CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218275Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Application Information

Application type	NDA
Application number	218275
Priority or standard	Priority
Submit date	8/3/2023
Received date	8/3/2023
PDUFA goal date	4/3/2024
Division/office	Division of Anti-Infectives (DAI)
Review completion date	3/29/2024
Established/proper name	Ceftobiprole medocaril sodium for injection
(Proposed) proprietary name	Zevtera
Pharmacologic class	Cephalosporin antibacterial
Other product name	Ceftobiprole
Applicant	BASILEA PHARMACEUTICA INTERNATIONAL LTD ALLSCHWIL
Dosage form/formulation	INJECTION, POWDER, LYOPHILIZED, FOR SOLUTION
Dosing regimen	***Staphylococcus aureus* Bacteremia (SAB) in Adults:** 667 mg every 6 hours on day 1 to 8, followed by every 8 hours from day 9 onwards over 2-hour infusion **ABSSSI and CABP in Adults:** 667 mg every 8 hours over 2 hour infusion **CABP in Pediatric Patients:** Adolescents: 12 to less than 18 years of age: 13.3 mg/kg (up to 667 mg) every 8 hours over 2-hour infusion Infants and children: 3 months and less than 12 years old: (b) (4) mg/kg (up to 667 mg) every 8 hours over 2 hour infusion Note: 667 mg of ceftobiprole medocaril sodium is equivalent to 500 mg of ceftobiprole. For pediatric patients: 13.3 mg/kg is equivalent to 10 mg/kg of ceftobiprole. (b) (4) mg/kg of ceftobiprole medocaril sodium is equivalent to (b) (4) mg/kg of ceftobiprole. Dosing adjustments for each indication are based on renal function

Applicant-proposed indications/ populations	1.Treatment of adult patients with *Staphylococcus aureus* bloodstream infection (bacteremia) (SAB), including those with right-sided infective endocarditis, caused by methicillin-susceptible and methicillin resistant isolates. 2.Treatment of adult patients with ABSSSI caused by susceptible isolates of the following gram-positive and gram-negative microorganisms: *Staphylococcus aureus* (methicillin-susceptible and methicillin-resistant isolates), *Streptococcus pyogenes,* [redacted] (b) (4) *and Klebsiella pneumoniae.* 3.Treatment of adult and pediatric patients (greater than or equal to 3 months to less than 18 years of age) with CABP caused by susceptible isolates of the following gram-positive and gram-negative microorganisms: *Staphylococcus aureus (methicillin-susceptible* [redacted] (b) (4) *isolates), Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae,* [redacted] (b) (4) *Escherichia coli, and Klebsiella pneumoniae*
SNOMED CT code for proposed indication disease term(s)1	406602003 |Infection caused by *Staphylococcus aureus* (disorder)| 128936008 |Bacterial infection of skin (disorder)| 385093006 |Community acquired pneumonia (disorder)|
Regulatory action	Approval
Approved dosage	See Tables below

Dosing in Adults

Indication[a]	Dose	Frequency
SAB	667 mg[b]	Every 6 hours on Days 1 to 8 Every 8 hours from Day 9
ABSSSI	667 mg[b]	Every 8 hours
CABP	667 mg[b]	Every 8 hours

[a] Duration of treatment **in adult patients** is up to 42 days for SAB and 5 days to 14 days for ABSSSI and CABP
[b] 667 mg of ceftobiprole medocaril sodium is equivalent to 500 mg of ceftobiprole. [b] 13.3 mg/kg of ceftobiprole medocaril sodium is equivalent to 10 mg/kg of ceftobiprole; 20 mg/kg ceftobiprole medocaril sodium is equivalent to 15 mg/kg of ceftobiprole. 667 mg ceftobiprole medocaril sodium is equivalent to 500 mg of ceftobiprole.
Dosing adjustments based on renal function.

Dosing in Pediatric Patients 3 Months to Less Than 18 Years Old

Pediatric Age Group	Dose[a]	Frequency
12 years to less than 18 years old	13.3 mg/kg (up to 667 mg/dose[b])	Every 8 Hours
3 months to less than 12 years old	20 mg/kg (up to 667 mg/dose[b])	Every 8 Hours

[a] Duration of treatment for CABP in **pediatric patients** is 7 days to14 days.
[b] 13.3 mg/kg of ceftobiprole medocaril sodium is equivalent to 10 mg/kg of ceftobiprole; 20 mg/kg ceftobiprole medocaril sodium is equivalent to 15 mg/kg of ceftobiprole. 667 mg ceftobiprole medocaril sodium is equivalent to 500 mg of ceftobiprole.
[redacted] (b) (4)

Approved indications/ populations	1. Treatment of adult patients with *Staphylococcus aureus* bloodstream infection (bacteremia), including those with right-sided infective endocarditis, caused by methicillin-susceptible and methicillin-resistant isolates 2. Treatment of adult patients with ABSSSI caused by susceptible isolates of the following gram-positive and gram-negative microorganisms: *Staphylococcus aureus* (methicillin-susceptible and methicillin-resistant isolates), *Streptococcus pyogenes*, and *Klebsiella pneumoniae* 3. Treatment of adult and pediatric patients (3 months to less than 18 years old) with community-acquired bacterial pneumonia (CABP) caused by susceptible isolates of the following gram-positive and gram-negative microorganisms: *Staphylococcus aureus* (methicillin-susceptible), *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Escherichia coli*, and *Klebsiella pneumoniae*
SNOMED CT code for approved indication disease term(s)[1]	406602003 |Infection caused by *Staphylococcus aureus* (disorder)| 128936008 |Bacterial infection of skin (disorder)| 385093006 |Community acquired pneumonia (disorder)|

[1] For internal tracking purposes only.
Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; CABP, community-acquired bacterial pneumonia; PDUFA, Prescription Drug User Fee Act; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms

Table of Tables xi
Table of Figures xxvii
Glossary xxxi
I. Executive Summary 34
1. Summary of Regulatory Action 34
2. Benefit-Risk Assessment 36
2.1. Benefit-Risk Framework 36
2.2. Conclusions Regarding Benefit-Risk 44
II. Interdisciplinary Assessment 46
3. Introduction 46
3.1. Review Issue List 48
3.1.1. Key Efficacy Review Issues 48
3.1.1.1. Re-Analysis of Trial CAP-3001 48
3.1.1.2. Clinical Success in Ukrainian Versus Non-Ukrainian Sites in Trial BPR-CS-009 48
3.1.2. Key Safety Review Issues 48
3.1.2.1. Higher Mortality for Ceftobiprole Patients with VABP in Trial BAP 248/307 48
3.1.2.2. Imbalance in Adverse Events Related to Thrombosis in Trial BPR-CS-009 48
3.2. Approach to the Clinical Review 48
4. Patient Experience Data 53
5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology 53
5.1. Nonclinical Assessment of Potential Effectiveness 53
5.2. Clinical Pharmacology/Pharmacokinetics 55
6. Efficacy (Evaluation of Benefit) 57
6.1. Assessment of Dose and Potential Effectiveness 57
6.2. Clinical Studies/Trials Intended to Demonstrate Efficacy 59
6.2.1. SAB, Trial BPR-CS-009 59
6.2.1.1. Design, Trial BPR-CS-009 59
6.2.1.2. Eligibility Criteria, Trial BPR-CS-009 61
6.2.1.3. Statistical Analysis Plan, Trial BPR-CS-009 63
6.2.1.4. Results of Analyses, Trial BPR-CS-009 69

Reference ID: 5357793

6.2.2. ABSSSI, Trial BPR-CS-008 76
6.2.2.1. Design, Trial BPR-CS-008 76
6.2.2.2. Eligibility Criteria, Trial BPR-CS-008 78
6.2.2.3. Statistical Analysis Plan, Trial BPR-CS-008 80
6.2.2.4. Results of Analyses, Trial BPR-CS-008 86
6.2.3. CABP, Trial CAP-3001 91
6.2.3.1. Design, Trial CAP-3001 91
6.2.3.2. Eligibility Criteria, Trial CAP-3001 94
6.2.3.3. Statistical Analysis Plan, Trial CAP-3001 96
6.2.3.4. Results of Analyses, Trial CAP-3001 104
6.2.4. Community-Acquired Bacterial Pneumonia, Trial BPR-PIP-002 107
6.3. Key Efficacy Review Issues 111
6.3.1. Re-Analysis of Trial CAP-3001 111
6.3.2. Clinical Success in Ukrainian Versus Non-Ukrainian Sites in Trial BPR-CS-009 121
7. Safety (Risk and Risk Management) 124
7.1. Potential Risks or Safety Concerns Based on Nonclinical Data 124
7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors 125
7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience 126
7.4. FDA Approach to the Safety Review 126
7.5. Adequacy of the Clinical Safety Database 128
7.6. Safety Results 129
7.6.1. SAB, Trial BPR-CS-009 129
7.6.1.1. Overview of Treatment-Emergent Adverse Events Summary, Trial BPR-CS-009 129
7.6.1.2. Deaths, Trial BPR-CS-009 130
7.6.1.3. Serious Treatment-Emergent Adverse Events, Trial BPR-CS-009 133
7.6.1.4. Adverse Events and FDA Medical Queries Leading to Treatment Discontinuation, Trial BPR-CS-009 137
7.6.1.5. Treatment-Emergent Adverse Events, Trial BPR-CS-009 139
7.6.1.6. Laboratory Findings, Trial BPR-CS-009 143
7.6.1.7. Assessment of Drug-Induced Liver Injury, Trial BPR-CS-009 150

Reference ID: 5357793

7.6.1.8. Vital Signs' Analyses, Trial BPR-CS-009 153
7.6.1.9. Subgroup Analyses, Trial BPR-CS-009 154
7.6.2. Acute Bacterial Skin/Soft Tissue Infection, Trial BPR-CS-008 155
7.6.2.1. Overview of Treatment-Emergent Adverse Events Summary, Trial BPR-CS-008 155
7.6.2.2. Deaths, Trial BPR-CS-008 156
7.6.2.3. Serious Treatment-Emergent Adverse Events, Trial BPR-CS-008 156
7.6.2.4. Adverse Events and FDA Medical Queries Leading to Treatment Discontinuation, Trial BPR-CS-008 159
7.6.2.5. Treatment-Emergent Adverse Events, Trial BPR-CS-008 160
7.6.2.6. Laboratory Findings, Trial BPR-CS-008 162
7.6.2.7. Assessment of Drug-Induced Liver Injury, Trial BPR-CS-008 167
7.6.2.8. Vital Signs' Analyses, Trial BPR-CS-008 171
7.6.2.9. Subgroup Analyses, Trial BPR-CS-008 171
7.6.3. Community-Acquired Bacterial Pneumonia, Trial CAP-3001 172
7.6.3.1. Overview of Treatment-Emergent Adverse Events Summary, Trial CAP-3001 172
7.6.3.2. Deaths, Trial CAP-3001 173
7.6.3.3. Serious Treatment-Emergent Adverse Events, Trial CAP-3001 174
7.6.3.4. Adverse Events Leading to Treatment Discontinuation, Trial CAP-3001 176
7.6.3.5. Treatment-Emergent Adverse Events, Trial CAP-3001 177
7.6.3.6. Laboratory Findings, Trial CAP-3001 180
7.6.3.7. Assessment of Drug-Induced Liver Injury, Trial CAP-3001 184
7.6.3.8. Vital Signs' Analyses, Trial CAP-3001 186
7.6.3.9. Subgroup Analyses, Trial CAP-3001 186
7.6.4. Community-Acquired Bacterial Pneumonia, Trial BPR-PIP-002 (Pediatric) 187
7.6.4.1. Overview of Treatment-Emergent Adverse Events Summary, Trial BPR-PIP-002 187
7.6.4.2. Deaths, Trial BPR-PIP-002 188
7.6.4.3. Serious Treatment-Emergent Adverse Events, Pediatric Trial BPR-PIP-002 188
7.6.4.4. Adverse Events and FDA Medical Queries Leading to Treatment Discontinuation, Trial BPR-PIP-002 191

Reference ID: 5357793

7.6.4.5. Treatment-Emergent Adverse Events, Trial BPR-PIP-002 192
7.6.4.6. Laboratory Findings, Trial BPR-PIP-002 193
7.6.4.7. Assessment of Drug-Induced Liver Injury, Trial BPR-PIP-002 196
7.6.4.8. Vital Signs' Analyses, Trial BPR-PIP-002 198
7.6.4.9. Subgroup Analyses, Trial BPR-PIP-002 200
7.6.5. Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia, Trial BAP 248/307 201
7.6.5.1. Overview of Treatment-Emergent Adverse Events Summary, Trial BAP 248/307 201
7.6.5.2. Deaths, Trial BAP 248/307 202
7.6.5.3. Serious Treatment-Emergent Adverse Events, Trial BAP 248/307 202
7.6.5.4. Adverse Events Leading to Treatment Discontinuation, Trial BAP 248/307 204
7.6.5.5. Treatment-Emergent Adverse Events, Trial BAP 248/307 208
7.6.5.6. Laboratory Findings, Trial BAP 248/307 209
7.6.5.7. Assessment of Drug-Induced Liver Injury, Trial BAP 248/307 213
7.6.5.8. Vital Signs' Analyses, Trial BAP 248/307 215
7.6.5.9. Subgroup Analyses, Trial BAP 248/307 215
7.7. Key Safety Review Issues 215
7.7.1. Higher Mortality for Ceftobiprole Patients With VABP in Trial BAP 248/307 215
7.7.2. Imbalance in Adverse Events Related to Thrombosis in Trial BPR-CS-009 217
8. Therapeutic Individualization 223
8.1. Intrinsic Factors 223
8.1.1. Renal Impairment 223
8.1.2. End-Stage Renal Disease and Patients Receiving Intermittent Hemodialysis 225
8.1.3. Patients With Augmented Renal Clearance 228
8.1.4. Pediatric Patients with Renal Impairment 229
8.1.5. Hepatic Impairment 233
8.1.6. Body Weight 233
8.1.7. Gender 233
8.1.8. Other Intrinsic Factors 233

Reference ID: 5357793

8.2. Extrinsic Factors 234
8.2.1. Pharmacokinetics Based Drug-Drug Interactions 234
8.3. Plans for Pediatric Drug Development 235
8.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential 236
9. Product Quality 236
9.1. Device or Combination Product Considerations 237
10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review 237
11. Advisory Committee Summary 238
III. Additional Analyses and Information 239
12. Summary of Regulatory History 239
13. Pharmacology Toxicology 242
13.1. Summary Review of Studies Submitted With the Investigational New Drug Application 242
13.1.1. Pharmacology 242
13.1.1.1. Safety Pharmacology 242
13.1.2. Toxicology 251
13.1.2.1. General Toxicology 251
13.1.2.2. Genetic Toxicology 269
13.1.2.3. Carcinogenicity 275
13.1.2.4. Reproductive Toxicology 275
13.1.2.5. Other Toxicology 287
13.2. Individual Reviews of Studies Submitted With the New Drug Application 304
14. Clinical Pharmacology 304
14.1. In Vitro Studies 304
14.1.1. Preclinical Studies to Determine the PK/PD Target of Ceftobiprole ..304
14.1.2. Protein Binding 309
14.1.3. Metabolism 310
14.1.4. Potential for CYP Enzyme-Mediated Drug-Drug Interactions 311
14.1.5. Potential for Transporter-Mediated Drug-Drug Interactions 312
14.2. In Vivo Studies 314
14.2.1. Single Ascending Dose 314

Reference ID: 5357793

14.2.2. Multiple Ascending Dose....324
14.2.3. Renal Impairment....327
14.2.4. Obesity....330
14.2.5. Drug Penetration....332
14.3. Bioanalytical Method Validation and Performance....335
14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety...339
14.5. Pharmacometrics Assessment....339
14.5.1. Population PK Analysis....339
14.5.1.1. Review Summary....339
14.5.1.2. Introduction of Analysis Reports....343
14.5.1.3. ABSSSI and CABP....344
14.5.1.4. *Staphylococcus aureus* Bacteremia....353
14.5.1.5. Pediatrics CABP....362
14.5.2. Exposure-Response Analysis and PTA....368
14.5.2.1. ABSSSI and CABP PK/PD Analysis....368
14.5.2.2. *Staphylococcus aureus* Bacteremia PK/PD Analysis....398
14.5.2.3. Assessment of End-Stage Renal Disease Dosing Regimen for Adults....412
14.5.2.4. Pediatrics CABP PK/PD Analysis....414
14.5.2.5. Assessment of Severe Renal Impairment Dosing Regimen for Adolescents....422
14.6. Pharmacogenetics....423
15. Study/Trial Design....423
16. Efficacy....423
17. Clinical Safety....423
17.1. Phase 1 Studies....423
17.2. *Staphylococcus aureus* Bacteremia, Trial BPR-CS-009....424
17.3. Acute Bacterial Skin/Soft Tissue Infection, Trial BPR-CS-008....438
17.4. Community-Acquired Bacterial Pneumonia, Trial CAP-3001....444
17.5. Community-Acquired Bacterial Pneumonia, Trial BPR-PIP-002 (Pediatric)....457
17.6. HABP/VABP, Trial BAP 248/307....458
18. Clinical Virology....485

Reference ID: 5357793

19. Clinical Microbiology 485
19.1. In Vitro Activity 485
19.2. Interaction With Other Antimicrobials 488
19.3. In Vivo Activity 488
19.4. PK/PD Studies 497
19.5. Clinical Studies 500
19.6. In Vitro Susceptibility Test Method 512
19.7. In Vitro Susceptibility Test Interpretive Criteria/Breakpoints 514
20. Mechanism of Action/Drug Resistance 519
20.1. Mechanism of Action 519
20.2. Mechanism of Resistance 525
21. Other Drug Development Considerations 529
22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections) 529
23. Labeling: Key Changes and Considerations 529
23.1. Approved Labeling Types 535
24. Postmarketing Requirements and Commitments 535
25. Financial Disclosure 537
26. References 538
27. Review Team 544
27.1. Reviewer Signatures 544

Table of Tables

Table 1. Application Information i

Table 2. Benefit-Risk Framework for Treatment of *Staphylococcus aureus* Bacteremia 36

Table 3. Benefit Risk Framework for Treatment of Acute Bacterial Skin/Soft Tissue Infection 39

Table 4. Benefit-Risk Framework for Treatment of Community-Acquired Bacterial Pneumonia....41

Table 5. Clinical Studies/Trials Submitted in Support of Efficacy and/or Safety Determinations[1] for Ceftobiprole....49

Table 6. Patient Experience Data Submitted or Considered....53

Table 7. Summary Statistics for Ceftobiprole Free-Drug Plasma %T>MIC Targets Associated With Net Bacterial Stasis and 1- and 2-log10 CFU Reductions From Baseline in a Neutropenic Murine Thigh Infection Model....54

Table 8. Summary of Clinical Pharmacology and Pharmacokinetics....55

Table 9. Day 3 Simulated Exposures of Ceftobiprole 55

Table 10. Ceftobiprole Dosage Evaluated in Phase 3 Trials 58

Table 11. Recommended Dosage in Pediatric Patients With CABP 59

Table 12. Reasons for Discontinuation From the Study and Discontinuation of Trial Treatment, Trial BPR-CS-009 65

Table 13. Baseline Demographic and Disease Characteristics (mITT Population) Trial BPR-CS-009 66

Table 14. Categories of Complicated *Staphylococcus aureus* Bacteremia at Baseline (mITT Population) Trial BPR-CS-009 67

Table 15. Overall Success Based on DRC Assessment at the PTE Visit (mITT Population), Trial -CS-009....70

Table 16. Key Secondary Endpoint Analyses (mITT), Trial BPR-CS-009....71

Table 17. Overall Success Based on DRC Assessment at the PTE Visit in Subgroups by Age, Gender, Race and Ethnicity (mITT Population), Trial BPR-CS-009 72

Table 18. Overall Success Based on DRC Assessment at the PTE Visit in Subgroups by Geographic Region (mITT Population), Trial BPR-CS-009 72

Table 19. Overall Success Based on DRC Assessment at the PTE Visit in Subgroups of Known Predisposing Risk Factors for *Staphylococcus aureus* Bacteremia and Infective Endocarditis, Trial BPR-CS-009 73

Table 20. Overall Success Based on DRC Assessment at the PTE Visit by Baseline Renal Function (mITT Population), Trial BPR-CS-009....73

Table 21. Major Protocol Deviations (ITT Population) Trial BPR-CS-009....74

Reference ID: 5357793

Table 22. Overall Success Based on DRC Assessment at the PTE Visit by MSSA or MRSA Designation (mITT Population) Trial BPR-CS-009....74

Table 23. DRC-Assessed and Investigator-Assessed Overall Success at the PTE Visit (mITT population) Trial BPR-CS-009....75

Table 24. Overall Success Based on DRC Assessment at the PTE Visit by Cohort (mITT Population), Trial BPR-CS-009....75

Table 25. Reasons for Discontinuation from Trial and Discontinuation of Trial (ITT Population), Trial BPR-CS-008....81

Table 26. Baseline Demographic and Disease Characteristics (mITT Population) Trial BPR-CS-008....83

Table 27. Primary Endpoint: Proportion of Subjects with Early Clinical Response 48–72 Hours After Start of Therapy, Trial BPR-CS-008....86

Table 28. Main Secondary Endpoint: Proportion of Subjects With Investigator-Assessed Clinical Success at the TOC Visit, Trial BPR-CS-008....87

Table 29. Other Secondary Endpoint Results, Trial BPR-CS-008....88

Table 30. Early Clinical Response at 48-72 hours after Start of Treatment by Age, Gender, Race, Ethnicity, Geographic Region, and Baseline ABSSSI Type (ITT Population), Trial BPR-CS-008....89

Table 31. Major Protocol Deviations, BPR-CS-008....91

Table 32. Reasons for Discontinuation From Trial (ITT Population), Trial CAP-3001 ...96

Table 33. Baseline Demographic and Disease Characteristics (ITT Population)....98

Table 34. Microbiological Outcome at the TOC Visit for Subjects With a Valid Pathogen at Baseline....102

Table 35. Analyses of Co-Primary Endpoints: Clinical Outcome at the TOC Visit in the CE and ITT Populations, Trial CAP-3001....104

Table 36. Analyses of Key Secondary Endpoints in Microbiological Eradication at the TOC Visit, Clinical Cure Rate at TOC in Subjects With PSI ≥91 and 30-day Pneumonia-Specific Mortality Rates, Trial CAP-3001....105

Table 37. Subgroup Analyses of Clinical Cure Rates at the TOC Visit by Baseline Characteristics (ITT Population)....106

Table 38. Analyses of Co-Primary Endpoints in Clinical Outcome at the TOC Visit in the CE and ITT Populations (Removing Dr. Yin-Ching Chuang's Site in Taiwan, Site id 886005), Trial CAP-3001....107

Table 39. Comparison of the Primary Endpoint Defined in the 2020 FDA CABP Guidance with the Equivalent pre-Specified Endpoint, CAP-3001....113

Table 40. Clinical, Radiographic, and Microbiologic Entry Criteria in the 2020 FDA CABP Guidance Compared to Inclusion Criteria for Trial CAP-3001 114

Reference ID: 5357793

Table 41. Baseline Demographic and Disease Characteristics (Prespecified ITT Population and re-Analysis Day 3-Modified ITT Population), CAP-3001 116

Table 42. (Re-Analysis): Results in Accordance With the 2020 FDA CABP, CAP-3001.....118

Table 43. CAP-3001: Subgroup Analyses of the re-Analysis Primary Endpoint in Accordance With the 2020 FDA CABP Guidance (Day 3-ITT and Day 3 Modified ITT Population).....119

Table 44. (Re-Analysis): Clinical Success at Day 3 by Causative Pathogen in Accordance With the 2020 FDA CABP Guidance, CAP-3001.....120

Table 45. Overview of the Distribution of Categories of Both Complicated and Potential *Staphylococcus aureus* Bacteremia Source Control Between Ukraine and Other Countries 123

Table 46. Duration of Exposure, Safety Population, Integrated Summary of Safety Dataset.....128

Table 47. Overview of Adverse Events, Safety Population, Trial BPR-CS-009.....129

Table 48. Deaths, Safety Population, Trial BPR-CS-009 131

Table 49. Adverse Event Leading to Deaths by Preferred Term, Safety Population, Trial BPR-CS-009.....132

Table 50. Subjects With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Trial BPR-CS-009, Cohorts 1 and 2 135

Table 51. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Trial BPR-CS-009, Cohorts 1 and 2 138

Table 52. Grouped Queries by Preferred Term, Showing Terms Occurring in at Least 1% of Subjects in the Ceftobiprole Arm, Safety Population Trial BPR-CS-009 142

Table 53. Subjects With One or More Chemistry Analyte Values With Elevated or Low Values Meeting Specified Levels, Safety Population, Trial BPR-CS-009, Cohorts 1 and 2 144

Table 54. Subjects With One or More Kidney Function Analyte Values Exceeding Specified Levels, Safety Population, Trial BPR-CS-009, Cohorts 1 and 2.....146

Table 55. Subjects With One or More Hematology Analyte Values Exceeding Specified Levels, Safety Population, Trial BPR-CS-009, Cohorts 1 and 2.....149

Table 56. Subjects in Each Quadrant for Potential Hepatocellular DILI Screening Plot, Safety Population, Trial BPR-CS-009, Cohorts 1 and 2 151

Table 57. Subjects With One or More Liver Biochemistry Analyte Values Exceeding Level 2, Safety Population, Trial BPR-CS-009, Cohorts 1 and 2.....151

Table 58. Adverse Events of Special Interest Assessment, Safety Population, Trial BPR-CS-009 152

Reference ID: 5357793

Table 59. Percentage of Subjects With Maximum Systolic Blood Pressure by Category of Blood Pressure Post-Baseline, Safety Population, Trial BPR-CS-009..153

Table 60. Percentage of Subjects With Maximum Diastolic Blood Pressure by Category of Blood Pressure Post-Baseline, Safety Population, Trial BPR-CS-009, Cohorts 1 and 2 154

Table 61. Overview of Adverse Events by Demographic Subgroup, Safety Population, Trial BPR-CS-009 154

Table 62. Overview of Adverse Events, Safety Population, Trial BPR-CS-008.....155

Table 63. Deaths, Safety Population, Trial BPR-CS-008.....156

Table 64. Subjects With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Trial BPR-CS-008.....157

Table 65. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Trial BPR-CS-008 160

Table 66. Grouped Queries by Preferred Term, Showing Terms Occurring in at Least 1% of Subjects in the Ceftobiprole Arm, Safety Population, Trial BPR-CS-008 162

Table 67. Subjects With Selected Chemistry Values Level 2 or Higher by Treatment Arm, Safety Population, Trial BPR-CS-008.....162

Table 68. Subjects With One or More Kidney Function Analyte Values Exceeding Level 2 or Higher, Safety Population, Trial BPR-CS-008.....164

Table 69. Subjects With One or More Hematology Analyte Values Exceeding Level 2 or Higher, Safety Population, Trial BPR-CS-008.....166

Table 70. Drug Induced Liver Injury Assessment, Safety Population, Trial BPR-CS-008.....169

Table 71. Subjects With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels, Safety Population, Trial BPR-CS-008 170

Table 72. Overview of Adverse Events by Demographic Subgroup, Safety Population, Trial BPR-CS-008 172

Table 73. Overview of Adverse Events, Safety Population, Trial CAP-3001.....173

Table 74. Overview of Deaths, Safety Population, Trial CAP-3001.....173

Table 75. Subjects With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Trial CAP-3001.....174

Table 76. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Trial CAP-3001 176

Table 77. Subjects With Common Adverse Events, Recoded, Occurring at ≥2% Frequency in the Ceftobiprole Arm, Safety Population, Trial CAP-3001.....179

Table 78. Subjects With One or More Chemistry Analyte Values With Elevated or Low Values Meeting Specified Levels, Safety Population, Trial CAP-3001.....180

Reference ID: 5357793

Table 79. Subjects With One or More Kidney Function Analyte Values Exceeding Specified Levels, Safety Population, Trial CAP-3001 181

Table 80. Subjects With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels, Safety Population, Trial CAP-3001 182

Table 81. Subjects With One or More Lipids Analyte Values Exceeding Specified Levels, Safety Population, Trial CAP-3001 182

Table 82. Subjects With One or More Hematology Analyte Values Exceeding Specified Levels, Safety Population, Trial CAP-3001 183

Table 83. Subjects in Each Quadrant for Potential Hepatocellular DILI Screening Plot, Safety Population, Trial CAP-3001.....186

Table 84. Overview of Adverse Events by Demographic Subgroup, IV Treatment Period, Safety Population, Trial CAP-3001.....186

Table 85. Overview of Adverse Events, Safety Population, Trial BPR-PIP-002.....187

Table 86. Subjects With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Trial BPR-PIP-002.....188

Table 87. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Trial BPR-PIP-002 ...191

Table 88. Subjects with Adverse Events, Safety Population, Trial BPR-PIP-002 193

Table 89. Subjects With One or More Chemistry Analyte Values With Elevated or Low Values Meeting Specified Levels, Safety Population, Trial BPR-PIP-002.....194

Table 90. Subjects With One or More Kidney Function Analyte Values Exceeding Specified Levels, Safety Population, Trial BPR-PIP-002 194

Table 91. Subjects With One or More Hematology Analyte Values Exceeding Specified Levels, Safety Population, Trial BPR-PIP-002 195

Table 92.Hepatic Enzyme Abnormalities Over Time in Subjec (b) (6) 197

Table 93, Hepatic Enzyme Abnormalities Over Time in Subject (b) (6) 197

Table 94. Hepatic Enzyme Abnormalities Over Time in Subject (b) (6) 197

Table 95. Percentage of Subjects Meeting Specific Hypotension Levels Post-Baseline, Safety Population, Trial BPR-PIP-002 200

Table 96. Overview of Adverse Events by Demographic Subgroup, IV Treatment Period, Safety Population, Trial BPR-PIP-002.....200

Table 97. Overview of Adverse Events, Safety Population, Trial BAP248/307.....201

Table 98. Subjects With Serious Adverse Events Occurring at ≥0.5% Frequency by System Organ Class and Preferred Term, Safety Population, Trial BAP248/307.....202

Table 99. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Trial BAP248/307.....205

Reference ID: 5357793

Table 100. Subjects With Common Adverse Events, Recoded, Occurring at ≥4% Frequency in the Ceftobiprole Arm, Safety Population, Trial BAP248/307.....208

Table 101. Subjects With One or More Chemistry Analyte Values With Elevated or Low Values Meeting Specified Levels, Safety Population, Trial BAP248/307.....210

Table 102. Subjects With One or More Kidney Function Analyte Values Exceeding Specified Levels, Safety Population, Trial BAP248/307.....211

Table 103. Subjects With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels, Safety Population, Trial BAP248/307.....211

Table 104. Subjects With One or More Lipids Analyte Values Exceeding Specified Levels, Safety Population, Trial BAP248/307.....212

Table 105. Subjects With One or More Hematology Analyte Values Exceeding Specified Levels, Safety Population, Trial BAP248/307.....212

Table 106. Subjects in Each Quadrant for Potential Hepatocellular DILI Screening Plot, Safety Population, Trial BAP248/307.....214

Table 107. Overview of Adverse Events by Demographic and Diagnosis Subgroup, Safety Population, Trial BAP248/307.....215

Table 108. Deaths and Drug Relatedness Determined by FDA Reviewer.....216

Table 109. Adverse Events Assessment of Thrombosis FDA Medical Query (Narrow), Safety Population, Trial BPR-CS-009, Cohorts 1 and 2.....218

Table 110. Case Overview (b) (6).....222

Table 111. Ceftobiprole Dosage for Adult Patients With Renal Impairment.....223

Table 112. Predicted Ceftobiprole C_{max} and AUC in Subjects With Normal and Impaired Renal Function Following the Proposed Dosage Adjustment in Adult Patients with Renal Impairment.....224

Table 113. Summary of Ceftobiprole Exposures by Indication and Renal Function.....226

Table 114. Subgroup Results for Overall Success at the PTE Visit in the Modified Intent-to-Treat Population by Baseline Creatinine Clearance and Dialysis.....228

Table 115. Subgroup Results for All-Cause Mortality at the PTE Visit in the Modified Intent-to-Treat Population by Baseline Creatinine Clearance and Dialysis.....228

Table 116. Ceftobiprole Recommended Dosage Regimens for Pediatric Patients With CABP and with Renal Impairment.....230

Table 117. Predicted PK-PD Target Attainment by Age Group in Patients With Renal Impairment Using the Population PK Model Fit to the Pooled Pediatric/Adult Data.....232

Table 118. In Vitro Transporter Inhibition Assessment Based on Calculated R Values.235

Table 119. In Vivo Cardiovascular Safety Study in Marmosets and Rats.....242

Table 120. In Vivo Cardiovascular Safety Study in Dogs.....243

Reference ID: 5357793

Table 121. In Vitro Cardiovascular Safety 243
Table 122. Central Nervous System 243
Table 123. In Vivo Pulmonary Function Study in Rats....244
Table 124. Metabolism of BAL5788 (Ceftobiprole Medocaril Sodium) 246
Table 125. Comparative Metabolism of Ceftobiprole Medocaril Sodium Summary....247
Table 126. Urinary Excretion of BAL9141 (% Dose Administered That is Recovered in 24 Hours) 247
Table 127. Toxicokinetic Studies Summary....249
Table 128. Study Information....251
Table 129. Observations and Results....252
Table 130. Plasma Histamine Concentrations (nm/L) in Dogs 253
Table 131. Study Information....253
Table 132. Observations and Results....253
Table 133. Plasma Concentrations of BAL5587 and BAL9141 10 Minutes Before the End of 4-Hour Intravenous Infusion of BAL5788 on Days 0 and 13....255
Table 134. Concentrations of BAL5587 and BAL9141 in Urine for 0 to 2, 2 to 4 and 4 to 6 Hours After Initiation of a 4-Hour Intravenous Infusion of BAL5788 to Rats on Days 0 and 13 256
Table 135. Study Information....257
Table 136. Observations and Results....257
Table 137. Study Information #BAP00046 258
Table 138. Observations and Results #BAP00046....258
Table 139. Incidence of Microscopic Observations in Rat....258
Table 140. Toxicokinetics Analysis....259
Table 141. Study Information....260
Table 142. Observations and Results....260
Table 143. Toxicokinetic Parameters 261
Table 144. Study Information....261
Table 145. Observations and Results....262
Table 146. Plasma Concentrations of BAL5788 and BAL9141 in Marmosets (mcg/mL) 263
Table 147. Study Information....264
Table 148. Observations and Results....265
Table 149. Plasma Toxicokinetic Parameters in Rats Treated IV With BAL5788 266

Reference ID: 5357793

Table 150. Study Information TOX7918 266
Table 151. Observations and Results TOX7918 267
Table 152. Plasma Levels in 13-Week Dog Study (mcg/mL) 267
Table 153. B167'797: Mutagenicity Evaluation of Ro 655788/001 in the Ames Test 269
Table 154. TOX8637 CHO/HPRT Forward Mutation Assay of JNJ-30982081 269
Table 155. Ro 9141/001 Mouse Lymphoma Cell Mutation Test (ML/TK) Research Report # B-167'775 271
Table 156. Ro 65-5700/001: Mouse Lymphoma Cell Mutation Test (ML/TK) Research Report # B-169'336 272
Table 157. Chromosome Aberration Test With Human Peripheral Blood Lymphocytes. Research Report # B-169'918 273
Table 158. Ro 65-5788/001: Micronucleus Test in Mouse Bone Marrow and Toxicokinetic Monitoring – Intravenous Administration Research Report # B-169'919 274
Table 159. Toxicokinetic Parameters of R0 63-9141 After Single Intravenous Administration of Ro 65-5788/001 to Mice in a Micronucleus Test 274
Table 160. Ro 65-5788/001: Measurement of Unscheduled DNA Synthesis in Rat Liver Using an in Vivo/in Vitro Procedure. Report # 1003801 275
Table 161. Methods, BAP00232 276
Table 162. Observations and Results, BAP00232 276
Table 163. Plasma Concentration (mcg/mL) of BAL5788 and BAL9141 in Female Rats, BAP00232 276
Table 164. Methods, BAP000231 277
Table 165. Observations and Results, BAP000231 277
Table 166. Method of Embryo-Fetal Developmental Study in Rats, BAP00173 278
Table 167. Observations and Results, BAP00173 278
Table 168. Plasma Levels of BAL5788 and BAL9141 in Pregnant Rats (mcg/mL on Gestation Day 6), BAP00173 279
Table 169. Plasma Levels of BAL5788 and BAL9141 in Pregnant Rats (mcg/mL on Gestation Day 17), BAP00173 279
Table 170. Method of Embryo-Fetal Developmental Study in Cynomolgus Monkeys, BAP00051 279
Table 171. Observations and Results, BAP00051 280
Table 172. Plasma levels of BAL5788 and BAL9141 in Pregnant Monkeys (mcg/mL), BAP00051 280
Table 173. Pre- and Post-Natal Development Study in Rats, BAP00640 281

Reference ID: 5357793

Table 174. Study Findings (F0 Generation), BAP00640.....281

Table 175. Study Findings (F1 Generation), BAP00640.....282

Table 176. Study Findings (F2 Generation), BAP00640.....282

Table 177. Concentration of BAL9141 and BAL5788 in Plasma of Female Rats (mcg/mL), BAP00640.....283

Table 178. Methods, TOX8611. Ceftobiprole Medocaril Sodium (BAL5788) 284

Table 179. Observations and Results, TOX8611. Ceftobiprole Medocaril Sodium (BAL5788).....285

Table 180. Toxicokinetics of BAL5788 (Ceftobiprole Medocaril Sodium).....286

Table 181. Toxicokinetics of BAL9141 (Ceftobiprole) 286

Table 182.183 Primary Packaging Container for Ceftobiprole Medocaril Sodium for Injection 289

Table 184. Drug Substance Impurities Not Fully Qualified in Toxicology Studies.....293

Table 185. Drug product Impurities Not Fully Qualified in Toxicology Studies.....294

Table 186: (b) (4): Bacterial Reverse Mutation Assay 296

Table 187. (b) (4): Bacterial Reverse Mutation Assay.....297

Table 188. (b) (4): Bacterial Reverse Mutation Assay.....297

Table 189. TOX8697: Bacterial Reverse Mutation Assay of (b) (4).....298

Table 190. *Salmonella typhimurium* and *Escherichia coli* Reverse Mutation Assay with (b) (4) 298

Table 191. In Vitro Chromosome Aberration Test in Chinese Hamster V79 Cells With (b) (4) (RMD854).....299

Table 192. Micronucleus Assay in Bone Marrow Cells of the Mouse With (b) (4)299

Table 193. Bone Marrow Micronucleus Assay in Mice Dosed by Intravenous Administration With (b) (4)Study TOX8696) 300

Table 194. CHO/HPRT Forward Mutation Assay of (b) (4) in Duplicate Cultures With Confirmatory Assay.....301

Table 195. TOX8809: Bacterial Reverse Mutation Assay of (b) (4).....302

Table 196. Summary of Genotoxicity Assay Results for (b) (4) (Ceftobiprole Medocaril Sodium and Ceftobiprole Are Included for Reference) 302

Table 197. Summary Statistics for Ceftobiprole Free-Drug Plasma %T>MIC Targets Associated With Net Bacterial Stasis and 1- and 2-log10 CFU Reductions From Baseline in a Neutropenic Murine-Thigh Infection Model.....306

Table 198. Activity of Ceftobiprole (Dosed as Ceftobiprole Medocaril Sodium) and Ceftriaxone in a Mouse Model of Acute Pneumococcal Pneumonia 307

Reference ID: 5357793

Table 199. %*f*T>MICs for Corresponding Effective Doses of Ceftobiprole Against *Staphylococcus aureus* Isolates in an Immunocompromised Murine Pneumonia Model 308

Table 200. Relationship Between Ceftobiprole Exposure, Expressed as %fT>MIC in Murine Plasma or %T>MIC in Murine ELF and Cell Kill for Eight Strains of *Staphylococcus aureus* 308

Table 201. Plasma Protein Binding of Ceftobiprole in Animal Species and Human 309

Table 202. Plasma Protein Binding of Ceftobiprole in Humans 310

Table 203. In Vitro Cytochrome P450 Inhibition Assessment 312

Table 204. Pharmacokinetic Parameters of Ceftobiprole After Single Ascending Intravenous Infusions (n=3) 315

Table 205. Urinary Excretion of Ceftobiprole and the β-Lactam Ring-Open metabolite (BAL2070) after Single Ascending Intravenous Infusions (N=3) 315

Table 206. Summary of Ceftobiprole Pharmacokinetic Parameters Following Single Intravenous Administration of 125, 250, 500, 750 and 1000 mg of Ceftobiprole Medocaril Sodium in Healthy, Male Subjects 316

Table 207. Individual And Mean Ceftobiprole Urine Pharmacokinetic Parameters Following Intravenous Infusion of Ceftobiprole 125 mg to Healthy Male Volunteers 317

Table 208. Summary of Ceftobiprole Pharmacokinetic Parameters Following Single Intravenous Administration of 750 mg of Ceftobiprole Medocaril Sodium in Healthy Male and Female Subjects 318

Table 209. Summary of Ceftobiprole Pharmacokinetic Parameters Following Single Intravenous Administration of 500 and 750 mg Infusions of Ceftobiprole Medocaril Sodium in Healthy Subjects 319

Table 210. Mean Plasma Concentrations of ceftobiprole at Various Times After the Start of Infusion Following Single Intravenous Administration of 500 mg and 750 mg Infusions of Ceftobiprole Medocaril Sodium in Healthy Subjects 319

Table 211. Summary of Ceftobiprole Pharmacokinetic Parameters Following Single (Day 1) and Multiple (Day 5) Intravenous Administration of Ceftobiprole Medocaril Sodium in Healthy Adults 321

Table 212. Summary of Open-Ring Metabolite Pharmacokinetic Parameters Following Single (Day 1) and Multiple (Day 5) Intravenous Administration of Ceftobiprole Medocaril Sodium in Healthy Adults 322

Table 213. Mean Urinary Recovery (Expressed as a Percentage of Dose) of Ceftobiprole Prodrug, Active Moiety, and Open Ring Metabolite Following Single (Day 1) and Multiple (Day 5) Intravenous Administration of Ceftobiprole Medocaril Sodium in Healthy Adults 322

Table 214. Mean (SD) Pharmacokinetic Parameters of Ceftobiprole per Age Group 323

Table 215. Summary of Ceftobiprole Pharmacokinetic Parameters Following Multiple Intravenous Administration of 500 and 750 mg of Ceftobiprole Medocaril Sodium in Healthy, Male Subjects 325

Table 216. Summary of Ceftobiprole Pharmacokinetic Parameters Following Multiple Intravenous Administration of 750 mg of Ceftobiprole Medocaril Sodium for 12 Days in Healthy, Male Subjects....326

Table 217. Summary of Ceftobiprole Pharmacokinetic Parameters Following Single Intravenous Administration of 250 mg of Ceftobiprole Medocaril Sodium in Healthy and Renally Impaired Male Subjects 327

Table 218. Mean (SD) Ceftobiprole PK Parameters in Healthy Subjects and End-Stage Renal Disease Subjects Following a Single Intravenous Infusion of 250 mg Ceftobiprole Administered Over 2 Hours....329

Table 219. Mean (SD) Plasma Ceftobiprole Pharmacokinetic Parameters Following a Single 2-Hour Infusion of Ceftobiprole 500 mg in Morbidly Obese and Non-Obese Subjects....331

Table 220. Mean (SD) Time Above MIC and Percent Time Above MIC for Ceftobiprole Following a 2-Hour Intravenous Infusion of Ceftobiprole 500 mg in Morbidly Obese and Non-Obese Subjects....331

Table 221. Mean (SD) Ceftobiprole Pharmacokinetic Parameters in Plasma, Skeletal Muscle, and Adipose Tissue Following a Single 2-Hour Intravenous Infusion of Ceftobiprole 500 mg to Healthy Subjects....333

Table 222. Mean Ceftobiprole Plasma PK Parameters on Day 2....334

Table 223. Mean (SD) Ceftobiprole Concentrations at BAL Sampling Time Points in the ELF and AM and the Ratios of the ELF and AM Concentrations on Day 2 Compared to Unbound Plasma Concentrations....334

Table 224. Bioanalytical Methods Used to Quantify Ceftobiprole Plasma, Urine, Ultrafiltrate, Dialysate, Bone and BAL Samples....336

Table 225. Specific Comments on Applicant's Final Population PK model....340

Table 226. Summary of Submitted PK and PK/PD Reports 343

Table 227. Summary of Studies Included in the PopPK Analysis 345

Table 228. Summary of Baseline Characteristics in Phase 1 Subjects....347

Table 229. Summary of Baseline Characteristics in Phase 3 Subjects....348

Table 230. Covariates Evaluated During Model Development....349

Table 231. Parameter Estimates for the Final PopPK Model for ABSSSI and CABP....350

Table 232. Summary of *Staphylococcus aureus* Bacteremia Clinical Trial....354

Table 233. Summary of Baseline Characteristics of Phase 3 *Staphylococcus aureus* Bacteremia Subjects and Phase 3 ABSSSI and CABP Subjects 354

Reference ID: 5357793

Table 234. Parameter Estimates for the Final PopPK Model for *Staphylococcus aureus* Bacteremia 355

Table 235. Summary of Ceftobiprole Exposures and PK Parameters for Phase 3 Subjects by Trial Including ABSSSI and CABP Studies 359

Table 236. Summary of Pediatric Studies.....363

Table 237. Summary of Baseline Characteristics for All Pediatric Subjects 364

Table 238. Parameter Estimates for the Final PopPK Model for Pediatric and Adult Subjects.....365

Table 239. Summary Statistics for Baseline MIC, Day 1 Free-Drug AUC, and %T>MIC in Analysis Populations.....369

Table 240. Summary of Successful Response for Efficacy Endpoints by Analysis Populations and Subpopulations.....370

Table 241. Summary Statistics for Baseline MIC, Day 1 Free-Drug AUC, and %T>MIC in Analysis Populations.....370

Table 242. Summary Statistics for Baseline MIC, Day 1 Free-Drug AUC, and %T>MIC in Pooled Analysis Populations.....371

Table 243. Summary of Percentage of Subjects in the Pooled ABSSSI, CABP, and HAP/VAP mITT and ME Analysis Populations Achieving Nonclinical Targets 372

Table 244. Ceftobiprole Regimens for Simulations 373

Table 245. Summary Statistics for Simulated Ceftobiprole Day 1 AUC Across Renal Function Groups for ABSSSI 376

Table 246. Summary Statistics for Simulated Ceftobiprole Day 1 C_{max} Across Renal Function Groups for ABSSSI 376

Table 247. Summary Statistics for Simulated Ceftobiprole Day 1 AUC Across Renal Function Groups for CABP 379

Table 248. Summary Statistics for Simulated Ceftobiprole Day 1 C_{max} Across Renal Function Groups for CABP 379

Table 249. PTA Results by MIC on Day 1 Based on Median Nonclinical Ceftobiprole Free-Drug Plasma %T>MIC Targets Associated With *Staphylococcus aureus* Efficacy.....380

Table 250. PTA Results by MIC on Day 1 Based on Randomly Assigned Nonclinical Ceftobiprole Free-Drug Plasma %T>MIC Targets Associated With *Staphylococcus aureus* Efficacy 381

Table 251. PTA Results by MIC on Day 1 Based on Median Nonclinical Ceftobiprole Free-Drug Plasma %T>MIC Targets Associated With *Streptococcus* species Efficacy.....383

Table 252. PTA Results by MIC on Day 1 Based on Randomly Assigned Non-Clinical Ceftobiprole Free-Drug Plasma %T>MIC Targets Associated With *Streptococcus* Species Efficacy 384

Reference ID: 5357793

Table 253. Ceftobiprole MIC Distributions (*Enterobacterales* Isolates) 386

Table 254. PTA Results by MIC on Day 1 Based on Median Nonclinical Ceftobiprole Free-Drug Plasma %T>MIC Targets Associated With *Enterobacterales* Efficacy ..387

Table 255. PTA Results by MIC on Day 1 Based on Randomly Assigned Nonclinical Ceftobiprole Free-Drug Plasma %T>MIC Targets Associated With *Enterobacterales* Efficacy 387

Table 256. PTA Results by MIC on Day 1 Based on Median Nonclinical Ceftobiprole Free-Drug Plasma %T>MIC Targets Associated With *Streptococcus pneumoniae* Efficacy 389

Table 257. PTA Results by MIC on Day 1 Based on Randomly Assigned Nonclinical Ceftobiprole Free-Drug Plasma %T>MIC Targets Associated With *Streptococcus pneumoniae* Efficacy 390

Table 258. PTA Results by MIC on Day 1 Based on Median Nonclinical Ceftobiprole Free-Drug Plasma %T>MIC Targets Associated With *Staphylococcus aureus* Efficacy 392

Table 259. PTA Results by MIC on Day 1 Based on Randomly Assigned Nonclinical Ceftobiprole Free-Drug Plasma %T>MIC Targets Associated With *Staphylococcus aureus* Efficacy 393

Table 260. PTA Results by MIC on Day 1 Based on Median Nonclinical Ceftobiprole Free-Drug Plasma %T>MIC Targets Associated With *Enterobacterales* Efficacy ..395

Table 261. PTA Results by MIC on Day 1 Based on Randomly Assigned Nonclinical Ceftobiprole Free-Drug Plasma %T>MIC Targets Associated With *Enterobacterales* Efficacy 396

Table 262. Dosing Regimens Studied in BPR-CS-009 399

Table 263. Summary of Response for Efficacy Endpoints by Visit 399

Table 264. Summary Statistics for Baseline MIC, Day 1 Free-Drug AUC, and %T>MIC in Analysis Populations 400

Table 265. Summary of Percentage of Subjects in the *Staphylococcus aureus* Bacteremia mITT and ME Analysis Populations Achieving Nonclinical Targets 400

Table 266. Ceftobiprole Regimens for Simulations 401

Table 267. Summary Statistics for Simulated Ceftobiprole Day 1 AUC Across Renal Function Groups for *Staphylococcus aureus* Bacteremia 406

Table 268. Summary Statistics for Simulated Ceftobiprole Day 10 AUC Across Renal Function Groups for *Staphylococcus aureus* Bacteremia 406

Table 269. Summary Statistics for Simulated Ceftobiprole Day 1 C_{max} Across Renal Function Groups for *Staphylococcus aureus* Bacteremia 406

Table 270. Summary Statistics for Simulated Ceftobiprole Day 10 C_{max} Across Renal Function Groups for *Staphylococcus aureus* Bacteremia 407

Reference ID: 5357793

Table 271. PTA Results by MIC on Day 1 Based on Median Nonclinical Ceftobiprole Free-Drug Plasma %T>MIC Targets Associated With *Staphylococcus aureus* Efficacy 408

Table 272. PTA Results by MIC on Day 1 Based on Randomly Assigned Nonclinical Ceftobiprole Free-Drug Plasma %T>MIC Targets Associated With *Staphylococcus aureus* Efficacy 409

Table 273. PTA Results by MIC on Day 10 Based on Median Nonclinical Ceftobiprole Free-Drug Plasma %T>MIC Targets Associated With *Staphylococcus aureus* Efficacy 411

Table 274. PTA Results by MIC on Day 10 Based on Randomly Assigned Nonclinical Ceftobiprole Free-Drug Plasma %T>MIC Targets Associated With *Staphylococcus aureus* Efficacy 412

Table 275. Summary of Ceftobiprole Exposures (Model-predicted) 413

Table 276. PTA for *Staphylococcus aureus* Bacteremia in ESRD Adult Subjects 413

Table 277. Summary Statistics of Predicted Exposures by Age Group 417

Table 278. Predicted PK/PD Target Attainment by Age Group....418

Table 279. Summary Statistics of Ceftobiprole in Subjects With Moderate Renal Impairment....420

Table 280. Summary Statistics of Ceftobiprole in Subjects With Severe Renal Impairment....421

Table 281. Predicted PK/PD Target Attainment by Age Group in Subjects With Renal Impairment....421

Table 282. Summary of Predicted Ceftobiprole AUC and C_{max} for Q24H and Q12H Dosing Interval for Adolescents With Severe Renal Impairment 422

Table 283. Grouped Queries by Preferred Term, Safety Population, Trial BPR-CS-009....424

Table 284. Grouped Queries by Preferred Term, Safety Population, Trial BPR-CS-008....438

Table 285. Full Listing of TEAEs by Preferred Term, Group Term, and FMQ, Safety Population, Trial CAP-3001 445

Table 286. Full Listing of Treatment-Emergent Adverse Events, Safety Population, Trial BPR-PIP-002....457

Table 287. Full Listing of TEAEs by Preferred Term, Group Term, and FMQ, Safety Population, Trial BAP248/307....459

Table 288. Ceftobiprole Antimicrobial Activity In Vitro Against Relevant Pathogens From Surveillance Studies 486

Table 289. Activity of Ceftobiprole Against Staphylococcal Clinical Isolates With Reduced Susceptibility to Vancomycin or Daptomycin, or Resistance to Linezolid or Tigecycline 487

Reference ID: 5357793

Table 290. Activity of Ceftobiprole Against Target Pathogens in Murine Septicemia Model 489

Table 291. Efficacy of Ceftobiprole Medocaril Sodium and Ampicillin Against *Enterococcus Faecalis* in a Murine Peritonitis Model 490

Table 292. Activity of Ceftobiprole in a Murine Model of Acute Pneumonia....491

Table 293. Efficacy of Ceftobiprole in Experimental Endocarditis 493

Table 294. Efficacy of Ceftobiprole in Experimental Meningitis and Osteomyelitis Models....495

Table 295. PD50s of Ceftobiprole and Other Antibiotics Against *Enterococcus Faecalis* Bla+ OG1 and Bla- OG1 Strains in a Mouse UTI Model....496

Table 296. Exposure Targets Required for a 1-Log Kill in Neutropenic Murine Thigh Infection Models (Gram-Positive Bacteria)....498

Table 297. Exposure Targets Required for a 1-Log Kill in Murine Pneumonia Models (Gram-Positive Bacteria) 498

Table 298. Exposure Targets Required for a 1-Log Kill in Neutropenic Murine Thigh Infection and Neutropenic Lung Infection Models (Gram-Negative Bacteria)....499

Table 299. Microbiological Eradication Rates in the mITT and CE Populations for Subject With Baseline *Staphylococcus aureus* Bacteremia....500

Table 300. Overall Success and Microbiological Eradication at PTE by Ceftobiprole MIC (mITT and CE Populations; DRC Assessment)....501

Table 301. Overall Success Based on DRC Assessment at the PTE Visit by MRSA Clonal Strain Type (mITT Population)....502

Table 302. Primary Efficacy Outcome by Pathogen From the Adult Phase 3 ABSSSI Trial....503

Table 303. Investigator-Assessed Early Clinical Response by 48 to 72 Hours and Investigator Assessed Clinical Success at TOC by Baseline Pathogen Susceptibility of Infection-Site Specimens in the Ceftobiprole Arm (mITT Population)....503

Table 304. Subjects With Baseline Pathogens Isolated From Blood Cultures (mITT Population)....505

Table 305. In Vitro Ceftobiprole Susceptibility of Baseline Pathogens From Infection-Site Specimens Isolated From Ceftobiprole-Treated Subjects (mITT Population)....505

Table 306. In Vitro Susceptibility of Baseline Pathogens Isolated From Blood Cultures–mITT Population 506

Table 307. Baseline Characteristics of Trial CAP3001 Subjects Reanalyzed Per 2020 FDA CABP Guidance Document 507

Table 308. Microbiological Eradication at the TOC Visit by Causative Pathogen (mITT and ME Populations, Pre-Specified Analysis), CAP-3001 508

Reference ID: 5357793

Table 309. Clinical Cure at the TOC Visit by Causative Pathogen (Pre-Specified analysis), CAP-3001 508

Table 310. Clinical Cure at TOC by Blood Culture Pathogens at Baseline (Pre-Specified Analysis; mITT and ME Populations), CAP-3001 510

Table 311. Clinical Cure at the TOC Visit, Early Clinical Response at Day 3, and Modified Early Clinical Response at Day 3 by Ceftobiprole MIC for Causative Pathogen (mITT Population), CAP-3001 510

Table 312. Microbiological Outcomes at TOC and LFU – mITT Population in Trial BPR-PIP-002 512

Table 313. Broth Microdilution Quality Control Results From an Eight-Laboratory Tier 2 QC Study as Specified by CLSI Document M23....513

Table 314. CLSI-Approved Disk Diffusion Quality Control Ranges for Ceftobiprole 5 mcg Disk 514

Table 315. Proposed Ceftobiprole Clinical Breakpoints and Disk Diffusion Zones....514

Table 316. Data for Ceftobiprole Breakpoint Determination for *Staphylococcus aureus*....515

Table 317. Data for Ceftobiprole Breakpoint Determination for *Streptococcus pneumoniae* 516

Table 318. Data for Ceftobiprole Breakpoint Determination for *Streptococcus pyogenes*....516

Table 319. Data for Ceftobiprole Breakpoint Determination for *Enterobacterales*....517

Table 320. Data for Ceftobiprole Breakpoint Determination for *Haemophilus influenzae* and *Haemophilus parainfluenzae* 518

Table 321. FDA Established Ceftobiprole Breakpoints 519

Table 322. Ceftobiprole Penicillin-Binding Proteins in Gram-Positive Bacterial Strains 520

Table 323. Penicillin-Binding Protein in Gram-Negative Bacteria 522

Table 324. Rates of Hydrolysis by Purified β-Lactamases....523

Table 325. β-Lactamase Hydrolysis Parameters for Ceftobiprole and Comparator Antibacterial Drugs....524

Table 326. Ceftobiprole Single Step Resistance Frequencies in Bacteria 527

Table 327. Key Labeling Changes and Considerations....529

Table 328. Covered Clinical Studies: BPR-CS-009, BPR-CS-008, CAP-3001, BAP-248/307, BPR-PIP-002 537

Table 329. Reviewers of Integrated Assessment 544

Table 330. Additional Reviewers of Application 544

Table 27-1 Signatures of Reviewers 544

Reference ID: 5357793

Table of Figures

Figure 1. Trial BPR-CS-009: Disposition of Subjects....64
Figure 2. Disposition of Patients, Trial BPR-CS-008 Subjects....82
Figure 3. Proportion of Early Clinical Response 48-72 hours After Start of Treatment (ITT population), Trial BPR-CS-008....90
Figure 4.: Trial Schema, CAP-3001....93
Figure 5. Disposition of Subjects, Trial CAP-3001....97
Figure 6. Mean Hemoglobin Data Change From Baseline Over Time, Safety Population, Trial BPR-CS-009....148
Figure 7. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Trial BPR-CS-009, Cohorts 1 and 2....150
Figure 8. Mean Laboratory (Kidney Function) Data Change From Baseline Over Time, Safety Population, Trial BPR-CS-008....164
Figure 9. Mean Laboratory (Hematology) Data Change From Baseline Over Time, Safety Population, Trial BPR-CS-008....166
Figure 10. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Trial BPR-CS-008....168
Figure 11. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Trial CAP-3001....185
Figure 12. Median and Interquartile Range of Pulse Rate Over Time by Treatment Arm, IV Treatment Period, Safety Population, Trial BPR-PIP-002....198
Figure 13. Median and Interquartile Range of Respiratory Rate Over Time by Treatment Arm, IV Treatment Period, Safety Population, Trial BPR-PIP-002....199
Figure 14. Median and Interquartile Range of Body Temperature Over Time by Treatment Arm, IV Treatment Period, Safety Population, Trial BPR-PIP-002....199
Figure 15. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Trial BAP248/307....214
Figure 16. Simulated Plasma Concentration-Time Profiles of Ceftobiprole Administered as 2-Hour Infusions for Subjects With Normal or Impaired Renal Function....224
Figure 17. Individual Ceftobiprole Concentration-Time Profiles in the Plasma Following a 2-Hour Intravenous Infusion of Ceftobiprole 250 mg to Subjects With ESRD Dosed After Hemodialysis....226
Figure 18. Dose-Normalized Plasma Concentrations vs. Time From Last Dose for all Subjects/Patients Used in the Model Fit Stratified by Sampling Time and Colored by ESRD With and Without Intermittent Hemodialysis....228

Reference ID: 5357793

Figure 19. Forest Plots Showing Impact of Statistically Significant Covariate-Parameter Relationships on Ceftobiprole 229

Figure 20. Distribution of Predicted Ceftobiprole AUC0-24 by Age Group in Renally Impaired Patients Using the Population PK Model Fit to Pooled Pediatric/Adult Data 231

Figure 21. Distribution of Predicted Ceftobiprole C_{max} by Age Group in Renally Impaired Patients Using the Population PK Model Fit to Pooled Pediatric/Adult Data 231

Figure 22. Structure of (b) (4) 291

Figure 23. Correlation of Ceftobiprole PK-PD Indices With Efficacy Against *Staphylococcus aureus* ATCC 33591. 305

Figure 24. In Vitro and In Vivo Metabolism of Ceftobiprole Medocaril Sodium.....311

Figure 25. Individual Ceftobiprole Concentration-Time Profiles in the Plasma Following a 2-Hour Intravenous Infusion of Ceftobiprole 250 mg to Subjects With ESRD Dosed After Hemodialysis. 330

Figure 26. Schematic of the Base Structural Model 349

Figure 27. Goodness-of-Fit Plots for the Final PopPK Model for ABSSSI and CABP ..350

Figure 28. Histograms of NPDE by Dose Levels and Scatterplot of NPDE by Time for the Final PopPK Model for ABSSSI and CABP 351

Figure 29. Prediction-corrected VPC Plot for the Final PopPK Model for ABSSSI and CABP 351

Figure 30. Prediction-Corrected VPC Plot for the Final PopPK Model for ABSSSI and CABP Using Phase 3 PK Data.....352

Figure 31. Forest Plot Showing Impact of Statistically Significant Covariate-Parameter Relationships on Day 1 AUC 352

Figure 32. Schematic of the Initial PopPK Model.....355

Figure 33. Goodness-of-Fit Plots for the Final PopPK Model for *Staphylococcus aureus* Bacteremia 356

Figure 34. Histograms of NPDE by Dose Levels and Scatterplot of NPDE by Time for the Final PopPK Model for *Staphylococcus aureus* Bacteremia 357

Figure 35. Prediction-Corrected VPC Plot for the Final PopPK Model Using the Pooled Dataset 357

Figure 36. Prediction-Corrected VPC Plot for the Final PopPK Model for *Staphylococcus aureus* Bacteremia Subjects Only 358

Figure 37. Forest Plot Showing Impact of Statistically Significant Covariate-parameter Relationships on Day 1 AUC.....359

Figure 38. Distributions of ETAs and NPDEs for Subjects in Trial BPR-CS-009 by Hemodialysis.....360

Reference ID: 5357793

Figure 39. Dose-normalized Ceftobiprole Plasma Concentrations Versus. Time Since Last Dose Stratified by ESRD and Hemodialysis Status....361

Figure 40. Prediction-Corrected VPC Plot for the Final PopPK Model Using the Pooled Dataset....366

Figure 41. Prediction-Corrected VPC Plot for the Final PopPK Model for Pediatric Subjects Only....366

Figure 42. Prediction-Corrected VPC Plot for the Final PopPK Model by Age Group for the Pooled Dataset....367

Figure 43. Comparison of PK Individual PK Parameters and Exposure Between the Pediatric PopPK Models....367

Figure 44. Scatterplot and Boxplots for Simulated Ceftobiprole Day 1 AUC Across Renal Function Groups for ABSSSI....374

Figure 45. Scatterplot and Boxplots for Simulated Ceftobiprole Day 1 C_{max} Across Renal Function Groups for ABSSSI....375

Figure 46. Scatterplot and Boxplots for Simulated Ceftobiprole Day 1 AUC Across Renal Function Groups for CABP....377

Figure 47. Scatterplot and Boxplots for Simulated Ceftobiprole Day 1 C_{max} Across Renal Function Groups for CABP....378

Figure 48. PTA on Day 1 Based on Median and Randomly Assigned Nonclinical Targets of %T>MIC for *Staphylococcus aureus*....382

Figure 49. PTA on Day 1 Based on Median and Randomly Assigned Nonclinical Targets of %T>MIC for *Streptococcus* Species....385

Figure 50. PTA on Day 1 Based on Median and Randomly Assigned Nonclinical Targets of %T>MIC for *Enterobacterales*....388

Figure 51. PTA on Day 1 Based on Median and Randomly Assigned Nonclinical Targets of %T>MIC for *Streptococcus pneumoniae*....391

Figure 52. PTA Results by MIC on Day 1 Based on Median Nonclinical Ceftobiprole Free-Drug Plasma %T>MIC Targets Associated With *Staphylococcus aureus* Efficacy....394

Figure 53. PTA on Day 1 Based on Median and Randomly Assigned Nonclinical Targets of %T>MIC for *Enterobacterales*....397

Figure 54. Scatterplot and Boxplots for Simulated Ceftobiprole Day 1 AUC Across Renal Function Groups for *Staphylococcus aureus* Bacteremia....402

Figure 55. Scatterplot and Boxplots for Simulated Ceftobiprole Day 10 AUC Across Renal Function Groups for *Staphylococcus aureus* Bacteremia....403

Figure 56. Scatterplot and Boxplots for Simulated Ceftobiprole Day 1 C_{max} Across Renal Function Groups for *Staphylococcus aureus* Bacteremia....404

Figure 57. Scatterplot and Boxplots for Simulated Ceftobiprole Day 10 C_{max} Across Renal Function Groups for *Staphylococcus aureus* Bacteremia....405

Reference ID: 5357793

Figure 58. PTA on Day 1 Based on Median and Randomly Assigned Nonclinical Targets of %T>MIC for *Staphylococcus aureus* 410

Figure 59. Characteristics of the Simulated Pediatric Population 415

Figure 60. Distribution of Predicted 24-Hour AUC by Age Group 415

Figure 61. Distribution of Predicted C_{max} by Age Group 416

Figure 62. Distribution of Predicted AUC and C_{max} by Age Group Compared Against Adult Subject Exposures....417

Figure 63. Distribution of Predicted 24-hour AUC by Age Group in Renal Impairment....419

Figure 64. Distribution of Predicted C_{max} by Age Group in Renal Impairment....419

Figure 65. Distribution of Predicted AUC and C_{max} by Age Group Compared Against Exposures in Adult Subject With Mild Renal Impairment....420

Reference ID: 5357793

Glossary

ABSSSI	acute bacterial skin and skin structure infections
ACM	all-cause mortality
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATCC	American type culture collection
AUC	area under the concentration-time curve
BAL	bronchoalveolar lavage
BCRP	breast cancer resistance protein
BSA	body surface area
BSEP	bile salt export pump
BSP	bromosulfalein
BUN	blood urea nitrogen
CABP	community-acquired bacterial pneumonia
CE	clinically evaluable
CFU	colony forming unit
CI	confidence interval
CL_{CR}	creatinine clearance
CLSI	Clinical & Laboratory Standards Institute
C_{max}	maximum plasma concentration
CMC	chemistry, manufacturing, and controls
CMH	Cochran-Mantel-Haenszel
CSF	cerebrospinal fluid
CSR	clinical study report
DILI	drug-induced liver injury
DMSO	dimethyl sulfoxide
DP	drug product
DRC	data review committee
DS	drug substance
DVT	deep vein thrombosis
ELF	epithelial lining fluid
EOT	end-of-treatment
ESBL	extended spectrum β-lactamase
ESRD	end-stage renal disease
FCA	Freund's complete adjuvant
FDA	Food and Drug Administration
FIA	Freund's incomplete adjuvant
FMQ	Food and Drug Administration Medical Dictionary for Regulatory Activities query
GD	gestation day
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GQ	grouped query

Reference ID: 5357793

HABP	hospital-acquired bacterial pneumonia
IC_{50}	half-maximal inhibitory concentration
ICH	International Council for Harmonisation
IDMC	independent data monitoring committee
IE	infective endocarditis
IIV	interindividual variability
IND	investigational new drug
ITT	intent-to-treat
IV	intravenous
LIE	left-sided infective endocarditis
ME	microbiologically evaluable
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
mITT	modified intent-to-treat
micro-ITT	microbiological intent-to-treat
MO	medical officer
MRHD	maximum recommended human dose
MRSA	methicillin-resistant *Staphylococcus aureus*
MSSA	methicillin-susceptible *Staphylococcus aureus*
NDA	new drug application
NI	noninferiority
NOAEL	no observed adverse effect level
NPDE	normalized prediction distribution errors
OATP	organic anion-transporting polypeptide
OFV	objective function value
OPQ	Office of Pharmaceutical Quality
OSI	Office of Scientific Investigations
PBP	penicillin-binding protein
PD	pharmacodynamic
PDE	permitted daily exposure
PDUFA	Prescription Drug User Fee Act
PI	prescribing information
PK	pharmacokinetic
PopPK	population PK
PORT	Pneumonia Outcomes Research Team
PSI	PORT Severity Index
PT	preferred term
PTA	probability of target attainment
PTE	post-treatment evaluation
QC	quality control
QIDP	Qualified Infectious Disease Product
QSAR	quantitative structure-activity relationship
RI	renal impairment
RIE	right-sided infective endocarditis
SAB	*Staphylococcus aureus* bacteremia
SAE	serious adverse event

Reference ID: 5357793

SBP	systolic blood pressure
SD	standard deviation
SIRS	systemic inflammatory response syndrome
SOC	system organ class
SPA	special protocol assessment
T	time
TEAE	treatment-emergent adverse event
TOC	test-of-cure
ULN	upper limit of normal
UVA	ultraviolet A
VABP	ventilator-associated bacterial pneumonia
VPC	visual predictive check
WBC	white blood cell

Reference ID: 5357793

I. Executive Summary

1. Summary of Regulatory Action

New drug application (NDA) 218275 for ceftobiprole medocaril sodium for injection was submitted by Basilea Pharmaceutica International Ltd, Allschwil (Applicant) for the following indications:

1. Treatment of adult patients with *Staphylococcus aureus* bacteremia (SAB), including those with right-sided infective endocarditis (RIE)
2. Treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI)
3. Treatment of adult and pediatric patients (greater than or equal to 3 months to less than 18 years of age) with community-acquired bacterial pneumonia (CABP)

The application was reviewed by the multidisciplinary review team. The review team has recommended approval, and I, the signatory for this application, concur with this recommendation.

Ceftobiprole medocaril sodium is a cephalosporin antibacterial drug which exerts its antibacterial activity by binding to penicillin-binding proteins and inhibiting synthesis of the bacterial cell wall. Ceftobiprole medocaril is the prodrug that rapidly converts to its active moiety, ceftobiprole. Ceftobiprole medocaril sodium is the salt form of ceftobiprole medocaril; ceftobiprole medocaril sodium is used interchangeably with ceftobiprole throughout this review. Ceftobiprole demonstrated in vitro and clinical activity against gram-positive and gram-negative bacteria including methicillin-susceptible *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA), *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Klebsiella pneumonia* and *Escherichia coli.*

The Applicant submitted a single, phase 3, randomized, double-blinded, active-controlled, noninferiority trial in adults for each of the indications (SAB, ABSSSI, and CABP) that demonstrated noninferiority to the comparators. Additionally, the Applicant submitted a phase 3, randomized, active-controlled trial in pediatric subjects with CABP and hospital-acquired bacterial pneumonia (HABP) and a phase 3 trial in adults with HABP and ventilator-associated bacterial pneumonia (VABP). Data from the pediatric CABP/HABP trial were primarily used to support the safety of ceftobiprole in pediatric subjects with CABP with efficacy extrapolated from the adult CABP trial. Indications for HABP/VABP in adults and HABP in pediatric subjects were not sought in this application and the data from the HABP/VABP subjects informed safety assessments.

The safety database consisted of 464 subjects who received at least one dose of ceftobiprole in phase 1 studies, and 1315 total subjects who received at least one dose of ceftobiprole at the to-be-marketed dose in the phase 3 trials. Overall, the safety findings observed with ceftobiprole were similar to other FDA-approved cephalosporins. The risks can be mitigated through labeling and further evaluated during routine pharmacovigilance.

Reference ID: 5357793

The overall benefit-risk profile is favorable to support approval of ceftobiprole for the treatment of:

1. Adult patients with SAB, including those with right-sided infective endocarditis (RIE), caused by methicillin-susceptible and methicillin-resistant isolates
2. Adult patients with ABSSSI caused by susceptible isolates of the following gram-positive and gram-negative microorganisms: *Staphylococcus aureus* (methicillin-susceptible and methicillin-resistant isolates), *Streptococcus pyogenes*, and *Klebsiella pneumoniae*
3. Adult and pediatric patients (3 months to less than 18 years old) with CABP caused by susceptible isolates of the following gram-positive and gram-negative microorganisms: *Staphylococcus aureus* (methicillin-susceptible), *Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, Escherichia coli, and Klebsiella pneumoniae*

The drug product established name and strength will be expressed in terms of the salt (i.e., ceftobiprole medocaril sodium for injection, 667 mg/vial) and labeling will include a statement stating that 667 mg of ceftobiprole medocaril sodium is equivalent to 500 mg of ceftobiprole (the active metabolite). This is an exception to the USP Salt Policy to eliminate having three different names/strengths in labeling (i.e., based on the prodrug, salt form, and active metabolite), thereby reducing the possibility for medication errors and harmonizing the US FDA labeling with existing medical literature and product labeling from other countries.

For detailed information supporting the basis for this approval, please refer to the reviews included in this interdisciplinary assessment and the product quality review.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework for Treatment of *Staphylococcus aureus* Bacteremia

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	• *Staphylococcus aureus* can cause invasive infections, sepsis and death. In 2017, nearly 120,000 bloodstream infections occurred with 20,000 associated deaths. *S. aureus* is an ongoing threat with community-onset methicillin-susceptible *S. aureus* (MSSA) infections increasing (3.9% per year, p<0.0001) from 2012 to 2017 (CDC 2019). Due to significant attempts to reduce MRSA bloodstream infections in healthcare settings, these infections had been decreasing by 17.1% each year from 2005 to 2012; however, no significant change was detected from 2013 to 2016. • MRSA bacteremia has a higher mortality rate than MSSA bacteremia; one meta-analysis showed an odds ratio of 1.93 (95% CI, 1.54-2.42) for in-hospital mortality compared with MSSA bacteremia. (Cosgrove et al. 2003). • RIE accounts for 5-10% of all IE cases. The most common cause of RIE is *S. aureus*, which accounts for an estimated 60-90% of cases and often requires 4-6 weeks of antibacterial drug therapy (Liu et al. 2011)	Bacteremia due to *S. aureus* remains a common cause of bloodstream infection with morbidity and mortality rates of up to 25%. IE is commonly caused by *S. aureus,* and native valve *S. aureus* endocarditis is often associated with a higher mortality as compared to other pathogens (Miro et al. 2005).
Current treatment options	• FDA-approved treatments for SAB, especially MRSA bacteremia, are limited. • Treatment for SAB and RIE caused by MSSA include cefazolin, nafcillin, oxacillin, and daptomycin. Vancomycin can be used in patients with beta-lactam allergy or in those who cannot receive other drugs. • There are fewer treatment options for SAB and RIE caused by MRSA; only vancomycin and daptomycin are approved for these indications. • Limitations of vancomycin include nephrotoxicity and ototoxicity, and the need for therapeutic drug monitoring. • Limitations of daptomycin include myalgias, rhabdomyolysis and eosinophilic pneumonia.	Approved treatment options for MRSA bacteremia and RIE are limited by toxicity and resistance necessitating the development of antibacterial drugs with improved adverse effect profiles.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Resistance to both vancomycin and daptomycin have been observed (McGuinness et al. 2017; Ernst and Peschel 2019).	
Benefit	• A phase 3, randomized, double-blind, double-dummy, active-controlled, multi-center trial in adult hospitalized subjects with SAB, including RIE was conducted to determine whether ceftobiprole was noninferior to daptomycin ± aztreonam (the comparator arm) for the primary endpoint of overall success at the post-treatment evaluation (PTE) visit at Day 70 after randomization in the mITT population that included subjects who received any dose of study medication, and had a blood culture positive for *S. aureus* at baseline. Overall success assessed by the data review committee (DRC) was defined as all of the following criteria being met: subject alive at Day 70, no new metastatic foci or complications of the SAB infection, resolution or improvement of SAB-related clinical signs and symptoms and two negative blood cultures for *S. aureus* at prespecified time points. The specified noninferiority margin was 15%. Key secondary endpoints included all-cause mortality (ACM) through PTE. • The ceftobiprole arm had an overall success rate of 69.8% (132/189); the comparator arm had an overall success rate of 68.7% (136/198); the difference (95% CI) was 2.0% (-7.1, 11.1), and the results of overall success at the PTE visit in the mITT population met the threshold for noninferiority. • All-cause mortality (ACM) through the Day 70 PTE visit in the mITT population was 9.0% (17/189) and 9.1% (18/198) in the ceftobiprole and comparator arms, respectively. • Additional analysis considered overall success at the PTE visit by pathogen. For MSSA, the overall success rates in the ceftobiprole vs. comparator arms were 70.9% (100/141) vs. 66.4% (97/146), respectively [difference (95% CI): 4.8 (−5.9, 15.5)]. For MRSA, the overall success rates in the ceftobiprole vs. comparator arms were 68.8% (31/45) vs. 77.6% (38/49), respectively [difference (95% CI): −8.3 (−25.3, 8.6)]. Of note, the microbiological eradication rates for MRSA at PTE in the ceftobiprole vs. comparator arms were 80.0% vs. 81.6%, respectively. • Overall success in subjects with definite RIE was similar between treatment arms [66.7% vs. 70% in the ceftobiprole vs. comparator arm, respectively, the difference (95% CI) was -6.6 (-40.1, 27.0)].	The phase 3 trial met its primary objective of demonstrating non-inferiority for the pre-specified primary endpoint of overall success based on DRC Assessment at the PTE (Day 70) visit. Outcomes of the secondary efficacy endpoints were similar between treatment arms. Overall, low ethnic/geographic diversity and differences in success rates by geographic region are not anticipated to significantly limit the efficacy assessment of ceftobiprole for SAB; these differences will be described in the labeling. Ceftobiprole provides an additional option for treatment of SAB, including RIE caused by both methicillin susceptible and methicillin resistant isolates.

Reference ID: 5357793

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Of note, overall success rates (ceftobiprole vs. comparator) based on DRC assessment at PTE in the Ukraine were: 74/88 (84.1%) vs. 82/92 (89.1%), respectively, versus 58/101 (57.4%) vs. 54/106 (50.9%), respectively, in other countries excluding the Ukraine. • Additionally, low racial and geographic diversity (96% were White and 93% were European) was observed in the trial.	
Risk and risk management	• The safety database included 191 subjects who received the proposed dose and duration of ceftobiprole. • Treatment-emergent adverse events (TEAEs) leading to death were similar in both treatment arms (approximately 9%). The deaths appeared to be related to underlying comorbidities and unrelated to ceftobiprole. • The incidence of SAEs was similar in the ceftobiprole arm and the daptomycin ± aztreonam arm (18.8% vs 22.7%). • The number of subjects who had TEAEs leading to treatment discontinuation was comparable in each arm (approximately 9%). The most common adverse reactions leading to treatment discontinuation were gastrointestinal symptoms, rash, and urticaria. • The most common adverse reactions occurring in ≥ 4% of ceftobiprole-treated subjects were anemia, nausea, hypokalemia, vomiting, hepatic enzyme and bilirubin increased, diarrhea, blood creatinine increased, and leukopenia. • Adverse events of special interest such as hypersensitivity reactions and seizures were both reported in 1.6% of subjects. • Thrombi formation at the injection site were seen in nonclinical studies, possibly due to mechanical irritation and higher concentrations of ceftobiprole than administered in clinical trials. In the SAB trial, thrombosis-related adverse events were reported in 5% of subjects in the ceftobiprole arm and 2% of subjects in the comparator arm. Thrombosis also occurred at a low frequency (1.6%) in other clinical trials. In all clinical trials, the majority of subjects with thromboses had underlying risk factors and thrombosis has not been reported in the postmarketing setting.	The safety profile of ceftobiprole appears acceptable in subjects with SAB. The TEAEs experienced in the study are generally compatible with the known safety profile of the cephalosporin drug class. The risks of ceftobiprole have been communicated in labeling. The Warning and Precautions section of the labeling will include hypersensitivity reactions and seizures and other central nervous system reactions. Monitoring for TEAEs of special interest will continue in the postmarketing phase.

Abbreviations: ACM, all-cause mortality; CI, confidence interval; DRC, data review committee; mITT, modified intent-to-treat; MRSA, methicillin-resistant S. aureus; MSSA, methicillin-susceptible *Staphylococcus aureus*; PTE, post-treatment evaluation; REMS, Risk Evaluation and Mitigation Strategy; RIE, right-sided infective endocarditis; SAB, *Staphylococcus aureus* Bacteremia; SAE, serious adverse event; TEAE, treatment-emergent adverse event

Table 3. Benefit Risk Framework for Treatment of Acute Bacterial Skin/Soft Tissue Infection

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	• The FDA Guidance for Industry (Acute Bacterial Skin and Skin structure Infections: Developing Drugs for Treatment) defines an ABSSSI as a bacterial infection of the skin with a lesion size of at least 75 cm^2 and encompassess diseases such as cellulitis/erysipelas, wound infections, and major cutaneous abscesses (October 2013). • ABSSSI are one of the most commonly diagnosed infectious diseases and account for an estimated 10.1% of all infectious disease-related hospitalizations (Christensen et al. 2009). • Treatment of cellulitis is usually directed towards the most common pathogens such as *S. aureus* and group A *Streptococcus* because the causative pathogen is rarely isolated. However, given the increased prevalence of community-associated MRSA, empiric therapy for MRSA may be considered (Chira and Miller 2010). • While gram-positive organisms are the predominant pathogens, the incidence of gram-negative organisms causing skin and soft tissue infections are on the rise (Jabbour and Kanj 2021).	ABSSSI are one of the most commonly diagnosed infectious diseases and are usually caused by *S. aureus* and group A *Streptococcus* but can be also caused by gram-negative bacteria.
Current treatment options	• While there are numerous treatment options for MSSA, *Streptococcus pyogenes*, and *group A streptococcus*, there are fewer options for treating MRSA. For MRSA infection, treatment options may include vancomycin, daptomycin, linezolid, dalbavancin, oritavancin, ceftaroline, clindamycin, tigecycline, omadacycline, doxycycline, trimethoprim-sulfamethoxazole, and delafloxacin. • There are currently numerous treatments for *K. pneumonia* which include but are not limited to cephalopsorins, β-lactams/β-lactamase inhibitor combinations, and fluoroquinolones. • Some treatment options are associated with toxicity or drug-drug interactions.	A single treatment option that combines MRSA and gram-negative antibacterial coverage may be useful in certain clinical settings.
Benefit	• A phase 3, randomized, double-blind, active-controlled, multicenter trial in adult hospitalized subjects with ABSSSI was conducted to determine whether ceftobiprole was noninferior to vancomycin and aztreonam for the primary endpoint of early clinical response based on percent reduction from baseline in lesion size at 48-72 hours after start of treatment, measured in subjects who did not receive rescue therapy, and were alive. The primary analysis was conducted in the (Intent-to-treat) ITT	The study met its primary objective of demonstrating non-inferiority. Secondary efficacy findings also favor ceftobiprole vs. vancomycin plus aztreonam. Ceftobiprole provides an additional option for treatment of ABSSSI caused by *Staphylococcus aureus* (methicillin-susceptible

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	population within a prespecificed noninferiority margin of 10%. Key secondary endpoints included investigator-assessed clinical success at the TOC visit 15-22 days after randomization. • The ceftobiprole group had an early clinical response rate of 91.3% (306/335); the vancomycin and aztreonam group had an early clinical response rate of 88.1% (303/344); the difference (95% CI) was 3.3% (-1.2, 7.8), and the results met the threshold for noninferiority. • For the main secondary endpoint of investigator-assessed clinical success at the TOC visit in the ITT population, the ceftobiprole group achieved a 90.1% success rate vs 89.0% success rate in the vancomycin plus aztreonam group with a difference (95% CI) of 1.0 (-3.5, 5.6). • Low racial diversity in the trial (95% White) was observed in the trial.	and methicillin-resistant isolates), *Streptococcus pyogenes, and Klebsiella pneumoniae.* Low racial diversity may limit generalizability of the trial results; however, an impact on overall efficacy is not anticipated.
Risk and risk management	• The safety database included 334 subjects • TEAEs leading to death occurred at a similar frequency in both treatment arms; the single death in the ceftobiprole arm was unrelated to ceftobiprole. • SAEs occurred in 1.8% in the ceftobiprole arm compared to 3.5% in the vancomycin and aztreonam arm. • The incidence of TEAEs that led to treatment discontinuation was similar in the ceftobiprole arm and the vancomycin and aztreonam arm (1.8% vs 2.9%). The adverse reactions that led to treatment discontinuation in the ceftobiprole arm included dysguesia, and both pruritis and rash. • The most common adverse reactions occurring in ≥ 2% of ceftobiprole-treated subjects were nausea, diarrhea, headache, injection site reaction, hepatic enzyme increased, rash, vomiting, and dysgeusia.	The safety profile of ceftobiprole appears acceptable as a treatment for ABSSSI. The TEAEs experienced in the study are compatible with the known safety profile of the cephalosporin drug class.

Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; CI, confidence interval; ITT, intent-to-treat; MRSA, methicillin-resistant S. aureus; MSSA, methicillin-susceptible *Staphylococcus aureus*; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TOC, Test of Cure

Table 4. Benefit-Risk Framework for Treatment of Community-Acquired Bacterial Pneumonia

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	• Community-acquired bacterial pneumonia (CABP) is generally defined as an infection of the lung parenchyma in patients without recent healthcare exposure. The microbiology of CABP typically includes *S. pneumoniae*, *H. influenzae*, *M. pneumoniae*, *S. aureus*, and *Enterobacterales.* The rise in the incidence of antibacterial resistance necessitates the use of broader spectrum antibacterial drugs for treatment. Despite treatment, CABP continues to have significant morbidity and mortality with mortality rates ranging from 5.1% to 36.5% depending on the severity at presentation, age, co-morbidities, and level of care required (Fine et al. 1996, Peters et al. 2022) (Fine et al. 1996; Peters et al. 2022)). • Community-acquired pneumonia, both bacterial and viral, is the most common cause of death in children under 5 years of age globally, causing nearly 15% of deaths in this age group (World Health Organization). In the US, CABP is among the most common causes of hospitalization in children of all ages with an annual incidence rate of approximately 15.7 hospitalizations per 10,000 children (Jain et al. 2016)(Jain et al. 2015).	In both adults and children, CABP is a serious infection that causes significant morbidity and mortality and may be caused by a variety of pathogens.
Current treatment options	• Initial treatment of CABP is empiric and is tailored to risk factors and severity of illness at presentation. FDA approved antibacterial drugs include beta-lactams, cephalosporins, macrolides, and fluoroquinolones with oral and parenteral formulations. • In pediatric patients, treatment of mild to moderate CABP in the outpatient setting involves empiric coverage of the most common causative organism, *S. pneumoniae*. For hospitalized patients, use of ampicillin demonstrates similar outcomes when compared to broader regimens (Messinger et al. 2017), but additional antibacterial coverage including cephalosporins and macrolides are recommended in patients with history of allergic reactions, recent influenza infection, or history of infection with MDR organisms.	There are many antibacterial drugs approved for treatment of CABP. However, with increasing antibacterial resistance, adverse reactions, including hypersensitivity, treatment options may be limited in some patients.
Benefit	• A phase 3 randomized, double-blind, active control, multicenter study conducted to evaluate the efficacy and safety of ceftobiprole in adult subjects diagnosed with CABP requiring	The submitted evidence showed non-inferiority of ceftobiprole to ceftriaxone ± linezolid.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	hospitalization found that ceftobiprole demonstrated noninferiority to ceftriaxone ± linezolid on the primary endpoint of clinical cure defined as the resolution of signs and symptoms of infection or improvement to such an extent that no further antimicrobial therapy was necessary and improvement/stabilization of chest X-ray findings with a pre-specified noninferiority margin of 15%. • The overall clinical cure rate was 86.6% for ceftobiprole compared with the overall clinical cure rate of 87.4% for the comparator group with a difference of -0.8%, 95% CI (-6.9, 5.3). The clinical cure rate in the ITT analysis was similar with 76.4% in the ceftobiprole group compared with 79.3% in the comparator group with a difference of -2.9%, 95% CI (-9.3, 3.6). • A post-hoc analysis using the currently recommend efficacy endpoint of clinical success at Day 3 confirmed that ceftobiprole was noninferior to the comparator. • Pediatrics: A phase 3, randomized, investigator blind, active control, multicenter study was conducted to evaluate the safety, tolerability, pharmacokinetics and efficacy of ceftobiprole in 138 pediatric subjects aged 3 months to < 18 years requiring hospitalization and IV antibacterial drugs for the treatment of CABP (vs. ceftriaxone ± vancomycin) and HABP (vs. ceftazidime ± vancomycin) with the primary objective of evaluating safety. Although the trial included subjects with both HABP and CABP, only 8 enrolled subjects had HABP. The Applicant is not seeking an indication for HABP. • A total of 94 subjects received ceftobiprole. Efficacy for CABP was extrapolated from the successful phase 3 CABP adult study described above.	Efficacy in the pediatric population was extrapolated from the adult trial. Ceftobiprole provides an additional option for treatment of CABP caused by *Staphylococcus aureus* (methicillin-susceptible), *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Haemophilus parainfluenzae*, *Escherichia coli*, and *Klebsiella pneumoniae*.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and risk management	• In the adult CABP study, there were 9 deaths in each treatment arm (2.8%). The deaths appeared to be related to underlying comorbidities and did not appear to be related to ceftobiprole. • Approximately 11.3% of subjects treated with ceftobiprole developed an SAE and 5.5% of subjects discontinued treatment due to an AE. These rates were similar to those observed in the comparator arm. • The most common adverse reactions occuring in ≥ 2% of ceftobiprole treated subjects were nausea, hepatic enzyme increased, vomiting, diarrhea, headache, rash, insomnia, abdominal pain, phlebitis, and dizziness. • No additional safety concerns were identified in this study. • No safety concerns were identified in the pediatric study. There were no deaths. Although a numerically greater number of subjects had SAEs in the ceftobiprole vs. comparator groups (7.9% vs 4.9%, respectively) and discontinued drug due to AEs (4.5% vs. 0, respectively), only hypersensitivity and urticaria in two subjects appeared related to ceftobiprole. • Occurrence of TEAEs was balanced between treatment groups (31.5% vs. 29.3% in the ceftobiprole vs. comparator groups, respectively). The most common adverse reactions occuring in ≥ 2% of ceftobiprole treated subjects were vomiting, headache, hepatic enzyme increased, diarrhea, infusion site reaction, phlebitis, and pyrexia.	The safety profile of ceftobiprole appears acceptable as a treatment for CABP. The TEAEs experienced in the adult and pediatric studies are compatible with the known safety profile of the cephalosporin drug class. The identified safety issues can be adequately addressed by labeling.

Abbreviations: AE, adverse event; CABP, community-acquired bacterial pneumonia; CI, confidence interval; HABP, hospital-acquired bacterial pneumonia; ITT, intent-to-treat; REMS, risk evaluation and mitigation strategy; SAE, serious adverse event; TEAE, treatment-emergent adverse event

2.2. Conclusions Regarding Benefit-Risk

All three of the proposed indications (SAB, ABSSSI, and CABP) are serious and often life-threatening infections with significant morbidity and mortality. While there are multiple antibacterial drugs currently approved to treat ABSSSI and CABP, the continued evolution of antibacterial resistance mechanisms, drug-drug interactions, and adverse effects of available antibacterial drugs can limit treatment options. There is an urgent need to develop antibacterial drugs which cover both gram-negative and gram-positive organisms, especially MRSA, which is a major cause of hospital and community-acquired infections worldwide . Current treatments for MRSA infections have certain limitations (e.g., vancomycin is associated with nephrotoxicity and the need for drug monitoring, linezolid has certain drug-drug interactions and toxicities, daptomycin does not penetrate the lung parenchyma, and ceftaroline is not FDA-approved for difficult to treat infections such as bacteremia and RIE). Approved treatments for SAB, including RIE due to MRSA are especially limited.

Ceftobiprole, an advanced generation cephalosporin antibacterial drug would provide an effective treatment option with a favorable safety profile for the indications sought (SAB, ABSSSI, and CABP). The Applicant submitted data demonstrating safety and effectiveness for all three indications.

Trial BPR-CS-009 demonstrated that ceftobiprole is noninferior to daptomycin ± aztreonam in the treatment of subjects with SAB, including those with RIE, caused by methicillin-susceptible and methicillin-resistant isolates in regard to the primary endpoint of overall success based on data review committee assessment at the post-treatment evaluation visit in the modified intent-to-treat population (ceftobiprole 69.8%, daptomycin 68.7% [difference 2.0%; 95% confidence interval (CI): -7.1, 11.1]), which met the prespecified 15% noninferiority (NI) margin.

Trial BPR-CS-008 demonstrated that ceftobiprole is noninferior to vancomycin plus aztreonam in the treatment of subjects with ABSSSI with respect to the primary endpoint of early clinical response in the intent-to-treat population (ceftobiprole 91.3%, vancomycin plus aztreonam 88.1% [difference 3.3%; 95% CI: -1.2, 7.8]), which met the prespecified 10% NI margin.

Trial CAP-3001 demonstrated that ceftobiprole is noninferior to ceftriaxone ± linezolid in the treatment of adult subjects with CABP. In the intent-to-treat population, the clinical cure rate in the ceftobiprole group was 76.4% compared with the comparator group at 79.3% with a treatment difference of -2.9%, 95 CI (-9.3, 3.6), which met the prespecified 10% NI margin. Efficacy for CABP in the pediatric population was extrapolated from the adult CABP Trial.

The safety database for ceftobiprole was adequate for the proposed dosing regimens, intended subject populations, and respective indications. Generally, the Applicant provided data demonstrating that the safety of ceftobiprole was similar to the active comparator in each trial. Overall, ceftobiprole has a favorable safety profile, and safety findings can be adequately addressed in labeling and by routine pharmacovigilance.

Based on review of all available efficacy and safety data, NDA 218275 for ceftobiprole provides substantial evidence of effectiveness and a favorable benefit-risk profile for the treatment of the following indications:

1. Treatment of adult patients with SAB, including those with right-sided infective endocarditis, caused by methicillin-susceptible and methicillin-resistant isolates
2. Treatment of adult patients with ABSSSI caused by susceptible isolates of the following gram-positive and gram-negative microorganisms: *Staphylococcus aureus* (methicillin-susceptible and methicillin-resistant isolates), *Streptococcus pyogenes*, and *Klebsiella pneumoniae*
3. Treatment of adult and pediatric patients (3 months to less than 18 years old) with CABP caused by susceptible isolates of the following gram-positive and gram-negative microorganisms: *Staphylococcus aureus* (methicillin-susceptible isolates), *Streptococcus pneumoniae, Haemophilus influenzae, Haemophilus parainfluenzae, Escherichia coli, and Klebsiella pneumoniae*

II. Interdisciplinary Assessment

3. Introduction

Ceftobiprole medocaril sodium for injection (Zevtera) is a cephalosporin antibacterial drug that binds to penicillin-binding proteins and inhibits their transpeptidase activity. The active ingredient (drug substance), ceftobiprole medocaril sodium, is a salt of a prodrug, ceftobiprole medocaril, and the active metabolite is ceftobiprole. The dosage form of the drug product is a powder for injection. Ceftobiprole is currently approved in several countries outside of the US for the treatment of community-acquired bacterial pneumonia (CABP) and hospital-acquired bacterial pneumonia (HABP).

Ceftobiprole was submitted under new drug application (NDA) 022132 for treatment of complicated skin and skin structure infections by the previous Applicant, Johnson and Johnson Pharmaceutical Research & Development LLC (J&J) on May 18, 2007. NDA 022132 received an Approvable Letter on March 17, 2008, a Complete Response Letter on November 21, 2008, and a Complete Response Letter on December 28, 2009. The Clinical Deficiencies cited in these letters concerned studies BAP 00154 and BAP 00414 which are not included in this new NDA 218275. Ownership of NDA 022132 was transferred back to Basilea Pharmaceutica Ltd. on January 24, 2011.

Ceftobiprole medocaril for injection was granted Qualified Infectious Disease Product designation for the CABP, acute bacterial skin and skin structure infections (ABSSSI), and *Staphylococcus aureus* bacteremia (SAB) indications on July 20, 2015, August 7, 2015, and December 8, 2017, respectively. Refer to Section 12 for a more detailed regulatory summary.

In this NDA submission, the proposed indications are for the treatment of adult patients with SAB, including right-sided infective endocarditis (RIE), ABSSSI, and CABP and for treatment of pediatric patients 3 months to less than 18 years old with CABP. For current available therapies and typical pathogens for each indication, refer to Section 2.1.

All three indications were supported by phase 3, multicenter, randomized, double-blind, active controlled noninferiority (NI) trials which met their respective primary endpoints within the prespecified NI margins. Refer to Section 6 and 7 for reviews of efficacy and safety for each trial.

The proposed dosing regimen is ceftobiprole 500 mg every 6 hours on Days 1 to 8, followed by every 8 hours from Day 9 up to 42 days for SAB and 500 mg every 8 hours for 5 to 14 days for ABSSSI and CABP with dosing adjustments based on renal function. The initial proposal by the Applicant was based on the strength of the amount of the "active moiety/metabolite" as 500 mg ceftobiprole/vial.

During the NDA review, the OPQ team recommended that the drug product established name and strength be revised following the USP Salt Policy to express the amount of the prodrug neutral form (i.e., ceftobiprole medocaril for injection, 646 mg/vial). In response, the Applicant requested exemption from the USP Salt Policy following the example of a previously approved product which was also a salt of a prodrug, Cresemba (isavuconazonium sulfate), for which the strength is expressed in terms of the salt in approved labeling.

The clinical team and the Division of Medication and Error Prevention Analysis (DMEPA) agreed with the Applicant that an exception to the USP Salt Policy would eliminate having three different names/strengths in labeling (i.e., based on the prodrug, salt form, and active metabolite), thereby reducing the possibility for medication errors and also harmonizing the US FDA labeling with existing medical literature and product labeling from other countries. Upon further discussion of the drug product name and strength between the Office of New Drugs (OND) and Office of Policy and Pharmaceutical Quality (OPPQ) teams, a consensus was reached that the drug product established name and strength should be expressed in terms of the salt (i.e., ceftobiprole medocaril sodium for injection, 667 mg/vial) and labeling would include a statement stating that 667 mg of ceftobiprole medocaril sodium is equivalent to 500 mg of ceftobiprole. For details regarding this decision, refer to the Memorandum filed in DARRTS on 3/21/24 by Jibril Abdus-Samad, OPQ/OPPQ/COSS.

Reference ID: 5357793

3.1. Review Issue List

3.1.1. Key Efficacy Review Issues

3.1.1.1. Re-Analysis of Trial CAP-3001

3.1.1.2. Clinical Success in Ukrainian Versus Non-Ukrainian Sites in Trial BPR-CS-009

3.1.2. Key Safety Review Issues

3.1.2.1. Higher Mortality for Ceftobiprole Patients with VABP in Trial BAP 248/307

3.1.2.2. Imbalance in Adverse Events Related to Thrombosis in Trial BPR-CS-009

3.2. Approach to the Clinical Review

The primary evidence of effectiveness and safety of ceftobiprole for the proposed indications of the treatment of SAB and ABSSSI in adults, and CABP in adult and pediatric patients were provided in five clinical trials. Four of the trials were submitted for efficacy evaluation of ceftobiprole. The HABP/ventilator-associated bacterial pneumonia (VABP) trial was submitted to support the safety evaluation. All five studies were randomized, double-blind, active-controlled, multicenter, phase 3 studies. The active control and the ceftobiprole dosing used in each study varied based on the clinical condition being treated. The endpoint evaluations in each trial were also adjusted based on the clinical indication. Additional data from post-marketing surveillance from other countries along with a review of literature publications were evaluated to support the safety evaluation. See Section 7.3 for further details.

Key review issues that were identified during the review are addressed in greater detail in Sections 6.3 for efficacy and Section 7.7 for safety. Overall, the submitted clinical trials were adequate for the safety and efficacy evaluation of ceftobiprole. Table 5 provides an overview of the clinical trials relevant to the review of ceftobiprole's efficacy and safety.

Table 5. Clinical Studies/Trials Submitted in Support of Efficacy and/or Safety Determinations[1] for Ceftobiprole

Study/ Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
BPR-CS-009 NCT # 03138733	Adult subjects with SAB, including right-sided infective endocarditis	Control type: Active concurrent non-inferiority Randomization: Standard randomization, 1:1 ratio Blinding: Double-blind Biomarkers: No biomarkers Innovative design features: None	Drug: Zevtera (Ceftobiprole medocaril sodium for injection) Dosage: 667 mg IV q6h on Days 1 to 8, 667 mg IV q8h Day 9 onwards Number treated: 191 Duration: Cohort 1: up to 28 d Cohort 2: up to 42 d Comparator: Daptomycin ± aztreonam Dosage: 6 mg/kg to 10 mg/kg IV q24h (daptomycin); standard dose per site (aztreonam) Number treated: 198 Duration: Cohort 1: up to 28 d Cohort 2: up to 42 d	Primary: Subjects alive at Day 70, no new metastatic foci or complications of SAB infection, improvement of SAB-related symptoms, two negative blood cultures for SAB Secondary: Mortality assessed at Day 70, microbiological eradication assessed at Day 70, overall success rate, development of new metastatic foci of SAB, time to SAB clearance, safety and tolerability, pharmacokinetics of ceftobiprole in PK population.	Planned: 415 Actual: 390	Centers: 60 Countries: 17

Study/ Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
BPR-CS-008 NCT # 03137173	Adult subjects with ABSSSI	Control type: Active concurrent non-inferiority Randomization: Standard randomization Blinding: Double-blind Biomarkers: No biomarkers Innovative design features: None	Drug: Zevtera (Ceftobiprole medocaril sodium for injection) Dosage: 667 mg IV q8h Number treated: 334 Duration: 5 to 14 d Comparator: Vancomycin plus aztreonam Dosage: 1 gram or 15 mg/kg q12h (vancomycin); 1 gram IV q12h (aztreonam) Number treated: 342 Duration: 5 to 14 d	Primary: Early clinical response resulting in ≥20% reduction from baseline in the area of the primary lesion, survival for ≥72 hours from the time of administration of the first dose, no use of concomitant antibacterial treatments and no additional unplanned surgical procedures. Secondary: Clinical success at the TOC visit 15 to 22 days after randomization, and at least 5 days after EOT visit.	Planned: 742 Actual: 679	Centers: 32 Countries: 4
CAP-3001 NCT # 00326287	Adult subjects with CABP	Control type: Active, concurrent, non-inferiority Randomization: Stratified randomization 1:1 Blinding: Double-blind Biomarkers: No biomarkers Innovative design features: None	Drug: Zevtera (Ceftobiprole medocaril sodium for injection) Dosage: 667 mg IV q8h Number treated: 310 Duration: 5 to 14 d Comparator: Ceftriaxone ± linezolid Dosage: 2 grams IV q24h (ceftriaxone); 600 mg IV q12h (linezolid) Number treated: 322 Duration: 5 to 14 d	Primary: Clinical cure rate at the TOC visit. Secondary: Microbiological eradication rate at the TOC visit. Clinical cure rate at the TOC visit for subjects who have a PSI score greater than or equal to 91. The 30-day pneumonia-specific mortality rate.	Planned: 532 Actual: 666	Centers: 103 Countries: 17

Reference ID: 5357793

Study/ Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
BAP-248/307 NCT # 00210964 and # 00229008	Adult subjects with HABP/VABP	Control type: Active concurrent non-inferiority Randomization: Standard randomization 1:1 Blinding: Double-blind Biomarkers: No biomarkers Innovative design features: None	Drug: Zevtera (Ceftobiprole medocaril sodium for injection) Dosage: 667 mg IV q8h Number treated: 386 Duration: 7 to 14 d Comparator: Ceftazidime ± linezolid Dosage: 2 grams IV q8h (ceftazidime); 600 mg IV q12h (linezolid) Number treated: 386 Duration: 7 to 14 d	Primary: Clinical cure rate at the TOC visit Secondary: Key endpoints included microbiological eradication rate at the TOC visit, clinical cure rate at TOC with nosocomial pneumonia caused by S. aureus, clinical cure rate at TOC visit in subjects with VABP	Planned: 770 Actual: 781	Centers: 157 Countries: 32

Reference ID: 5357793

Study/ Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized[2]	Number of Centers and Countries
BPR-PIP-002 NCT # 03439124	Pediatric subjects aged 3 months to <18 years of age with CABP/HABP	Control type: Active concurrent Randomization: 2:1 Randomization Blinding: Investigator-blind Biomarkers: None Innovative design features: None	Drug: Zevtera (ceftobiprole medocaril sodium for injection) Dosage: 13.3 mg/kg to 26.7 mg/kg IV q8h, age-adjusted Number treated: 94 Duration: 7 to 14 d including minimum of 3 d of study drug treatment and subsequent switch to defined age-appropriate oral antibacterial drug Comparator: Standard of care cephalosporin ± vancomycin Dosage: per site Number treated: 44 Duration: 7 to 14 d including minimum of 3 d of study drug treatment and subsequent switch to defined age-appropriate oral antibacterial drug	Primary: Adverse events during the first 3 days of treatment and at EOT, TOC and LFU Secondary: Comparison between treatment arms for clinical response at Day 4 and EOT, clinical cure at TOC and LFU, microbiological eradication rates at TOC and LFU and microbiological relapse rates at LFU	Planned: 138 Actual: 138	Centers: 12 Countries: 4

Source: Reviewer.
* Note: 667 mg of ceftobiprole medocaril sodium is equivalent to 500 mg of ceftobiprole. For pediatric patients: 13.3 mg/kg is equivalent to 10 mg/kg of ceftobiprole. 26.7 mg/kg of ceftobiprole medocaril sodium is equivalent to 20 mg/kg of ceftobiprole. Dosing adjustments for each indication are based on renal function
[1] Includes all submitted clinical trials, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.
[2] If no randomization, then replace with "Actual Enrolled."
Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; BID, twice daily; d, day; CABP, community-acquired bacterial pneumonia; DB, double-blind; EOT, end of treatment; h, hour; HABP, hospital-acquired bacterial pneumonia; LFU, last follow-up; LTE, long-term extension; MC, multicenter; mo, month(s); N, number of subjects; NCT, national clinical trial; OL, open-label; PC, placebo-controlled; PG, parallel group; PK, pharmacokinetic; PSI, Pneumonia Outcomes Research Team (PORT) Severity Index; q6h, every 6 hours, q8h, every 8 hours; q12h, every 12 hours, q24h, every 24 hours, R, randomized; SAB, *Staphylococcus aureus* Bacteremia; TOC, test-of-cure; VABP, ventilator-associated bacterial pneumonia; wk, week(s); y, year(s)

Reference ID: 5357793

4. Patient Experience Data

Table 6. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	**Type of Data**	**Section Where Discussed, if Applicable**
Clinical Outcome Assessment Data Submitted in the Application		
☐	Patient-reported outcome	Section 6. Definitions of Secondary Endpoints
☐	Observer-reported outcome	
☒	Clinician-reported outcome	
☐	Performance outcome	
Other Patient Experience Data Submitted in the Application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

5.1. Nonclinical Assessment of Potential Effectiveness

Nonclinical Ceftobiprole PK/PD Information

Several studies were conducted to examine the nonclinical pharmacokinetics (PK)/ pharmacodynamics (PD) of ceftobiprole in murine thigh and pneumonia models. Percent of time that free-drug concentrations remain above the minimum inhibitory concentration (%*f*T>MIC) was best correlated with ceftobiprole efficacy, indicating that antibacterial activity of ceftobiprole is time dependent, similar to other beta-lactams (see Section 14.1.1 for more information).

Identification of PK/PD Target

An efficacy study was performed in neutropenic thigh-infected mice given single subcutaneous doses (0.2 mL/ dose) of ceftobiprole medocaril sodium (10, 40, and 160 mg/kg). A sigmoid dose-response model derived from the four-parameter Hill equation was used to calculate the dose of ceftobiprole producing a net bacteriostatic effect and 1-log10 kill over 24 hours. The free time above MIC (*f*T > MIC) values for each static and 1-log kill dose were estimated from PK and MICs. Ceftobiprole was tested against a total of 14 gram-positive strains and five strains of gram-negative bacteria, including *E. coli*, *K. pneumoniae* and *P. aeruginosa* and *E. cloacae* (see Section 14.1.1 for more information). The results of %*f*T > MIC to achieve bacteriostasis, 1-log10 kill and 2-log kill are presented in Table 7.

Table 7. Summary Statistics for Ceftobiprole Free-Drug Plasma %T>MIC Targets Associated With Net Bacterial Stasis and 1- and 2-log10 CFU Reductions From Baseline in a Neutropenic Murine Thigh Infection Model

Pathogen	Measure	Free-drug plasma %T>MIC by bacterial reduction endpoint[a]		
		Net bacterial stasis	1-log_{10} CFU reduction from baseline[b]	2-log_{10} CFU reduction from baseline
S. aureus (n = 8)	Minimum	14.1	20.3	24.4
	Median	21.1	24.7	28.5
	Maximum	25.4	32.1	39.1
S. pneumoniae (n = 6)	Minimum	15.2	17.4	18.4
	Median	19.0	23.1	25.9
	Maximum	22.2	26.6	31.8
Enterobacterales (n = 4)	Minimum	35.6	38.3	40.9
	Median	41.6	50.0	58.5
	Maximum	44.6	72.3	100

Note: Abbreviations are provided in the Abbreviation Listing.
a. Free-drug plasma %T>MIC targets associated with net bacterial stasis and a 2-log_{10} CFU reduction from baseline were based on Hill-type models for individual isolates, as described in reference 20.
b. Free-drug plasma %T>MIC targets associated with a 1-log_{10} CFU reduction from baseline were interpolated.
Source: Craig 2008
Abbreviations: CFU, colony forming unit; MIC, minimum inhibitory concentration

Since free-drug plasma %T>MIC targets from this study were only reported for net bacterial stasis and a 2-log10 colony forming unit (CFU) reduction from Baseline, free-drug plasma %T>MIC targets associated with a 1-log10 CFU reduction from baseline were linearly interpolated by averaging the targets for net bacterial stasis and a 2-log10 CFU reduction from Baseline.

Based on these results, the Applicant chose ceftobiprole bactericidal (1-log kill) %*f*T>MIC values of 30% and 50% for the treatment of infections caused by gram-positive and gram-negative pathogens, respectively.

5.2. Clinical Pharmacology / Pharmacokinetics

Information on general pharmacology and PK characteristics is shown Table 8.

Table 8. Summary of Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class (EPC)	Cephalosporin antibacterial
Mechanism of action	Inhibition of bacterial cell wall synthesis by binding to essential penicillin-binding proteins (PBPs) and inhibiting transpeptidase activity, which is essential for the synthesis of the peptidoglycan layer of the bacterial cell wall.
Active moieties	Ceftobiprole
QT prolongation	At a single intravenous dose of 500 mg and 1000 mg (2 times the recommended dose), ceftobiprole does not prolong the QT interval to any clinically relevant extent (Study CSI-1003).
	General Information
Bioanalysis	Validated HPLC-MS/MS and LC-MS/MS methods were used to determine the concentrations of ceftobiprole medocaril sodium and ceftobiprole concentrations in human plasma, urine, BAL fluid, bone, ultrafiltrate and dialysate.
Healthy subjects versus subjects	SAB: AUC is approximately 17% less in subjects vs. healthy subjects (95% CI, 0.12-0.20) ABSSSI/CAP: AUC is approximately 26% less in subjects vs. healthy subjects (95% CI, 0.23-0.28)
Drug exposure at steady state following the therapeutic dosing regimen	Day 3 simulated exposures of ceftobiprole in subjects following administration of 500 mg/kg q8h or q6h IV ceftobiprole is shown below:
Maximally tolerated dose or exposure	1,000 mg IV ceftobiprole is the maximally tolerated single dose (Study BAP00006) 1,000 mg q8h IV ceftobiprole is the maximally tolerated daily dose but is also the highest tested dose in the MAD study (Study BAP00393).
Dose proportionality	Ceftobiprole AUC and C_{max} increase in a roughly dose proportional manner from of 125 to 1000 mg, infused over 30 minutes (Study NP16104, Study BAP00010 and Study BAP00393).

Table 9. Day 3 Simulated Exposures of Ceftobiprole

Indication	$AUC_{0\text{-}24h}$ (µg[a]h/mL)	C_{max} (ug/mL)
ABSSSI[b]	197 (39.6%)	17.4 (27.7%)
CABP[b]	270 (42.1%)	21.6 (28.3%)
SAB[c]	338 (54.2%)	20.9 (41.5%)

Source:
[a] all values are presented as geometric mean (geometric CV%)
[b] following administration of 500 mg IV q8h
[c] following administration of 500 mg IV q6h
Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; AUC, area under the concentration-time curve; $AUC_{0\text{-}24}$, area under the concentration-time curve from time 0 to 24 hours; CABP, community-acquired bacterial pneumonia; C_{max}, maximum plasma concentration; SAB, *Staphylococcus aureus* bacteremia

Characteristic	Drug Information
Accumulation	The accumulation ratio for the dosing regimen of 500 mg every 8 hours at steady state (Day 5) was 1.14 (Study CSI-1004).
Time to achieve steady-state	In healthy subjects receiving four doses of ceftobiprole 500 mg q8 hours, steady-state was achieved for most subjects before the fourth infusion on Day 2 (Study CSI-1005).
Bridge between to-be-marketed and clinical trial/study formulations	The to-be-marketed ceftobiprole medocaril sodium formulation was used in the pivotal efficacy studies.
	Absorption
Bioavailability	N/A
T_{max}	2 hours (Study CSI1004)
Food effect (fed/fasted) Geometric least square mean and 90% CI	N/A
	Distribution
Volume of distribution	18 L
Plasma protein binding	The protein binding of ceftobiprole is 16% and is independent of ceftobiprole concentration across the range of 0.5 to 100 µg/mL (Study FK5789 and Study FK6157).
Drug as substrate of transporters	Ceftobiprole is not a substrate of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), multidrug resistance protein 2 (MRP2), BSEP, organic anion-transporting polypeptide (OATP) 1B1, OATP1B3, or OCT1. Ceftobiprole is a substrate of the renal uptake transporters organic anion transporter 1 (OAT1) and organic cation transporter 2 (OCT2) but not OAT3 (Study XT138008).
	Elimination
Mass balance results	A mass balance study for ceftobiprole medocaril sodium was not submitted for review.
Clearance	5 L/hr
Half-life	The terminal half-life of ceftobiprole is approximately 3 hours, ranging from 2.4 to 4.11 hours across the phase 1 studies.
Metabolic pathway(s)	Ceftobiprole medocaril sodium is the active pharmaceutical ingredient. Ceftobiprole medocaril is the prodrug of the active form, ceftobiprole. Conversion from ceftobiprole medocaril sodium to ceftobiprole occurs rapidly and is mediated by non-specific plasma esterases. Ceftobiprole undergoes minimal metabolism to an open-ring metabolite which is microbiologically inactive. Systemic exposure of the open-ring metabolite is approximately 4% of the parent exposure.
Primary excretion pathways (% dose)	The main route of elimination of ceftobiprole is by renal excretion, by glomerular filtration. Following single dose administration, approximately 89% of the administered dose is recovered in the urine as active ceftobiprole (83%), the open-ring metabolite (5%) and ceftobiprole medocaril sodium (<1%; Study CSI-1004).
	Intrinsic Factors and Specific Populations
Body weight	No clinically significant differences in the PK of ceftobiprole were observed in adults based on body weight. Dose adjustment is not needed.

Characteristic	Drug Information
Age	No clinically significant differences in the PK of ceftobiprole were observed in adults based on age. Dose adjustment is not needed.
Renal impairment	Ceftobiprole AUC increase was 2.5-fold and 3.3-fold higher in adult subjects with moderate renal impairment (CL_{CR} 30 to < 50 mL/min), and 3.3-fold in severe renal impairment (CL_{CR} < 30 mL/min). Dose adjustment is recommended in moderate and severe renal impairment in adults and in pediatric patients > 2 years of age. No clinically significant difference in the PK of ceftobiprole were observed in adult patients with ESRD (CL_{CR} < 15 mL/min) compared to healthy adult subjects based on limited PK data and PK modeling and simulation. Ceftobiprole was demonstrated to be hemodialysable in patients receiving ceftobiprole
Hepatic impairment	The effect of hepatic impairment on the PK of ceftobiprole was not evaluated. However, hepatic impairment is not expected to alter the elimination of ceftobiprole because ceftobiprole is mainly excreted by the kidneys. Dose adjustment is not needed.
	Drug Interaction Liability (Drug as Perpetrator)
Inhibition/induction of metabolism	In vitro studies did not show a clinically relevant inhibitory or induction potential of ceftobiprole toward cytochrome P450 (CYP) 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5 (Studies 1009572, FK6366, and FK6604, FK5831/XT053012, FK6603/XT083004, and XT223040)
Inhibition/induction of transporter systems	In vitro studies suggest ceftobiprole is not an inhibitor of P-gp, BCRP, OAT1, OAT3, OCT1, or OCT2 (XT138008, XT228043). Ceftobiprole inhibits OATP1B1 and OATP1B3 in vitro (Study XT138008). Concomitant administration of ceftobiprole and substrates of OATP1B1 and OATP1B3 is not recommended (see Section 8.2.1 and 14.1.5). As ceftobiprole is not an inducer of CYP3A4 in vitro, no evaluation was done for P-gp induction.

Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; AUC, area under the concentration-time curve; AUC_{0-24}, area under the concentration-time curve from time 0 to 24 hours; BAL, bronchoalveolar lavage; BCRP, breast cancer resistance protein; BSEP, bile salt export pump; CABP, community-acquired bacterial pneumonia; CL_{CR}, creatine clearance; C_{max}, maximum plasma concentration; CI, confidence interval; CV, coefficient of variation; CYP, cytochrome P450; EPC, established pharmacologic class; ESRD, end-stage renal disease IV, intravenous; MRP2, multidrug resistance protein 2; OATP, organic anion-transporting polypeptide; OAT1, organic anion transporter 1; OAT2, organic anion transporter 2; PBP, penicillin binding proteins; P-gp, P-glycoprotein; PK, pharmacokinetic; QT, qualification threshold; q6h, every 6 hours; q8h, every 8 hours; SAB, *Staphylococcus aureus* Bacteremia; T_{max}, time to maximum concentration

6. Efficacy (Evaluation of Benefit)

6.1. Assessment of Dose and Potential Effectiveness

The Applicant conducted probability of target attainment (PTA) analyses based on nonclinical PK/PD targets to support the adequacy of the proposed dose regimens including the renal function-based dose adjustments.

Based on the observed PK and MIC data from the subjects evaluated in the phase 3 trials, the percentage of subjects who achieved the PK/PD targets associated with stasis and 1-log kill were determined.

The Applicant's proposed dosages were evaluated in a single phase 3 trial for each respective indication (Table 10). The dosages used in the phase 3 clinical trials reflect the final

Reference ID: 5357793

recommended dosages. Dose adjustments are required for patients with renal impairment (See Section 8.1 for more information).

Table 10. Ceftobiprole Dosage Evaluated in Phase 3 Trials

Indication	Dose	Frequency	Infusion Duration	Duration of Therapy
Staphylococcus aureus bacteremia	500 mg	Every 6 hours on Days 1 to 8 Every 8 hours from Day 9	2 hours	Up to 42 days
Acute bacterial skin and skin structure infections	500 mg	Every 8 hours		5 to 14 days
Community acquired bacterial pneumonia	500 mg	Every 8 hours		5 to 14 days

Source: BPR-CS-009; BPR-CS-008; CAP-3001
500 mg of ceftobiprole is equivalent to 667 mg of ceftobiprole medocaril sodium

These dosages were evaluated in target attainment analyses using simulated subjects by creatinine clearance (CL_{CR}) group and those resembling the clinical trial population on Day 1 (and Day 10 for the SAB indication). Target attainment was assessed based on median and randomly assigned free-drug plasma %fT>MIC targets associated with net bacterial stasis and a 1-log10 CFU reduction from Baseline.

Among simulated subjects with SAB, the percent probabilities of target attainment were >99% for both stasis and 1-log10 CFU reduction over the MIC distributions on Day 1 and Day 10. For the ABSSSI and CABP indication, Day 1 target attainment rates differed slightly based on the bacterial species with >99.9% for *S. aureus*, 100% for *Streptococcus* species, and ranged from 87.2 to 87.6% for *Enterobacterales* in simulated subjects with ABSSSI and 100% for *S. pneumoniae*, >99.9% for *S. aureus*, and ranged from 87.0 to 87.4% for *Enterobacterales* in simulated subjects with CABP (see Section 14.5 for analysis results).

Dosage in Pediatric Patients with CABP

The recommended dosage in pediatric subjects with CABP is outlined in Table 11. Evidence of effectiveness for the proposed ceftobiprole dosage in CABP pediatric patients ages 3 months and older is based on safety and PK data in pediatric patients as well as extrapolation of effectiveness from adult CABP patients. Because CABP is pathophysiologically similar in adults and pediatric patients aged 3 months and older, the efficacious ceftobiprole exposures in adults are expected to also be effective in pediatric patients. Population PK analyses demonstrate that estimated ceftobiprole exposures resulting from the proposed dosage in pediatric CABP patients are similar to the efficacious exposures in adults, thus enabling extrapolation of effectiveness from adults to pediatric patients. Additionally, supportive evidence of effectiveness for the proposed dosage is provided by the results of probability of PK/PD target attainment analysis (see Section 14.5 for more information).

Table 11. Recommended Dosage in Pediatric Patients With CABP

Pediatric Age Group	Dose	Frequency	Infusion Duration
12 years to less than 18 years	10 mg/kg (maximum 500 mg/dose)	Every 8 hours	2-hour infusion
Greater than or equal to 3 months and less than 12 years	15 mg/kg (maximum 500 mg/dose)		

Source: Applicant's Population PK Report 00616-3A
Abbreviations: CABP, community-acquired bacterial pneumonia
10 mg/kg of ceftobiprole is equivalent to 13.3 mg/kg of ceftobiprole medocaril sodium; 15 mg/kg of ceftobiprole is equivalent to 20 mg/kg ceftobiprole medocaril sodium; 500 mg of ceftobiprole is equivalent to 667 mg ceftobiprole medocaril sodium

Dose adjustment is recommended in pediatric patients greater than or equal to 2 years of age with renal impairment. For patients aged <2 years, there is insufficient information to recommend dosage adjustments in the setting of renal impairment due to the complexity of renal maturation and the lack of PK data in this subpopulation (see Section 8.1.4 for more information).

6.2. Clinical Studies/Trials Intended to Demonstrate Efficacy

6.2.1. SAB, Trial BPR-CS-009

6.2.1.1. Design, Trial BPR-CS-009

Trial BPR-CS-009 was conducted from August 2018 to March 2022. The trial protocol was reviewed as a special protocol assessment (SPA) under investigational new drug application (IND) 64407. This was a randomized, double-blind, double-dummy, active-controlled, parallel-arm, multi-center trial in adult hospitalized subjects with SAB, including infective endocarditis (IE), which was conducted in two parts. Part 1 enrolled an initial cohort of subjects (Cohort 1) for a maximum treatment duration of 28 days as animal studies had indicated the potential of an increased risk of convulsions with prolonged ceftobiprole treatment duration (> 4 weeks) and no prior clinical studies of ceftobiprole with this treatment duration had been conducted. Based on a safety evaluation of Cohort 1, the Data and Safety Monitoring Board decided that it was safe to proceed to Part 2. Part 2 allowed a longer treatment duration of up to 42 days and the inclusion of subjects with more difficult to treat infections such as osteomyelitis and epidural or cerebral abscess who were excluded from Cohort 1. Subjects with left-sided infective endocarditis (LIE) diagnosed after randomization were also permitted to continue in the trial.

Following a screening period of up to 72 hours, subjects were randomized 1:1 to receive intravenous (IV) ceftobiprole or daptomycin ± aztreonam. The randomization was stratified by Trial site, dialysis status, and prior antibacterial treatment use within 7 days before randomization. Following the completion of treatment, visits were scheduled at end-of-treatment (EOT) (within 72 hours of the last Trial drug administration), Day 35 (± 3 days), Day 42 (± 3 days), and at post-treatment evaluation (PTE) on Day 70 (± 5 days) post-randomization. Note that the Day 35 and Day 42 visits could have been active treatment periods for subjects in Part 2

requiring up to 42 days of treatment. The total duration of the Trial for each subject was approximately 10 weeks.

A total of 390 subjects were planned to be randomized, and a total of 390 subjects were actually randomized and comprised the intent-to-treat (ITT) population (ceftobiprole n = 192; comparator n = 198). An independent blinded data review committee (DRC) comprising six infectious diseases experts was assembled to review detailed subject profiles, including imaging and microbiological and laboratory results, of all subjects in the ITT population, to assess the baseline categories of complicated SAB, the response outcome for the primary endpoint, and the secondary endpoints of microbiological outcomes and death attributed to SAB.

Primary Endpoint

Overall success assessed by the DRC at the PTE visit assessed in the modified intent-to-treat population.

Overall success was defined as all of the following criteria being met:

1. Subject alive at Day 70 (± 5 days) post-randomization
2. No new metastatic foci or complications of the SAB infection
3. Resolution or improvement of SAB-related clinical signs and symptoms
4. Two negative blood cultures for *S. aureus* (without any subsequent positive blood culture for *S. aureus*):
    - At least one while the subject was on active study treatment; AND
    - Confirmed by at least one subsequent negative blood culture for *S. aureus*
        a. Either in the period between 7 days after the EOT Visit and the PTE Visit
        b. Or at the PTE Visit

Treatment failure was defined as any of the following:

1. Premature discontinuation of study treatment due to DRC assessed lack of efficacy or for adverse events (AEs) that represented manifestation of disease progression or relapse, at any time between first dose of study drug and the PTE visit.
2. Development of new metastatic or other complications related to SAB between Day 8 and the PTE visit.
3. SAB relapse/reinfection based on evidence from a blood culture positive for *S. aureus* (after documented clearance of *S. aureus* from the bloodstream and clinical improvement) between the EOT and PTE visits.
4. Receipt of systemic non-study antibacterial treatment, other than those permitted under the protocol, for the treatment of SAB. This included subjects who were prematurely discontinued from study therapy due to an AE, but who required continuation of antibacterial treatment for SAB.
5. Treatment of infections other than SAB with systemic non-study antibacterial treatment which was potentially effective against *S. aureus*, and which was considered by the DRC to

Reference ID: 5357793

have a relevant impact on the primary endpoint in accordance with guidelines provided in the protocol.

6. Death for any reason between first administration of study drug and the PTE visit.
7. Indeterminate outcome, defined as any data needed to determine whether the outcome was success or failure was missing at the PTE visit, including but not limited to:
   - Missing PTE visit, or missing key data to evaluate the primary endpoint
   - Lost-to-follow-up, or subjects who withdrew consent prior to the PTE visit
   - Subjects not meeting the criteria for success or failure, or subjects not meeting all criteria for overall success
8. Requirement for systemic antibacterial treatment for SAB beyond EOT.

Secondary Endpoints

1. All-cause mortality assessed at Day 70 (PTE Visit) in the mITT population (ITT subjects who received any dose of study medication, and had a blood culture positive for *S. aureus* at Baseline).
2. Microbiological eradication assessed by the DRC at Day 70 (PTE Visit) in the mITT population.
3. The overall success rate in the ITT, mITT, and clinically evaluable (CE) populations:
   - At the EOT and PTE (ITT and CE populations only) visits
   - At the EOT and PTE visits, for RIE versus non-IE SAB
   - At the EOT and PTE visits, by renal-function status
4. Development of new metastatic foci or other complications of SAB after Day 7 were assessed in the mITT and CE populations.
5. Time to *S. aureus* bloodstream clearance in the mITT and CE populations, defined as the elapsed time (days) from randomization to bloodstream clearance, with bloodstream clearance defined as the occurrence of two consecutive study days with blood-culture-negative assessments for *S. aureus*; bloodstream clearance in subjects with intermittent positive on treatment blood cultures started after the last positive blood culture. Subjects with *S. aureus* relapse or reinfection as per DRC assessment were not considered as bloodstream clearance.
6. Safety and tolerability.
7. Pharmacokinetics.

6.2.1.2. Eligibility Criteria, Trial BPR-CS-009

The trial enrolled adult subjects with complicated SAB, defined as subjects with at least one positive blood culture for *S. aureus* at Baseline, signs and symptoms of bacteremia (fever, white blood cell [WBC] count, tachycardia, and/or hypotension), and one of the following underlying conditions or complications: chronic intermittent hemodialysis or peritoneal dialysis,

Reference ID: 5357793

persistent SAB, definitive native-valve RIE, ABSSSIs, or metastatic infections of native tissue (e.g., septic arthritis, septic/suppurative thrombophlebitis, visceral abscess, septic pulmonary emboli).

Subjects with osteomyelitis or cerebral/epidural abscess were to be enrolled in Part 2 only.

Subjects who received treatment with potentially effective anti-staphylococcal systemic antibacterial treatment for more than 48 hours within 7 days before randomization were excluded from the trial unless they met the criteria for persistent SAB.

Inclusion Criteria

Subjects meeting all of Inclusion Criteria 1 – 5 and at least one of Inclusion Criteria 6 – 11 were eligible for enrollment:

1. Male or female ≥18 years of age.
2. Informed consent signed by the subject (or by their legally acceptable representative, if appropriate) indicating that they understood the purpose of, and procedures required for, the trial and were willing to participate in the trial.
3. SAB, based on at least one positive blood culture obtained within the 72 hours prior to randomization:
    - Identified by culture laboratory report, or
    - Positive diagnostic test for *S. aureus* (e.g., polymerase chain reaction [PCR], tube coagulase test and fluorescent in situ hybridization) obtained from a blood culture.

At least one of the following signs or symptoms of bacteremia within the 72 hours prior to randomization (may be based on measurements obtained before or after informed consent but within the 72 hours prior to randomization):

1. Fever >38°C / 100.4°F measured orally, >38.5°C / 101.3°F measured tympanically, >37.5°C / 99.5°F measured by axillary method, or >39°C /102.2°F measured rectally
2. WBC count >10.0 x 10^9/L or <4.0 x10^9/L, or >10% immature neutrophils (bands)
3. Tachycardia (heart rate >90 beats per minute [bpm])
4. Hypotension (systolic blood pressure [SBP] <90 mm Hg)
5. Required duration of study antibacterial treatment ≤42 days.
6. SAB in subjects undergoing chronic intermittent hemodialysis or peritoneal dialysis.
7. Persistent SAB: documented failure of bloodstream clearance, defined as a positive blood culture for *S. aureus* within the 72 hours prior to randomization, after prior appropriate anti-staphylococcal treatment (except failure under daptomycin therapy) of at least 3 complete days.
8. Other forms of complicated SAB, including the following:
    - ABSSSIs
    - Metastatic infection of native tissue. Examples include but were not limited to:
9. Septic arthritis or bacterial joint infection/empyema

Reference ID: 5357793

10. Septic or suppurative thrombophlebitis
11. Visceral soft-tissue abscesses requiring ≤42 days of study antibacterial treatment
12. Septic pulmonary emboli/infarction
13. Definite native-valve RIE by Modified Duke's Criteria.

Prohibited Concomitant Medications

Concomitant systemic antibacterials that provide activity against *S. aureus* were prohibited during the period from randomization up to the PTE visit. The use of non-study antibacterial treatment during the trial was not necessarily considered to be an outcome of 'failure'. The significance of concomitant potentially effective non-study antibacterial treatment (except aztreonam, metronidazole, nitrofurantoin, and oral vancomycin) was assessed in accordance with the guidelines provided in the clinical study report (CSR) to determine whether the treatment had an impact on the primary endpoint.

Permitted Antibacterial Treatments

The following concomitant antibacterial medications were permitted:

1. In the daptomycin treatment arm, aztreonam using a standard-dose regimen at the site for coverage of gram-negative infections (i.e., for polymicrobial bloodstream infections, or gram-negative non-bloodstream infections). Subjects randomized to the ceftobiprole arm who were considered to require coverage against gram-negative infections received dummy treatment with placebo so that blinding was maintained during the active treatment phase.
2. In both treatment arms:
    - Nitrofurantoin for urinary tract infections
    - Metronidazole using a standard-dose regimen at the site for coverage of anaerobic infections
    - Oral vancomycin was considered a non-systemic antibiotic and was permitted for use at any time during the trial.

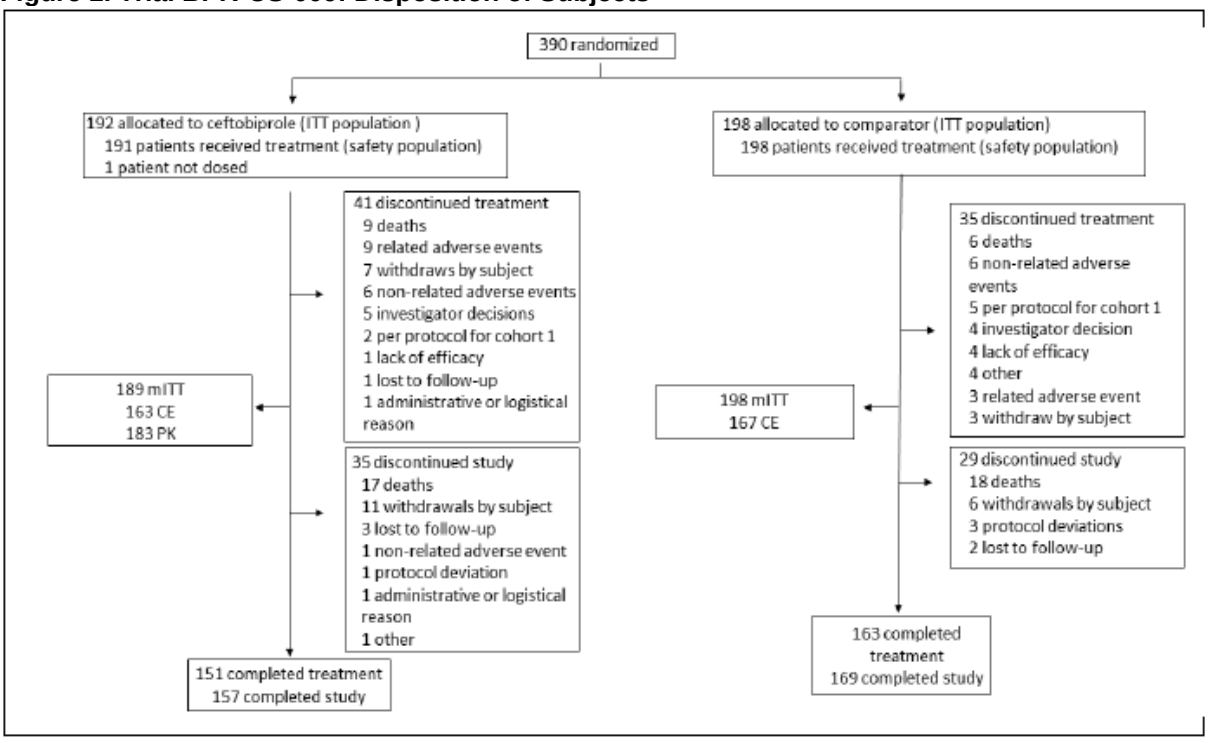
6.2.1.3. Statistical Analysis Plan, Trial BPR-CS-009

Disposition of Subjects

The disposition of subjects is described in Figure 1. A total of 390 subjects were randomized to receive either the ceftobiprole (n = 192) or daptomycin (n = 198) treatment. Three subjects did not receive study treatment (1 in ceftobiprole arm and 2 in the daptomycin arm). Two subjects, both in the ceftobiprole arm, were determined by central laboratory results not to have a confirmed positive blood culture for *S. aureus* at Baseline.

Reference ID: 5357793

Figure 1. Trial BPR-CS-009: Disposition of Subjects



Source: Figure 1 of CSR
Abbreviations: CE, clinically evaluable; ITT, intent-to-treat; , modified intent-to-treat; PK, pharmacokinetic

As shown in Figure 1 and Table 12, there were 35 ITT subjects (18.2%) in the ceftobiprole arm and 29 ITT subjects (14.6%) in the comparator arm who were discontinued from the Trial. The main reasons for study discontinuation were deaths, (17 (8.9%) in the ceftobiprole arm and 18 (9.1%) in the daptomycin arm) and withdrawal by subjects, (11 (5.7%) in the ceftobiprole arm and 6 (3.0%) in the daptomycin arm). A total of 76 subjects (19.5%) discontinued study treatment, 41 (21.4%) and 35 (17.7%) in the ceftobiprole and daptomycin arms, respectively. The most common reason for treatment discontinuation was having a death which was observed in 9 ceftobiprole subjects (4.7%) and 3 daptomycin subjects (3.0%). There were also 9 subjects (4.7%) in the ceftobiprole arm and 6 subjects (3.0%) in the daptomycin arm who discontinued Trial treatment due to related AEs and 1 subject (0.5%) in the ceftobiprole arm and 4 subjects (2.0%) in the daptomycin arm who discontinued due to lack of efficacy.

Table 12. Reasons for Discontinuation From the Study and Discontinuation of Trial Treatment, Trial BPR-CS-009

Categories	Ceftobiprole (N=192) n (%)	Daptomycin (N=198) n (%)	Total (N=390) n (%)
Completed study	157 (81.8)	169 (85.4)	326 (83.6)
Discontinued from study	35 (18.2)	29 (14.6)	64 (16.4)
Primary reason			
Administrative or logistical reasons	1 (0.5)	0	1 (0.3)
Death	17 (8.9)	18 (9.1)	35 (9.0)
Lost to follow-up	3 (1.6)	2 (1.0)	5 (1.3)
Non-related adverse event	1 (0.5)	0	1 (0.3)
Protocol deviation	1 (0.5)	3 (1.5)	4 (1.0)
Withdrawal by subject	11 (5.7)	6 (3.0)	17 (4.4)
Other	1 (0.5)	0	1 (0.3)
Completed study treatment	151 (78.6)	163 (82.3)	314 (80.5)
Discontinued study treatment	41(21.4)	35 (17.7)	76 (19.5)
Primary reason			
Administrative or logistical reasons	1 (0.5)	0	1 (0.3)
Death	9 (4.7)	6 (3.0)	15 (3.8)
Investigator decision	5 (2.6)	4 (2.0)	9 (2.3)
Lack of efficacy	1 (0.5)	4 (2.0)	5 (1.3)
Lost to follow-up	1 (0.5)	0	1 (0.3)
Non-related adverse event	6 (3.1)	6 (3.0)	12 (3.1)
Per protocol for Cohort 1	2 (1.0)	5 (2.5)	7 (1.8)
Related adverse event	9 (4.7)	3 (1.5)	12 (3.1)
Withdrawal by subject	7 (3.6)	3 (1.5)	10 (2.6)
Other	0	4 (2.0)	4 (1.0)

Source: Table10 in CSR
Abbreviations: N, number of subjects in treatment arm; n, number of subjects within category

Baseline demographic and disease characteristics

As shown in Table 13**,** the baseline demographic and disease characteristics in the mITT population were generally balanced across the treatment arms. Subjects in the mITT were mostly White (96%), European (93%) or male (69%) with a median age of 58 years. Approximately 8% of subjects were Hispanic or Latino. Of note, 54% of subjects had a fever at baseline, 13% were on chronic dialysis and 40% had an abnormal WBC at baseline. Prior antibacterial medication use was common at 70% and concomitant (allowed) antibacterial medication use was also common using aztreonam (34%) or metronidazole (6%).

Reviewer Comments

The large percentage of White subjects (96%) may limit the generalizability of the trial's findings to other races.

Reference ID: 5357793

Table 13. Baseline Demographic and Disease Characteristics (mITT Population) Trial BPR-CS-009

Categories	Ceftobiprole N=189	Daptomycin N=198	Total N=387
Age (years)			
Mean (SD)	55.5 (15.18)	56.5 (15.33)	56.0 (15.25)
Median	57.0	58.0	58.0
Min, max	20, 89	19, 91	19, 91
Age categories (years) n (%)			
18 – 34	20 (10.6)	19 (9.6)	39 (10.1)
35 – 64	111 (58.7)	116 (58.6)	227 (58.7)
65 – 74	41 (21.7)	42 (21.2)	83 (21.4)
≥75	17 (9.0)	21 (10.6)	38 (9.8)
Sex n (%)			
Male	128 (67.7)	140 (70.7)	268 (69.3)
Female	61 (32.3)	58 (29.3)	119 (30.7)
Race n (%)			
White	174 (94.7)	192 (97.0)	371 (95.9)
Black	4 (2.1)	5 (2.5)	9 (2.3)
Other	5 (2.6)	0	5 (1.3)
Ethnicity n (%)			
Hispanic or Latino	14 (7.4)	15 (7.6)	29 (7.5)
Not Hispanic or Latino	174 (92.1)	182 (91.9)	356 (92.0)
Not reported	1 (0.5)	1 (0.5)	2 (0.5)
Geographic regions n (%)			
Europe	175 (92.6)	185 (93.4)	360 (93.0)
North America	5 (2.6)	5 (2.5)	10 (2.6)
Other	9 (4.8)	8 (4.0)	17 (4.4)
Prior antibiotic medication n (%)			
Yes	139 (73.5)	134 (67.7)	273 (70.5)
No	50 (26.5)	64 (32.3)	114 (29.5)
Concomitant (allowed) antibacterial medication n (%)			
Aztreonam/placebo	69 (36.5)	62 (31.3)	131 (33.9)
Metronidazole	9 (4.8)	15 (7.6)	24 (6.2)
Creatinine clearance (mL/min) n (%)f			
Chronic dialysis	24 (12.7)	25 (12.6)	49 (12.7)
Not on chronic dialysis			
CL_{CR} <30 mL/min	5 (2.6)	8 (4.0)	13 (3.4)
CL_{CR} 30-50 mL/min	12 (6.3)	6 (3.0)	18 (4.7)
CL_{CR} 50-80 mL/min	33 (17.5)	35 (17.7)	68 (17.6)
CL_{CR} >80 mL/min	115 (60.8)	124 (62.6)	239 (61.8)
Fever status n (%)			
Fever	104 (55.0)	105 (53.0)	209 (54.0)
No Fever	85 (45.0)	93 (47.0)	178 (46.0)
WBC count n (%)			
Normal (4.0 x 10^9/L ≤WBC ≤10.0 x 10^9/L)	72 (38.1)	78 (39.4)	150 (38.8)
Abnormal (WBC<4.0 x 10^9/L or WBC >10.0 x 10^9/L)	70 (37.0)	84 (42.4)	154 (39.8)
Missing	47 (24.9)	36 (18.2)	83 (21.4)

Source: Partially Adapted from Table 13 of CSR
Abbreviations: CL_{CR}, creatine clearance; mITT, modified intent-to-treat; N, number of subjects in treatment arm; n, number of subjects within category; WBC, white blood cell

Table 14 provides a summary of the categories of complicated SAB at Baseline in the mITT population. Categories of complicated SAB were based on Investigator assessment, except for persistent SAB at Baseline; this was based on the DRC assessment, as the DRC had access to central microbiology laboratory results including susceptibility.

The most frequent baseline categories of complicated SAB were ABSSSI (61.2%), intra-abdominal abscesses (14.2%), chronic intermittent dialysis (12.7%), septic arthritis (10.6%), definite native valve IE (8.3%), and osteomyelitis (7.8%). A total of 6.5% of subjects had definite RIE with slightly higher rates in the ceftobiprole arm (ceftobiprole 7.9%, 15/189, comparator 5.1% 10/198). However, treatment arms generally showed similar percentages for baseline categories of complicated SAB.

Table 14. Categories of Complicated *Staphylococcus aureus* Bacteremia at Baseline (mITT Population) Trial BPR-CS-009

Categories	Ceftobiprole N=189	Daptomycin N=198	Total N=387
Uncomplicated SAB	0	0	0
Any complicated SAB	189 (100)	198 (100)	387 (100)
Chronic intermittent dialysis	24 (12.7)	25 (12.6)	49 (12.7)
Graft (synthetic conduit)	0	0	0
Tunneled catheter	12 (6.3)	7 (3.5)	19 (4.9)
Fistula (natural vessel only)	2 (1.1)	5 (2.5)	7 (1.8)
Temporary catheter	13 (6.9)	13 (6.6)	26 (6.7)
Other	0	0	0
Peritoneal dialysis	0	0	0
Persistent SAB	16 (8.5)	16 (8.1)	32 (8.3)
Other forms of complicated SAB	169 (89.4)	179 (90.4)	348 (89.9)
ABSSSIs	116 (61.4)	121 (61.1)	237 (61.2)
Metastatic infection of native tissue	68 (36.0)	65 (32.8)	133 (34.4)
Intra-abdominal abscess	26 (13.8)	29 (14.6)	55 (14.2)
Hepatic abscess[a]	5 (2.6)	7 (3.5)	12 (3.1)
Psoas abscess	9 (4.8)	9 (4.5)	18 (4.7)
Pancreatic/omental abscess[a]	5 (2.6)	6 (3.0)	11 (2.8)
Other intra-abdominal abscess[a]	7 (3.7)	8 (4.0)	15 (3.9)
Thoracic abscess	7 (3.7)	10 (5.1)	17 (4.4)
Pleural empyema/lung abscess[a]	3 (1.6)	7 (3.5)	10 (2.6)
Mediastinitis[a]	4 (2.1)	3 (1.5)	7 (1.8)
Septic arthritis	22 (11.6)	19 (9.6)	41 (10.6)
Septic or suppurative thrombophlebitis	9 (4.8)	5 (2.5)	14 (3.6)
Septic pulmonary emboli/infarction	11 (5.8)	4 (2.0)	15 (3.9)
Other metastatic infection of native tissue	7 (3.7)	6 (3.0)	13 (3.4)
Osteomyelitis	13 (6.9)	17 (8.6)	30 (7.8)
Epidural or cerebral abscess	2 (1.1)	6 (3.0)	8 (2.1)
Other	1 (0.5)	1 (0.5)	2 (0.5)
Definite native-valve IE[a]	19 (10.1)	13 (6.6)	32 (8.3)
Definite native-valve RIE	15 (7.9)	10 (5.1)	25 (6.5)
Definite native-valve LIE[a]	5 (2.6)	3 (1.5)	8 (2.1)

Source: Partially Adapted from Table 15 of CSR
Note: Diagnosis of categories of complicated SAB at baseline could be done up to 7 days post-randomization. Subjects could have more than one category of complicated SAB.
Note: All categories were assessed by Investigator except persistent SAB at baseline that was assessed by DRC.
[a] Identified based on medical review of terms reported under 'Other' or 'Other Metastatic Infection of Native Tissue' field on the Categories of Complicated SAB CRF page.
Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; IE, infective endocarditis; LIE, left sided infective endocarditis; N, number of subjects in treatment arm; RIE, right-sided infective endocarditis; SAB, *Staphylococcus aureus* Bacteremia

Analysis Sets

The analysis sets defined in the trial were as follows:

ITT Population

All randomized subjects.

The Safety Population

All randomized subjects who received at least one dose of study drug.

mITT Population

ITT subjects who received any dose of study medication, and who had a blood culture positive for *S. aureus* at baseline.

CE Population

Protocol-compliant ITT subjects who complied with important aspects of the study.

Sample Size Determination

The sample size estimate was based on:

- A point estimate for overall success of 40% in each treatment arm in the mITT population
- One-sided alpha level of 0.025
- Power of >80%
- Non-inferiority margin of 15% for the between-arm difference in the primary endpoint

With these assumptions, enrollment of 175 subjects per treatment arm (total of 350 subjects) was required for the mITT population. Assuming that approximately 90% of subjects in the ITT population had confirmed SAB and therefore were to be included in the mITT population, it was necessary for 195 subjects per arm (total of 390 subjects) to be randomized and receive Trial treatment.

Statistical Methods

Primary Analysis

The Trial was designed to determine whether ceftobiprole was non-inferior to daptomycin for the primary outcome measure of overall success at the PTE Visit at Day 70 (± 5 days) after randomization, in the mITT population. The specified NI margin was 15%.

Reviewer Comments

This 15% NI margin was based on 7 studies from the pre-penicillin era reporting clinical outcome (survival) in untreated subjects with SAB which combined suggested all-cause mortality (ACM) of 76% (95% confidence interval *[CI]: 71%, 79%) as well as 3 studies of mortality in SAB subjects receiving antibacterial treatment which suggested an ACM of 16% (95% CI: 12%, 20%). The M1 is estimated to be 51% for ACM. The protocol stated that "An estimation of M1 for an overall success endpoint is not possible, as this was not reported in the historical studies,*

Reference ID: 5357793

which considered survival to be success" but that "the mortality data suggest that M1 for a clinical/overall success outcome for SAB would similarly be very large, i.e., in the range of 50%, when outcomes are compared for untreated subjects and subjects who received effective antibacterial treatment." The NI margin of 15% was chosen based on clinical judgement. With a sample size of 250–350 subjects (in the mITT population), an NI margin of 15% would allow for the determination of noninferiority only if the point estimate between ceftobiprole and daptomycin is <5%.

The difference in the percentage of responders (i.e., subjects with overall success at PTE) (ceftobiprole arm minus the comparator arm) was determined, and a two-sided 95% CI for the difference was computed, with adjustment for actual dialysis status, and prior antibacterial treatment use (defined as receipt of medications within 7 days prior to randomization that were categorized as potentially effective systemic antibacterial treatments). Cochran-Mantel-Haenszel (CMH) weights were used for the stratum weight in the calculation of the CI. The non-inferiority hypothesis test was a one-sided hypothesis test performed at the 2.5% level of significance. If the lower limit of the two-sided 95% CI for the difference in response rates in the mITT population was greater than −15%, the noninferiority of ceftobiprole to daptomycin therapy was concluded.

Secondary Analyses

Secondary analyses considered the above approach for overall success assessed by the DRC at the EOT visit in the ITT and CE populations. All-cause mortality was assessed in the mITT and ITT populations and time to death was calculated using Kaplan-Meier methods. Survival rates (event-free probability estimates) at Day 28 and Day 70 in the ITT and mITT populations were provided and associated two-sided 95% CIs were calculated using the Greenwood formula. The hazard ratio for all-cause mortality and associated 95% CI were provided using a Cox proportional-hazard model, with treatment and actual stratum (dialysis status and prior antibacterial treatment use) as covariates. *S. aureus* clearance was analyzed in a similar manner as all-cause mortality.

6.2.1.4. Results of Analyses, Trial BPR-CS-009

Primary and Key Secondary Endpoint Analyses

Table 15 shows the results from the primary analysis and reasons for failure. For the primary endpoint of overall success at the PTE visit at Day 70 (± 5 days) after randomization in the mITT population, noninferiority was demonstrated with an adjusted difference (Ceftobiprole – Daptomycin) of 2.0% with a lower 95% confidence limit of -7.1% which exceeded the pre-specified NI margin of -15%. Similar findings were observed when considering the primary endpoint in the CE population.

Reasons for failure were generally similar between the treatment arms; however, there was a lower proportion of failures due to 'Requirement for systemic antibacterial treatment for SAB beyond protocol-defined maximum study treatment duration' in the ceftobiprole arm, 9/57 (15.2%) vs. 15/62 (24.2%). A slightly lower proportion of failures due to SAB relapse/reinfection was also observed in the ceftobiprole arm, 2/57 (3.5%) vs. 4/62 (6.5%). The most common reason for treatment failure in both treatment arms was 'Treatment of SAB with systemic non-study antibacterial treatment, other than those permitted under the protocol' which

Reference ID: 5357793

was more common in the ceftobiprole arm accounting for 20/57 (39.1%) versus 19/61 (30.6%) of failures.

Table 15. Overall Success Based on DRC Assessment at the PTE Visit (mITT Population), Trial - CS-009

Categories	Ceftobiprole (N=189)	Daptomycin (N=198)
Number of responders n (%)	132 (69.8)	136 (68.7)
95% CI[a]	62.8, 76.3	61.7, 75.1
Number of non-responders n (%)	57 (30.2)	62 (31.3)
Reasons for failure[b]		
Premature discontinuation of study treatment due to lack of efficacy	9 (15.8)	10 (16.1)
Development of new metastatic or other complications related to SAB	11 (19.3)	11 (17.7)
SAB relapse/reinfection	2 (3.5)	4 (6.5)
Treatment of SAB with systemic non-study antibacterial treatment, other than those permitted under the protocol	20 (35.1)	19 (30.6)
Treatment of infections other than SAB with systemic non-study antibacterial treatment potentially effective against *S. aureus*		13 (21.0)
Death for any reason after first administration of study drug	17 (29.8)	18 (29.0)
Indeterminate outcome, defined as any data needed to determine whether the outcome is success or failure missing	16 (28.1)	17 (27.4)
Requirement for systemic antibacterial treatment for SAB Beyond protocol-defined maximum study treatment duration	9 (15.8)	15 (24.2)
Proportion difference (95% CI) (%)[c] 2.0 (–7.1, 11.1)		

Source: Table 22 of CSR
[a] Computed using binomial exact method.
[b] Denominators for percentages are based on the number of non-responders. A subject may have been counted in more than one category.
[c] Proportion difference of ceftobiprole minus daptomycin. Computed using Cochran-Mantel-Haenszel (CMH) weights method adjusted for actual stratum (dialysis status and prior antibacterial treatment use).
Abbreviations: CI, confidence interval; mITT, modified intent-to-treat N, number of subjects in treatment arm; n, number of subjects within category; SAB, *Staphylococcus aureus* Bacteremia

As shown in Table 16, the outcomes of the secondary efficacy endpoints were also similar between treatment arms. All-cause mortality (ACM) through the Day 70 PTE visit in the mITT population showed rates of 17/189 (9.0%) and 18/198 (9.1%), in the treatment and comparator arms, respectively, and 7/189 (3.7%) and 6/198 (3.0%) when considering ACM due to SAB. For microbiological eradication at the PTE visit in the mITT population, rates were 155/189 (82.0%) and 153/198 (77.3%). Rates of development of new metastatic foci or other complications of SAB after Day 7 in the mITT population were 11/189 (5.8%) and 11/198 (5.6%). The median time to *S. aureus* bloodstream clearance in the mITT population was 4 days in both treatment arms.

Table 16. Key Secondary Endpoint Analyses (mITT), Trial BPR-CS-009

	Ceftobiprole	Daptomycin	Adjusted Difference (Ceftobiprole – Daptomycin) (95% CI)
ACM through PTE, n/N (%)	17/189 (9.0)	18/198 (9.1)	−0.5% (−6.2, 5.2)
Death due to SAB (DRC), n/N (%)	7/189 (3.7)	6/198 (3.0)	0.4% (−3.2, 4.0)
Microbiological response at PTE, n/N (%)	155/189 (82.0)	153/198 (77.3)	5.1% (−2.9, 13.0)
Subjects with development of new metastatic foci or other complications of SAB after Day 7, n/N (%)	11/189 (5.8)	11/198 (5.6)	0.1% (−4.6, 4.8)
Time (days) to *S. aureus* bloodstream clearance, Median (95% CI)	4 (3,5)	4 (3,5)	

Source: Partially adapted from Applicant Tables 24-27
Abbreviations: CI, confidence interval; DRC, data review committee; mITT, modified intent-to-treat; N, number of subjects in treatment arm; n, number of subjects within category; PTE, post-treatment evaluation; SAB, *Staphylococcus aureus* Bacteremia

Subgroup Analyses

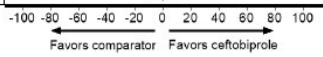
Subgroup analyses for the primary endpoint, 'overall success based on DRC assessment at the PTE visit' by gender, race and ethnicity are shown in Table 17**.** Treatment differences tended to be more favorable in ceftobiprole subjects among subjects who were 18-34 years, male, White and Hispanic/Latino. There were a few other notable findings. Among subjects 18 to 34 years of age, overall success rates were 17/20 (85%) versus 11/19 (57.9%) which showed a nominally significant treatment difference of 26.7% (95 CI: 0.4, 53.0) favoring ceftobiprole. Also, among non-White subjects, overall success rates were 0/5 (0%) for subjects in the ceftobiprole arm versus 5/6 (66.7%) for subjects in the daptomycin arm which showed a nominally significant treatment difference of -55.6% (95 CI: -100.0, -10.5) favoring daptomycin.

Reviewer Comments

The small number of non-White subjects combined with the nominally significant difference in non-White subjects favoring daptomycin may make generalizing trial results to non-White subjects more difficult. Of note, this difference was likely due to the small sample size and random variation since the subjects' reasons for failure were often not directly related to a lack of treatment effect.

Table 17. Overall Success Based on DRC Assessment at the PTE Visit in Subgroups by Age, Gender, Race and Ethnicity (mITT Population), Trial BPR-CS-009

Subgroup	Ceftobiprole n/N (%)	Daptomycin n/N (%)	Forest plot	Difference (95% CI)[a]
Overall	132/189 (69.8)	136/198 (68.7)		2.0 (−7.1, 11.1)
Age (2 categories)				
≥ 18 to < 65yr	98/131 (74.8)	101/135 (74.8)		0.6 (−9.8, 10.9)
≥ 65yr	34/58 (58.6)	35/63 (55.9)		6.9 (−10.5, 24.3)
Age (4 categories)				
18 to 34yr	17/20 (85.0)	11/19 (57.9)		26.7 (0.4, 53.0)
35 to 64yr	81/111 (73.0)	90/116 (77.6)		−4.0 (−15.1, 7.0)
65 to 74yr	27/41 (65.9)	27/42 (64,3)		3.5 (−17.3, 24.4)
≥ 75yr	7/17 (41.2)	8/21 (38.1)		19.5 (−7.2, 46.3)
Gender				
Male	93/128 (72.7)	92/140 (65.7)		8.0 (−2.8, 18.8)
Female	39/61 (63.9)	44/58 (75.9)		−11.3 (−27.7, 5.1)
Race				
White	127/179 (70.9)	131/192 (68.2)		3.5 (−5.8, 12.8)
Non-white	5/10 (50.0)	5/6 (83.3)		−55.6 (−100.0, −10.5)
Ethnicity				
Hispanic or Latino	9/14 (64.3)	7/15 (46.7)		15.4 (−23.6, 54.4)
Not Hispanic or Latino	122/174 (70.1)	128/182 (70.3)		0.6 (−8.9, 10.0)

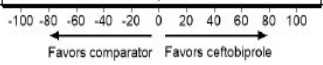


Source: Table 28 of CSR
Abbreviations: CI, confidence interval; DRC, data review committee; mITT, modified intent-to-treat; N, number of subjects in treatment arm; n, number of subjects within category; PTE, post-treatment evaluation

Subgroup analyses by geographic region are shown in Table 18**.** Treatment differences tended to be more favorable in ceftobiprole subjects among subjects who were from 'Other Regions' (non-European/North American) and in 'Other Countries (excluding Ukraine)'. Although there were no significant differences among any geographic regions, it was noted that success rates in Ukraine for both treatment arms were substantially higher than in other regions.

Table 18. Overall Success Based on DRC Assessment at the PTE Visit in Subgroups by Geographic Region (mITT Population), Trial BPR-CS-009

Subgroup	Ceftobiprole n/N (%)	Daptomycin n/N (%)	Forest plot	Difference (95% CI)[a]
Overall	132/189 (69.8)	136/198 (68.7)		2.0 (−7.1, 11.1)
Region				
Europe	126/175 (72.0)	129/185 (69.7)		2.9 (−6.5, 12.2)
North America	0/5 (0.0)	3/5 (60.0)		−60.0 (−100.0, −17.1)
Other Regions	6/9 (66.7)	4/8 (50.0)		5.4 (−44.7, 55.5)
Ukraine vs Other countries				
Ukraine	74/88 (84.1)	82/92 (89.1)		−3.8 (−13.7, 6.1)
Other countries (excl. Ukraine)	58/101 (57.4)	54/106 (50.9)		6.6 (−6.9, 20.1)

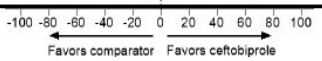


Source: Table 29 of CSR
Abbreviations: CI, confidence interval; DRC, data review committee; mITT, modified intent-to-treat; N, number of subjects in treatment arm; n, number of subjects within category; PTE, post-treatment evaluation

Subgroup analyses by known predisposing risk factors for SAB and infective endocarditis are shown in Table 19. Treatment differences tended to be less favorable for ceftobiprole in subjects who used concomitant antibacterial treatment. However, findings did not reach significance in either of these groups. There were no other notable findings.

Table 19. Overall Success Based on DRC Assessment at the PTE Visit in Subgroups of Known Predisposing Risk Factors for *Staphylococcus aureus* Bacteremia and Infective Endocarditis, Trial BPR-CS-009

Subgroup	Ceftobiprole n/N (%)	Daptomycin n/N (%)	Forest Plot	Difference (95% CI)[a]
Overall	132/189 (69.8)	136/198 (68.7)		2.0 (−7.1, 11.1)
Known predisposing risk factors				
Any predisposing risk factor	91/137 (66.4)	95/144 (66.0)		1.5 (−9.6, 12.5)
Surgery within 30 days	52/73 (71.2)	64/83 (77.1)		−5.0 (−18.7, 8.8)
Diabetes mellitus	45/69 (65.2)	39/66 (59.1)		8.2 (−7.9, 24.4)
Chronic renal insufficiency	18/36 (50.0)	16/32 (50.0)		−1.1 (−24.4, 22.2)
Hemodialysis dependence*	13/24 (54.2)	15/24 (62.5)		−7.2 (−35.4, 20.9)
Trauma within 30 days	17/24 (70.8)	7/13 (53.8)		16.4 (−17.4, 50.3)
History of injection drug use	5/13 (38.5)	4/10 (40.0)		−10.0 (−51.6, 31.6)
Type of device at baseline				
Intravascular	71/97 (73.2)	80/99 (80.8)		−7.1 (−18.6, 4.3)
Extravascular	2/4 (50.0)	1/1 (100.0)		−50.0 (−100.0, 19.3)
Baseline fever status				
Fever	83/104 (79.8)	76/105 (72.4)		7.2 (−4.4, 18.8)
No Fever	49/85 (57.6)	60/93 (64.5)		−4.6 (−18.3, 9.2)
Prior antibacterial treatment				
Yes	92/139 (66.2)	85/134 (63.4)		2.9 (−8.4, 14.2)
No	40/50 (80.0)	51/64 (79.7)		−0.2 (−15.0, 14.6)
Concomitant antibacterial treatment				
Yes	5/32 (15.6)	14/50 (28.0)		−11.7 (−29.2, 5.7)
No	127/157 (80.9)	122/148 (82.4)		−1.3 (−10.0, 7.4)

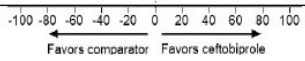


Source: Table 30 of CSR
Abbreviations: CI, confidence interval; DRC, data review committee; mITT, modified intent-to-treat; N, number of subjects in treatment arm; n, number of subjects within category; PTE, post-treatment evaluation; SAB, *Staphylococcus aureus* Bacteremia

Subgroup analyses by baseline renal status are shown in Table 20. There were no notable findings.

Table 20. Overall Success Based on DRC Assessment at the PTE Visit by Baseline Renal Function (mITT Population), Trial BPR-CS-009

Subgroup	Ceftobiprole n/N (%)	Daptomycin n/N (%)	Forest Plot	Difference (95% CI)[a]
Overall	132/189 (69.8)	136/198 (68.7)		2.0 (−7.1, 11.1)
Baseline creatinine clearance				
Chronic dialysis	13/24 (54.2)	15/25 (60.0)		−4.6 (−32.5, 23.3)
<30 mL/min	3/5 (60.0)	2/8 (25.0)		35.0 (−17.4, 87.4)
30 to < 50 mL/min	6/12 (50.0)	3/6 (50.0)		2.0 (−50.5, 54.5)
50 to 80 mL/min	22/33 (66.7)	24/35 (68.6)		1.9 (−20.4, 24.2)
>80 mL/min	88/115 (76.5)	92/124 (74.2)		2.6 (−8.2, 13.5)



Source: Table 31 of CSR
Abbreviations: CI, confidence interval; DRC, data review committee; mITT, modified intent-to-treat; N, number of subjects in treatment arm; n, number of subjects within category; PTE, post-treatment evaluation

Major Protocol Deviations

Relevant deviations related to Trial entry criteria were observed for three subjects; one subject with suspected RIE that was not confirmed (this subject was randomized but withdrew consent prior to receiving study drug), and two subjects with implanted cardiac devices. These deviations were considered major (Table 21), and the subjects were excluded from the CE population.

For the primary endpoint assessment, three subjects (one in the ceftobiprole arm and two in the daptomycin arm) had a missing PTE visit; all three subjects were failures for the primary endpoint, and two of the three subjects had other reasons for failure than the missing PTE Visit.

Table 21. Major Protocol Deviations (ITT Population) Trial BPR-CS-009

	Ceftobiprole (N=192) n (%)	Daptomycin (N=198) n (%)	Total (N=390) n (%)
Inclusion Criteria	1 (0.5)	0	1 (0.3)
IN6–11: Subject enrolled without confirmed or suspected complicated SAB	1 (0.5)	0	1 (0.3)
Exclusion Criteria	1 (0.5)	1 (0.5)	2 (0.5)
EX05: Presence of cardiac devices or prosthetic valves at study entry	1 (0.5)	1 (0.5)	2 (0.5)
Concomitant Medication	2 (1.0)	6 (3.0)	8 (2.1)
Prohibited systemic antibiotic medication that provides activity against *S. aureus* prior to the PTE visit	2 (1.0)	6 (3.0)	8 (2.1)

Source: Table 11 of CSR
Note: Denominators for percentages are the number of subjects in the ITT Population. Subjects may have had more than one major protocol deviation
Abbreviations: EX, exclusion criteria; IN, inclusion criteria; ITT, intent-to-treat; N, number of subjects in treatment arm; n, number of subjects within category; PTE, post-treatment evaluation; SAB, *Staphylococcus aureus* Bacteremia

Additional Analyses

Additional analyses considered overall success at the PTE visit by methicillin-susceptible *Staphylococcus aureus* (MSSA) or methicillin-resistant *Staphylococcus aureus* (MRSA) designation, concordance of DRC-assessed and investigator-assessed overall success at the PTE visit and overall success based on DRC assessment at the PTE visit by cohort. These analyses were performed in the mITT population.

As shown in Table 22, the treatment difference tended to favor ceftobiprole in subjects with MSSA and daptomycin in subjects with MRSA. Of the 287 mITT subjects with a blood culture positive for MSSA at baseline, overall success at the PTE Visit was 70.9% (100/141) in the ceftobiprole arm, versus 66.4% (97/146) in the comparator arm. The adjusted between-arm difference was 4.8% (95% CI: −5.9, 15.5) in favor of ceftobiprole. In 94/387 subjects (24.3%) with a blood culture positive for MRSA at Baseline in the mITT population, overall success at the PTE visit was 68.9% (31/45) in the ceftobiprole arm, vs. 77.6% (38/49) in the comparator arm. The adjusted between-arm difference was -8.3% (95% CI: −26.3, 8.6) in favor of daptomycin.

Table 22. Overall Success Based on DRC Assessment at the PTE Visit by MSSA or MRSA Designation (mITT Population) Trial BPR-CS-009

	N_{Total}	Ceftobiprole n/N (%)	Daptomycin n/N (%)	Difference (95% CI)[a]
Overall	387	132/189 (69.8)	136/198 (68.7)	2.0 (−7.1, 11.1)
MSSA	287	100/141 (70.9)	97/146 (66.4)	4.8 (–5.9, 15.5)
MRSA	94	31/45 (68.9)	38/49 (77.6)	−8.3% (−25.3, 8.6)

Source: Partially Adapted from Table 35 of CSR
MSSA or MRSA designation was not assessed in three subjects in each treatment arm
A Proportion difference of ceftobiprole minus daptomycin. Computed using CMH weights method adjusted for actual stratum (dialysis status and prior antibacterial treatment use).
Abbreviations: CI, confidence interval; DRC, data review committee; mITT, modified intent-to-treat; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; N, number of subjects in treatment arm; N_{Total}, total number of subjects; n, number of subjects within category; PTE, post-treatment evaluation

An overview of concordance between the DRC- and investigator-assessed overall success at the PTE Visit in the mITT population (the primary endpoint) is provided in Table 23. Concordance

was defined as the conditional probability that if the DRC or the Investigator makes an assessment of overall success (or failure) then the other (i.e., the Investigator or the DRC) will also make an assessment of overall success (or failure). There was 98.0% agreement between the DRC and investigator assessments for overall success, and 95.2% agreement for failure.

Table 23. DRC-Assessed and Investigator-Assessed Overall Success at the PTE Visit (mITT population) Trial BPR-CS-009

	Summary of Ratings		
	Investigator	DRC	
	Total	Overall Success	Failure
Total	387	268	119
Overall Success	277	267	10
Failure	110	1	109

Source: Table 43 of CSR
267 of the 277 assessments of overall success by the Investigator were also rated as overall success by the DRC, and 267 of the 268 assessments of overall success by the DRC were also rated as overall success by the Investigator. Concordance for overall success was calculated as the total number of agreements in overall success ratings between the Investigator and the DRC (n = 534, 267 + 267) divided by the total number of overall success ratings by either the Investigator or the DRC (N = 545, 277 + 268), resulting in a concordance of overall success of 98.0% (534/545).
109 of the 110 assessments of failure by the Investigator were also rated as failures by the DRC, and 109 of the 119 assessments of failure by the DRC were also rated as failure by the Investigator. Concordance for failure was calculated as the total number of agreements in failure between the Investigator and the DRC (n = 218, 109 + 109) divided by the total number of failures rated by either the investigator or the DRC (N = 229, 110 + 119), resulting in a concordance of failure of 95.2% (218/229).
Abbreviations: DRC, data review committee; mITT, modified intent-to-treat; PTE, post-treatment evaluation

Table 24 summarizes a post-hoc analysis of the proportion of subjects with overall success by cohort. There were no significant differences between the results in Cohort 1 (maximum treatment duration of 28 days) and the results in Cohort 2 (maximum treatment duration of 42 days). However, success rates in the daptomycin arm appeared to be higher in Cohort 2. Consequently, adjusted differences were less favorable for ceftobiprole subjects when considering Cohort 2 versus Cohort 1.

Table 24. Overall Success Based on DRC Assessment at the PTE Visit by Cohort (mITT Population), Trial BPR-CS-009

	Ceftobiprole n/N (%)	Daptomycin n/N (%)	Difference (95% CI)[a]
Overall	132/189 (69.8)	136/198 (68.7)	2.0 (-7.1, 11.1)
Cohort 1	68/97 (70.1)	62/96 (64.6)	7.6 (–5.6, 20.8)
Cohort 2	64/92 (69.6)	74/102 (72.5)	-3.4 (-16.1, 9.3)

Source: Table 43 of CSR
A Proportion difference of ceftobiprole minus daptomycin. Computed using CMH weights method adjusted for actual stratum (dialysis status and prior antibacterial treatment use).
Abbreviations: CI, confidence interval; DRC, data review committee; mITT, modified intent-to-treat; N, number of subjects in treatment arm; n, number of subjects within category; PTE, post-treatment evaluation

Conclusions

Trial BPR-CS-009 met its primary objective of demonstrating noninferiority for the pre-specified primary endpoint of overall success based on DRC Assessment at the PTE (Day 70) Visit. Key secondary endpoints also appeared to be generally consistent with noninferiority. Overall, there were no major concerns regarding the evidence of effectiveness.

Minor concerns are related to subject selection with approximately 96% of subjects being ‘White,’ which may limit the generalizability of efficacy findings to other races. There were also less favorable treatment differences in a few subgroups receiving ceftobiprole (‘non-White’,

'U.S.', 'MRSA' and 'polymicrobial BSIs'), although sample sizes tended to be small. Findings of large regional differences in clinical overall success rates at PTE (e.g., Ukrainian vs. Ex-Ukrainian sites) may also limit generalizability. Although the high success rates at the Ukrainian sites did not positively affect the estimated treatment difference in this trial, they could affect the assumptions used in the justification of the NI margin (see 6.3 for more details).

6.2.2. ABSSSI, Trial BPR-CS-008

6.2.2.1. Design, Trial BPR-CS-008

Trial BPR-CS-008 was conducted from August 2018 to March 2022. The protocol was reviewed as a SPA under IND 64407. The design of pivotal trial BPR-CS-008 was based on the current FDA Guidance for Industry Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment, October 2013, including with respect to the efficacy endpoints, timing of assessments, and statistical considerations.

This was a randomized, double-blind, active-controlled, parallel-arm, multicenter trial in adult hospitalized subjects to establish the safety and efficacy of ceftobiprole compared with vancomycin plus aztreonam in the treatment of ABSSSIs. The trial had a noninferiority design, with vancomycin plus aztreonam selected as an established comparator regimen. Vancomycin, recognized in current guidelines as the standard treatment for ABSSSI, is effective against gram-positive bacteria, including MRSA. Aztreonam was added to vancomycin due to its efficacy against gram-negative bacteria.

Trial BPR-CS-008 was conducted in three phases:

1. Pre-treatment: Screening and baseline, duration up to 24 hours.
2. Active treatment: Randomization and at least 5 days, and up to 10 days, of study drug administration. Study treatment could be extended up to 14 days if required.
3. Post-treatment: An EOT visit within 24 hours after last treatment, a test-of-cure (TOC) visit 15 – 22 days after randomization and at least 5 days after EOT, and a last follow-up visit 28 – 35 days after last treatment. In addition, survival status (Alive; Dead; Lost to Follow-up) was to be verified for evaluation of all-cause mortality. Survival status (by telephone or visit) was to be obtained at Day 28 (± 2 days).

The total duration of the study for each subject was approximately 5 – 7 weeks.

The selected ceftobiprole dose was the dose approved for the HABP and CABP indications in non-U.S. countries: 500 mg administered as a 2-hour IV infusion every 8 hours, to be adjusted for subjects with moderate or severe renal impairment (500 mg of ceftobiprole is equivalent to 667 mg of ceftobiprole medocaril sodium). The dose of vancomycin was 1,000 mg or 15 mg/kg administered as a 2-hour IV infusion every 12 hours; this could be modified for renal function. The dose of aztreonam was 1,000 mg per 0.5-hour IV infusion every 12 hours, to be adjusted for subjects with severe renal impairment; the need for treatment with aztreonam was to be reassessed at the 72-hour study Visit.

Other design considerations:

- Primary measurement of the target lesion size was to be performed using a flexible ruler, measuring longest length, and maximum width perpendicular to the length.
- Measurements were to be performed at Screening (prior to randomization and within the 6 hours prior to first dose of study drug), twice on Day 2, Day 3, and Day 4, and once on Day 8, and the EOT, TOC, and last follow-up visits. On days when two measurements were obtained, the measurements were to be taken at least 8 hours apart. Infection-site assessment includes incision/drainage, erythema, heat/localized warmth, pain/tenderness to palpation, fluctuance, and swelling/induration.
- A digital photograph was to be obtained at Screening, at the early clinical response assessment (48–72 hours after first treatment), and at the EOT and TOC Visit, for each subject (primary ABSSSI lesion), and was to be used for documentation purposes and as source data. Digital photography was not to be used for the measurement of the ABSSSI lesion size area; the determination of the ABSSSI lesion size area was to be solely based on the ruler measurements.
- Clinical success was to be assessed by the investigator using a four-point scale relative to the baseline assessment: cured, improved, stable, or worsened. In case of worsened (e.g., bacteremia, osteomyelitis, amputation), signs and symptoms needed to be documented as AEs.
- Concomitant antibacterial therapies, other drug therapies, and non-drug procedures were to be assessed at all scheduled study visits.
- Survival status (by telephone or visit) was to be obtained at Day 28.

The primary objective for Trial BPR-CS-008 was to demonstrate the non-inferiority of ceftobiprole to vancomycin plus aztreonam in subjects with ABSSSI with respect to early clinical response based on percent reduction in lesion size at 48 – 72 hours after first treatment in the ITT population.

The main secondary objective was to demonstrate the non-inferiority of ceftobiprole to vancomycin plus aztreonam in subjects with ABSSSI with respect to investigator-assessed clinical success at the TOC visit 15 – 22 days after randomization in the ITT and Clinically Evaluable populations.

Primary Endpoint

Early clinical response based on percent reduction from baseline in lesion size at 48 – 72 hours after first study-drug administration, measured in subjects who did not receive rescue therapy, and were alive. A clinical response was defined as a percentage reduction in lesion size greater than or equal to 20 percent compared to baseline.

The Main Secondary Endpoint

Investigator-assessed clinical success at the TOC visit 15 – 22 days after randomization, and at least 5 days after the EOT, assessed in the ITT and CE populations.

Reference ID: 5357793

6.2.2.2. Eligibility Criteria, Trial BPR-CS-008

The eligible subject population for trial BPR-CS-008 included adults who were diagnosed with ABSSSI (cellulitis/erysipelas, major cutaneous abscess, wound infection) with regional or systemic signs of infection, who were hospitalized (in a hospital or equivalent medical confinement or clinical research unit) and required IV antibacterial treatment. Subjects with other forms of ABSSSI or uncomplicated skin and skin structure infections were excluded, as were those with infections related to prosthetic devices, or infections which required more than two surgical interventions.

Subjects who had received any systemic antibacterial treatment within 14 days, or topical antibacterial on the primary lesion within 96 hours, before first infusion of study drug, were also excluded.

The minimum lesion size had to be 75 cm^2 using standardized measurements (longest length of the lesion by widest width perpendicular to that length) with a flexible plastic ruler. The proportion of subjects with major cutaneous abscesses was also not to exceed 30% of the total subject population included.

Inclusion Criteria

Subjects meeting all of the following:

1. Male or female, aged ≥18 years.
2. Diagnosis of ABSSSI, meeting at least one of the definitions in (a) to (c) below. Local symptoms must have started within the 7 days prior to the Screening visit.
3. Cellulitis/erysipelas, defined as a diffuse skin infection characterized by all of the following within 24 h:
    a. Rapidly spreading areas of erythema, edema, and/or induration with a minimum total lesion surface area of 75 cm^2.
    b. No collection of pus apparent upon visual examination.
    c. At least two of the following local signs of infection:
        - erythema
        - induration
        - localized warmth
        - pain or tenderness on palpation
        - swelling/edema

Reference ID: 5357793

4. Major cutaneous abscess, defined as infection characterized by a collection of pus within the dermis or deeper that is apparent upon visual examination before or after therapeutic intervention and is accompanied by all of the following within 24 h:
   - Erythema, edema and/or induration with a minimum total lesion surface area of 75 cm^2.
   - At least two of the following local signs of infection:
     a. fluctuance
     b. incision and drainage required
     c. purulent or seropurulent drainage
     d. localized warmth
     e. pain or tenderness on palpation

14. Wound infection, defined as infection of any apparent break in the skin characterized by at least one of the following:
   - Superficial incision/surgical site infection meeting all the following criteria:
     a. involves only the skin or subcutaneous tissue around the incision (does not involve fascia).
     b. occurs within 30 days of procedure.
     c. purulent drainage (spontaneous or therapeutic) with surrounding erythema, edema and/or induration with a minimum total lesion surface area of 75 cm^2.
     d. Post-traumatic wound (including penetrating trauma, e.g., needle, nail, knife, insect and spider bites) meeting the following criterion within 24 h:
     e. Purulent drainage (spontaneous or therapeutic) with surrounding erythema, edema and/or induration with a minimum total lesion surface area of 75 cm^2.

15. At least one of the following regional or systemic signs of infection at the Screening visit:
   a. Lymph node tenderness and volume increase, or palpable lymph node proximal to the primary ABSSSI.
   b. Fever ≥38°C/100.4°F (regardless of method of measurement).
   c. WBC count >10.0 x 10^9/L or <4.0 x 10^9/L.
   d. >10% immature neutrophils (band forms).

16. Requirement for IV antibacterial treatment.

17. Willing and able to adhere to study procedures (including prohibitions and restrictions) as specified in this protocol.

18. Willing and able to remain hospitalized (in a hospital or equivalent medical confinement or clinical research unit) until completion of the early-clinical-response assessment for the primary endpoint.

19. Informed consent signed by the subject, or their legally acceptable representative if appropriate, indicating that they understand the purpose of, and procedures required for, the trial, and are willing to participate.

Reference ID: 5357793

Prohibited Concomitant Medications

Concomitant systemic antibacterial drugs were prohibited during the trial up to the TOC visit, with the following exceptions:

1. Vancomycin PO 125 mg or 250 mg every 6 hours, fidaxomicin PO 200 mg q12h, or metronidazole IV or PO 500 mg q8h, in both treatment arms, for the treatment of *Clostridium difficile* infections.
2. Metronidazole IV as adjunctive therapy in both treatment arms for coverage of anaerobic bacteria.
3. Nitrofurantoin at any time during the trial in both treatment arms as it does not achieve therapeutic blood levels.

All NSAIDs were prohibited until 72 hours after start of treatment, and were then permitted only after early clinical response had been determined.

The administration of steroids (>40 mg per day prednisolone, or equivalent), or immunosuppressants was prohibited between administration of first study drug and the TOC Visit.

Chronic systemic therapy with calcineurin-inhibitors (e.g., tacrolimus, or cyclosporin), mycophenolate mofetil or mycophenolate sodium, azathioprine, sirolimus, and topical antibacterial drugs on the primary lesion was prohibited from randomization to the TOC Visit.

Non-Drug Adjunctive Therapy

Adjuvant surgical treatment was recognized as appropriate and necessary for adequate treatment of wound infections and abscesses. Subjects were evaluated at Screening to determine whether more than one intra-operative surgical intervention was required. Those expected to require more than two surgical interventions in the operating room for the ABSSSI were to be excluded from the trial.

When indicated, the initial surgical procedure was to be performed before randomization, and subsequent procedures performed no later than 48 hours after the start of treatment.

Adjunctive therapies permitted for the treatment of ABSSSI at any time were debridement at the bedside, topical solutions, including antiseptic agents such as povidone-iodine (topical solutions did not contain anti-microbial agents), and local bedside wound care in accordance with hospital protocols.

6.2.2.3. Statistical Analysis Plan, Trial BPR-CS-008

Disposition of Subjects

The disposition of subjects is described in Figure 2.**.** Overall, there were no notable imbalances between the treatment arms. A total of 679 subjects were randomized to receive either the ceftobiprole (n=335) or vancomycin plus aztreonam (n=344) treatment. Three subjects did not receive trial treatment (1 in ceftobiprole arm and 2 in the vancomycin plus aztreonam arm). In

the ITT population, 26 subjects in the ceftobiprole arm and 36 subjects in the vancomycin plus aztreonam arm discontinued the study.[1]

As shown in Table 25, sixty-two (9.1%) of subjects discontinued the study. The main reasons for study discontinuation were lost to follow-up (4.6%) and withdrawal by subjects (3.1%). Four subjects (0.6%) died, 1 (0.3%) in the ceftobiprole and 3 (0.9%) in the comparator arm. Fifty-six subjects (8.2%) discontinued study treatment, 7.5% in ceftobiprole arm versus 9.0% in the vancomycin plus aztreonam arm. Eleven subjects (3.3%) in the ceftobiprole arm and 14 subjects (4.1%) in the vancomycin plus aztreonam arm withdrew consent. Three subjects (0.9%) in the ceftobiprole arm, and 6 subjects (1.7%) in the vancomycin plus aztreonam arm, discontinued study treatment due to AEs. Four subjects (1.2%) in each treatment arm discontinued study treatment due to lack of efficacy.

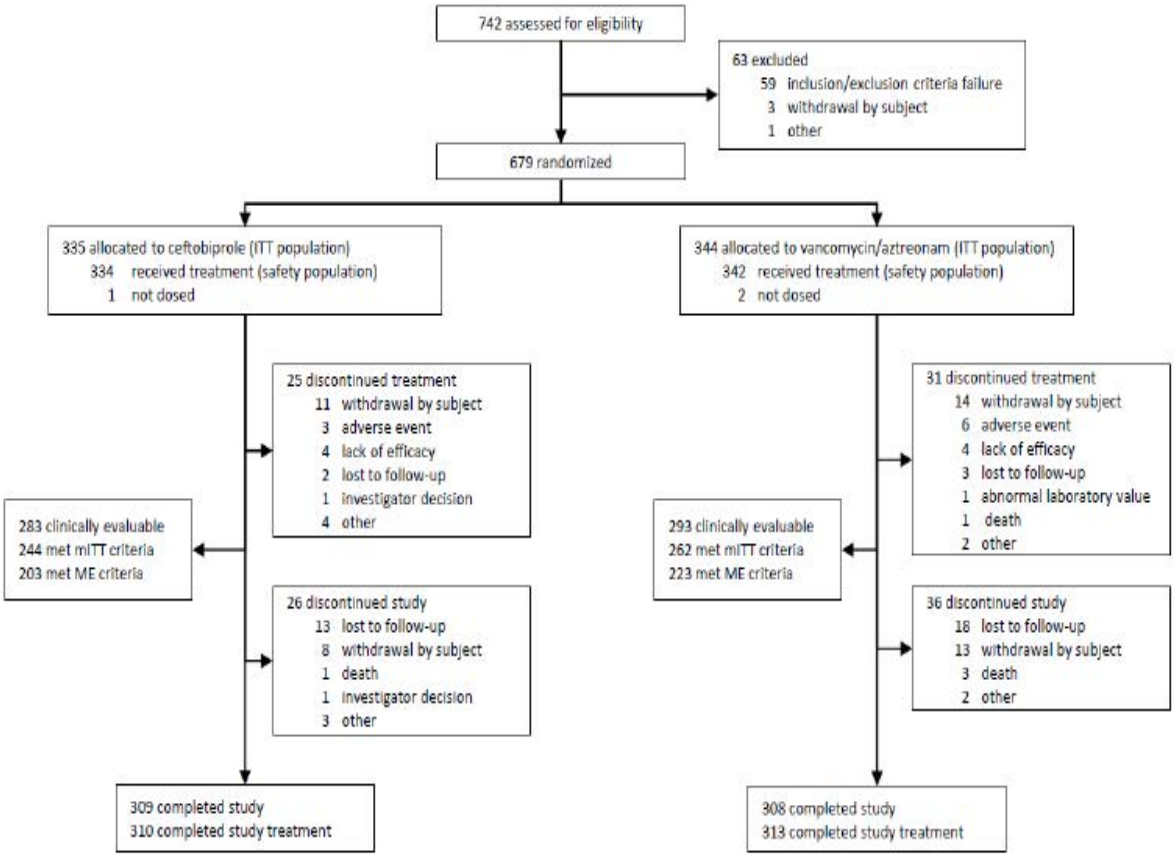
Table 25. Reasons for Discontinuation from Trial and Discontinuation of Trial (ITT Population), Trial BPR-CS-008

Categories	Ceftobiprole (N=335) n (%)	Vancomycin Plus Aztreonam (N=344) n (%)	Total (N=679) n (%)
Completed study	309 (92.2)	308 (89.5)	617 (90.9)
Discontinued from study	26 (7.8)	36 (10.5)	62 (9.1)
Primary reason			
Death	1 (0.3)	3 (0.9)	4 (0.6)
Investigator decision	1 (0.3)	0	1 (0.1)
Lost to follow-up	13 (3.9)	18 (5.2)	31 (4.6)
Withdrawal by subject	8 (2.4)	13 (3.8)	21 (3.1)
Other	3 (0.9)	2 (0.6)	5 (0.7)
Completed study treatment	310 (92.5)	313 (91.0)	623 (91.8)
Discontinued study treatment	25 (7.5)	31 (9.0)	56 (8.2)
Primary reason			
Abnormal laboratory value	0	1 (0.3)	1 (0.1)
Adverse event	3 (0.9)	6 (1.7)	9 (1.3)
Death	0	1 (0.3)	1 (0.1)
Investigator decision	1 (0.3)	0	1 (0.1)
Lack of efficacy	4 (1.2)	4 (1.2)	8 (1.2)
Lost to follow-up	2 (0.6)	3 (0.9)	5 (0.7)
Withdrawal by subject	11 (3.3)	14 (4.1)	25 (3.7)
Other	4 (1.2)	2 (0.6)	6 (0.9)

Source: Table 8 in CSR
Abbreviations: ITT, intent-to-treat; N, number of subjects in treatment arm; n, number of subjects within category

[1] Two additional subjects in the comparator arm completed the EOT and LFU visits and were recorded as completing the trial but did not complete the TOC visit.

Figure 2. Disposition of Patients, Trial BPR-CS-008 Subjects



Source: Figure 2 in CSR
Abbreviations: ITT, intent-to-treat; ME, microbiologically evaluable; mITT, modified intent-to-treat

Baseline Demographic and Disease Characteristics

As shown in Table 26, the baseline demographic and disease characteristics in the mITT population were generally balanced across the treatment arms. Subjects were mostly White, males, and approximately 50 years of age. All subjects were from North American or European sites. Approximately 32% of subjects identified as being Hispanic or Latino. Approximately 12% of subjects had diabetes mellitus at baseline, 35% of subjects had fever at baseline, 16% had CrCL <80 mL/min and 35% had abnormal WBC at baseline. Systemic prior antibacterial medication use and concomitant antibacterial medication use were rare, each being less than 1%.

Table 26. Baseline Demographic and Disease Characteristics (mITT Population) Trial BPR-CS-008

Categories	Ceftobiprole N=335	Vancomycin Plus Aztreonam N=344	Total N=679
Age (years)			
Mean (SD)	49.1 (13.85)	49.0 (14.69)	49.1 (14.27)
Median	51.0	50.0	50.0
Min, max	18, 89	20, 87	18, 89
Age categories (years), n (%)			
18 – 34	58 (17.3)	67 (19.5)	125 (18.4)
35 – 64	236 (70.4)	225 (65.4)	461 (67.9)
65 – 74	27 (8.1)	36 (10.5)	63 (9.3)
≥75	14 (4.2)	16 (4.7)	30 (4.4)
Sex, n (%)			
Male	198 (59.1)	201 (58.4)	399 (58.8)
Female	137 (40.9)	143 (41.6)	280 (41.2)
Race, n (%)			
White	318 (94.9)	330 (95.9)	648 (95.4)
Black	7 (2.1)	8 (2.3)	15 (2.2)
Other	10 (3.4)	6 (1.7)	16 (2.4)
Ethnicity, n (%)			
Hispanic or Latino	103 (30.7)	115 (33.4)	218 (32.1)
Not Hispanic or Latino	232 (69.3)	229 (66.6)	461 (67.9)
Geographic region, n (%)			
North America	203 (60.6)	215 (62.5)	418 (61.6)
Europe	132 (39.4)	129 (37.5)	261 (38.4)
Diabetes Mellitus, n (%)			
Yes	36 (10.7)	42 (12.2)	78 (11.5)
No	299 (89.3)	302 (87.8)	601 (88.5)
Systemic Prior antibiotic medication, n (%)			
Yes	0	1 (0.3)	1 (0.1)
No	335 (100)	343 (99.7)	678 (99.9)
Concomitant antibacterial medication, n (%)			
Metronidazole	1 (0.3)	4 (1.2)	5 (0.7)
Creatinine clearance (mL/min), n (%)			
CL_{CR} <30 mL/min	0	1 (0.3)	1 (0.1)
CL_{CR} 30-50 mL/min	10 (3.0))	11 (3.2	21 (3.1)
CL_{CR} 50-80 mL/min	43 (12.8)	44 (12.8)	87 (12.8)
CL_{CR} >80 mL/min	282 (84.2)	288 (83.7)	570 (83.9)
Fever status, n (%)			
Fever	120 (35.8))	120 (34.9	240 (35.3)
No Fever	214 (63.9)	224 (65.1)	438 (64.5)
Missing	1 (0.3)	0	0
WBC count, n (%)			
Normal (4.0 x 10^9/L ≤WBC ≤10.0 x 10^9/L)	222 (66.3)	218 (63.4)	440 (64.8)
Abnormal (WBC<4.0 x 10^9/L or WBC >10.0 x 10^9/L)	113 (33.7)	126 (36.6)	239 (35.2)

Source: Partially Adapted from Table 11 of CSR
Abbreviations: CL_{CR}, creatine clearance; mITT, modified intent-to-treat; N, number of subjects in treatment arm; n, number of subjects within category; WBC, white blood cell

Analysis Populations

The ITT Population

Included all randomized subjects, analyzed according to the treatment they were randomized to receive, and if different, not according to what they actually received.

The Microbiological ITT Population

Was the subset of subjects in the ITT population who had causative (i.e., infecting) pathogens identified by the central microbiology laboratory from skin lesion or blood cultures; local laboratory identification results were only used if the corresponding causative pathogen was not available for identification by the central laboratory. Subjects with no pathogens isolated at Baseline (microbiologically non-evaluable) were excluded from the microbiological ITT (micro-ITT) population.

CE Population

Was the subset of subjects in the ITT population who complied with important aspects of the trial until the TOC visit, i.e., with no major protocol deviations (e.g., a completed response outcome assessment, and no concomitant systemic antibacterial treatment or topical antibacterial applied to the primary lesion).

The Microbiologically Evaluable Population

Was the subset of subjects in the micro-ITT population who were also in the CE population. Analysis at each time point was performed on subjects with available response at that time point (excluding those with microbiological response of ‘Not Evaluable’ or missing).

Sample Size Determination

A sample size of 674 subjects (337 per arm) provided at least 90% power to reject the null hypothesis (H0) against the alternative hypothesis (HA) at the one-sided alpha level of 0.025 as follows, using a two-arm large-sample normal approximation test of Proportions. Early clinical response rates of an at least 20% reduction in lesion area size (primary endpoint) and clinical cure rates at the TOC visit (main secondary endpoint) were based on recent phase 3 studies in ABSSSI. The sample size estimate was based on a point estimate for early clinical response of 80% in each treatment arm in the ITT and CE population, a one-sided alpha level of 0.025, a non-inferiority margin of 10 percentage points for the between-arm difference of the primary endpoint.

Data Monitoring and Interim Analyses

Investigators, Applicant employees, and others involved in the conduct and analysis of the Trial (with the exception of the unblinded pharmacist or delegate) remained blinded to the treatment codes and interim analysis results until all monitoring decisions were made, and the database locked for the final analysis.

A blinded interim analysis for sample size re-estimation assessed whether the initial sample size estimate was adequate for evaluating the primary endpoint, and to select a larger sample size if warranted.

Reference ID: 5357793

The blinded interim analysis was performed in November 2018, and was based on pooled information across the two treatment arms when early clinical response data were available for 60% of the subjects planned to be randomized (approximately 404 subjects). The number and percentage of responders and non-responders based on the primary Endpoint (and Clinical Success / No-Success based on the main secondary endpoint) were provided.

Reviewer Comments:

The interim analyses appeared to be conducted appropriately and there were no major concerns. Note that no statistical adjustment was required, and the sample size specified in the protocol remained unchanged after the blinded review of the primary and secondary endpoints.

Statistical Methods

Trial BPR-CS-008 was designed to determine whether ceftobiprole was non-inferior to vancomycin plus aztreonam for both the primary endpoint of early clinical response and the main secondary endpoint of investigator-assessed clinical success at the TOC visit. The main primary analysis was based on the ITT population consisting of all randomized subjects. The weighted difference in percentage of responders at 48–72 h (ceftobiprole arm minus the vancomycin plus aztreonam arm), and the 95% CI for the weighted difference was computed using CMH weights method adjusted for geographical region (North America and Europe), and actual type of ABSSSI.

The non-inferiority hypothesis test was a one-sided hypothesis test performed at the 2.5% level of significance. If the lower limit of the two-sided 95% CI for the difference in response rates (ceftobiprole minus vancomycin plus aztreonam) in the ITT population was greater than -10%, the non-inferiority of ceftobiprole to vancomycin plus aztreonam would be concluded. If non-inferiority was declared at the one-sided significance level of 0.025, then the difference would be tested for superiority. Superiority would be declared if the lower limit of the two-sided 95% CI exceeded 0 (or equivalently p-value less than 0.05 using CMH test). The same analysis was repeated on the CE population.

Reviewer Comments

The overall data from two studies by Snodgrass in 1937, both of which compared ultraviolet light against a sulfonamide antibacterial drug, in subjects with cellulitis/erysipelas for an outcome of cessation of spread of lesion at 48-72 hours, support a treatment difference of 18%. Because this is thought to be conservatively estimated at 18 percent for antibacterial drugs in the treatment of ABSSSI for the endpoint based on lesion size assessment, further discounting of the treatment effect may not be necessary and thus M1 is estimated to be 18 percent. These scientific data provide support for the selection of a noninferiority margin of 10 percent that preserves some of M1 based on an endpoint of lesion size assessment. Refer to the ABSSSI Guidance[2] for further details on the justification of a 10% NI margin for ABSSSI.

The main secondary analysis was based on the weighted difference in percentage of clinical success at the TOC visit (ceftobiprole arm minus the vancomycin plus aztreonam arm), and the

[2] FDA Guidance for Industry, Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment, October 2013

Reference ID: 5357793

95% CI for the weighted difference was computed using CMH weights method, adjusted for geographical region (North America and Europe), and actual type of ABSSSI.

Superiority would be declared if the lower limit of the two-sided 95% CI exceeds 0 (or equivalently p value less than 0.05 using CMH test).

6.2.2.4. Results of Analyses, Trial BPR-CS-008

Primary Analysis

As shown in Table 27, ceftobiprole met the primary objective of this trial by demonstrating the non-inferiority of ceftobiprole (greater than the pre-specified 10% non-inferiority margin) to vancomycin plus aztreonam for the primary endpoint of early clinical response based on a 20% or more reduction from baseline in lesion size at 48–72 hours after start of trial drug administration. In the ITT population (primary analysis population), 306 subjects (91.3%) in the ceftobiprole arm were responders (95% CI: 87.8, 94.1) versus 303 (88.1%) subjects in the vancomycin plus aztreonam arm (95% CI: 84.2, 91.3). The proportion difference (ceftobiprole minus vancomycin plus aztreonam) was 3.3% (95% CI: −1.2, 7.8). Since −1.2% (the lower limit of this 95% CI) exceeded the required NI limit of −10%, non-inferiority was demonstrated.

There were 29 (8.7%) and 41 (11.9%) non-responders in the ceftobiprole and vancomycin plus aztreonam arms, respectively. The most common reason for non-responders at 48-72 hours after start of treatment was <20% reduction from baseline in surface area of primary lesion which included 65.5% of ceftobiprole non-responders and 70.7% of vancomycin plus aztreonam non-responders. In general, there were no notable treatment differences regarding the reasons for non-response.

Table 27. Primary Endpoint: Proportion of Subjects with Early Clinical Response 48–72 Hours After Start of Therapy, Trial BPR-CS-008

Categories	Ceftobiprole (N=335)	Vancomycin Plus Aztreonam (N=344)
Number of responders, n (%)	306 (91.3)	303 (88.1)
95% CI	(87.8, 94.1)	(84.2, 91.3)
Number of non-responders, n (%)	29 (8.7)	41 (11.9)
Reason for non-responders, n (%)[1]		
Missing surface area of primary lesion at baseline	1 (3.4)	0
48–72 hours after start of treatment	8 (27.6)	12 (29.3)
<20% reduction from baseline in surface area of primary lesion	19 (65.5)	29 (70.7)
Death prior to 72 hours from time of first dose of study drug	0	2 (4.9)
Concomitant antibacterial treatment	0	1 (2.4)
Additional unplanned surgical procedure for ABSSSI	1 (3.4)	1 (2.4)
Proportion difference (95% CI) (%)[2]	3.3 (−1.2, 7.8)	
p-Value for testing superiority	0.1543	

Source: Table 34 of CSR
[1] Denominators for percentages are based on the number of non-responders. A subject may be counted in more than one category.
[2] Ceftobiprole minus vancomycin plus aztreonam.
Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects within category

Secondary Analyses

As shown in Table 28, the main secondary endpoint was also supportive of non-inferiority in the primary analysis. The proportion of clinical successes at TOC was slightly higher in the ceftobiprole arm versus vancomycin plus aztreonam arm, 302/335 (90.1%) versus 306/344 (89.0%), respectively. The proportion difference (ceftobiprole minus vancomycin plus aztreonam) was 1.0% (95% CI: −3.5, 5.6). There were no concerns related to reasons for nonclinical success which were mostly comparable between arms.

There were 33 (9.9%) and 38 (11.0%) nonclinical successes at TOC in the ceftobiprole and vancomycin plus aztreonam arms, respectively. The most common reason for nonclinical success was 'Missing assessment at TOC' which occurred in 60.6% of ceftobiprole non-successes and 60.5% of vancomycin plus aztreonam non-successes. In general, there were no notable treatment differences regarding the reasons for non-success. A slightly greater proportion of subjects in the vancomycin plus aztreonam arm were non-successes due to 'Unplanned surgical procedure for the ABSSSI after start of therapy and prior to TOC' (13.2% versus 6.1%) and there were 2 (5.2%) of non-successes due to 'death prior to TOC' in the vancomycin plus aztreonam arm versus 0 (0.0%) in the ceftobiprole arm.

Table 28. Main Secondary Endpoint: Proportion of Subjects With Investigator-Assessed Clinical Success at the TOC Visit, Trial BPR-CS-008

Categories	Ceftobiprole (N=335)	Vancomycin Plus Aztreonam (N=344)
Number of clinical successes, n (%)	302 (90.1)	306 (89.0)
95% CI	(86.4, 93.1)	(85.2, 92.1)
Number of nonclinical successes, n (%)	33 (9.9)	38 (11.0)
Reason for nonclinical successes, n (%)[1]		
No clinical success at TOC	7 (21.2)	9 (23.7)
Missing assessment at TOC	20 (60.6)	23 (60.5)
Not evaluable assessment at TOC	6 (18.2)	29 (15.8)
Additional antibacterial therapy received for treatment of primary lesion prior to TOC	7 (21.2)	6 (15.8)
Initiation of non-study antibacterial treatment of another infection prior to TOC	3 (9.1)	3 (7.9)
Unplanned surgical procedure for ABSSSI after start of therapy and prior to TOC	2 (6.1)	5 (13.2)
Death prior to TOC	0	2 (5.3)
Proportion difference (95% CI) (%)[2]	1.0 (-3.5, 5.6)	
p-Value for testing superiority	0.6562	

Source: Table 45 of CSR
[1] Denominators for percentages are based on the number of non-responders. A subject may be counted in more than one category.
[2] Ceftobiprole minus vancomycin plus aztreonam.
Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects within category; TOC, test-of-cure

In analyses of other secondary endpoints (Table 29), results were generally favorable tending to slightly favor ceftobiprole over the comparator. These results show that the clinical response observed at 48-72 hours in the primary analysis was sustained at later visits. In addition, findings were robust to the choice of population (ITT, CE), the timing of assessment (EOT, TOC), and defined outcome (clinical response, sustained reduction in lesion size, investigator-assessed clinical success, and all-cause mortality at Day 28.

Table 29. Other Secondary Endpoint Results, Trial BPR-CS-008

Categories	Ceftobiprole	Vancomycin Plus Aztreonam	Difference In Proportion % (95% CI)[1]
Clinical response[2]			
ITT population, n (%)	N=335	N=344	
At EOT	283 (84.5)	277 (80.5)	
At TOC	290 (86.6)	293 (85.2)	
At both EOT and TOC	269 (80.3)	262 (76.2)	4.2 (−2.0, 10.3)
CE population, n (%)	N=283	N=293	
At EOT	251 (88.7)	246 (84.0)	
At TOC	267 (94.3)	267 (91.1)	
At both EOT and TOC	248 (87.6)	240 (81.9)	6.0 (0.2, 11.8)
Sustained reduction in lesion size[3]			
ITT population, n (%)	N=335	N=344	
At TOC and EOT	284 (84.8)	278 (80.8)	4.0 (−1.6, 9.6)
Investigator-assessed clinical success[4]			
ITT population, n (%)	N=335	N=344	
48–72 hours after start of treatment	311 (92.8)	307 (89.2)	3.6 (−0.7, 7.8)
At TOC	302 (90.1)	306 (89.0)	1.0 (−3.5, 5.6)
Sustained at LFU	293 (87.5)	288 (83.7)	3.5 (−1.7, 8.7)
CE population, n (%)	N=283	N=293	
48–72 hours after start of treatment	264 (93.3)	264 (90.1)	3.1 (−1.3, 7.5)
At TOC	277 (97.9)	279 (95.2)	2.7 (−0.3, 5.6)
Sustained at LFU	269 (95.1)	264 (90.1)	4.8 (0.6, 9.1)
All-cause mortality at Day 28			
ITT population, n (%)	N=335	N=344	
KM survival rate estimate (95% CI)[5]	100.0 (100.0, 100.0)	99.1 (97.2, 99.7)	
CE population, n (%)	N=283	N=293	
KM survival rate estimate (95% CI)[5]	100.0 (100.0, 100.0)	99.3 (97.3, 99.8)	

Source: Table 53 of CSR

[1] Ceftobiprole minus vancomycin plus aztreonam; computed using Cochran-Mantel-Haenszel (CMH) weights method adjusted for geographic region (North America, Europe) and actual type of ABSSSI (cellulitis/erysipelas, major cutaneous abscess, wound infection).

[2] Defined as ≥ 80% decrease in lesion area at the EOT visit, and ≥ 90% decrease at the TOC visit, with improvement of local signs of infection, no use of any concomitant systemic antibacterial (or topical at the primary lesion), and no unplanned surgical procedures.

[3] Defined as ≥ 20% decrease in lesion area 48–72 hours after the start of treatment (U.S. FDA-defined primary endpoint) sustained at the EOT and TOC visits.

[4] Clinical success at TOC defined as complete or near complete resolution of baseline signs and symptoms of the primary infection, with no further need for antibacterial treatment; sustained clinical success at LFU required no new signs or symptoms of the ABSSSI between the TOC and LFU visits.

[5] Survival rate was the estimated probability that a subject remained event-free up to the specified time point; survival rate was obtained from the KM survival estimate. CIs of KM estimate used Greenwood formula

Abbreviations: CE, clinically evaluable; CI, confidence interval; EOT, end of treatment; ITT, intent-to-treat; KM, Kaplan-Meier; LFU, last follow-up; N, number of subjects in treatment arm; n, number of subjects within category; TOC, test-of-cure

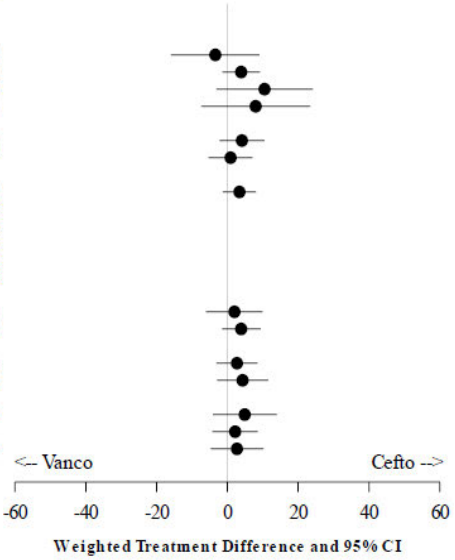
Subgroup Analyses

Subgroup analyses for the primary endpoint, ‘Proportion for Early Clinical Response 48—72 h after Start of Treatment’ in the ITT Population by age, gender, race, ethnicity, geographic region, and baseline ABSSSI type are shown in Table 30. Treatment differences tended to be more favorable in ceftobiprole subjects among most subgroups as would be expected given that the overall primary analysis numerically favored ceftobiprole. However, it was observed that the

treatment difference tended to be more favorable for ceftobiprole subjects who were males or at least 35 years of age. There were no other notable findings.

Table 30. Early Clinical Response at 48-72 hours after Start of Treatment by Age, Gender, Race, Ethnicity, Geographic Region, and Baseline ABSSSI Type (ITT Population), Trial BPR-CS-008

Subgroup	Ceftobiprole medocaril	Vancomycin plus Aztreonam	Difference (95% CI)	p-value
Age				
18-34	49 (84.5)	59 (88.1)	-3.4 (-15.9 , 9.0)	0.5852
35-64	217 (91.9)	199 (88.4)	3.9 (-1.4 , 9.2)	0.1482
65-74	26 (96.3)	31 (86.1)	10.5 (-3.1 , 24.1)	0.1798
>= 75	14 (100)	14 (87.5)	8.0 (-7.4 , 23.4)	0.3173
Gender				
Male	179 (90.4)	171 (85.1)	4.1 (-2.2 , 10.5)	0.2079
Female	127 (92.7)	132 (92.3)	0.9 (-5.3 , 7.1)	0.7817
Race				
White	289 (90.9)	289 (87.6)	3.4 (-1.3 , 8.1)	0.1619
Black or African American	7 (100)	8 (100)	NE (NE , NE)	NE
Asian	0	1 (100)	NE (NE , NE)	NE
American Indian or Alaska Native	4 (100)	3 (100)	NE (NE , NE)	NE
Native Hawaiian or Other Pacific Islander	1 (100)	0	NE (NE , NE)	NE
Other	5 (100)	2 (100)	NE (NE , NE)	NE
Ethnicity				
Hispanic or Latino	93 (90.3)	102 (88.7)	2.0 (-6.0 , 9.9)	0.6324
Not Hispanic or Latino	213 (91.8)	201 (87.8)	3.9 (-1.5 , 9.4)	0.1599
Geographic Region				
North America	185 (91.1)	190 (88.4)	2.7 (-3.1 , 8.5)	0.3654
Europe	121 (91.7)	113 (87.6)	4.3 (-2.9 , 11.5)	0.2468
Baseline Abssi Type				
Cellulitis Erysipelas	99 (88.4)	93 (83.8)	4.9 (-4.1 , 13.9)	0.2890
Major Cutaneous Abscess	92 (95.8)	87 (93.5)	2.2 (-4.2 , 8.6)	0.4961
Wound Infection	115 (90.6)	123 (87.9)	2.7 (-4.7 , 10.2)	0.4730

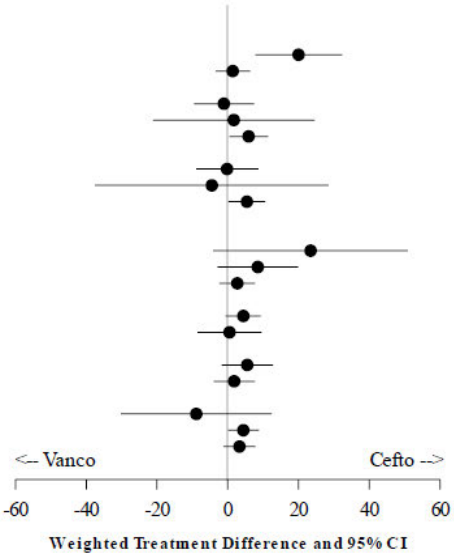


Source: Figure 14.2.1.2.1 of CSR
Note: Proportions difference (95% CI) (Ceftobiprole medocaril sodium minus Vancomycin plus Aztreonam) are computed using Cochran-Mantel-Haenszel (CMH) weights method adjusted for geographical region and actual type of ABSSSI. P-value are computed using CMH test for general association between treatment arm and response.
Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; ITT, intent-to-treat

Subgroup analyses by other baseline disease characteristics including diabetes mellitus, illicit drug use, IV drug use, creatinine clearance, white blood cell count, fever status, >10% immature neutrophils are shown in Table 30. Treatment differences were more favorable and nominally significant for various subgroups of subjects including those with diabetes mellitus, those never using injection drugs, and those not having >10% immature neutrophils at baseline. The most significant findings were observed in subjects with diabetes mellitus at baseline where clinical response rates at 48-72 hours were 36/36 (100%) in the ceftobiprole arm versus 35/42 (83.3%) in the vancomycin plus aztreonam arm with an adjusted treatment difference of 20.0% (95% CI: 7.8, 32.3).

Figure 3. Proportion of Early Clinical Response 48-72 hours After Start of Treatment (ITT population), Trial BPR-CS-008

Subgroup	Ceftobiprole medocaril	Vancomycin plus Aztreonam	Difference (95% CI)	p-value
Diabetes Mellitus				
Yes	36 (100)	35 (83.3)	20.0 (7.8 , 32.3)	0.0029
No	270 (90.3)	268 (88.7)	1.4 (-3.4 , 6.3)	0.5627
Illicit Drug Use				
Current	102 (86.4)	111 (87.4)	-1.1 (-9.5 , 7.4)	0.8075
Previous	12 (92.3)	19 (90.5)	1.7 (-21.1 , 24.5)	0.8721
Never	192 (94.1)	173 (88.3)	5.9 (0.5 , 11.4)	0.0337
Injection Drug Use				
Current	94 (87.0)	102 (87.2)	-0.2 (-8.9 , 8.6)	0.9694
Previous	9 (81.8)	13 (86.7)	-4.5 (-37.5 , 28.5)	0.7681
Never	203 (94.0)	188 (88.7)	5.4 (0.2 , 10.6)	0.0435
Baseline Creatinine Clearance				
<30	0	1 (100)	NE (NE , NE)	NE
30 - <50	10 (100)	9 (81.8)	23.4 (-4.1 , 50.9)	0.1161
50 - 80	41 (95.3)	40 (90.9)	8.5 (-2.9 , 19.9)	0.1174
>80	255 (90.4)	253 (87.8)	2.7 (-2.4 , 7.7)	0.2978
Baseline White Blood Cell				
Normal	210 (94.6)	196 (89.9)	4.4 (-0.6 , 9.3)	0.0846
Abnormal	96 (85.0)	107 (84.9)	0.5 (-8.5 , 9.6)	0.9100
Baseline Fever Status				
Fever	111 (92.5)	105 (87.5)	5.5 (-1.7 , 12.8)	0.1418
No Fever	194 (90.7)	198 (88.4)	1.8 (-3.9 , 7.6)	0.5329
Baseline >10% Immature Neutrophils				
Yes	19 (70.4)	30 (83.3)	-8.9 (-30.2 , 12.4)	0.4206
No	261 (94.9)	245 (90.4)	4.4 (0.1 , 8.8)	0.0470
Overall	306 (91.3)	303 (88.1)	3.3 (-1.2 , 7.8)	0.1543



Source: Figure 14.2.1.2.1 of CSR
Note: Proportions difference (95% CI) (Ceftobiprole medocaril sodium minus Vancomycin plus Aztreonam) are computed using Cochran-Mantel-Haenszel (CMH) weights method adjusted for geographical region and actual type of ABSSSI. P-value are computed using CMH test for general association between treatment arm and response.
Abbreviations: ITT, intent-to-treat

Major Protocol Deviations

Major protocol deviations were defined as those that could potentially bias either the efficacy or safety conclusions of the trial. These are presented in Table 31. Overall, there were a large number of deviations. However, they were generally balanced between treatment arms.

Table 31. Major Protocol Deviations, BPR-CS-008

Type of Deviation	Ceftobiprole (N=335) n (%)	Vancomycin Plus Aztreonam (N=344) n (%)	Total (N=679) n (%)
Overall deviations	52 (15.5)	51 (14.8)	103 (15.2)
ICH/GCP deviations	3 (0.9)	6 (1.7)	9 (1.3)
Incomplete source documentation	3 (0.9)	6 (1.7)	9 (1.3)
Protocol deviations	51 (15.2)	46 (13.4)	97 (14.3)
Non-study antibiotic[1]	9 (2.7)	5 (1.5)	14 (2.1)
Inadvertent unblinding	2 (0.6)	0	2 (0.3)
ABSSSI diagnosis[2]	0	2 (0.6)	2 (0.3)
Prohibited medication[3]	0	1 (0.3)	1 (0.1)
Prohibited non-antibiotics[4]	14 (4.2)	12 (3.5)	26 (3.8)
Less than 80% compliance[5]	1 (0.3)	0	1 (0.1)
Treatment duration <5 days	17 (5.1)	16 (4.7)	33 (4.9)
Visit missed	19 (5.7)	18 (5.2)	37 (5.4)
Visit out of window	5 (1.5)	5 (1.5)	10 (1.5)

Source: Table 9 of CSR
[1]. Concomitant systemic antibacterials and/or topical antibacterials applied to the primary lesion prior to the TOC visit, other than allowed by the protocol.
[2]. ABSSSI diagnosis lacking at randomization.
[3]. Prohibited medication taken within 14 days prior to the first investigational product of the study.
[4]. Prohibited non-antibiotic medication before TOC.
[5]. Subject randomized, compliance < 80% (based on total doses for overall treatment duration).
Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; GCP, good clinical practice; ICH, International Conference for Harmonisation; N, number of subjects in treatment arm; n, number of subjects within category

Additional Analyses

There were no additional analyses performed.

Conclusions

Trial BPR-CS-008 met its primary objective of demonstrating non-inferiority for the primary endpoint. In general, primary and secondary efficacy findings tended to numerically favor ceftobiprole to vancomycin plus aztreonam. Early clinical response appeared to be sustained at later timepoints. Overall, there are no major concerns with the evidence of effectiveness.

Minor concerns were that over 95% of subjects in the ITT population were White, which may limit the generalizability of findings to other races. (b) (4) [redacted]

6.2.3. CABP, Trial CAP-3001

6.2.3.1. Design, Trial CAP-3001

This was a randomized, double-blind, multicenter trial of ceftobiprole versus ceftriaxone with or without linezolid designed to assess the efficacy and safety of ceftobiprole in adult subjects with CABP requiring hospitalization. The trial was conducted from June 2006 to July 2007.

The primary objective of this trial was to demonstrate the noninferiority of ceftobiprole compared with ceftriaxone with or without linezolid with respect to the clinical cure rate at the TOC visit in subjects hospitalized with CABP.

The secondary objectives were to compare the following in hospitalized CABP subjects after treatment with ceftobiprole versus treatment with the comparator:

- The microbiological eradication rate at the TOC Visit
- The clinical cure rate and the microbiological eradication rate at the TOC Visit of subjects who required mechanical ventilation within the first 48 hours of enrollment
- The clinical and microbiological relapse rates at the late follow-up visit
- The 30-day pneumonia-specific mortality rates.

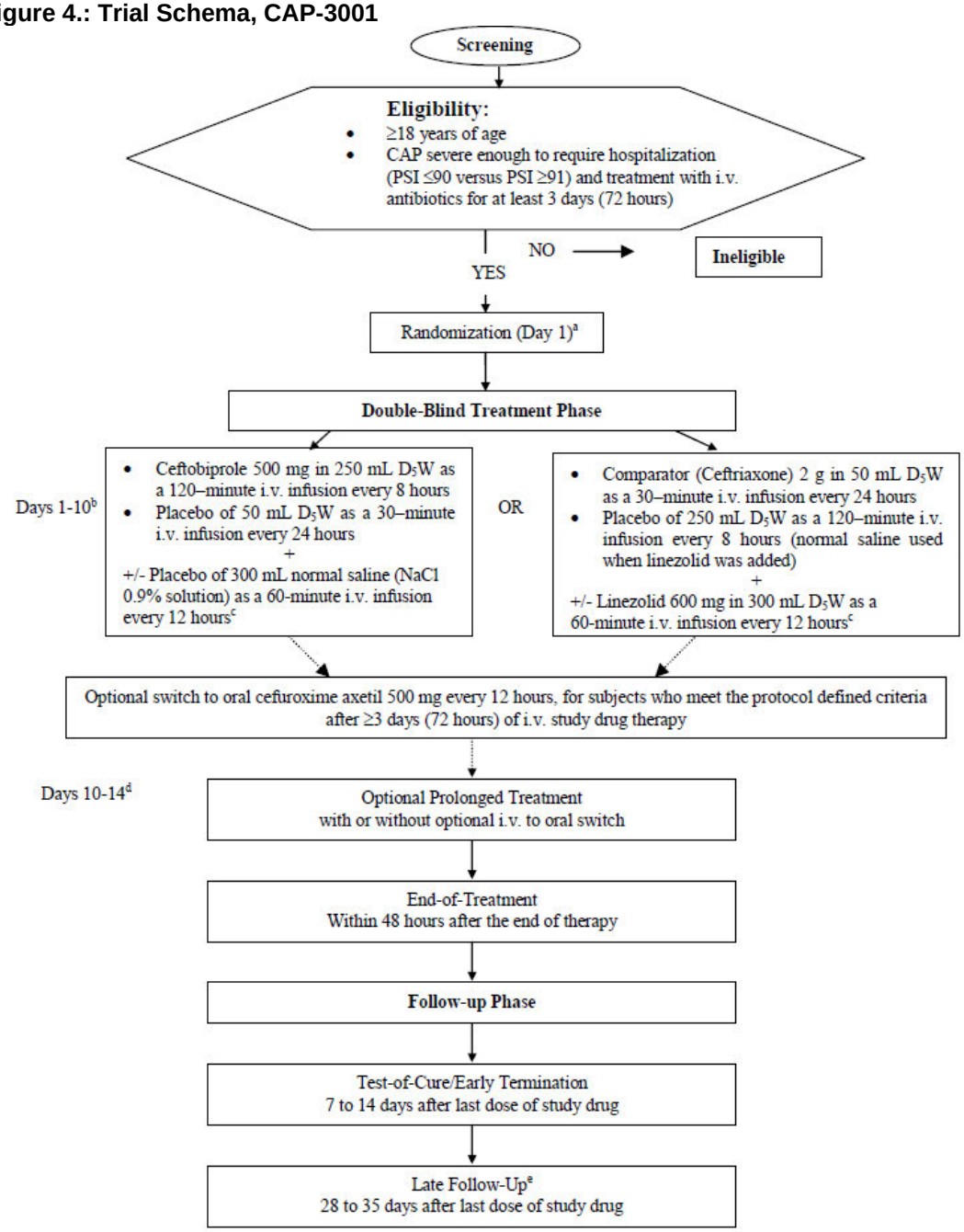
Since many subjects in this trial would not require hospitalization for the entire duration of antibacterial therapy, a switch from IV study drugs to oral cefuroxime axetil (500 mg every 12 hours) was allowed after a minimum of 3 days of IV therapy, but only for those subjects who met all protocol-specified criteria for improvement and were candidates for hospital discharge. The use of cefuroxime axetil was consistent with the recommendation of practice guidelines.

All subjects continued to receive intravenous therapy while hospitalized and trial sites were encouraged to keep subjects on IV therapy as long as appropriate in order to maximize the number of subjects receiving a full course of IV study medication. In addition, subjects with a positive blood culture at baseline were required to receive IV study drug for a minimum of 5 days pending results of repeat blood cultures.

The total duration of study drug therapy (IV plus oral) for all subjects was a minimum of 5 days and a target of 7 days. If in the investigator's opinion a subject required additional days of study therapy, the duration of the therapy could have been extended up to a maximum of 10 days. Therapy could have been further extended to a maximum of 14 days.

At the discretion of the investigator, subjects were allowed to receive study drug infusions as outpatients or through a home-care agency, provided they met all other protocol requirements, but all IV study drug infusions had to be administered and monitored by a qualified nurse, a qualified member of the trial staff, or an infusion specialist. No concomitant administration of antibacterial treatments was permitted. The treatment and follow-up schedules are summarized in Figure 4.

Figure 4.: Trial Schema, CAP-3001



Note: D_5W = 5% dextrose solution in water

[a] Day of the first infusion. Baseline assessments were performed before first infusion.

[b] The 30-minute infusion was administered first (placebo or ceftriaxone), followed by the 120-minute infusion (ceftobiprole or placebo). The target duration of study drug treatment (i.v. and oral) for all subjects was a minimum of 5 days to a target of 7 days. If, in the investigator's opinion, a subject required additional days of study therapy, the duration of the therapy may have been extended (up to a maximum of 10 days). Subjects were evaluated at Days 5 and 10 while on therapy.

[c] Linezolid or placebo was added as concomitant therapy based on initial signs and symptoms suggestive of MRSA or *S. aureus*. Linezolid or placebo should have been discontinued by 48 hours if infection with MRSA or CRSP was not confirmed by culture.

[d] Therapy could have been further extended to a maximum of 14 days after approval by the Sponsor's Medical Monitor. Subjects were evaluated at Day 14 while on prolonged therapy.

[e] Late Follow-up Visit was by telephone contact. Subjects reporting signs or symptoms consistent with pulmonary infection were evaluated in person.

Source: Figure 1 in CSR

An independent data monitoring committee (IDMC) was established to monitor data on an ongoing basis to ensure the continuing safety of subjects enrolled in this trial and the efficacy of

Reference ID: 5357793

the study drug. The IDMC included independent experts, not affiliated with the Applicant, in internal medicine, critical care medicine, infectious diseases, and biostatistics. The IDMC could call upon experts in other specialties to attend IDMC meetings to provide information regarding unanticipated findings or issues. The committee met on 3 occasions (14 October 2006, 23 January 2007, and 24 May 2007) to review data collected in this Trial and made recommendations after each review to continue conduct of the trial as planned.

6.2.3.2. Eligibility Criteria, Trial CAP-3001

Approximately 670 subjects hospitalized with CABP severe enough to require treatment with IV antibacterials for at least 3 days, were to be enrolled to achieve 532 (266 in each treatment arm) clinically evaluable subjects. In total, 666 subjects at 103 sites worldwide were randomly assigned centrally in a 1:1 ratio to treatment with either ceftobiprole (500 mg every 8 hours as a 120-minute IV infusion) or ceftriaxone (2 g once daily as a 30-minute IV infusion) with or without linezolid (600 mg every 12 hours as a 60-minute IV infusion). Subjects were stratified by the Pneumonia Outcomes Research Team (PORT) Severity Index (PSI) score at randomization (PSI ≤90 versus PSI ≥91), and by the need for anti-staphylococcal therapy (linezolid or placebo) based on signs, symptoms, and medical history at enrollment.

Reference ID: 5357793

Inclusion Criteria

Subjects meeting all the following:

- Men or women, 18 years of age or older who provided written informed consent.
- Women must have been postmenopausal (for at least 1 year), surgically sterile or practiced an effective method of birth control.
- Subjects had a diagnosis of CABP severe enough to require hospitalization and treatment with IV antibacterial drugs for at least 3 days (72 hours), defined as meeting all the following criteria:
- Subjects had a diagnosis of CABP severe enough to require hospitalization and treatment with IV antibacterials for at least 3 days (72 hours), defined as meeting all of the following criteria (must meet a, b, c, d, and e):

  a) Clinical diagnosis of acute bacterial pneumonia acquired in the community. Subjects must have resided in the community (i.e., not in a chronic care facility such as a nursing home or rehabilitation facility) and must not have been hospitalized during the 14 days before the onset of symptoms of pneumonia. Residence in an assisted-living facility where the subject had regular access to the community was allowed.

  b) Clinical signs or symptoms of acute bacterial pneumonia with at least 2 of the following criteria:

     – Cough (new or increased over usual state)

     – Production of purulent sputum or a worsening in the character of sputum

     – Auscultatory findings on pulmonary examination of rales or evidence of pulmonary consolidation (dullness on percussion, bronchial breath sounds, or egophony)

     – Dyspnea or tachypnea (respiratory rate ≥20 breaths per minute), that was new or worse than usual state

     – New onset hypoxemia on room air (PO2 <60 mm Hg on arterial blood gas or O2 saturation <90% by pulse oximetry), or respiratory failure that required mechanical ventilation.

  c) New radiographic infiltrates (not related to another disease process) consistent with the diagnosis of bacterial pneumonia

  d) Fever or leukocytosis/leukopenia (temporally associated with the onset of pneumonia symptoms)

     – Fever (in the absence of antipyretics) defined as an axillary temperature >37.5°C, an oral temperature >38°C, a tympanic temperature >38.5°C, a rectal temperature >39°C, or hypothermia, defined as a rectal body temperature of <35°C

     – Leukocytosis defined as an elevated total peripheral WBC count ≥10 x 10^9/L or ≥15% immature neutrophils (bands), regardless of total peripheral white count; or leukopenia with total WBC ≤4.5 x 10^9/L

  e) Severity of pneumonia required IV antibacterial therapy

Reference ID: 5357793

6.2.3.3. Statistical Analysis Plan, Trial CAP-3001

Disposition of Subjects

A total of 706 subjects were enrolled into this trial, Figure 5. Sixty-eight subjects were not included in the ITT analysis set (i.e., the ITT population of all randomized subjects) including 40 subjects who were screen failures and 28 subjects who were randomly assigned to treatment with ceftobiprole (14 subjects) or ceftriaxone with or without linezolid (14 subjects) at site 506002[3]. A total of 638 subjects were randomized to receive either the ceftobiprole (n = 314) or ceftriaxone with or without linezolid (n = 324) treatment.

One subject was randomly assigned to the comparator arm but was treated with ceftobiprole.

As shown in Table 32**,** a total of 532 of 638 (83%) of ITT subjects completed the study. Of the 17% of subjects who discontinued the study, the main reasons for study discontinuation were subjects having AEs (5%) or being lost to follow-up (3%). Overall, there were no notable imbalances between the treatment arms regarding reasons for discontinuation from the study.

Table 32. Reasons for Discontinuation From Trial (ITT Population), Trial CAP-3001

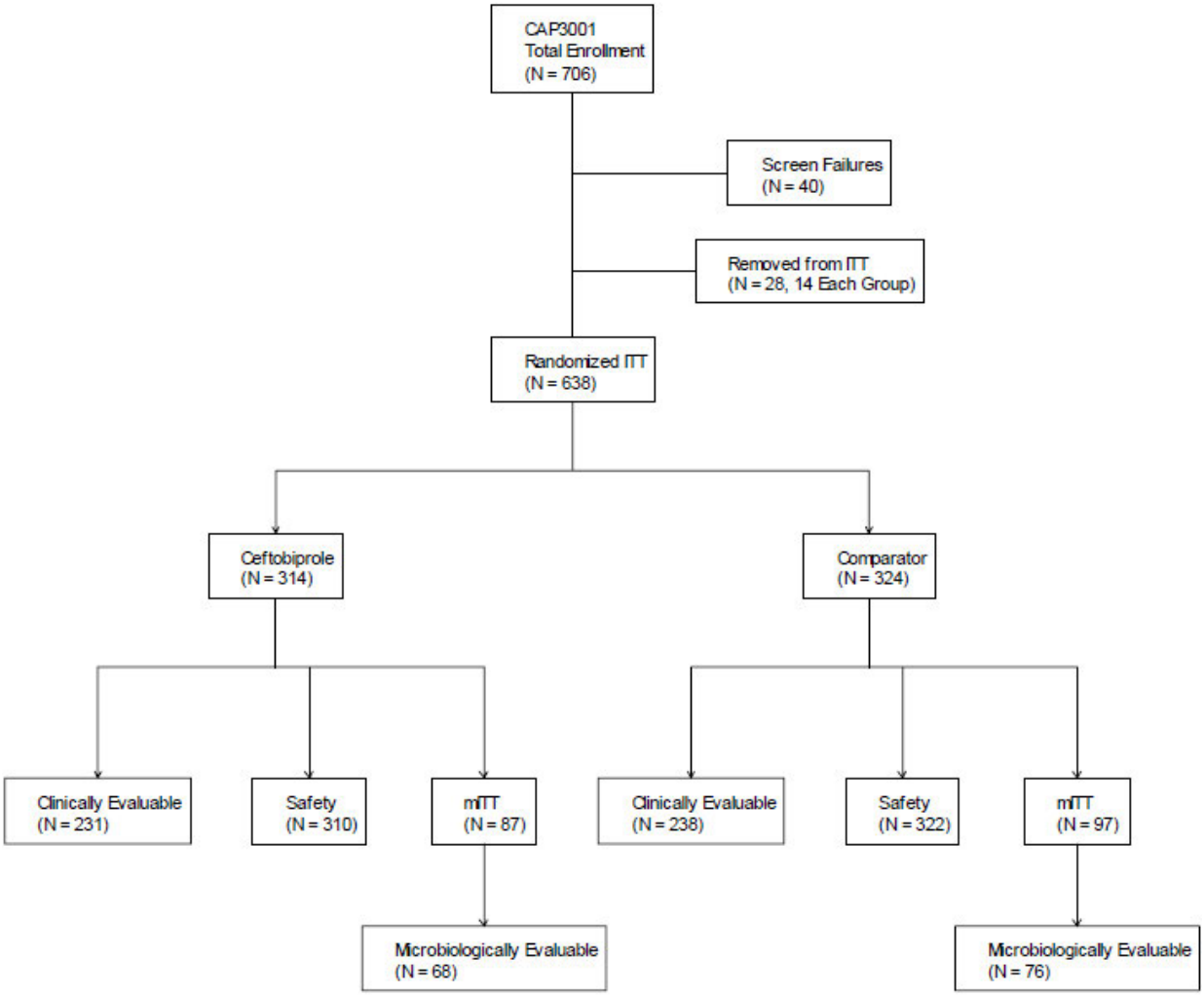
Categories	Ceftobiprole (N=314) n (%)	Ceftriaxone (N=324) n (%)	Total (N=638) n (%)
Completed study	258 (82)	274 (85)	532 (83)
Discontinued from study	56 (18)	50 (15)	106 (17)
Primary reason			
Adverse event	19 (6)	14 (4)	33 (5)
Subject choice (subject withdrew consent)	12 (4)	12 (4)	24 (4)
Lost to follow-up	8 (3)	9 (3)	17 (3)
Lack of efficacy	5 (2)	5 (2)	10 (2)
Death	6 (2)	3 (1)	9 (1)
Other	6 (2)	7 (2)	13 (2)

Source: Table 9 in CSR
Abbreviations: ITT, intent-to-treat; N, number of subjects in treatment arm; n, number of subjects within category

[3] During the course of the study, routine medical monitoring identified discrepancies regarding chest x-ray confirmation of pneumonia at a single site (506002). Specifically, protocol-specified central review of the subjects' baseline chest x-rays determined that 22 (79%) of the 28 subjects enrolled at this site did not have findings consistent with CAP. After the database lock, the Sponsor reassessed available information on study site performance at all sites that participated in this study. Based on these issues the Applicant decided to exclude all data generated from this site from all analyses.

Reference ID: 5357793

Figure 5. Disposition of Subjects, Trial CAP-3001



Source: Figure 2 in CSR
Abbreviations: ITT, intent-to-treat; mITT, modified intent-to-treat; N, number of subjects in specified group

Baseline Demographic and Disease Characteristics

As shown in Table 33**,** the baseline demographic characteristics in the ITT population were generally balanced across the treatment arms. Overall, subjects had a median age of 56 years and tended to be males (57%), White (62%) or not Hispanic or Latino (75%). Approximately 13% of subjects were from North American sites and 41% were from European sites. Disease characteristics were also balanced across the treatment arms. Overall, 22% of subjects had a PSI ≥ 91, 49% had a PORT Risk Class of ≥ III and 54% had systemic inflammatory response syndrome (SIRS) at baseline. Concomitant use of linezolid was observed in 11% of subjects. The percentage of ITT subjects with a valid pathogen at baseline was 29%.

Table 33. Baseline Demographic and Disease Characteristics (ITT Population)

Categories	Ceftobiprole N=314	Ceftriaxone N=324	Total N=638
Age (years)			
Mean (SD)	53.8 (19.31)	55.2 (19.20)	54.5 (19.25)
Median	56.0	55.5	56.0
Min, max	18,90	18,94	18,9
Age categories (years) n (%)			
≥65	111 (35)	126 (39)	237 (37)
≥75	54 (17)	62 (19)	116 (18)
Sex n (%)			
Male	179 (57)	187 (58)	366 (57)
Female	135 (43)	137 (42)	272 (43)
Race n (%)			
White	193 (61)	204 (63)	397 (62)
Black	18 (6)	18 (6)	36 (6)
Asian	69 (22	72 (22)	141 (22)
Other	34 (11)	30 (9)	64 (10)
Ethnicity n (%)			
Hispanic or Latino	72 (23)	84 (26)	156 (25)
Not Hispanic or Latino	242 (77)	238 (4)	480 (75)
Geographic regions n (%)			
North America	41 (13)	41 (13)	82 (13)
Europe	132 (42)	132 (41)	264 (41)
Other	141 (45)	151 (47)	292 (46)
PSI Group			
≤90	245 (78)	252 (78)	497 (78)
≥91	69 (22)	72 (22)	141 (22)
PORT Class			
I	19 (6)	14 (4)	33 (5)
II	137 (44)	159 (49)	296 (46)
III	89 (28)	77 (24)	166 (26)
IV	65 (21)	65 (20)	130 (20)
V	4 (1)	7 (2)	11 (2)
Missing	0	2 (1)	2 (<1)
Valid Pathogen at Baseline n (%)			
Yes	87 (28)	97 (30)	184 (29)
No	227 (72)	227 (70)	454 (71)
SIRS n (%)			
No	146 (47)	144 (45)	290 (46)
Yes	164 (53)	178 (55)	342 (54)
Concomitant antibacterial medication n (%)			
Linezolid	30 (10)	40 (12)	70 (11)

Source: Partially Adapted from Tables 10 and 11 of CSR
Abbreviations: ITT, intent-to-treat; N, number of subjects in treatment arm; n, number of subjects within category; PORT, Pneumonia Outcomes Research Team; PSI, Pneumonia Outcomes Research Team (PORT) Severity Index; SIRS, systemic inflammatory response syndrome

Sample Size Determination

The sample size was determined to show the noninferiority of ceftobiprole compared with ceftriaxone with or without linezolid in terms of the clinical cure rate at the TOC visit.
The sample size calculation was based on the following assumptions for the ITT analysis set:

- The clinical cure rate is 70% in both treatment arms,
- The non-inferiority margin is 10%,
- The power (1-β) is 80%,
- The level of significance is 2-sided 5%,
- The clinically evaluable rate is 80%.

Based on the above, 670 subjects needed to be randomly assigned to treatment, providing 335 subjects in each treatment arm.

Efficacy Analysis Sets

- **ITT Analysis Set:** included all subjects randomly assigned to treatment.
- **mITT Analysis Set:** a subset of the ITT analysis set that included all ITT subjects who had a valid pathogen at Baseline.
- **Clinically Evaluable Analysis Set:** a subset of the ITT analysis set that included all the ITT subjects who received at least 48 hours of Trial medication but excluded those subjects with a derived clinical outcome of Not Evaluable at the TOC Visit. The derived clinical outcome was based on clinical assessment and evaluability of a subject, whereas the clinical outcome collected in the electronic case report form was based on the investigator's assessment.
- **Clinically Evaluable Analysis Set at the Late Follow-Up Visit:** included all clinically evaluable subjects with a derived clinical outcome of cure at the TOC visit and who were clinically evaluable at the late follow-up visit.
- **Microbiologically Evaluable Analysis Set:** a subset of the mITT analysis set that included all mITT subjects who were also clinically evaluable subjects, excluding those with a microbiological outcome of 'Not Evaluable' at the TOC Visit.
- **Microbiologically Evaluable Analysis Set at the Late Follow-Up Visit:** included all microbiologically evaluable subjects with a microbiological outcome of eradication or presumed eradication at the TOC visit and who were microbiologically evaluable at the late follow-up visit.
- **Safety Analysis Set:** The safety analysis set is a subset of the ITT analysis set and included all the subjects in the ITT analysis set who were exposed to any Trial medication.

Derived Clinical Outcome at the TOC Visit

In the ITT and mITT analyses subjects whose clinical outcomes were assessed as 'Not Evaluable' by the investigator were considered failures. Subjects who were considered clinically cured by the investigator at the TOC Visit but received effective concomitant therapy for any reason, were also considered failures in the ITT and mITT analyses.

Reference ID: 5357793

Cure

A subject was considered a ‘derived clinical cure’ at the TOC visit if the clinical outcome at the TOC visit was cure and the subject was not a ‘derived failure’ as defined below.

Failure

A subject was considered a clinical failure at TOC if he or she took study medication for at least 48 hours and met any of the following criteria:

- Clinical outcome at the TOC visit was failure
- Subject withdrew from the treatment because of a treatment-related adverse event
- Subject died due to pneumonia after 48 hours of treatment
- Subject withdrew from the Trial due to lack of efficacy
- Subject missed a TOC visit assessment and the final clinical assessment before the TOC visit was ‘Unchanged’ or ‘Worsened from Baseline’,
- Subject received non-study systemic antibiotics for treatment of pneumonia prior to the TOC Visit.

Subjects who withdrew from treatment because of an adverse event but received a full course of therapy (5 to 14 days) were regarded as clinical cures if the clinical outcome at the TOC Visit was cure.

Non-evaluable

A subject was considered ‘non-evaluable’ at the TOC visit if the following criteria were satisfied:

- Subject did not meet the criteria for cure or failure (as defined above), and
- Subject had missing TOC visit or the investigator’s assessment of the clinical outcome at the TOC visit was ‘Not Evaluable’.

Reference ID: 5357793

Evaluability at the TOC Visit

A subject was deemed clinically evaluable at the TOC visit unless he or she met any of the following criteria:

- Clinical Diagnosis Unconfirmed: Per the investigator, the inclusion criterion related to a diagnosis of CABP was not satisfied.
- Community-Acquired Pneumonia Unconfirmed: The baseline infiltrate was not consistent with pneumonia by central x-ray evaluation.
- Mortality:
  - Early Mortality: The subject died within 48 hours after the first infusion.
  - Unrelated Mortality: The mortality was unrelated to pneumonia and the last clinical assessment was not worsened, and the subject had no treatment-related adverse event, did not withdraw due to lack of efficacy, and had no TOC visit.
  - Effective Concomitant Therapy: The subject took a systemic antibacterial drug (administered for a reason other than CABP), against gram-positive or gram-negative pathogens. Subjects who received a concomitant medication with purely anaerobic (e.g., metronidazole), anti-fungal, or antiviral activity were considered evaluable. Subjects who received non-absorbable antibacterial drugs s (e.g., oral vancomycin, neomycin) or topical antibacterial drugs were also evaluable.
  - Other Protocol Violations: The presence of neutropenia (absolute neutrophil count ≥0.5x109/L).
  - Resistant to Study Drugs:
    i. Subjects whose cultures yielded pathogens resistant to both treatment arms of the trial based on central laboratory results (MIC values ≥ 16 mg/mL), or
    ii. Subjects who withdrew due to “resistant organism at baseline” based on local laboratory results.
- Inappropriate Clinical Evaluation:
  - The subject did not meet the definition of failure and the TOC visit was not completed 6 to 21 days following the last dose of study drug.
- Course Too Short:
  - The subject took study medication for less than 48 hours, or
  - The subject had a clinical outcome of ‘Cure’ at the TOC visit but took study medication for less than 120 hours, or
  - The subject took less than 80% of scheduled IV study medication.
- Missing TOC Visit: Subjects who missed the TOC visit and did not meet the definition of cure or failure.

Reference ID: 5357793

Derived Clinical Outcome at the Late Follow-Up Visit

Clinical Relapse

A subject was considered a clinical relapse at the late follow-up visit if the subject was an evaluable cure at the TOC visit and any of the following applied:

- The outcome at the late follow-up visit was relapse, or
- The subject died due to pneumonia prior to the late follow-up visit, or
- The subject took effective concomitant therapy for pneumonia between the TOC visit and the late follow-up visit.

Evaluability at the Late Follow-Up Visit

A subject was considered clinically evaluable at the late follow-up visit if the following criteria were met:

- The subject was evaluable and had a clinical outcome of cure at the TOC visit.
- The subject did not take effective concomitant therapy for a reason other than pneumonia during the period between the TOC and late follow-up visits, OR the subject took effective concomitant therapy for a reason other than pneumonia and was a clinical relapse at the late follow-up visit.
- The subject had a clinical evaluation at the late follow-up visit or the subject died of pneumonia prior to the late follow-up visit.

Microbiological Outcome at the TOC Visit

Microbiological outcome at the subject level was not directly collected in the electronic case report form, but was obtained through a combination of the clinical assessment, infection symptoms, and the microbiological assessment at the baseline, TOC, and late follow-up visits. For all subjects with a valid pathogen at baseline, the microbiological outcome at the TOC visit was derived following the mapping shown in Table 34 below.

Table 34. Microbiological Outcome at the TOC Visit for Subjects With a Valid Pathogen at Baseline

	Derived Clinical Outcome at TOC Visit	
Microbiological Result at TOC	**Cure**	**Failure**
No Culture Possible	Presumed Eradication	Presumed Persistence
No Growth	Eradication	Eradication
Initial Pathogen	Persistence	Persistence
New Pathogen	Colonization	Superinfection

Source: Table 4 of CSR
Note: Subjects with no microbiological and clinical assessment at TOC were not evaluable. Any subject with a missing TOC visit or who was not clinically evaluable was considered microbiologically nonevaluable at the TOC visit. Any subject with a persistent baseline pathogen was considered to have an outcome of persistence at the TOC visit.
Abbreviations: TOC, test-of-cure

Subjects who were clinical failures and received non-study systemic antibacterial drugs for the primary infection prior to the TOC visit were considered to have a microbiological outcome of 'Presumed Persistence' in the absence of a culture at the TOC visit.

Reference ID: 5357793

Microbiological Evaluability at the TOC Visit

A subject was considered microbiologically evaluable at the TOC visit if the following criteria were met:

- Subject was clinically evaluable at the TOC visit
- Subject had a valid pathogen isolated at baseline. To be considered valid, a pathogen must have met the following isolation criteria:
  - Tracheal aspirate, bronchoalveolar lavage, PBS, or other
  - Expectorated samples with less than 10 squamous epithelial cells and greater than 25 leukocytes/lpf.

Primary Efficacy Analysis

The primary efficacy analysis was performed on the clinically evaluable and the ITT co-primary analysis sets. The primary efficacy endpoint was the clinical cure rate at the TOC visit, defined as the ratio of the number of subjects who had a derived clinical outcome of cure at the TOC visit to the total number of the subjects in the analysis set under consideration.
The hypotheses tested were:

H0: The clinical cure rate of the ceftobiprole arm is more than 10% inferior to that of the ceftriaxone with or without linezolid arm.

H1: The clinical cure rate of the ceftobiprole arm is no more than 10% inferior to that of the ceftriaxone with or without linezolid arm.

A 2-sided 95% confidence interval based on the Normal approximation for the difference of two binomial proportions was calculated for the between-treatment difference (ceftobiprole minus ceftriaxone with or without linezolid) at the TOC Visit. Noninferiority of ceftobiprole compared with ceftriaxone with or without linezolid was concluded if the lower limit of this confidence interval was greater than or equal to –10%.

Secondary Efficacy Analyses

The secondary efficacy endpoints were tested using a step-down hierarchical procedure in the following order:

1) microbiological eradication rate at the TOC visit,
2) clinical cure rate at the TOC visit for subjects who had a PSI score ≥91,
3) the 30-day pneumonia-specific mortality rates.

The microbiological eradication rate at the TOC Visit was defined as the ratio of the number of subjects with a microbiological outcome of Eradication or Presumed Eradication at the TOC visit to the total number of subjects in the analysis set under consideration at the TOC visit. This analysis was performed on the microbiologically evaluable analysis set.
The clinical cure rate for subjects who had a PSI score ≥91 was defined as the ratio of the number of subjects with PSI score ≥91 who had a clinical outcome of cure at the TOC visit to the total number of the subjects with a PSI score ≥91 in the analysis set under consideration. The analysis of the clinical cure rate for subjects who had a PSI score ≥91 was performed on the clinically evaluable and ITT analysis sets.

Noninferiority hypotheses similar to the primary hypothesis were tested for the microbiological eradication rate and the clinical response rate in subjects with a PSI score ≥91.

Reference ID: 5357793

The 30-day pneumonia-specific mortality rate was defined as the ratio of the number of deaths due to pneumonia to the total number of subjects in the analysis set under consideration. This analysis was performed on the clinically evaluable and ITT analysis sets.

Given the limited sample sizes for these tests, a 15% noninferiority margin was used to test all secondary hypotheses. This was documented prior to database lock, but was not prespecified in the protocol or the analysis plan. The 2-sided 95% confidence interval was computed in the same way as for the primary efficacy analysis.

6.2.3.4. Results of Analyses, Trial CAP-3001

Primary Efficacy Analysis

The protocol specified two co-primary endpoints to be analyzed in the primary efficacy analysis, which included the clinical cure rate at the TOC visit in the CE and ITT populations. For both co-primary endpoints, treatment differences were shown to satisfy a 10% NI margin based on the respective lower confidence limits exceeding -10% (Table 35**)**. In the clinically evaluable analysis set, the clinical cure rate at the TOC visit was 86.6% (ceftobiprole) versus 87.4% (comparator), a treatment difference of -0.8% (95% CI: -6.9, 5.3) which indicated NI since the lower bound of -6.9% exceeded a -10% limit. In the ITT analysis set, the clinical cure rate at the TOC visit was 76.4% (ceftobiprole) versus 79.3% (comparator), a treatment difference of -2.9% (95% CI: -9.3, 3.6) which indicated NI since the lower bound of -9.3% exceeded the -10% limit.

Table 35. Analyses of Co-Primary Endpoints: Clinical Outcome at the TOC Visit in the CE and ITT Populations, Trial CAP-3001

Categories	Ceftobiprole n (%)	Ceftriaxone n (%)	Diff[b](%)	95% CI[c]
CE Population	**N=231**	**N=238**		
Cure	200 (86.6)	208 (87.4)	-0.8	(-6.9; 5.3)
Failure	31 (13.4)	30 (12.6)		
ITT Population[a]	**N=314**	**N=324**		
Cure	240 (76.4)	257 (79.3)	-2.9	(-9.3; 3.6)
Failure	74 (23.6)	67 (20.7)		

Source: Partially Adapted from Tables 17 and 18 of CSR
[a] Subjects were counted as Cure in the ITT Analysis Set only when the subject had a clinical outcome of Cure without effective concomitant therapy, otherwise, the subject was counted as Failure.
[b] Ceftobiprole minus ceftriaxone with/without linezolid.
[c] 2-sided 95% C.I. is based on the Normal approximation to the difference of the 2 proportions.
Abbreviations: CE, clinically evaluable; CI, confidence interval; ITT, intent-to-treat; N, number of subjects in treatment arm; n, number of subjects within category; TOC, Test of Cure

Secondary Efficacy Analyses

The secondary efficacy endpoints were tested using a step-down hierarchical procedure in the following order using an NI margin of 15%:

1) Microbiological eradication rate at the TOC visit,
2) Clinical cure rate at the TOC visit for subjects who had a PSI score ≥91,
3) The 30-day pneumonia-specific mortality rates.

Findings for key secondary endpoints were generally consistent with the non-inferiority finding in the primary analysis.

Reviewer Comments

The Applicant cannot demonstrate non-inferiority for these endpoints due to uncertainty regarding the NI margin. The specified NI margin for the above secondary endpoints has not been scientifically justified and therefore the interpretation of findings for these endpoints may not be clear unless superiority is shown. These endpoints were therefore considered to be descriptive.

Table 36. Analyses of Key Secondary Endpoints in Microbiological Eradication at the TOC Visit, Clinical Cure Rate at TOC in Subjects With PSI ≥91 and 30-day Pneumonia-Specific Mortality Rates, Trial CAP-3001

Categories	Ceftobiprole n (%)	Ceftriaxone n (%)	Diff[b](%)	95% CI[c]
Microbiological Eradication at TOC Endpoints				
ME Population	N=68	N=76		
Eradication	60 (88.2)	69 (90.8)	-2.6	(-12.6; 7.5)
mITT Population[a]	N=87	N=97		
Eradication	70 (80.5)	79 (81.4)	-1.0	(-12.4; 10.4)
Clinical Cure Rate at TOC in Subjects with PSI ≥91				
CE Population	N=51	N=58		
Clinical Cure	46 (90.2)	49 (84.5)	5.7	(-6.7; 18.1)
ITT Population[a]	N=69	N=72		
Clinical Cure	56 (81.2)	56 (77.8)	3.4	(-9.9; 16.7)
30-day Pneumonia-Specific Mortality Rates				
CE Population	N=231	N=238		
Deaths	0 (0.0)	2 (0.8)	-0.8	(-2.0; 0.3)
ITT Population[a]	N=314	N=324		
Deaths	1 (0.3)	3 (0.9)	-0.6	(-1.8; 0.6)

Source: Partially Adapted from Tables 17 and 18 of CSR
[a] Subjects were counted as Cure in the ITT Analysis Set only when the subject had a clinical outcome of Cure without effective concomitant therapy, otherwise, the subject was counted as Failure.
[b] Ceftobiprole minus ceftriaxone with/without linezolid.
[c] 2-sided 95% C.I. is based on the Normal approximation to the difference of the 2 proportions.
Abbreviations: CE, clinically evaluable; CI, confidence interval; ITT, intent-to-treat; ME, microbiologically evaluable; mITT, modified intent-to-treat; N, number of subjects in treatment arm; n, number of subjects within category; PSI, Pneumonia Outcomes Research Team (PORT) Severity Index; TOC, test-of-cure

Subgroup Analyses

Subgroup analyses for the primary endpoint 'Clinical Cure Rate at TOC' in the ITT Population by age (<65, ≥65), sex (M/F), race (White, Black, Asian, other), geographic region (U.S./Non-U.S), PSI Score (≤90, ≥91), PORT class (I-V), gram-positive pathogen (Y/N), gram-negative pathogen (Y/N), oral switch (Y/N), received linezolid/placebo (Y/N), SIRS (Y/N), bacteremia (Y/N) and dose reduction (Y/N) are shown in Table 37. Overall, treatment differences appeared to be generally similar between treatment arms across all subgroups. There were no notable findings. Similar trends were observed in the CE population.

Table 37. Subgroup Analyses of Clinical Cure Rates at the TOC Visit by Baseline Characteristics (ITT Population)

Categories	Ceftobiprole n/N (%)	Ceftriaxone n/N (%)	Diff.[a] (95% CI[b])
Age			
<65	150/203 (73.9)	152/198 (76.8)	-2.9 (-9.3, 2.6)
≥65	90/111 (81.1)	105/126 (83.3)	-2.3 (-12.0, 7.5)
Sex			
Male	142/179 (79.3)	146/187 (78.1)	1.3 (-7.1, 9.6)
Female	98/135 (72.6)	111/ 137 (81.0)	-8.4 (-18.4, 1.6)
Race			
White	150/193 (77.7)	165/204 (80.9)	-3.2 (-11.1, 4.8)
Black	9/18 (50.0)	13/18 (72.2)	-22.2 (-53.2, 8.8)
Asian	51/69 (73.9)	51/72 (70.8)	3.1 (-11.7, 17.8)
Other	30/34 (88.2)	28/30 (93.3)	-5.1 (-19.1, 8.9)
Region			
U.S.	23/ 41 (56.1)	29/41 (70.7)	-14.6 (-35.2,6.0)
Non-U.S.	217/273 (79.5)	228/283 (80.6)	-1.1 (-7.7, 5.6)
PSI Score			
≤90	184/245 (75.1)	201/252 (79.8)	-4.7 (-12.0, 2.7)
≥91	56 /69 (81.2)	56/72 (77.8)	3.4 (-9.9, 16.7)
PORT Risk Class			
I	14/19 (73.7)	12/ 14 (85.7)	-12.0 (-39.0, 15.0)
II	101/ 137 (73.7)	128/159 (80.5)	-6.8 (-16.4, 2.8)
III	69/ 89 (77.5)	61/77 (79.2)	-1.7 (-14.2, 10.9)
IV	53/65 (81.5)	50/65 (76.9)	4.6 (-9.3, 18.5)
V	3/ 4 (75.0)	6/7 (85.7)	-10.7 (-60.4, 39.0)
Baseline gram-positive pathogen			
Yes	37/48 (77.1)	40/53 (75.5)	1.6 (-15.0, 18.2)
No	203/266 (76.3)	217/271 (80.1)	-3.8 (-10.7, 3.2)
Baseline gram-negative pathogen			
Yes	39/49 (79.6)	43/51 (84.3)	-4.7 (-19.8, 10.3)
No	201/265 (75.8)	214/273 (78.4)	-2.5 (-9.6, 4.6)
Oral Switch			
Yes	153/ 166 (92.2)	158/ 168 (94.0)	-1.9 (-7.3, 3.6)
No	87/ 144 (60.4)	99/154 (64.3)	-3.9 (-14.9, 7.1)
Received linezolid/placebo			
Yes	23/30 (76.7)	27/40 (67.5)	9.2 (-11.8, 30.1)
No	217/280 (77.5)	230/282 (81.6)	-4.1 (-10.7, 2.6)
SIRS[c]			
Yes	126/164 (76.8)	144/178 (80.9)	-4.1 (-12.7, 4.6)
No	114/146 (78.1)	113/144 (78.5)	-0.4 (-9.9, 9.1)

Source: Attachment 3.2.2 of CSR
[a] Ceftobiprole minus ceftriaxone with/without linezolid.
[b] 2-sided 95% C.I. is based on the Normal approximation to the difference of the 2 proportions.
[c] Systemic Inflammatory Response Syndrome (SIRS) is defined as the existence of at least two out of the following:
(1) temperature > 38° or < 36°, (2) heart rate > 90/min, (3) respiratory rate > 20 breaths/min or
(4) WBC count > 12000 cells/μL or < 4000 cells/μL (or > 10% band forms).
Abbreviations: Diff, difference; ITT, intent-to-treat; N, number of subjects in treatment arm; n, number of subjects within category; PORT, Pneumonia Outcomes Research Team; PSI, PORT Severity Index; SIRS, systemic inflammatory response syndrome; TOC, test-of-cure

Additional Analyses

A sensitivity analysis was performed removing Dr. Yin-Ching Chuang's site in Taiwan (site id = 886005). This site was identified by the Office of Scientific Investigations (OSI) in a preliminary inspection and there may have been issues with both missing records and subjects not meeting CABP diagnoses. As a result, the Reviewer performed a sensitivity analysis in which 30 subjects from this site were removed. Findings from this analysis showed slightly less favorable results in the primary efficacy analysis results however non-inferiority within a 10% margin would still have been met (Table 38**)**.

Table 38. Analyses of Co-Primary Endpoints in Clinical Outcome at the TOC Visit in the CE and ITT Populations (Removing Dr. Yin-Ching Chuang's Site in Taiwan, Site id 886005), Trial CAP-3001

Categories	Ceftobiprole n (%)	Ceftriaxone n (%)	Diff[b](%)	95% CI[c]
CE Population	N=225	N=224		
Cure	194 (86.2)	196 (87.5)	-1.3	(-7.5, 5.0)
Failure	31 (13.8)	28 (12.5)		
ITT Population[a]	N=301	N=307		
Cure	229 (76.1)	244 (79.5)	-3.4	(-10.0, 3.2)
Failure	72 (23.9)	63 (20.5)		

Source: FDA Reviewer
[a] Subjects were counted as cure in the ITT analysis set only when the subject had a me of cure without effective concomitant therapy, otherwise, the subject was counted as failure.
[b] Ceftobiprole minus ceftriaxone with/without linezolid.
[c] 2-sided 95% CI is based on the Normal approximation to the difference of the 2 proportions.
Abbreviations: CE, clinically evaluable; CI, confidence interval; ITT, intent-to-treat; N, number of subjects in treatment arm; n, number of subjects within category; TOC, test-of-cure

Conclusions

Based on findings from the re-analyses which followed the guidelines of the CABP 2020 Guidance, Trial CAP-3001was considered to provide an adequate level of evidence provided there is support from positive trial findings in the other two indications (SAB and ABSSSI). See Section 6.3.1 for further details on the re-analyses.

There were no other major concerns. Minor concerns related to there being very few subjects from U.S. sites included in the Day 3 mITT population (i.e., 7 subjects in the ceftobiprole arm and 10 in the ceftriaxone arm). In addition, only 3 of these 7 subjects (43%) had an early clinical success compared to 7 of 10 (70%) in the ceftriaxone arm.

6.2.4. Community-Acquired Bacterial Pneumonia, Trial BPR-PIP-002

BPR-PIP-002 was a multicenter, randomized, investigator-blind, active-controlled trial conducted in pediatric subjects ages 3 months to less than 18 years with CABP or HABP requiring hospitalization and treatment with IV antibacterial drugs. The primary objective of this trial was to evaluate the safety of ceftobiprole. The trial was not powered for comparative inferential efficacy analysis, and no efficacy endpoint was identified as primary.

Randomization was stratified by 4 age groups (3 months to <2 years; 2 years to <6 years; 6 years to <12 years; 12 years to <18 years) and by diagnosis of HABP or CABP. Subjects were randomized 2:1 within each group to receive either ceftobiprole or the comparator which was an

IV standard-of-care cephalosporin with optional antibacterial coverage for MRSA (ceftazidime with or without vancomycin for subjects with HABP; ceftriaxone with or without vancomycin for subjects with CABP) for 7-14 days. Subjects were to receive IV antibacterial treatment for at least 3 days but then could be switched to oral antibacterial drugs if clinical improvement criteria for IV to oral switch were met. Ceftobiprole was administered at a dose of 10-20 mg/kg IV every 8 hours, age-adjusted for dose and infusion duration (maximum daily dose was 1500 mg).

Inclusion criteria included:

1. Male or female aged 3 months to <18 years
2. Body weight of ≥5 kg
3. Diagnosis of either CABP or HABP requiring hospitalization and characterized by:
    - Fever (>38.5°C) or hypothermia (<35°C), and
    - Leukocytosis or leukopenia (relevant to subject age and institutional normal ranges)
    - At least two of the following signs or symptoms: cough, lower respiratory tract secretions, auscultatory findings of pneumonia, dyspnea/tachypnea, increased work of breathing (retractions, nasal flaring, or grunting), hypoxemia/oxygen saturation <92% (on room air)
    - Subjects with CAP had to present with ≥1 of the following conditions:
      Admission to an intensive care unit, intermediate care unit, or a unit with the ability to provide constant and close monitoring and care
    - Suspected infection with multi-drug resistant pneumococci or MRSA
    - History of absent or incomplete pneumococcal vaccination (did not receive all vaccinations as per schedule)
    - Recent clinical diagnosis of influenza with exacerbation of fever and respiratory symptoms after initial improvement in the symptoms of acute influenza
    - Failure to clinically improve on initial antibiotic therapy for ≥48 hours and need for antibiotic treatment change
    - Oxygen saturation on room air ≤90%
4. New or progressive imaging findings consistent with bacterial pneumonia (e.g., X-ray, ultrasound, or computed tomography)
5. Requirement for IV antibacterial treatment for pneumonia
6. Sufficient vascular access to receive IV study drug
7. Informed consent from the parent(s) or legally acceptable representative(s) to participate in the study, and child's assent, as appropriate
8. Female subjects who were not pregnant or breast-feeding and met one of the following conditions:
    - Pre-menarchal, or
    - A negative serum or urine pregnancy test and willing to use a highly reliable method of contraception during the study until the last follow-up visit

Exclusion criteria included:

1. Known resistance of the causative pathogen to ceftobiprole or IV standard-of-care cephalosporin treatment (± vancomycin)
2. On mechanical ventilation at the time of Screening for >48 hours
3. Chest trauma with severe lung contusion or flail chest
4. Acute respiratory distress syndrome
5. Empyema or lung abscess
6. Anatomical bronchial obstruction
7. Documented or suspected active or currently treated pulmonary tuberculosis
8. Documented or suspected atypical bacterial pneumonia, or viral pneumonia without bacterial superinfection, or need for antibiotic coverage with a macrolide
9. Known positive result from a rapid diagnostic test for influenza or respiratory syncytial virus, unless bacterial pneumonia secondary to viral respiratory illness is suspected based on a clinical history of exacerbation of fever and respiratory symptoms after initial improvement in the symptoms of an acute respiratory infection
10. Documented or suspected pertussis, chemical pneumonitis (e.g., aspiration of gastric contents, inhalation injury), or cystic fibrosis
11. Severe immunodeficiency (human immunodeficiency virus [HIV] infection, or congenital or acquired immunodeficiency syndrome)
12. Significant laboratory abnormalities (based on local laboratory results) including:
    - Hematocrit <20%
    - Absolute neutrophil count <0.5 x 109/L
    - Platelet count <50 x 10^9/L
    - Alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin >5 x the age-specific upper limit of normal
    - Creatinine clearance of <50 mL/min/1.73 m^2, or requirement for any form of renal dialysis therapy
13. Use of systemic antimicrobial therapy for > 24 hours in the 48 hours before randomization for the current episode of pneumonia. Exception: CAP subjects with failure to clinically improve on initial antibiotic therapy for ≥48 hours and need for antibiotic treatment change (see Inclusion criterion 3).
14. History of a previous clinically relevant hypersensitivity or serious adverse reaction to beta-lactam antibiotics or to vancomycin
15. Poorly controlled seizure disorder (>1 seizure in the month preceding randomization)

The trial comprised the following phases:

- A pre-dosing screening phase of up to 24 hours
- A treatment phase of 7-14 days
- A post-treatment TOC assessment 7–14 days after the EOT visit
- An last follow-up assessment 28–35 days after the last treatment to monitor relapse of pneumonia and safety

The total duration of the study for each subject was to be approximately 5 to 7 weeks.

Reference ID: 5357793

A subject was to be discontinued from study drug if any of the following events occurred:

- No adequate response to the antibiotic treatment within 3 days of treatment
- Need for the use of macrolides concomitant to study drug treatment
- Pregnancy

Additionally, a subject could be discontinued from study drug for the following reasons:

- Adverse event
- Abnormal laboratory value
- Abnormal test procedure result
- Intercurrent illness that prevented or interfered with further administration of treatment
- Death
- Protocol deviation
- Lost to follow-up
- Administrative/logistical reasons

For all subjects who discontinued Trial drug, AE monitoring was to be continued up to and including an last follow-up visit 28–35 days after EOT.

The primary endpoint was analysis of AEs on the first 3 days of Trial treatment, at the EOT, TOC and last follow-up visits, though AEs were assessed for the full study period. Secondary endpoints included clinical response at Day 4 and EOT visits, and clinical cure rates at the TOC and last follow-up visits in the ITT and CE populations, and microbiological eradication rates at the TOC and last follow-up visits. Clinical response was assessed by the blinded investigator at Day 4 and EOT as cured (no signs or symptoms of pneumonia), improved (clinically relevant improvement in signs and symptoms), unchanged (no or minor change from baseline) or worsened (clinically relevant increased in severity of signs and symptoms). Clinical cure was assessed by the blinded investigator at the TOC Visit and defined as signs and symptoms of pneumonia normalized or improved to an extent that further antibiotic therapy was not necessary, and stabilization or improvement of chest X-rays post-baseline if these were available. Pharmacokinetic assessments were also performed.

The Trial population consisted of 138 subjects (94 in the ceftobiprole arm, 44 in the comparator arm), of which 94.7% and 100% respectively, completed Trial treatment. Of the subjects in the ceftobiprole arm, 18 were ages 12 to <18 years old, 27 were 6 to <12 years old, 37 were 2 to <6 years old, and 12 were aged 3 months to <2 years. The majority of subjects (94.2%) had CABP, and only 6 subjects had a pathogen identified at baseline. Subjects with ventilator-associated HABP were excluded from the Trial. The median duration of exposure to IV treatment was similar for the ceftobiprole and comparator arms (6 versus 7 days respectively) as was the median duration of exposure to oral treatment (5 days in each arm).

The clinical response was determined at study Day 4, the EOT visit (7-14 days after randomization), and at the TOC Visit (7-14 days after the EOT visit). The ITT population included all subjects who were randomized.

In the ITT population, the clinical response rates in the ceftobiprole and comparator arms were respectively 95.7% and 93.2% on Day 4 (between-arm difference 2.6% [95% confidence interval CI: 5.5, 14.7]), 96.8% and 100% at the EOT visit (between-arm difference -3.2% [95% CI: -9.1, 5.5]), and 90.4% and 97.7% at the TOC visit (between-arm difference -7.3% [95% CI: -15.7, 3.6]).

Evaluation of safety in Trial BPR-PIP-002 was centered on subjects with CABP as there were only two AEs occurring in 8 subjects with HABP in either treatment arm; neither AE was considered a serious adverse event (SAE).

6.3. Key Efficacy Review Issues

6.3.1. Re-Analysis of Trial CAP-3001

Issue

CAP-3001 was conducted prior to the CABP Guidance of 2020 and was not designed to assess an early clinical success endpoint (Day 4) in an appropriate Trial population (e.g., PORT Risk Class ≥ III) in which a non-inferiority margin could be scientifically justified. Therefore, the Applicant provided several post-hoc re-analyses which considered new analysis populations, endpoints, and selection criteria which closely followed those outlined in the CABP Guidance[4].

Background

Since Trial CAP-3001 was conducted from June 2006 to July 2007, i.e., before the current FDA CABP Guidance for Industry was issued in June 2020, the Applicant included CSR Addendum 2 in this NDA submission. Addendum 2 included additional post-hoc analyses that were performed after completion of the original CSR (dated November 3, 2009). These new analyses shown in the tables below were taken directly from Addendum 2 of the CSR. These analyses were critical in assessing the overall evidence obtained from this Trial and the Trial's ability to meet the current recommendations for CABP trials outlined in the FDA Guidance.

The endpoints and Trial populations specified in the re-analysis were similar to those described in the Guidance. The primary endpoint in Trial CAP-3001 was clinical cure at the TOC visit which clearly differed from the endpoint of clinical success at Day 4 stipulated in the current guidance. Therefore, the re-analyses considered an early clinical response endpoint at Day 3 (prior to IV to oral switch) which resembled the Guidance endpoint at Day 4, as shown in Table 39. There were also differences in the Trial populations of CAP-3001 and the Guidance. The Applicant modified the analysis populations to be more consistent with the FDA Guidance. There were also differences between the original entry criteria of CAP-3001 and those outlined in the Guidance are shown in Table 40**.**

[4] FDA guidance for CABP "Community- Acquired Bacterial Pneumonia: Developing Drugs for Treatment, June 2020" (U.S. Department of Health Human Services) (FDA 2020)

Reference ID: 5357793

Analysis Populations for the Re-analysis

In total, four analysis populations were used for the re-analyses using the primary endpoint stipulated in the 2020 FDA CABP guidance:

- The 'Day 3-ITT population' comprised all randomized subjects who had at least two of the following symptoms at baseline: tachypnea, cough, production of purulent sputum, or chest pain. Subjects were analyzed according to the study medication assigned at randomization.
- The Day 3-modified ITT population comprised the subset of subjects in the Day 3-ITT population who met all of the following additional criteria: 1. At least one of new-onset hypoxemia, rales or pulmonary consolidation, and leukocytosis or leukopenia. 2. At least two of fever, hypothermia, hypotension, tachycardia, and tachypnea.
- The Day 3-mITT population was the subset of the Day 3-ITT subjects who had a valid pathogen at baseline.
- The Day 3-modified mITT population was the subset of the Day 3-modified ITT subjects who had a valid pathogen at baseline.

The Baseline demographic and disease characteristics in the 'Day 3-ITT population' and the 'Day 3-modified ITT population' are shown in Table 39**.**

Primary Efficacy Analysis in Re-analysis

The re-analysis was performed to determine whether ceftobiprole is non-inferior to ceftriaxone ± linezolid for the primary endpoint of clinical success at Day 3. Analysis of the primary endpoint was based on the Day 3-ITT population and the Day 3-modified ITT population.

A two-sided 95% confidence interval using the Normal approximation to the difference of two binomial proportions, was calculated for the between-treatment difference (ceftobiprole minus ceftriaxone ± linezolid) at the TOC Visit.

The result for the primary endpoint of the re-analysis was interpreted in the context of a 12.5% non-inferiority margin, i.e., non-inferiority of ceftobiprole compared with ceftriaxone with or without linezolid was interpreted if the lower limit of this confidence interval was greater than or equal to −12.5%.

The same subgroup analyses were performed for the re-analysis of the primary endpoint in accordance with the 2020 FDA CABP guidance as described for the pre-specified primary endpoint of derived clinical cure at the TOC Visit (CAP-3001 CSR Appendix 2.2.1.1). The exception is the subgroup analysis by oral switch status, as none of the subjects in the Trial had switched to oral therapy at the Day 3 assessment.

Reviewer Comments

The 12.5% NI margin mentioned above was chosen by the Applicant to be wider than the 10% NI margin for the original primary analysis to account for additional variability from having to reduce the size of the analysis populations to be consistent with the guidelines for populations specified in the 2020 CABP Guidance. However, since a NI margin of 10% was satisfied in the re-analyses for early clinical success in the Day 3 ITT and Day 3 mITT populations (as discussed later in this section), this change in the margin did not impact conclusions.

Reference ID: 5357793

Secondary and other efficacy analyses

For all secondary and other analysis included in the re-analysis, a two-sided 95% confidence interval using the Normal approximation to the difference of two binomial proportions was calculated for the between-treatment difference (ceftobiprole minus ceftriaxone ± linezolid). Analyses of the secondary and other endpoints were descriptive with no testing against an interpretative non-inferiority margin.

Table 39. Comparison of the Primary Endpoint Defined in the 2020 FDA CABP Guidance with the Equivalent pre-Specified Endpoint, CAP-3001

2020 FDA CABP guidance primary endpoint[a]	CAP-3001 equivalent endpoint
Clinical success as improvement at Day 4 in at least two (with no worsening) of the following symptoms: 1. Chest pain 2. Cough 3. Amount of productive sputum 4. Difficulty breathing These symptoms are to be scored on a four-point scale as – Absent – Mild – Moderate – Severe	Clinical success as improvement at Day 3 in at least two (with no worsening) of the following symptoms: 1. Pleuritic chest pain 2. Cough 3. Purulent sputum production or respiratory secretion 4. Tachypnea Each of these symptoms was scored on a five-point scale as: – Present – Absent – Worsened – Unchanged – Improved
Improvement is defined as at least a one-point improvement from baseline to the assessment at Day 4 (with no worsening of other symptoms), i.e.: – Severe to moderate (or mild, or absent) – Moderate to mild (or absent) – Mild to absent	Improvement is defined as at least a one-point improvement from baseline to the assessment at Day 3 (with no worsening of other symptoms, including pleuritic chest pain, cough, purulent sputum production or respiratory secretion, tachypnea, but also rigor or shaking chills, hypoxemia, and rales or pulmonary consolidation), i.e.: – Present to absent (considered as resolution) – Improved

CABP = community-acquired bacterial pneumonia; FDA = Food and Drug Administration.

[a] Guidance for Industry. *Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment* U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), June 2020.

Source: CSR Addendum 2, Section 2.3.1
Abbreviations: CABP, community-acquired bacterial pneumonia

Table 40. Clinical, Radiographic, and Microbiologic Entry Criteria in the 2020 FDA CABP Guidance Compared to Inclusion Criteria for Trial CAP-3001

2020 FDA CABP Guidance[1] entry criteria	CAP-3001 inclusion criteria[2]
At least two of the following symptoms: – Difficulty breathing – Cough – Production of purulent sputum – Chest pain	**At least two of the following criteria:** – **Dyspnea or tachypnea** – **Cough (new or increased over usual state)** – **Production of purulent sputum** – Note: pleuritic chest pain was assessed but not used as an entry criterion
At least two vital sign abnormalities: – Fever – Hypothermia – Hypotension – Tachycardia – Tachypnea	– **Fever or hypothermia or leukocytosis/leukopenia** – Note: hypotension and/or tachycardia were assessed through vital signs but not used as an entry criterion – See above (Dyspnea or tachypnea)
At least one finding of other clinical signs/laboratory abnormalities: – Hypoxemia – Clinical evidence of pulmonary consolidation – An elevated total white blood cell count or leukopenia	– **New-onset hypoxemia on room air** – **Auscultatory rales or pulmonary consolidation** – See above: Fever or hypothermia or leukocytosis/leukopenia
Radiographic evidence	X-ray: New radiographic infiltrates (not related to another disease) consistent with the diagnosis of bacterial pneumonia
Appropriate microbiological sample	Respiratory culture and Gram stain was to be obtained at screening, and to be repeated within 24 hours if an inadequate specimen was obtained.
2020 CABP Draft Guidance[1] exclusion criteria	**CAP-3001 exclusion criteria[2]**
– Aspiration pneumonia – Hospital-acquired bacterial pneumonia or ventilator-associated bacterial pneumonia – Patients with known bronchial obstruction or a history of post-obstructive pneumonia (this criterion does not exclude patients who have chronic obstructive pulmonary disease) – Patients with primary or metastatic lung cancer – Patients with cystic fibrosis, known or suspected *Pneumocystis jiroveci* pneumonia, or known or suspected active tuberculosis	– Suspected or known pneumonia due to aspiration – HABP or VABP patients were not included – Known bronchial obstruction or a history of post-obstructive pneumonia (patients with asthma or chronic obstructive pulmonary disease were not excluded provided they met the criteria of acute new-onset pneumonia) – Primary lung cancer or another malignancy to the lungs unless surgically resected – Cystic fibrosis, lung abscess, … active tuberculosis, suspected or known pneumonia due to atypical bacteria…, or *Pneumocystis jiroveci* (carinii)

CABP = community-acquired bacterial pneumonia; HABP = hospital-acquired bacterial pneumonia; VABP = ventilator-acquired bacterial pneumonia.

1 Guidance for Industry. *Community-Acquired Bacterial Pneumonia: Developing Drugs for Treatment* U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), June 2020.

2 **CAP-3001 CSR, Section 3.2.3**

Source: CSR Addendum 2, Section 2.2
Abbreviations: CABP, community-acquired bacterial pneumonia; HABP, hospital-acquired bacterial pneumonia; VABP, ventilator-associated bacterial pneumonia

Approximately 97% (618/638) of CAP-3001 ITT subjects had at least two of the following symptoms at baseline: difficulty breathing, cough, production of purulent sputum, or chest pain; this was required to assess the 2020 FDA CABP guidance primary endpoint of early clinical success. For the purposes of the re-analysis against the current guidance, the Applicant defined this group of 618 subjects as the 'Day 3-ITT population,' and used this as the ITT population for the re-analyses of both the current guidance primary and secondary efficacy endpoints. In addition, a second 'Day 3-modified ITT population' was used for the re-analyses of primary and secondary efficacy endpoints stipulated in the 2020 FDA CABP guidance; this population very closely matched the 2020 FDA CABP guidance in terms of entry criteria, and includes 187 subjects (97 treated with ceftobiprole and 90 with the comparator), who met all of the following criteria:

- A baseline PORT classification of PORT Risk Class ≥ III
- At least two of tachypnea (as surrogate for "difficulty breathing"), cough, production of purulent sputum, and pleuritic chest pain
- At least two of fever, hypothermia, hypotension, tachycardia, and tachypnea
- At least one of new-onset hypoxemia, rales or pulmonary consolidation, and leukocytosis or leukopenia
- New radiographic infiltrates (not related to another disease process) consistent with the diagnosis of bacterial pneumonia

Assessment

Baseline Demographic and Disease Characteristics

Baseline demographic and disease characteristics for Day 3 ITT population and Day 3-modified ITT are shown in Table 41. In the Day 3 ITT population, the median age was 56 years, 62% of subjects were White, 66% were not Hispanic or Latino, 87% were from ex-U.S. sites, 29% had a valid pathogen at baseline, 22% of subjects had PORT Risk Class ≥ IV and 31% had SIRS at baseline. Compared to the Day 3 ITT population, the Day 3-modified ITT included older subjects (median age of 67 versus 56 years) and a greater percentage of subjects with PORT Risk Class ≥ IV (50% vs. 22%) or SIRS (65% vs. 31%). This would be expected given that the Day 3-modified ITT population excluded a large number of lower risk subjects with PORT Risk Classes of I and II (i.e., approximately 51% of the Day 3 ITT population).

In general, there were no major imbalances between the treatment arms in either of these populations which would raise serious concerns. However, in the Day 3-modified ITT population, a slightly lower percentage of subjects with PORT Risk Class ≥ IV observed in the ceftobiprole arm (45% versus 54%).

Reference ID: 5357793

Table 41. Baseline Demographic and Disease Characteristics (Prespecified ITT Population and re-Analysis Day 3-Modified ITT Population), CAP-3001

	Day 3 ITT population			Day 3-modified ITT population		
	Ceftobiprole (N = 307)	Ceftriaxone* (N = 311)	Total (N = 618)	Ceftobiprole (N = 97)	Ceftriaxone* (N = 90)	Total (N = 187)
Median age (years), (range)	56.0 (18–90)	55.0 (18–94)	56.0 (18–94)	65.0 (21–86)	71.0 (24–89)	67.0 (21–89)
Gender, n (%)						
Female	133 (43.3)	132 (42.4)	265 (42.9)	37 (38.1)	32 (35.6)	69 (36.9)
Male	174 (56.7)	179 (57.6)	353 (57.1)	60 (61.9)	58 (64.4)	118 (63.1)
Race, n (%)						
White	189 (61.6)	194 (62.4)	383 (62.0)	69 (71.1)	65 (72.2)	134 (71.7)
Black.	18 (5.9)	17 (5.5)	35 (5.7)	2 (2.1)	3 (3.3)	5 (2.7)
Asian	66 (21.5)	70 (22.5)	136 (22.0)	11 (11.3)	12 (13.3)	23 (12.3)
Other[a]	34 (11.1)	30 (9.6)	64 (10.4)	15 (15.5)	10 (11.1)	25 (13.4)
Ethnicity, n (%)						
Hispanic or Latino ethnicity	72 (23.5)	81 (26.0)	153 (24.8)	33 (34.0)	32 (35.6)	65 (34.8)
Not Hispanic or Latino	235 (76.5)	228 (73.3)	463 (74.9)	64 (66.0)	57 (63.3)	121 (64.7)
Geographic regions, n (%)						
USA	40 (13.0)	39 (12.5)	79 (12.8)	7 (7.2)	10 (11.2)	17 (9.1)
Europe[b]	129 (42.0)	126 (40.5)	255 (41.3)	43 (44.3)	36 (40.0)	79 (42.2)
Other[c]	138 (45.0)	146 (46.9)	284 (46.0)	47 (48.5)	44 (48.9)	91 (48.7)
Patients with any valid baseline pathogen, n (%)	85 (27.7)	96 (30.9)	181 (29.3)	32 (33.0)	27 (30.0)	59 (31.6)
Gram-positive pathogen	46 (15.0)	52 (16.7)	98 (15.9)	18 (18.6)	14 (15.6)	32 (17.1)
Gram-negative pathogen	49 (16.0)	51 (16.4)	100 (16.2)	19 (19.6)	14 (15.6)	33 (17.6)
Monomicrobial	69 (22.5)	88 (28.3)	157 (25.4)	25 (25.8)	26 (28.9)	51 (27.3)
Polymicrobial	16 (5.2)	8 (2.6)	24 (3.9)	7 (7.2)	1 (1.1)	8 (4.3)
PORT classification[d], n (%)						
≤ III	238 (77.5)	241 (77.5)	479 (77.5)	53 (54.6)	41 (45.6)	94 (50.3)
≥ IV	69 (22.5)	69 (22.2)	138 (22.3)	44 (45.4)	49 (54.4)	93 (49.7)
PORT classification, n (%)						
I	18 (5.9)	14 (4.5)	32 (5.2)	0 (0.0)	0 (0.0)	0 (0.0)
II	133 (43.3)	152 (48.9)	285 (46.1)	0 (0.0)	0 (0.0)	0 (0.0)
III	87 (28.3)	75 (24.1)	162 (26.2)	53 (54.6)	41 (45.6)	94 (50.3)
IV	65 (21.2)	62 (19.9)	127 (20.6)	41 (42.3)	43 (47.8)	84 (44.9)
V	4 (1.3)	7 (2.3)	11 (1.8)	3 (3.1)	6 (6.7)	9 (4.8)
Missing	0	1 (0.3)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
Received linezolid/placebo (%)[e]	26 (8.5)	36 (11.6)	62 (10.0)	7 (7.2)	13 (14.4)	20 (10.7)
From baseline	26 (8.5)	31 (10.0)	57 (9.2)	7 (7.2)	11 (12.2)	18 (9.6)

	Day 3 ITT population			Day 3-modified ITT population		
	Ceftobiprole (N = 307)	Ceftriaxone* (N = 311)	Total (N = 618)	Ceftobiprole (N = 97)	Ceftriaxone* (N = 90)	Total (N = 187)
Started after baseline	0 (0.0)	5 (1.6)	5 (0.8)	0 (0.0)	2 (2.2)	2 (1.1)
Had SIRS n (%)	162 (52.8)	170 (54.7)	332 (53.7)	70 (72.2)	52 (57.8)	122 (65.2)
Prior antibiotic therapy n (%)[f]	180 (58.6)	190 (61.1)	370 (59.9)	57 (58.8)	58 (64.4)	115 (61.5)
Switch to oral medication n (%)	NA	NA	NA	NA	NA	102 (54.5)

Source: CAP-3001 CSR Addendum 2, Post-text Table 1.1. and Table 1.2
ITT = Intent-to-Treat; NA: not applicable; PORT = Pneumonia Outcomes Research Team; PSI = Pneumonia Severity Index; SIRS = systemic inflammatory response syndrome.
* With or without linezolid.
[a] Includes Hispanic and mixed race patients.
[b] Czech Republic, Germany, Hungary, Lithuania, Poland, Russia, Ukraine.
[c] Argentina, Brazil, Costa Rica, Hong Kong, Mexico, Panama, People's Republic of China, Republic of Korea, Taiwan.
[d] PSI score ≤ 90 corresponds to PORT classifications I, II, III; PSI score ≥ 91 corresponds to PORT classifications IV, V.
[e] Up to and including Day 3.
[f] Refers to any prior antibiotic used within 30 days prior to first dose.

Source: CSR Addendum 2, Table 1
Abbreviations: ITT, intent-to-treat; N, number of subjects in treatment arm; n, number of subjects within category; NA, not applicable; PORT, Pneumonia Outcomes Research Team; SIRS, systemic inflammatory response syndrome

Main Efficacy Results

The main efficacy results of the Applicant's re-analysis are presented in Table 42,. For the clinical success at Day 3 endpoint in the Day 3 ITT population, success rates were 71.0% (ceftobiprole) versus 71.1% (ceftriaxone), a treatment difference (ceftobiprole – ceftriaxone) of -0.1% (95% CI: -7.2, 7.1). For the clinical success at Day 3 endpoint in the Day 3 modified-ITT population, success rates were 71.1% (ceftobiprole) versus 67% (ceftriaxone), a treatment difference (ceftobiprole – ceftriaxone) of 4.5% (95% CI: -8.8, 17.7). Treatment differences in these analyses were more favorable than those in the originally specified primary analysis of clinical cure rates at TOC (Table 42). These findings appeared to be consistent with the finding of non-inferiority within a 10% NI margin observed in the original primary analysis.

Findings for other efficacy endpoints also tended to be comparable between the treatment arms and generally consistent with non-inferiority. A notable finding was that in the Day 3-modified ITT population, the 28-day ACM rate was observed to be substantially lower in the ceftobiprole arm (2.1%) compared to the ceftriaxone arm (7.8%) with a treatment difference of -5.7% (95% CI: -11.9, 0.5) which approached nominal significance in favor of the ceftobiprole arm.

Reference ID: 5357793

Table 42. (Re-Analysis): Results in Accordance With the 2020 FDA CABP, CAP-3001

	Ceftobiprole n/N (%)	Ceftriaxone* N (%)	Difference† (95% CI)
Efficacy analyses (Day 3-ITT population)			
Clinical success at Day 3	218/307 (71.0)	221/311 (71.1)	−0.1% (−7.2, 7.1)
28-day all-cause mortality	5/307 (1.6)	8/311 (2.6)	−0.9% (−3.2, 1.3)
Clinical success at Day 3 and improvement in vital signs	178/307 (58.0)	177/311 (56.9)	1.1% (−6.7, 8.9)
Clinical cure or improvement at EOT‡	255/307 (83.1)	264/311 (84.9)	−1.8% (−7.6, 4.0)
Clinical cure at TOC	235/307 (76.5)	249/311 (80.1)	−3.5 (−10.0, 3.0)
Efficacy analyses (Day 3-modified ITT population)			
Clinical success at Day 3	69/97 (71.1)	60/90 (66.7)	4.5% (−8.8; 17.7)
28-day all-cause mortality	2/97 (2.1)	7/90 (7.8)	−5.7% (−11.9; 0.5)
Clinical success at Day 3 and improvement in vital signs	45/97 (46.4)	47/90 (52.2)	−5.8% (−20.1; 8.5)
Clinical cure or improvement at EOT‡	83/97 (85.6)	74/90 (82.2)	3.3% (−7.2; 13.9)
Clinical cure at TOC	77/97 (79.4)	70/90 (77.8)	1.6 (−10.2, 13.4)

Source: **CAP-3001 CSR Addendum 2, Post-text Table 2.1 and Table 2.2**
n = number of patients with respective outcome; N = total number of patients in the respective category.
CE = Clinically evaluable; CI = confidence interval; EOT = End-of-treatment, ITT = Intent-to-Treat.
* With or without linezolid.
† Difference of ceftobiprole minus ceftriaxone with or without linezolid. The two-sided 95% CI was based on the Normal approximation to the difference of the two proportions.
‡ Based on investigator assessment.

Source: CSR Addendum 2, Table 2
Abbreviations: CABP, community-acquired bacterial pneumonia; CI, confidence interval; EOT, end of treatment; ITT, intent-to-treat; N, number of subjects in treatment arm; n, number of subjects within category ;TOC, test-of-cure

Subgroup Analysis Results

As shown in Table 43, analyses of subgroups in the re-analysis were limited due to the reduced sample size, especially in the Day 3-modified ITT population. There were no nominally significant comparisons observed in the subgroup analyses conducted in the Day 3-modified ITT population. However, there were some notable findings in this population. For example, ceftobiprole tended to have greater efficacy in more severe cases of CABP. For example, in subjects with PORT classes of ≥ IV, response rates at Day 3 were 77.3% (ceftobiprole) versus 61.2% (ceftriaxone) whereas comparisons among subjects with PORT classes of III were 66.2% versus 73.0%, respectively. Subgroup comparisons also favored the ceftobiprole arm in subjects with gram-positive pathogens at baseline (13/18 (72.2%) versus 6/14 (42.9%) with pronounced differences also observed for the Day 3 ITT population.

A more detailed comparison of clinical efficacy in subjects with gram-positive and gram-negative causative pathogens is shown in Table 44**.** Clinical success rate in infections due to *Streptococcus pneumoniae*, the most commonly isolated pathogen, was higher in the ceftobiprole as compared to ceftriaxone group, 27/33 (81.8%) versus 27/41 (65.9%), respectively. Among gram-negative pathogens, *E. coli*, *K. pneumonia*, *H. influenzae*, and *H. parainfluenzae* occurred in sufficient numbers of subjects across the treatment arms and will be included in the indication for CABP in labeling.

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Table 43. CAP-3001: Subgroup Analyses of the re-Analysis Primary Endpoint in Accordance With the 2020 FDA CABP Guidance (Day 3-ITT and Day 3 Modified ITT Population)

Subgroup	Ceftobiprole n/N (%)	Ceftriaxone* n/N (%)	Forest plot	Difference (95% CI)[a]
All Day 3 ITT	218/307 (71.0)	221/311 (71.1)		−0.1 (−7.2, 7.1)
Age group 1				
<65 yr	137/199 (68.8)	137/189 (72.5)		−3.6 (−12.7, 5.4)
≥65yr	81/108 (75.0)	84/122 (68.9)		6.1 (−5.4, 17.7)
Age group 2				
<75 yr	177/254 (69.7)	180/252 (71.4)		−1.7 (−9.7, 6.2)
≥75yr	41/53 (77.4)	41/59 (69.5)		7.9 (−8.4, 24.1)
Gender				
Male	121/174 (69.5)	126/179 (70.4)		−0.9 (−10.4, 8.7)
Female	97/133 (72.9)	95/132 (72.0)		1.0 (−9.8, 11.7)
Race				
White	131/189 (69.3)	135/194 (69.6)		−0.3 (−9.5, 9.0)
Black[b]	12/18 (66.7)	15/17 (88.2)		−21.6 (−48.2, 5.1)
Asian	45/66 (68.2)	46/70 (65.7)		2.5 (−13.3, 18.3)
Other[c]	30/34 (88.2)	25/30 (83.3)		4.9 (−12.3, 22.1)
Region 1				
U.S.	28/40 (70.0)	26/39 (66.7)		3.3 (−17.2, 23.8)
Europe[d]	85/129 (65.9)	88/126 (69.8)		−3.9 (−15.4, 7.5)
Other	105/138 (76.1)	107/146 (73.3)		2.8 (−7.3, 12.9)
Region 2				
U.S.	28/40 (70.0)	26/39 (66.7)		3.3 (−17.2, 23.8)
Non-U.S.	190/267 (71.2)	195/272 (71.7)		−0.5 (−8.2, 7.1)
PORT classification[e]				
≤III	164/238 (68.9)	178/242 (73.6)		−4.6 (−12.7, 3.4)
≥IV	54/69 (78.3)	43/69 (62.3)		15.9 (0.9, 31.0)
Gram-positive pathogen[f]				
Yes	36/46 (78.3)	35/52 (67.3)		11.0 (−6.5, 28.4)
No	182/261 (69.7)	186/259 (71.8)		−2.1 (−9.9, 5.7)
Gram-negative pathogen[f]				
Yes	35/49 (71.4)	40/51 (78.4)		−7.0 (−24.0, 10.0)
No	183/258 (70.9)	181/260 (69.6)		1.3 (−6.6, 9.2)
Received linezolid/placebo[h]				
Yes	17/26 (65.4)	20/36 (55.6)		9.8 (−14.6, 34.3)
No	201/281 (71.5)	201/275 (73.1)		−1.6 (−9.0, 5.9)
SIRS[i]				
Yes	109/162 (67.3)	116/170 (68.2)		−1.0 (−11.0, 9.1)
No	109/141 (77.3)	105/140 (75.0)		2.3 (−7.7, 12.3)
Bacteremia[g]				
Yes	7/10 (70.0)	10/17 (58.8)		11.2 (−25.6, 48.0)
No	211/297 (71.0)	211/294 (71.8)		−0.7 (−8.0, 6.6)
Dose reduction				
Yes	25/34 (73.5)	28/38 (73.7)		−0.2 (−20.5, 20.2)
No	193/273 (70.7)	193/273 (70.7)		0.0 (−7.6, 7.6)

-50 -40 -30 -20 -10 0 10 20 30 40 50
Favors comparator Favors ceftobiprole

Subgroup	Ceftobiprole n/N (%)	Ceftriaxone* n/N (%)	Forest plot	Difference (95% CI)[a]
All Day 3 modified ITT	69/97 (71.1)	60/90 (66.7)		4.5 (−8.8, 17.7)
Age group 1				
<65 yr	35/48 (72.9)	21/31 (67.7)		5.2 (−15.5, 25.9)
≥65yr	34/49 (69.4)	39/59 (66.1)		3.3 (−14.4, 21.0)
Age group 2				
<75 yr	51/71 (71.8)	38/59 (64.4)		7.4 (−8.7, 23.5)
≥75yr	18/26 (69.2)	22/31 (71.0)		−1.7 (−25.6, 22.1)
Gender				
Male	40/60 (66.7)	39/58 (67.2)		−0.6 (−17.6, 16.4)
Female	29/37 (78.4)	21/32 (65.6)		12.8 (−8.4, 33.9)
Race				
White	47/69 (68.1)	43/65 (66.2)		2.0 (−14.0, 17.9)
Black[b]	2/2 (100.0)	3/3 (100.0)		NA
Asian	8/11 (72.7)	7/12 (58.3)		14.4 (−24.0, 52.7)
Other[c]	12/15 (80.0)	7/10 (70.0)		10.0 (−24.9, 44.9)
Region 1				
U.S.	3/7 (42.9)	7/10 (70.0)		−27.1 (−73.5, 19.2)
Europe[d]	30/43 (69.8)	24/36 (66.7)		3.1 (−17.5, 23.7)
Other	36/47 (76.6)	29/44 (65.9)		10.7 (−7.8, 29.2)
Region 2				
U.S.	3/7 (42.9)	7/10 (70.0)		−27.1 (−73.5, 19.2)
Non-U.S.	66/90 (73.3)	53/80 (66.3)		7.1 (−6.7, 20.9)
PORT classification[e]				
III	35/53 (66.0)	30/41 (73.2)		−7.1 (−25.7, 11.5)
≥IV	34/44 (77.3)	30/49 (61.2)		16.0 (−2.4, 34.5)
Gram-positive pathogen[f]				
Yes	13/18 (72.2)	6/14 (42.9)		29.4 (−3.8, 62.5)
No	56/79 (70.9)	54/76 (71.1)		−0.2 (−14.5, 14.1)
Gram-negative pathogen[f]				
Yes	13/19 (68.4)	11/14 (78.6)		−10.2 (−40.1, 19.8)
No	56/78 (71.8)	49/76 (64.5)		7.3 (−7.4, 22.0)
Received linezolid/placebo[h]				
Yes	4/7 (57.1)	7/13 (53.8)		3.3 (−42.3, 48.9)
No	65/90 (72.2)	53/77 (68.8)		3.4 (−10.5, 17.3)
SIRS[i]				
Yes	52/70 (74.3)	33/52 (63.5)		10.8 (−5.8, 27.4)
No	17/27 (63.0)	27/38 (71.1)		−8.1 (−31.3, 15.1)
Bacteremia[g]				
Yes	4/6 (66.7)	2/6 (33.3)		33.3 (−20.0, 86.7)
No	65/91 (71.4)	58/84 (69.0)		2.4 (−11.2, 15.9)
Dose reduction				
Yes	9/14 (64.3)	14/19 (73.7)		−9.4 (−41.4, 22.6)
No	60/83 (72.3)	46/71 (64.8)		7.5 (−7.2, 22.2)

-60 -50 -40 -30 -20 -10 0 10 20 30 40 50 60
Favors comparator Favors ceftobiprole

Source: **CAP-3001 CSR Addendum 2, Post-text Table 3.**

n = number of patients with response; N = total number of patients in the respective category.

* With or without linezolid.

[a] Ceftobiprole minus ceftriaxone ± linezolid; the 95% confidence interval (CI) is based on the Normal approximation to the difference of the two proportions. [b] Includes African American. [c] Includes Hispanic and mixed-race patients. [d] Czech Republic, Germany, Hungary, Lithuania, Poland, Russia, Ukraine. [e] Argentina, Brazil, Costa Rica, Hong Kong, Mexico, Panama, China, South Korea, Taiwan. [f] PORT ≤ III corresponds to a Pneumonia Severity Index (PSI) score ≤ 90; PORT ≥ IV corresponds to a PSI score ≥ 90 (two patients in the comparator group had a missing PORT classification). [g] At baseline. [h] Up to and including Day 3. [i] Systemic Inflammatory Response syndrome (SIRS) was defined as the presence of at least two of the following: (1) temperature > 38 °C or < 36 °C, (2) heart rate > 90 beats per minute, (3) respiratory rate > 20 breaths per minute, (4) White blood cell count > 12.0×10^9/L or < 4.0×10^9/L (or > 10% band forms).

Source: CSR Addendum 2, Table 3

Abbreviations: CABP, community-acquired bacterial pneumonia; ITT, intent-to-treat; N, number of subjects in treatment arm; n, number of subjects within category; PORT, Pneumonia Outcomes Research Team; SIRS, systemic inflammatory response syndrome

Table 44. (Re-Analysis): Clinical Success at Day 3 by Causative Pathogen in Accordance With the 2020 FDA CABP Guidance, CAP-3001

	Clinical success at Day 3 (Day 3-mITT)		Clinical success at Day 3 (Day 3-modified mITT)	
Pathogen	**Ceftobiprole (N = 85) n/N (%)**	**Ceftriaxone* (N = 96) n/N (%)**	**Ceftobiprole (N = 32) n/N (%)**	**Ceftriaxone* (N = 27) n/N (%)**
Any Gram-positive	**36/46 (78.3)**	**35/52 (67.3)**	**13/18 (72.2)**	**6/14 (42.9)**
Streptococcus pneumoniae	27/33 (81.8)	27/41 (65.9)	11/14 (78.6)	4/9 (44.4)
Staphylococcus aureus	10/14 (71.4)	7/10 (70.0)	3/4 (75.0)	1/4 (25.0)
MRSA	2/2 (100.0)	0/0 (NA)	0/0 (NA)	0/0 (NA)
MSSA	8/12 (66.7)	7/10 (70.0)	3/4 (75.0)	1/4 (25.0)
Any Gram-negative	**35/49 (71.4)**	**40/51 (78.4)**	**13/19 (68.4)**	**11/14 (78.6)**
Enterobacterales	14/18 (77.8)	13/16 (81.3)	5/7 (71.4)	6/7 (85.7)
Enterobacter cloacae	0/1 (0.0)	3/3 (100.0)	0/1 (0.0)	2/2 (100.0)
Escherichia coli	6/6 (100.0)	2/4 (50.0)	2/2 (100.0)	1/2 (50.0)
Klebsiella pneumoniae	7/8 (87.5)	7/8 (87.5)	2/3 (66.7)	2/2 (100.0)
Haemophilus influenzae	4/10 (40.0)	11/16 (68.8)	2/3 (66.7)	3/5 (60.0)
Haemophilus parainfluenzae	8/9 (88.9)	8/8 (100.0)	2/2 (100.0)	1/1 (100.0)
Moraxella catarrhalis	2/4 (50.0)	4/5 (80.0)	1/3 (33.3)	1/1 (100.0)
Pseudomonas aeruginosa	2/2 (100.0)	3/4 (75.0)	1/1 (100.0)	0/0 (NA)
Acinetobacter baumannii	2/3 (66.7)	1/1 (100.0)	1/2 (50.0)	0/0 (NA)

Source: **CSR Addendum 2, Post-text Table 6.**
n = number of patients with a response; N = total number of patients in the respective category.
mITT = microbiological Intent-to-Treat; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *Staphylococcus aureus*.
* Ceftriaxone with or without linezolid.

Source: CSR Addendum 2, Table 5
Abbreviations: CABP, community-acquired bacterial pneumonia; mITT, modified intent-to-treat; MRSA, methicillin-*resistant S. aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; N, number of subjects in treatment arm; n, number of subjects within category

Conclusions

Trial CAP-3001, as originally designed, met its primary objective. When reviewing this Trial under current FDA guidance recommendations, Trial CAP-3001 was considered to have major limitations. However, although the re-analysis was conducted in a post-hoc manner and involved limited sample sizes, findings appeared to be consistent with the assumption of non-inferiority. Findings in the re-analysis showed that treatment differences tended to favor ceftobiprole when considering an earlier time point (i.e., Day 3) as well as a population that excluded subjects with PORT Risk Classes of 1 or 2 (i.e., Day 3 mITT). Positive findings for the CAP-3001 Trial are considered adequate as evidence of effectiveness for the CABP indication provided they are supported by positive findings for the studies of the SAB and ABSSSI indications.

Reference ID: 5357793

6.3.2. Clinical Success in Ukrainian Versus Non-Ukrainian Sites in Trial BPR-CS-009

Issue

In Trial BPR-CS-009, it was observed that sites in Ukraine showed substantially higher overall success rates compared to sites in other countries. Due to large site-specific efficacy and fewer AEs, these sites were identified for inspection but could not be inspected due to the current travel restrictions to Ukraine. Thus, in addition to clinical site inspections, an Applicant inspection was also conducted (see Section 10 for details), and higher overall success in Ukraine was evaluated in further detail.

Background

There may be limitations with generalizing Trial findings across different geographical regions. Overall response rates in non-Ukrainian countries may be lower than rates observed in the Trial BPR-CS-009, which included Ukrainian sites with high response rates. Ukraine was also the highest-enrolling country in the Trial, with 46.5% of subjects (180/387) in the mITT population. This may also have implications for the assumptions used in justifying the non-inferiority margin since the subject populations of Ukraine may not be appropriate for inclusion due to inherently lower risk factors and more effective therapeutic interventions compared to those of the assumed study population.

Based on post-hoc analyses, subjects enrolled in Ukraine were younger and had a more favorable distribution of Baseline categories for complicated SAB, e.g., the percentage of subjects on chronic dialysis was 0.6% (1/180) in Ukraine compared to 23.2% (48/207) in other countries, and there were no subjects with LIE from Ukraine vs 4.8% (10/207) in other countries. Therapeutic interventions with the potential for achieving source control for SAB were performed more often within 72 hours before, or within 7 days after, randomization, in subjects from Ukraine than in other countries, e.g., in 70.5% for abdominal abscesses in Ukraine compared to 9.1% in abdominal abscesses in other countries, and in 67.9% (74/109) in ABSSSIs/soft tissue infections in Ukraine compared to 30.5% (30/128) in other countries. (Table 45).

Reference ID: 5357793

Assessment

Significantly higher overall success rates based on DRC at the PTE visit were observed in Ukraine (86.7%, 156/180 across treatment arms) versus other countries excluding Ukraine (54.1%. 112/207 across treatment arm). The rate difference (Ukraine – non-Ukraine) was highly significant at 86.7% versus 54.1%, difference favoring Ukraine by 32.6% (95% CI: 23.9, 40.8), $p<0.0001$.

As shown in Table 45, treatment comparisons of overall success rates based on DRC assessment at PTE were 74/88 (84.1%) vs. 82/92 (89.1%) in Ukraine versus 58/101 (57.4%) versus 54/106 (50.9%) in other countries (excluding Ukraine). Since comparisons in Ukraine were less favorable for the ceftobiprole arm, the inclusion of Ukrainian sites likely did not positively influence the overall finding of non-inferiority.

Conclusion

As noted above, concerns were lessened since the between-arm difference was not more favorable in Ukraine versus the other countries. However, real life comparisons of rates may be lower than what was observed in this Trial due to the high rates observed in Ukraine, therefore comparisons of rates in the potential labeling should describe the strong differences in overall success rates between Ukrainian and non-Ukrainian sites.

Reference ID: 5357793

Table 45. Overview of the Distribution of Categories of Both Complicated and Potential *Staphylococcus aureus* Bacteremia Source Control Between Ukraine and Other Countries

Attachment 6 Analyses in patients from Ukraine and other countries

Attachment Table 6-1 Overview of the distribution of categories of complicated SAB and potential SAB source control between Ukraine and other countries

Category of complicated SAB	Prevalence of cSAB categories in Ukraine vs other countries			Prevalence of potential SAB source control in Ukraine vs other countries		
	Ukraine n/N (%)	Other n/N (%)	Difference % (UKR−Other)	Ukraine n/N (%)	Other n/N (%)	Difference % (UKR−Other)
Complicated SAB overall	180/180 (100.0)	207/207 (100.0)	NA			
Chronic dialysis	1/180 (0.6)	48/207 (23.2)	−22.6	0/1 (0.0)	4/48 (8.3)	−8.3
Persistent SAB	5/180 (2.8)	27/207 (13.0)	−10.3	0/5 (0.0)	0/27 (0.0)	0.0
Septic or suppurative thrombophlebitis	0/180 (0.0)	14/207 (6.8)	−6.8	0/0 (NA)	0/14 (0.0)	NA
Septic PEI	1/180 (0.6)	14/207 (6.8)	−6.2	0/1 (0.0)	0/14 (0.0)	0.0
LIE	0/180 (0.0)	8/207 (3.9)	−3.9	0/0 (NA)	0/8 (0.0)	NA
ABSSSI	109/180 (60.6)	128/207 (61.8)	−1.3	74/109 (67.9)	39/128 (30.5)	37.4
Other metastatic infection of native tissue	5/180 (2.8)	8/207 (3.9)	−1.1	2/5 (40.0)	0/8 (0.0)	40.0
Other	0/180 (0.0)	2/207 (1.0)	−1.0	0/0 (NA)	0/2 (0.0)	NA
Epidural/cerebral abscess	3/180 (1.7)	5/207 (2.4)	−0.7	0/3	0/5 (0.0)	0.0
Osteomyelitis	15/180 (8.3)	157207 (7.2)	1.1	6/15 (40.0)	3/15 (20.0)	20.0
Definite RIE	13/180 (7.2)	12/207 (5.8)	1.4	0/13 (0.0)	0/12 (0.0)	0.0
Thoracic abscess	12/180 (6.7)	5/207 (2.4)	4.3	6/12 (50.0)	2/5 (40.0)	10.0
Septic arthritis	30/180 (16.7)	11/207 (5.3)	11.4	22/30 (73.3)	4/11 (36.4)	37.0
Intraabdominal abscess	44/180 (24.4)	11/207 (5.3)	19.1	31/44 (70.5)	1/11 (9.1)	61.4

ABSSSI = acute skin and skin structure infections; LIE = left-sided infective endocarditis; NA = not applicable; PEI = pulmonary embolism/infarction; RIE = right-sided infective endocarditis; SAB = *Staphylococcus aureus* bacteremia, UKR = Ukraine.
The medical review to determine interventions suggestive of potential source control was performed separately for each category of complicated SAB. For example, removal of dialysis catheters were considered potential measures of source control for chronic dialysis, abscess drainage for abdominal abscesses, debridement, amputation or drainage for ABSSSI or osteoarticular infections.
Source: Table 14.4.2.5

Source: CSR Table 14.4.2.5
Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; LEI, left sided infective endocarditis; PEI, pulmonary embolism/infraction; RIE, right sided infective endocarditis; SAB, *Staphylococcus aureus* Bacteremia

7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

The nonclinical safety profile of ceftobiprole medocaril sodium has been explored in single and repeat-dose studies in mice, rats, dogs, rabbits and monkeys for up to 3 months duration; in vitro and in vivo genotoxicity studies; reproductive and developmental toxicity studies including fertility studies in male and female rats, embryofetal developmental studies in rats and monkeys, and pre- and post-natal developmental toxicity study in rats; and PK and toxicokinetic studies to support ceftobiprole medocaril sodium development and to compare PK in animals and humans. The target organs of toxicity that may be relevant to human risks are described below.

Injection Site Reactions, Thrombi, Emboli, Convulsions, Mortality

Thrombi formation at the injection site was a consistent finding in toxicological studies across species, including rats, marmosets and dogs with severity increasing with dosing duration. In 2-4- and 13-week studies in rats, marmosets, and dogs, injection site findings included thrombus formation, accumulation of inflammatory cells, thickening of the vascular wall in the periphery of the dosing catheter, granulomas, edema/hemorrhage and/or necrosis of tissues around the catheter. No other significant toxicities were observed in 2-week studies in rats and in 4-week studies in rats and marmosets administered ceftobiprole medocaril sodium (at doses up to 360 mg/kg/day (1.4-times the maximum recommended human dose [MRHD] based on body surface area [BSA] comparisons) and 200 mg/kg/day respectively, (0.75 times the MRHD, based on BSA comparisons). However, in the 13-week studies in the rats and marmosets at similar doses to those used in shorter term studies, convulsions and mortality were observed (≥50 mg/kg in marmosets, 0.2 times the MRHD; ≥250 mg/kg in rats, 0.94 times the MRHD, based on BSA comparisons). Thrombi/emboli were seen in marmosets in several tissues distal to the site of injection, including in skeletal muscle, heart, and lungs, that were attributed to the cause of mortality at all doses tested. In the rat 13-week study, mortality was primarily attributed to kidney failure (see kidney toxicity information below). Although no seizures or thrombi (except at the injection site) were reported in the dog 13-week study (up to 32 mg/kg/day, 0.4 timed the MRHD, based on BSA comparisons), the dosing catheter in many animals did not remain patent for the duration of the study and was found to be filled with fibrin, erythrocyte clumps and inflammatory cell infiltrate. In mice, tonic/clonic convulsions were observed after ceftobiprole medocaril sodium was administered as a single intravenous dose at ≥250 mg/kg (0.75 times the MRHD, based on BSA comparisons).

Kidney Toxicity

No significant kidney toxicities were observed in 2- or 4-week studies in rats or in 4-week studies in marmosets. However, in a 13-week rat study at doses up to 750 mg/kg/day in males (2.8 times the MRHD, based on BSA comparisons) and 376 mg/kg/day in females (1.42 time the MRHD, based on BSA comparisons), significant kidney toxicity (dose dependent increases in tubular/duct eosinophilic bodies, and presence of foreign material) was observed at ≥250 mg/kg/day potentially due to precipitation of test article; kidney interstitial fibrosis (moderate) was observed in males at the high dose. Mortality was observed at ≥250 mg/kg/day,

Reference ID: 5357793

primarily on study Days 34 to 87 and attributed to kidney failure due to obstruction with foreign material. Mice administered a single dose of ceftobiprole medocaril sodium intravenously at ≥250 mg/kg showed kidney tubules deposits (moderate to marked), dilation, congestion, degeneration of distal tubules and necrosis. In this study the lethal dose in mice was ≥500 mg/kg (0.94 the MRHD based on BSA comparisons).

Hypersensitivity

In a 2-week dog study, ceftobiprole medocaril sodium administered intravenously at ≥50 mg/kg/day (0.6 times the MRHD based on BSA comparisons) induced a histaminergic reaction (reddening of the skin, face edema, injection of the oral mucosa, vomiting and salivation) primarily associated with a relatively short infusion time (30 minutes). Findings significantly decreased with a longer infusion time (2 hours) for the high and medium dosed animals. These finding correlated with a dose dependent increase in plasma levels of histamine that returned to control levels after approximately 4 hours from start of infusion. In a 13-week dog study, ceftobiprole medocaril sodium administered intravenously at up to 32 mg/kg/day (0.4 times the MRHD based on BSA comparisons) caused sporadic reddening of the gums of some dogs primarily during the first 3 weeks of dosing. Ceftobiprole medocaril sodium administered to guinea pigs by the intravenous or subcutaneous route, at a dose up to 100 mg/kg (0.5 times the MRHD based on BSA comparisons), showed moderate antigenic potential.

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Ceftobiprole is a cephalosporin antibacterial drug. In general, cephalosporins have a favorable safety profile and have been well-tolerated with extensive use worldwide. Common adverse reactions associated with their use include nausea, vomiting, diarrhea, abdominal pain, and rash. Labeled Warnings and Precautions across the five generations of cephalosporins include serious hypersensitivity/anaphylactic reactions, *Clostridioides difficile* associated diarrhea, neurotoxicity including seizures and encephalopathy, development of drug-resistant bacteria with prolonged or inappropriate use, and laboratory-based abnormalities such as direct Coombs' test seroconversion and decrease in prothrombin activity. Almost all cephalosporins require dose adjustment in subjects with impaired renal function. The second generation cephalosporins carry a risk of hearing loss in pediatric subjects while third generation cephalosporins such as ceftriaxone may interact with calcium containing products, or cause pancreatitis, biliary sludge, gallbladder pseudolithiasis, and hemolytic anemia. Third and fourth generation cephalosporins have rarely been associated with electrolyte derangements including hyponatremia and hyperkalemia.

Reported post-marketing adverse events for cephalosporins include serum sickness-like reaction, acute tubulointerstitial nephritis, and acute generalized exanthematous pustulosis. A few cases of neonatal death in subjects receiving ceftriaxone in conjunction with calcium-containing fluids have been reported. Hepatotoxicity or drug induced liver injury due to cephalosporins are uncommon with the exception of ceftriaxone which as noted above can cause biliary sludge related to the formation of ceftriaxone-calcium salt. Finally, there have been reports of life-threatening or fatal occurrences of encephalopathy, myoclonus and seizures related to cefepime use. This was primarily observed in subjects with renal impairment who exceeded recommended dosages but have also occurred in subjects in whom doses were appropriately adjusted.

Reference ID: 5357793

Given its drug class, the risks and safety concerns for ceftobiprole are anticipated to be similar to those associated with cephalosporins already on the market as summarized above. Adverse events of special interest monitored by the Applicant during the clinical development program of ceftobiprole included hypersensitivity/anaphylactic reaction, *C. difficile* colitis, convulsions, acute renal failure, increased hepatic enzymes, hyponatremia, nausea, vomiting, and thrombosis.

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

A review of the literature regarding the postmarketing experience for ceftobiprole yielded a retrospective case series conducted in Italy reporting on 29 patients who received ceftobiprole; 2 patients developed myoclonus and 1 patient developed a rash that were attributed to ceftobiprole (Durante-Mangoni et al. 2020). No deaths occurred in patients while receiving ceftobiprole. Another published case reported agranulocytosis in a patient receiving ceftobiprole after DRESS associated with vancomycin and rifampin (Wendland et al. 2011). After discontinuation of ceftobiprole, the patient's neutrophils recovered without further issues. The Applicant has also submitted postmarketing surveillance data in their application highlighting cases of serious hypersensitivity reactions including Stevens-Johnson syndrome, urticaria, and angioedema.

The FDA Adverse Event Reporting System was also queried for AEs reported with ceftobiprole. Upon review, AEs that were deemed potentially related to ceftobiprole were leukopenia, encephalopathy, rash, agranulocytosis, hyponatremia, and seizures.

Review of the labeling from Canada, the United Kingdom, and Australia did not identify any new safety issues. Safety issues and adverse reactions reported in the ex-US labeling were derived from the clinical studies covered in this review. No additional postmarketing experiences were identified.

7.4. FDA Approach to the Safety Review

Please see the discussion in Section 3.2 for a description of the clinical trials and any other data used in the review of safety and whether the trials submitted were fit for purpose. The studies submitted for safety were analyzed individually as described in this section. Pooling of safety results was not deemed to be appropriate given clinically distinct subject populations and differences in study design and conduct across pivotal trials. No major data quality or integrity issues were identified that would preclude performing a safety review for this NDA. There were no major identified issues with respect to recording, coding and categorizing AEs. A few preferred terms (PTs) were reclassified based on the verbatim terms. The clinical data scientist performed standard safety analyses including Food and Drug Administration Medical Dictionary for Regulatory Activities queries (FMQs) to determine safety signals, and additional analyses as requested by the clinical team. The clinical review team performed a grouped query (GQ) analysis for selected treatment-emergent adverse events (TEAEs) to evaluate potential splitting of similar AEs and these are discussed in the TEAE section of each indication. Review of subject narratives and graphical subject profiles (created using JMP clinical version 17) were used in some instances to help determine causality. AE and TEAE are used interchangeably in this review.

Reference ID: 5357793

Safety evaluations included recording of AEs, vital signs (including electrocardiogram results), and collection of laboratory parameters. For all studies, AEs included any untoward medical occurred associated with the use of the drug in humans, whether or not considered drug related. An AE could arise with any use of the drug (e.g., off-label use, use in combination with another drug) and with any route of administration, formulation, or dose, including an overdose. If there was a suspicion that a GQ was related to ceftobiprole, subject narratives and graphical subject profiles (created using JMP clinical version 17) were used to help determine causality.

For Trial BPR-CS-009, AEs were collected continuously from the start of first dosing up to and including the scheduled PTE visit (Day 70 ± 5 days post-randomization). For Trial BPR-CS-008, AEs were collected continuously from start of first dosing up to and including the scheduled last follow-up visit (28-35 days after last treatment). The Medical Dictionary for Regulatory activities (MedDRA) version 24.0 was used for both Trials. In order to assess severity, a 3-point grading scale was used (mild, moderate, severe). For Trial CAP-3001, AEs were collected from the time of informed consent up to completion of the last trial-related procedure. For BAP 248307, AEs were collected from the first study related procedure up to the last trial-related procedure. MedDRA version 10.0 was used for studies CAP-3001 and BAP 248307. For Trial BPR-PIP-002, AEs were collected continuously from time of first study drug administration up to and including the scheduled last follow-up visit (28-35 days after EOT). MedDRA version 22.1 was used for this Trial.

Reference ID: 5357793

7.5. Adequacy of the Clinical Safety Database

The Applicant conducted eighteen phase 1 studies in adults and two phase 1 studies in pediatric subjects for a total of 464 subjects. The studies enrolled 385 adult subjects and 79 pediatric subjects who received ceftobiprole. The ceftobiprole dose ranged from 125 mg to 1000 mg. Additional information on the phase 1 safety database can be found in Section 17.

The duration of exposure in each of the studies submitted for safety evaluation are noted in the table below. A total of 1315 subjects were treated with ceftobiprole in these studies. The dosing, duration, and number of subjects in the safety database of all submitted phase 3 studies were considered sufficient to conduct a safety review.

Table 46. Duration of Exposure, Safety Population, Integrated Summary of Safety Dataset

	BPR-CS-009		BPR-CS-008		CAP-3001		BAP248/307		BPR-PIP-002		TOTAL	
Parameter	Ceftobiprole N=191 n (%)	Daptomycin +/- Aztreonam N=198 n (%)	Ceftobiprole N=334 n (%)	Vancomycin + Aztreonam N=342 n (%)	Ceftobiprole N=310 n (%)	Ceftriaxone +/- Linezolid N=322 n (%)	Ceftobiprole N=386 n (%)	Ceftazidime + Linezolid N=386 n (%)	Ceftobiprole N=94 n (%)	Cephalosporin +/- vancomycin N=44 n (%)	Total Ceftobiprole N=1315 n (%)	Total Comparator N=1292 n (%)
Duration of treatment, days												
Mean (SD)	21 (7.5)	20.8 (6.7)	6.8 (2.4)	7 (2.7)	8.7 (2.9)	8.6 (2.7)	8.5 (3.4)	9 (3.4)	6.3 (2.5)	6.5 (2.1)	9.8 (6.1)	10.1 (6)
Median (Q1, Q3)	21 (21, 25)	21 (21, 22.8)	6 (5, 8)	7 (5, 9)	9 (7.2, 10)	9 (7, 10)	8 (7, 10)	8 (8, 11)	6 (4, 8)	7 (5, 8)	8 (6, 11)	8 (7, 11)
Min, Max	1, 42	1, 42	1, 14	1, 14	1, 18	1, 16	1, 16	1, 23	2, 14	3, 12	1, 42	1, 42
Total exposure (person years)	11	11	6	7	7	8	9	10	2	1	35	36
Subjects treated, by duration, n (%)												
<5 days	9 (4.7)	7 (3.5)	15 (4.5)	18 (5.3)	34 (11.0)	24 (7.5)	50 (13.0)	38 (9.8)	30 (31.9)	8 (18.2)	138 (10.5)	95 (7.4)
≥5 to <8 days	9 (4.7)	7 (3.5)	217 (65.0)	205 (59.9)	44 (14.2)	78 (24.2)	54 (14.0)	53 (13.7)	37 (39.4)	22 (50.0)	361 (27.5)	365 (28.3)
≥8 to <11 days	4 (2.1)	5 (2.5)	91 (27.2)	99 (28.9)	162 (52.3)	164 (50.9)	186 (48.2)	178 (46.1)	20 (21.3)	12 (27.3)	463 (35.2)	458 (35.4)
≥11 to <15 days	7 (3.7)	6 (3.0)	11 (3.3)	20 (5.8)	63 (20.3)	52 (16.1)	67 (17.4)	81 (21.0)	7 (7.4)	2 (4.5)	155 (11.8)	161 (12.5)
≥15 to <22 days	102 (53.4)	115 (58.1)	0	0	7 (2.3)	4 (1.2)	29 (7.5)	35 (9.1)	0	0	138 (10.5)	154 (11.9)
≥22 to <29 days	49 (25.7)	54 (27.3)	0	0	0	0	0	1 (0.3)	0	0	49 (3.7)	55 (4.3)
≥29 days	11 (5.8)	4 (2.0)	0	0	0	0	0	0	0	0	11 (0.8)	4 (0.3)

Source: adex.xpt and adsl.xpt; Software: R
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation

Reference ID: 5357793

7.6. Safety Results

7.6.1. SAB, Trial BPR-CS-009

7.6.1.1. Overview of Treatment-Emergent Adverse Events Summary, Trial BPR-CS-009

As shown in Table 47 the overall incidence of TEAEs was 63.4% in the ceftobiprole arm and 59.1% in the daptomycin arm. Most of the TEAEs in the ceftobiprole arm were of moderate severity and there were slightly fewer severe TEAEs as compared to the daptomycin arm. There was an overall lower incidence of SAEs in the ceftobiprole arm compared to the daptomycin arm, respectively (18.8% versus 22.7%). The number of deaths and TEAEs leading to discontinuation were similar between treatment arms.

There were four subjects in the ceftobiprole arm and none in the comparator arm with TEAEs leading to dose modification of the study drug. In the ceftobiprole arm, two subjects each required dose reduction and dose interruption, described below:

- Subject (b) (6) had a reported TEAE of acute kidney injury resulting in reduction of the ceftobiprole dose on Day 6. However, on the same day, the subject also developed SAEs of respiratory failure and staphylococcal pneumonia which led to the permanent discontinuation of ceftobiprole.
- Subject (b) (6) had a reported SAE of renal impairment on Day 6 resulting in ceftobiprole dose reduction. The dose was reduced for 2 days until the creatinine improved. Ultimately, the subject died from cardiopulmonary failure.
- Subject (b) (6) had a reported TEAE of allergic dermatitis on Day 16 which led to ceftobiprole dose interruption and treatment for the rash on the same day. Ceftobiprole was permanently discontinued on Day 18 after a positive dechallenge and rechallenge associated with fevers and an elevated eosinophil count 8.5% (reference range 0-6). The subject recovered and no other signs of hypersensitivity were reported.
- Subject (b) (6) had a reported TEAE of dyspnea resulting in ceftobiprole dose interruption on Day 4 which was considered possibly related by the investigator. However, dyspnea resolved upon continuation of ceftobiprole.

Table 47. Overview of Adverse Events, Safety Population, Trial BPR-CS-009

Event Category	Ceftobiprole N=191 n (%)	Daptomycin N=198 n (%)
SAE	36 (18.8)	45 (22.7)
SAEs with fatal outcome	17 (8.9)	18 (9.1)
Life-threatening SAEs	13 (6.8)	10 (5.1)

Event Category	Ceftobiprole N=191 n (%)	Daptomycin N=198 n (%)
AE leading to permanent discontinuation of study drug	18 (9.4)	18 (9.1)
AE leading to dose modification of study drug	4 (2.1)	0
AE leading to interruption of study drug	2 (1.0)	0
AE leading to reduction of study drug	2 (1.0)	0
AE leading to dose delay of study drug	0	0
Any AE	121 (63.4)	117 (59.1)
Severe and worse	29 (15.2)	38 (19.2)
Moderate	60 (31.4)	52 (26.3)
Mild	32 (16.8)	27 (13.6)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as adverse events which occurred between the start of the first dosing up to and including the scheduled post treatment evaluation visit.
Duration is up to 42 days plus the follow-up period up to Day 70.
Severity as assessed by the Applicant.
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event

7.6.1.2. Deaths, Trial BPR-CS-009

There were no imbalances in TEAEs leading to death between the treatment arms (17/191 (8.9%) in the ceftobiprole and 18/198 (9.1%) in the daptomycin arm). In both arms, the most commonly reported TEAE leading to death was multiple organ dysfunction syndrome and septic shock.

None of the TEAEs leading to death were assessed as drug related by the investigator or by the FDA reviewer upon a detailed review of the case narratives. The case narratives and subject profiles suggested that the deaths appeared to be related to underlying comorbidities and complications arising from the underlying infection, which is not unexpected for subjects with SAB. A meta-analysis performed in 2022 estimated that the all-cause mortality rate of SAB in a total of 341 studies (536,791 subjects, spanning from January 1, 1991 to May 7, 2021) was 10.4% (95% CI, 9.0%–12.1%) at 7 days, 13.3% (95% CI, 11.1%–15.8%) at 2 weeks, 18.1% (95% CI, 16.3%–20.0%) at 1 month, 27.0% (95% CI, 21.5%–33.3%) at 3 months, and 30.2% (95% CI, 22.4%–39.3%) at 1 year (Bai et al. 2022).

The mortality rate in the BPR-CS-009 trial of 8.9% at Day 70 was less than what was seen in the meta-analysis by Bai et al. described above, possibly due to mortality being assessed in a clinical trial setting.

Table 48. Deaths, Safety Population, Trial BPR-CS-009

Preferred Term	Ceftobiprole N=191 n (%)	Daptomycin N=198 n (%)
Any AE leading to death	17 (8.9)	18 (9.1)
Multiple organ dysfunction syndrome	3 (1.6)	2 (1.0)
Acute myocardial infarction	1 (0.5)	0
Acute respiratory failure	1 (0.5)	0
Arrhythmia	1 (0.5)	0
Candida sepsis	1 (0.5)	0
Cardiac arrest	1 (0.5)	0
Death	1 (0.5)	0
Cardiac failure acute	1 (0.5)	1 (0.5)
Cardiopulmonary failure	1 (0.5)	1 (0.5)
COVID-19 pneumonia	1 (0.5)	1 (0.5)
Myocardial infarction	1 (0.5)	1 (0.5)
Sepsis	1 (0.5)	1 (0.5)
Shock hemorrhagic	1 (0.5)	1 (0.5)
Respiratory failure	1 (0.5)	2 (1.0)
Cardiac failure	0	1 (0.5)
Gastrointestinal hemorrhage	0	1 (0.5)
Pneumonia	0	1 (0.5)
Pulmonary edema	0	1 (0.5)
Squamous cell carcinoma of skin	0	1 (0.5)
Septic shock	2 (1.0)	4 (2.0)
Pancreatitis necrotizing	0	2 (1.0)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as adverse events which occurred between the start of the first dosing up to and including the scheduled post treatment evaluation visit.
Duration is up to 42 days plus the follow-up period up to Day 70.
For subject-level data, see the table “List of Adverse Events Leading to Death…”
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with adverse event

Deaths were further stratified by treatment duration (≤21 days versus >21 days) to evaluate for any differences in the timing of death between the treatment arms as related to a specific TEAE leading to death. The cut-off of 21 days was used in the analysis as this was the average duration of therapy and half of the maximum allowed treatment duration of 42 days. No discernable patterns related to duration were noted and the number of deaths in the group treated with >21 days of was too small to make any meaningful conclusions.

Reference ID: 5357793

Table 49. Adverse Event Leading to Deaths by Preferred Term, Safety Population, Trial BPR-CS-009

	Treatment Duration ≤21 Days		Treatment Duration >21 Days	
	Ceftobiprole 500 mg N=131	Daptomycin 6 mg/kg N=141	Ceftobiprole 500 mg N=60	Daptomycin 6 mg/kg N=57
Preferred Term	n (%)	n (%)	n (%)	n (%)
Any AE leading to death	14 (10.7)	17 (12.1)	3 (5.0)	1 (1.8)
Multiple organ dysfunction syndrome	3 (2.3)	2 (1.4)	0	0
Acute myocardial infarction	1 (0.8)	0	0	0
Acute respiratory failure	1 (0.8)	0	0	0
Arrhythmia	1 (0.8)	0	0	0
Candida sepsis	1 (0.8)	0	0	0
Cardiac arrest	1 (0.8)	0	0	0
Death	1 (0.8)	0	0	0
Cardiopulmonary failure	1 (0.8)	1 (0.7)	0	0
Myocardial infarction	1 (0.8)	1 (0.7)	0	0
Respiratory failure	1 (0.8)	1 (0.7)	0	1 (1.8)
Shock hemorrhagic	1 (0.8)	1 (0.7)	0	0
Cardiac failure	0	0	0	1 (1.8)
Cardiac failure acute	0	1 (0.7)	1 (1.7)	0
COVID-19 pneumonia	0	1 (0.7)	1 (1.7)	0
Gastrointestinal hemorrhage	0	1 (0.7)	0	0
Pneumonia	0	1 (0.7)	0	0
Pulmonary edema	0	1 (0.7)	0	0
Sepsis	0	1 (0.7)	1 (1.7)	0
Squamous cell carcinoma of skin	0	1 (0.7)	0	0
Septic shock	2 (1.5)	4 (2.8)	0	0
Pancreatitis necrotizing	0	2 (1.4)	0	0

Source: adae.xpt; Software: R
AVAL variable in adexsum.xpt dataset is used for treatment duration categorization.
Treatment-emergent adverse events defined as adverse events which occurred between the start of the first dosing up to and including the scheduled post treatment evaluation visit. Follow-up duration is 70 days
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with adverse event

Reference ID: 5357793

In addition, the incidence of deaths was examined in the subgroup of subjects with endocarditis (n = 15 in ceftobiprole arm, n = 10 in daptomycin arm) as these subjects would be expected to have greater severity of illness and underlying comorbidities. Overall, there were no major imbalances in death among subjects with endocarditis. In subjects with RIE, there was one death (b) (6) in the ceftobiprole arm (6.7%) compared to none in the daptomycin arm. The TEAE leading to death in the ceftobiprole arm was cardiopulmonary failure, attributed to underlying cardiopulmonary comorbidities (history of cardiac failure and multiple cardiac valvular abnormalities).

7.6.1.3. Serious Treatment-Emergent Adverse Events, Trial BPR-CS-009

The incidence of SAEs was lower in the ceftobiprole arm compared to the daptomycin arm (18.8% versus 22.7%). Most SAEs occurring in both arms were related to the Infections and Infestations system organ class (SOC) (9.4% in the ceftobiprole versus 12.6% in the daptomycin arm). Multiple organ dysfunction syndrome was the only SAE that had a greater than 1% risk difference in the ceftobiprole arm versus the daptomycin arm. After reviewing the narratives of the subjects who experienced an SAE of multiple organ dysfunction syndrome while on ceftobiprole ((b) (6)), none of these SAEs appeared to be drug-related, or due to failure of treatment with ceftobiprole.

Additional SAEs were evaluated to determine relatedness to ceftobiprole, and selected SAEs are described below by SOC. The FDA reviewer agreed with the investigator that two SAEs (seizure and leukopenia) could have been related to ceftobiprole. There were two additional SAEs (tonic-clonic seizure and cutaneous vasculitis) may also have been related to ceftobiprole, and the FDA reviewer's causality assessment for these selected SAEs is noted below:

Blood and Lymphatic System Disorders

- Subject (b) (6) had an SAE of leukopenia on Day 14. On that day, his WBC decreased to 3.02 x 10^3 /uL (9.95 x 10^3 /uL) with an absolute neutrophil count of 1.76 x 10^3 /uL. On Day 18, ceftobiprole was discontinued due to leukopenia. The subject was switched to vancomycin and the next recorded neutrophil count occurred on Day 21 where the absolute neutrophil count was 1.52 x 10^3 /uL. He was lost to follow-up, and it was unknown if the WBC recovered. Concomitant medications included metamizole, potassium supplements, bromhexine, and tramadol. The FDA reviewer agrees with the investigator that this SAE was possibly related to ceftobiprole.

Infections and Infestations

- Subjects (b) (6) in the ceftobiprole arm had SAEs of pneumonia (2 fatal). There did not appear to be a relationship between these SAEs and ceftobiprole as pneumonia was likely acquired nosocomially due to complicated medical histories and prolonged hospitalization prior to starting ceftobiprole. Both SAEs occurred on Day 2 of ceftobiprole treatment in two subjects who had organisms isolated other than *S. aureus*: (b) (6) had pneumonia due to *Acinetobacter bereziniae*, with an MIC of 0.12 to ceftobiprole; (b) (6) had *K. pneumonia* bacteremia likely to pre-existing mediastinitis, complicated by pericarditis, pneumonia, and multiple organ dysfunction). The other subject (b) (6)) developed pneumonia on Day 16, 12 days after leaving against medical advice. All three subjects were considered treatment failures.

Nervous System Disorders

As described below, two subjects in the ceftobiprole arm, who had no past medical history of seizures, developed SAEs of seizures that were temporally associated with ceftobiprole. Cephalosporins can precipitate seizures and seizures are noted as warnings in the labeling of several drugs in this class (Bora et al. 2016). The FDA reviewer agrees with the inclusion of seizures and other central nervous system disorders in the warnings section of labeling as proposed by the Applicant.

- Subject (b) (6) had no medical history of seizure and developed an SAE of a generalized tonic-clonic seizure on Day 15 while on ceftobiprole, in the setting of worsening renal function, and other TEAEs including nausea, vomiting, hypotension, multiple organ failure with respiratory distress requiring endotracheal intubation. While there may have been confounding factors such as hypotension and possible hypoxia due to respiratory distress requiring intubation, an association to ceftobiprole cannot be completely excluded.
- Subject (b) (6) had a medical history of alcohol abuse but no history of seizures and developed an SAE of seizure on Day 11 during infusion of ceftobiprole which led discontinuation. At the time of the seizure, the subject was still conscious but was unresponsive to a verbal challenge with a fixed glare. There were no concomitant medications or events at the time that would predispose to seizures, and there was no renal impairment. The FDA reviewer agrees with the investigator that this SAE was probably related to ceftobiprole.

Renal and Urinary Disorders

- Subject (b) (6) had an SAE of acute kidney injury on Day 24, two days after completion of treatment with ceftobiprole. The baseline creatinine was 1.02 mg/dL (Day -1) and increased to 1.3 mg/dL on Day 14 and 2.92 mg/dL on Day 21. On Day 34, a biopsy of the kidney was performed which showed acute glomerulonephritis with IgA deposits associated with *S. aureus* infection. Due to the biopsy results, it is unlikely that there was a direct relationship between acute kidney injury and ceftobiprole. On Day 66, the subject died due to respiratory failure.
- Subject (b) (6) had an SAE of renal impairment on Day 6 (see 7.6.1.4). It is unlikely that the renal impairment was primarily caused by ceftobiprole as the creatinine decreased while on ceftobiprole, and there were other confounding factors (i.e., infection, diuretic usage, cardiac issues).

Skin and Subcutaneous Disorders

- Subject (b) (6) had an SAE of cutaneous vasculitis on Day 27, 6 days after the last dose of ceftobiprole. It was characterized by petechiae on the subject's hands for which a biopsy was performed and showed leukocytoclastic vasculitis with transepidermal ischemic necrosis. After topical treatment, the SAE resolved. Ceftobiprole may have been associated with this SAE as other beta-lactams have been shown to cause leukocytoclastic vasculitis (Baigrie 2024). However, cutaneous vasculitis can also be idiopathic or associated with infections.

Table 50. Subjects With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Trial BPR-CS-009, Cohorts 1 and 2

System Organ Class Preferred Term	Ceftobiprole N=191 n (%)	Daptomycin N=198 n (%)
Any SAE	36 (18.8)	45 (22.7)
Blood and lymphatic system disorders (SOC)	2 (1.0)	1 (0.5)
Leukopenia	1 (0.5)	0
Anemia	1 (0.5)	1 (0.5)
Hypocoagulable state	0	1 (0.5)
Cardiac disorders (SOC)	7 (3.7)	7 (3.5)
Acute myocardial infarction	1 (0.5)	0
Arrhythmia	1 (0.5)	0
Atrial thrombosis	1 (0.5)	0
Cardiac arrest	1 (0.5)	1 (0.5)
Cardiac failure acute	1 (0.5)	1 (0.5)
Cardiopulmonary failure	1 (0.5)	1 (0.5)
Myocardial infarction	1 (0.5)	1 (0.5)
Angina unstable	0	1 (0.5)
Cardiac failure	0	3 (1.5)
Gastrointestinal disorders (SOC)	3 (1.6)	5 (2.5)
Intra-abdominal hemorrhage	1 (0.5)	0
Esophageal varices hemorrhage	1 (0.5)	0
Retroperitoneal hematoma	1 (0.5)	0
Lower gastrointestinal hemorrhage	0	1 (0.5)
Pancreatic hemorrhage	0	1 (0.5)
Gastrointestinal hemorrhage	0	2 (1.0)
Pancreatitis necrotizing	0	2 (1.0)
General disorders and administration site conditions (SOC)	5 (2.6)	3 (1.5)
Multiple organ dysfunction syndrome	4 (2.1)	2 (1.0)
Death	1 (0.5)	0
Pyrexia	0	1 (0.5)
Hepatobiliary disorders (SOC)	1 (0.5)	0
Cholestasis	1 (0.5)	0

System Organ Class Preferred Term	Ceftobiprole N=191 n (%)	Daptomycin N=198 n (%)
Infections and infestations (SOC)	18 (9.4)	25 (12.6)
Pneumonia	3 (1.6)	2 (1.0)
Bacteremia	1 (0.5)	0
Candida sepsis	1 (0.5)	0
Infectious pleural effusion	1 (0.5)	0
Lung abscess	1 (0.5)	0
Mediastinitis	1 (0.5)	0
Purulent pericarditis	1 (0.5)	0
Pyelonephritis acute	1 (0.5)	0
Skin bacterial infection	1 (0.5)	0
Endocarditis staphylococcal	1 (0.5)	1 (0.5)
Gangrene	1 (0.5)	1 (0.5)
Osteomyelitis	1 (0.5)	1 (0.5)
Pneumonia staphylococcal	1 (0.5)	1 (0.5)
Sepsis	1 (0.5)	1 (0.5)
Urosepsis	1 (0.5)	1 (0.5)
COVID-19 pneumonia	2 (1.0)	3 (1.5)
Abdominal abscess	0	1 (0.5)
Abscess limb	0	1 (0.5)
Bacterial sepsis	0	1 (0.5)
Cardiac valve vegetation	0	1 (0.5)
Escherichia bacteraemia	0	1 (0.5)
Hematoma infection	0	1 (0.5)
Laryngitis	0	1 (0.5)
Muscle abscess	0	1 (0.5)
Psoas abscess	0	1 (0.5)
Septic necrosis	0	1 (0.5)
Superinfection bacterial	0	1 (0.5)
Intervertebral discitis	0	2 (1.0)
Staphylococcal bacteremia	0	3 (1.5)
Septic shock	4 (2.1)	8 (4.0)
Injury, poisoning and procedural complications (SOC)	4 (2.1)	2 (1.0)
Arteriovenous fistula thrombosis	1 (0.5)	0
Hemodialysis complication	1 (0.5)	0
Kidney rupture	1 (0.5)	0
Post procedural hemorrhage	1 (0.5)	0
Foot fracture	0	1 (0.5)
Vascular pseudoaneurysm	0	1 (0.5)
Investigations (SOC)	1 (0.5)	1 (0.5)
Wound healing normal	1 (0.5)	1 (0.5)
Musculoskeletal and connective tissue disorders (SOC)	0	2 (1.0)
Myopathy	0	1 (0.5)
Neck pain	0	1 (0.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	1 (0.5)	1 (0.5)
Chloroma	1 (0.5)	0
Squamous cell carcinoma of skin	0	1 (0.5)

System Organ Class Preferred Term	Ceftobiprole N=191 n (%)	Daptomycin N=198 n (%)
Nervous system disorders (SOC)	4 (2.1)	4 (2.0)
Generalized tonic-clonic seizure	1 (0.5)	0
Headache	1 (0.5)	0
Hypoglycemic seizure	1 (0.5)	0
Seizure	1 (0.5)	1 (0.5)
Ischemic stroke	0	1 (0.5)
Presyncope	0	1 (0.5)
Status epilepticus	0	1 (0.5)
Renal and urinary disorders (SOC)	4 (2.1)	3 (1.5)
Hydronephrosis	1 (0.5)	0
Renal hematoma	1 (0.5)	0
Acute kidney injury	1 (0.5)	1 (0.5)
Renal impairment	1 (0.5)	1 (0.5)
Hematuria	0	1 (0.5)
Respiratory, thoracic and mediastinal disorders (SOC)	7 (3.7)	6 (3.0)
Acute respiratory distress syndrome	2 (1.0)	0
Acute respiratory failure	2 (1.0)	0
Pneumonia aspiration	1 (0.5)	0
Respiratory failure	2 (1.0)	2 (1.0)
Acute pulmonary edema	0	1 (0.5)
Eosinophilic pneumonia	0	1 (0.5)
Eosinophilic pneumonia acute	0	1 (0.5)
Pulmonary edema	0	1 (0.5)
Skin and subcutaneous tissue disorders (SOC)	1 (0.5)	1 (0.5)
Cutaneous vasculitis	1 (0.5)	0
Pemphigoid	0	1 (0.5)
Surgical and medical procedures (SOC)	1 (0.5)	1 (0.5)
Leg amputation	1 (0.5)	1 (0.5)
Vascular disorders (SOC)	2 (1.0)	3 (1.5)
Extremity necrosis	1 (0.5)	1 (0.5)
Shock hemorrhagic	1 (0.5)	1 (0.5)
Deep vein thrombosis	0	1 (0.5)
Peripheral ischemia	0	1 (0.5)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as adverse events which occurred between the start of the first dosing up to and including the scheduled post treatment evaluation visit.
Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Treatment duration is up to 42 days plus the follow-up period up to Day 70.
Abbreviations: incl, including; N, number of subjects in treatment arm; n, number of subjects with adverse event; SAE, serious adverse event; SOC, system organ class

7.6.1.4. Adverse Events and FDA Medical Queries Leading to Treatment Discontinuation, Trial BPR-CS-009

In both arms, the number of subjects who had AEs leading to treatment discontinuation was comparable (9.4% in the ceftobiprole arm and 9.1% in the daptomycin arm). The most common types of TEAEs that led to treatment discontinuation were related to the Infections and Infestations SOC.

The AEs considered possibly related to the study drug by the investigator and leading to treatment discontinuation in the ceftobiprole arm were leukopenia (n = 1), gastrointestinal

Reference ID: 5357793

disorders (n = 3), seizure (n = 1), allergic dermatitis (n = 2), urticaria (n = 2), and liver enzyme elevation (n = 1). These subjects are described below:

- Subject (b) (6) had AEs of nausea, vomiting, gamma-glutamyl transferase increased (93 U/L on Day 1 to 528 U/L on Day 10), blood alkaline phosphatase increased (166 U/L on Day 1 to 708 U/L on Day 10), ALT increased (19 U/L on Day 1 to 229 U/L on Day 10), AST increased (21 on Day 1 to 165 U/L on Day 10) on Day 8 resulting in treatment discontinuation on Day 9. Nausea resolved by Day 15 and liver enzymes were within normal limits by Day 35.
- Subject (b) (6) had an AE of urticaria on Day 15 which was characterized by itching and a rash on the thorax, abdomen, and extremities. Symptoms improved initially with desloratadine, but the subject reported intensified itching and worsening rash which required intravenous methylprednisolone. On Day 16, the urticaria intensified again and ceftobiprole was discontinued.
- Subject (b) (6) had an AE of urticaria on Day 18 which was also characterized by a rash that disappeared spontaneously but reappeared at a different site the following day. Because of the continuous symptoms, ceftobiprole was discontinued.
- Subject (b) (6) had an AE of allergic dermatitis (verbatim term was a macular-papular skin rash) on Day 9 which continued the following day. The subject was treated with chloropyramine and ceftobiprole was discontinued with resolution of the subject's rash by Day 13.
- Subject (b) (6) had an AE of allergic dermatitis on Day 16. The subject had a reported fever of 38.4°C along with a raspberry-colored shallow rash. Ceftobiprole was temporarily interrupted (i.e., 1 dose was skipped) and the subject was treated with prednisolone and chloropyramine leading to disappearance of the rash. On Day 18, after infusion of ceftobiprole, the rash and fever recurred, leading to permanent discontinuation.
- Subject (b) (6) had an SAE of seizure on Day 11 leading to discontinuation of ceftobiprole. Subject was discussed in the SAE section.
- Subject (b) (6) had an SAE of leukopenia on Day 14 leading to discontinuation of ceftobiprole. Subject was discussed in the SAE Section (7.6.1.3).

The FDA reviewer agrees with the Applicant about the possible causality between the above AEs (leukopenia, gastrointestinal disorders, seizure, allergic dermatitis, urticaria and liver enzyme elevation) and ceftobiprole. In addition, the most common adverse reactions leading to discontinuation (nausea, vomiting, rash, and urticaria) will be proposed in Section 6 in labeling.

Table 51. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Trial BPR-CS-009, Cohorts 1 and 2

System Organ Class Preferred Term	Ceftobiprole N=191 n (%)	Daptomycin N=198 n (%)
Any AE leading to discontinuation	18 (9.4)	18 (9.1)
Blood and lymphatic system disorders (SOC)	1 (0.5)	0
Leukopenia	1 (0.5)	0
Gastrointestinal disorders (SOC)	3 (1.6)	0
Nausea	2 (1.0)	0
Vomiting	2 (1.0)	0
General disorders and administration site conditions (SOC)	2 (1.0)	1 (0.5)
Multiple organ dysfunction syndrome	2 (1.0)	1 (0.5)

System Organ Class Preferred Term	Ceftobiprole N=191 n (%)	Daptomycin N=198 n (%)
Infections and infestations (SOC)	9 (4.7)	14 (7.1)
Septic shock	3 (1.6)	2 (1.0)
Candida sepsis	1 (0.5)	0
Osteomyelitis	1 (0.5)	0
COVID-19 pneumonia	1 (0.5)	1 (0.5)
Pneumonia staphylococcal	1 (0.5)	1 (0.5)
Bacteremia	0	1 (0.5)
Cardiac valve vegetation	0	1 (0.5)
COVID-19	0	1 (0.5)
Intervertebral discitis	0	1 (0.5)
Pathogen resistance	0	1 (0.5)
Psoas abscess	0	1 (0.5)
Renal abscess	0	1 (0.5)
Endocarditis staphylococcal	2 (1.0)	5 (2.5)
Investigations (SOC)	1 (0.5)	0
Alanine aminotransferase increased	1 (0.5)	0
Aspartate aminotransferase increased	1 (0.5)	0
Blood alkaline phosphatase increased	1 (0.5)	0
Gamma-glutamyltransferase increased	1 (0.5)	0
Musculoskeletal and connective tissue disorders (SOC)	0	1 (0.5)
Myopathy	0	1 (0.5)
Nervous system disorders (SOC)	1 (0.5)	0
Seizure	1 (0.5)	0
Respiratory, thoracic and mediastinal disorders (SOC)	2 (1.0)	3 (1.5)
Acute respiratory distress syndrome	1 (0.5)	0
Respiratory failure	1 (0.5)	0
Eosinophilic pneumonia	0	1 (0.5)
Eosinophilic pneumonia acute	0	1 (0.5)
Pulmonary edema	0	1 (0.5)
Skin and subcutaneous tissue disorders (SOC)	4 (2.1)	0
Dermatitis allergic	2 (1.0)	0
Urticaria	2 (1.0)	0

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as adverse events which occurred between the start of the first dosing up to and including the scheduled post treatment evaluation visit.
Duration is up to 42 days plus the follow-up period up to Day 70.
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with adverse event; SOC, system organ class

7.6.1.5. Treatment-Emergent Adverse Events, Trial BPR-CS-009

TEAEs occurred in 63.4% of the subjects in the ceftobiprole arm and 59.1% in the daptomycin arm with a risk difference of 4.3%. The GQs demonstrating a risk difference of at least 4% or higher in the ceftobiprole arm compared to the daptomycin arm were nausea, vomiting, hypokalemia, pneumonia, and diarrhea; these are described below. Hypokalemia is discussed in the laboratory Section 7.6.1.6. Although the GQ of bacterial infections were common in both arms, it was not considered an adverse reaction as they were likely related to underlying medical conditions and was not caused by ceftobiprole.

Gastrointestinal Symptoms

Most TEAEs of either nausea, vomiting, or diarrhea were of mild to moderate severity and did not lead to discontinuation. About half of the TEAEs of nausea or vomiting were related to ceftobiprole by the investigator.

There were no reports of diarrhea associated with *Clostridioides difficile*. Gastrointestinal symptoms such as nausea, vomiting, and diarrhea are often considered common adverse reactions associated with antibacterial drugs, and are proposed by the Applicant in Section 6 of labeling.

Pneumonia

The narrow FMQ of pneumonia encompassed the PTs of pneumonia, pneumonia staphylococcal, pneumonia aspiration, lung abscess, pneumonia pseudomonal, pneumonia viral, and infectious pleural effusion. Although the number of subjects with pneumonia was higher in the ceftobiprole arm compared to the daptomycin arm [16 (8.4%) versus 5 (2.5%)], review of subject profiles and narratives did not reveal a link between ceftobiprole and the PTs in the narrow FMQ. Out of the 16 subjects with FMQs of pneumonia, 2 were due to aspiration and 1 was due to a viral cause. In most of the cases the subjects had comorbidities which made pneumonia more likely to occur (presence of endotracheal tube, immunosuppression, prolonged hospitalization). There was also no information about the pathogen except in 4 cases, where all but one of the pathogens isolated was gram negative. The subject with a *S. aureus* pneumonia is described below:

- One subject, (b) (6), had an AE of pneumonia staphylococcal on Day 7. The subject was on cefazolin for 6 days for persistent SAB prior to randomization. After 6 days of ceftobiprole, the subject experienced an SAE of respiratory failure and MSSA was isolated from lavage from the endotracheal tube; ceftobiprole was discontinued and changed to imipenem-cilastatin. The AEs of pneumonia staphylococcal and respiratory failure were resolved 2 days later. Overall, given that the AE occurred even after 6 days of cefazolin and 6 days of ceftobiprole but resolved after 2 days of imipenem-cilastatin suggests either a source control issue or an issue related to incomplete duration of treatment. This subject was considered a treatment failure due to use of non-study antibacterial drugs.

Analysis of the following adverse events of special interest were performed as these AEs have been observed with use of other cephalosporins or noted in the nonclinical studies using ceftobiprole: renal impairment, leukopenia, liver enzyme increased, thrombosis, rash, hypersensitivity reactions, and seizure. Leukopenia and liver enzyme increased are discussed in the laboratory section. Thrombosis will be discussed in Section 7.7.2, key safety review issues.

Renal Impairment

There were 13 subjects (6.8%) who experienced AEs related to the GQ of renal impairment (renal impairment, blood creatinine increased, creatinine renal clearance decreased, acute kidney injury, and oliguria) in the ceftobiprole arm, and there was a similar frequency in the daptomycin arm. Although none appeared to have a definitive association between renal impairment and ceftobiprole, there was a possible association in 2 subjects ((b) (6). Blood creatinine increased was proposed by the Applicant in labeling, and a few additional PTs noted in this section will be added.

- Subject (b) (6) is an 82-year-old male with a medical history of cellulitis and creatinine renal clearance decrease. As he finished his 28-day course of ceftobiprole, his

creatinine slowly increased and on the final day of ceftobiprole, the creatinine was measured at 1.81 mg/dL (1.37 mg/dL on Day 1). Concomitant medications which could have also caused the increase in creatinine included metamizole and omeprazole. Overall, the contribution of ceftobiprole cannot be completely excluded. However, there were confounding factors such as history of renal impairment, advanced age, and concomitant medications.

- Subject (b) (6) is a 66-year-old male with a medical history of diabetes mellitus and hypertension. Levels of creatinine started to increase from Day 14 from 1.07 mg/dL to 1.49 mg/dL on Day 28, the day that ceftobiprole treatment was completed. Concomitant medications included omeprazole, furosemide, and ketoprofen. On Day 29, his creatinine improved to 1.1 mg/dL. Although there were confounding factors such as concomitant medications and underlying comorbidities which could have caused the increase in creatinine, the contribution of ceftobiprole cannot be completely excluded.

Rash/ Hypersensitivity

There were 3 (1.6%) subjects each in the ceftobiprole arm with the AEs of rash ((b) (6) (b) (6) and hypersensitivity (b) (6) (b) (6) compared to 2 (1%) subjects in the daptomycin arm with the AE of rash and 1 (0.5%) subject in the daptomycin arm with the AE of hypersensitivity.

In the subjects with AEs of rash, 2 of the 3 subjects ((b) (6) were considered by both the Applicant and the MO to have been related to ceftobiprole. These cases are discussed in AEs leading to discontinuation.

In subjects with AEs related to hypersensitivity, the MO considered that all three AEs could have been related to ceftobiprole. Subjects (b) (6) experienced the AE of urticaria are discussed in the AEs leading to discontinuation section and subject (b) (6) experienced the AE of cutaneous vasculitis and is discussed in the SAE section.

Seizure

There were 3 (1.6%) subjects in the ceftobiprole arm with AEs related to seizure ((b) (6) (b) (6) Subjects (b) (6) discussed in the SAE section, had seizures that may been associated with ceftobiprole. However, for subject (b) (6) the seizure was clearly attributed to hypoglycemia as multiple episodes of hypoglycemia (nadir of 23.4 mg/dl) were reported. None of the subjects had a past medical history of seizures.

Table 52. Grouped Queries by Preferred Term, Showing Terms Occurring in at Least 1% of Subjects in the Ceftobiprole Arm, Safety Population Trial BPR-CS-009

Grouped Query Preferred Term	Ceftobiprole N=191 n (%)	Daptomycin N=198 n (%)
Anemia[a]	22 (11.5)	26 (13.1)
Bacterial Infection[b]	22 (11.5)	33 (16.7)
Nausea	20 (10.5)	8 (4.0)
Hypokalemia[c]	17 (8.9)	5 (2.5)
Pneumonia[d]	16 (8.4)	5 (2.5)
Vomiting	16 (8.4)	4 (2.0)
Liver enzyme increased[e]	15 (7.9)	20 (10.1)
Diarrhea	13 (6.8)	5 (2.5)
Renal impairment[f]	13 (6.8)	11 (5.6)
Hemorrhage[g]	11 (5.8)	9 (4.5)
Respiratory failure[h]	10 (5.2)	4 (2.0)
Viral infection[i]	10 (5.2)	7 (3.5)
Hypertension[j]	10 (5.2)	4 (2.0)
Leukopenia[k]	8 (4.2)	5 (2.5)
Pyrexia[l]	8 (4.2)	5 (2.5)
Arthritis[m]	7 (3.7)	7 (3.5)
Thrombosis[n]	7 (3.7)	2 (1.0)
Abdominal pain[o]	6 (3.1)	2 (1.0)
Constipation	6 (3.1)	7 (3.5)
Cardiac failure[p]	5 (2.6)	9 (4.5)
Fungal infection[q]	5 (2.6)	3 (1.5)
Headache	5 (2.6)	6 (3.0)
Septic shock	5 (2.6)	8 (4.0)
Ascites	4 (2.1)	0
Dyspnea[r]	4 (2.1)	2 (1.0)
Hydrothorax	4 (2.1)	5 (2.5)
Hypoglycemia	4 (2.1)	6 (3.0)
Multiple organ dysfunction syndrome	4 (2.1)	2 (1.0)
Pleural effusion	4 (2.1)	2 (1.0)
Purulent material[s]	4 (2.1)	9 (4.5)
Renal & urinary tract infection[t]	4 (2.1)	7 (3.5)
Arrhythmia[u]	3 (1.6)	1 (0.5)
Hepatic injury[v]	3 (1.6)	5 (2.5)
Hyperglycemia[w]	3 (1.6)	4 (2.0)
Hypersensitivity[x]	3 (1.6)	1 (0.5)
Hypoalbuminemia[y]	3 (1.6)	2 (1.0)
Hypomagnesemia[z]	3 (1.6)	2 (1.0)
Hypotension[aa]	3 (1.6)	3 (1.5)
Insomnia	3 (1.6)	0
Pancreatitis[bb]	3 (1.6)	3 (1.5)
Pericardial effusion	3 (1.6)	0
Peripheral edema[cc]	3 (1.6)	4 (2.0)
Phlebitis[dd]	3 (1.6)	1 (0.5)
Rash[ee]	3 (1.6)	1 (0.5)
Seizure[ff]	3 (1.6)	2 (1.0)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any adverse event which occurred between the start of the first dosing up to and including the scheduled last follow-up.
Duration is up to 42 days plus the follow-up period up to Day 70.
Recoded terms are defined based on the dictionary created in conjunction with the clinical team.
Adverse Events are sorted by prevalence in the Ceftobiprole arm.
[a] Anemia includes anemia, hypochromic anemia, hemoglobin decreased, and normochromic normocytic anemia
[b] Bacterial infection includes pyelonephritis acute, cellulitis, endocarditis staphylococcal, abdominal abscess, arthritis bacterial, bacteremia, bacterial infection, cholecystitis chronic, endotoxemia, Escherichia infection, gangrene, lung abscess, pneumonia

Reference ID: 5357793

pseudomonal, pneumonia staphylococcal, pseudomonas infection, psoas abscess, sepsis, skin bacterial infection, staphylococcal bacteremia, subcutaneous abscess, urinary tract infection, urosepsis, wound infection, abscess limb, bacterial sepsis, catheter site infection, Enterobacter bacteremia, Escherichia bacteremia, extradural abscess, genitourinary tract infection, infected gouty tophus, muscle abscess, pancreatic abscess, postoperative wound infection, pseudomonal bacteremia, pyelonephritis, renal abscess, superinfection bacterial.
[c] Hypokalemia includes blood potassium decreased.
[d] Pneumonia includes pneumonia, infectious pleural effusion, pneumonia aspiration, lung abscess, pneumonia pseudomonal, pneumonia staphylococcal, pneumonia viral.
[e] Liver enzyme increased includes gamma-glutamyltransferase increased, alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood bilirubin increased, hyperbilirubinemia.
[f]Renal impairment includes blood creatinine increased, creatinine renal clearance decreased, acute kidney injury, renal impairment, oliguria.
[g] Hemorrhage includes blood loss anemia, hematuria, epistaxis, intra-abdominal hemorrhage, esophageal varices hemorrhage, petechiae, post procedural hemorrhage, rectal hemorrhage, renal hematoma, respiratory tract hemorrhage, retroperitoneal hematoma, shock hemorrhagic, arterial hemorrhage, arteriovenous fistula site hemorrhage, gastrointestinal hemorrhage, hematoma infection, lower gastrointestinal hemorrhage, pancreatic hemorrhage.
[h] Respiratory failure includes respiratory failure, acute respiratory failure, acute respiratory distress syndrome, cyanosis, oxygen saturation decreased, hypoxia.
[i] Viral infection includes COVID-19, COVID-19 pneumonia, herpes simplex reactivation, herpes zoster, herpes zoster reactivation, human herpesvirus 6 infection, pneumonia viral, SARS-CoV-2 test positive.
[j] Hypertension includes hypertension, blood pressure increased, hypertensive crisis
[k] Leukopenia includes leukopenia, lymphocyte count decreased, neutropenia, white blood cell count decreased, lymphopenia, neutrophil count decreased.
[l] Pyrexia includes pyrexia, hyperthermia.
[m] Arthritis includes arthritis, intervertebral discitis, arthritis bacterial, arthritis reactive, spinal osteoarthritis, synovitis, osteoarthritis, rheumatoid arthritis.
[n] Thrombosis includes venous thrombosis limb, arteriovenous fistula thrombosis, atrial thrombosis, deep vein thrombosis, portal vein thrombosis, thrombosis, splenic infarction.
[o] Abdominal pain includes abdominal pain upper, abdominal tenderness.
[p] Cardiac failure includes cardiac failure, cardiac failure acute, cardiopulmonary failure, acute pulmonary edema, cardiac failure congestive, pulmonary edema.
[q] Fungal infection includes oral candidiasis, candida infection, candida sepsis, vulvovaginal candidiasis, fungal test positive, tinea pedis.
[r] Dyspnea includes dyspnea, respiratory distress.
[s] Purulent material includes abdominal abscess, lung abscess, psoas abscess, subcutaneous abscess, abscess limb, extradural abscess, muscle abscess, pancreatic abscess, renal abscess.
[t] Renal and urinary tract infection includes pyelonephritis acute, urinary tract infection, urosepsis, genitourinary tract infection, pyelonephritis, renal abscess.
[u] Arrhythmia includes arrhythmia, atrial fibrillation, supraventricular extrasystoles.
[v] Hepatic injury includes cholestasis, esophageal varices hemorrhage, hepatomegaly, liver disorder, pneumobilia, portal hypertension.
[w] Hyperglycemia includes diabetes mellitus, diabetic retinopathy, hyperglycemia.
[x] Hypersensitivity includes urticaria, cutaneous vasculitis, red man syndrome.
[y] Hypoalbuminemia includes blood albumin decreased.
[z] Hypomagnesemia includes blood magnesium decreased.
[aa] Hypotension includes hypotension, orthostatic hypotension.
[bb] Pancreatitis includes pancreatitis acute, pancreatitis chronic, obstructive pancreatitis, pancreatic abscess, pancreatic hemorrhage, pancreatitis necrotizing.
[cc] Peripheral edema includes edema peripheral, peripheral swelling.
[dd] Phlebitis includes catheter site phlebitis, infusion site phlebitis, thrombophlebitis.
[ee] Rash includes dermatitis allergic, rash, rash macular.
[ff] Seizure includes generalized tonic-clonic seizure, hypoglycemic seizure, seizure, status epilepticus.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with adverse event

7.6.1.6. Laboratory Findings, Trial BPR-CS-009

Chemistry

Chemistry findings between the two arms were similar with exception of decreased potassium, elevated chloride, elevated random glucose, elevated albumin and elevated blood urea nitrogen (BUN) which had more than a 2% risk difference of occurring in the ceftobiprole arm than in the daptomycin arm. None of the differences in the chemistry findings, with exception to hypokalemia, were felt to be directly due to ceftobiprole given that chemistry derangements are

common in critically ill subjects. There were no laboratory measurements for lipase, amylase, phosphate, magnesium, calcium, and bicarbonate.

Hypokalemia

There was a greater frequency of AEs of blood potassium increased (GQ of hypokalemia) in the ceftobiprole arm as compared with the daptomycin arm, as shown in Table 52 above; this correlated with an increased number of subjects in the ceftobiprole arm with low potassium values as noted in the table below. Hypokalemia could be explained by increased gastrointestinal losses caused by diarrhea and vomiting; both of which were higher in the ceftobiprole arm. As such, hypokalemia will be added to the Applicant's proposed labeling as an adverse reaction.

Moreover, in the ceftobiprole arm, there were 14 subjects with a low potassium value of level 3. In contrast, 9 subjects in the daptomycin arm had the same level with a risk difference of 2.8%, higher in the ceftobiprole arm. Subject profiles were evaluated for cardiac events that could be associated with hypokalemia. Upon examination of the 14 subjects, two subjects had AEs related to cardiac arrythmias, atrial fibrillation and arrhythmia, described below:

- Subject (b) (6) reported an AE of arrhythmia on Day 12. The subject had a medical history of hypertension, myocardial ischemia, myocardial infarction, diabetes mellitus, renal failure, cardiac ventricular thrombosis, decubitus ulcer, intermittent hypokalemia, intermittent hypernatremia, and atrial fibrillation. The nadir for potassium measurement occurred on Day 3 where it was measured at 2.3 mmol/L and the subject was given potassium chloride. On Day 12, the subject experienced an SAE of arrhythmia and despite cardiopulmonary resuscitation and adrenaline, the subject died. No potassium level was recorded on this day with the last potassium level of 3.2 mmol/L being recorded on Day 7.
- Subject (b) (6) reported an AE of atrial fibrillation on Day 5. The subject had a medical history of atrial fibrillation, venous thrombosis, and aortic valve sclerosis. The lowest potassium measurement occurred on Day 21 where it was measured at 2.8 mmol/L. The subject did not receive any potassium supplementation for hypokalemia but was on a standing order of electrolyte replacement (calcium chloride, magnesium chloride, potassium chloride and sodium chloride).

Table 53. Subjects With One or More Chemistry Analyte Values With Elevated or Low Values Meeting Specified Levels, Safety Population, Trial BPR-CS-009, Cohorts 1 and 2

Laboratory Parameter	Ceftobiprole N=191 n/N_w (%)	Daptomycin N=198 n/N_w (%)
Sodium, low (mEq/L)		
Level 1 (<132)	30/189 (15.9)	29/194 (14.9)
Level 2 (<130)	8/189 (4.2)	18/194 (9.3)
Level 3 (<125)	1/189 (0.5)	3/194 (1.5)
Sodium, high (mEq/L)		
Level 1 (>150)	5/189 (2.6)	2/194 (1.0)
Level 2 (>155)	2/189 (1.1)	1/194 (0.5)
Level 3 (>160)	0/189 (0)	0/194 (0)
Potassium, low (mEq/L)		
Level 1 (<3.6)	71/189 (37.6)	54/194 (27.8)
Level 2 (<3.4)	45/189 (23.8)	35/194 (18.0)
Level 3 (<3)	14/189 (7.4)	9/194 (4.6)

Laboratory Parameter	Ceftobiprole N=191 n/N_w (%)	Daptomycin N=198 n/N_w (%)
Potassium, high (mEq/L)		
Level 1 (>5.5)	39/189 (20.6)	41/194 (21.1)
Level 2 (>6)	12/189 (6.3)	17/194 (8.8)
Level 3 (>6.5)	0/189 (0)	3/194 (1.5)
Chloride, low (mEq/L)		
Level 1 (<95)	40/189 (21.2)	41/193 (21.2)
Level 2 (<88)	3/189 (1.6)	6/193 (3.1)
Level 3 (<80)	1/189 (0.5)	1/193 (0.5)
Chloride, high (mEq/L)		
Level 1 (>108)	32/189 (16.9)	19/193 (9.8)
Level 2 (>112)	7/189 (3.7)	6/193 (3.1)
Level 3 (>115)	6/189 (3.2)	2/193 (1.0)
Glucose, low (mg/dL)		
Level 1 (<70)	29/189 (15.3)	32/194 (16.5)
Level 2 (<54)	9/189 (4.8)	6/194 (3.1)
Level 3 (<40)	0/189 (0)	1/194 (0.5)
Glucose, fasting, high (mg/dL)		
Missing	NA	NA
Glucose, random, high (mg/dL)		
Level 2 (≥200)	53/189 (28.0)	46/194 (23.7)
Level 3 (>250)	29/189 (15.3)	25/194 (12.9)
Protein, total, low (g/dL)		
Level 1 (<6)	102/189 (54.0)	92/193 (47.7)
Level 2 (<5.4)	41/189 (21.7)	46/193 (23.8)
Level 3 (<5)	23/189 (12.2)	21/193 (10.9)
Albumin, low (g/dL)		
Level 1 (<3.1)	104/189 (55.0)	103/194 (53.1)
Level 2 (<2.5)	50/189 (26.5)	47/194 (24.2)
Level 3 (<2)	10/189 (5.3)	14/194 (7.2)
CPK, high (U/L)		
Level 1 (>3X ULN)	11/189 (5.8)	18/193 (9.3)
Level 2 (>5X ULN)	6/189 (3.2)	6/193 (3.1)
Level 3 (>10X ULN)	1/189 (0.5)	3/193 (1.6)
Blood urea nitrogen, high (mg/dL)		
Level 1 (>23)	71/189 (37.6)	69/193 (35.8)
Level 2 (>27)	62/189 (32.8)	58/193 (30.1)
Level 3 (>31)	53/189 (28.0)	50/193 (25.9)

Source: adlb.xpt; Software: R
Note that glucose values for hyperglycemia do not follow a nested format like the other labs. Level 1 corresponds to the diagnosis of prediabetes and is not inclusive of Level 2 and 3. Level 2 corresponds to the diagnosis of diabetes. Level 3 represents significant hyperglycemia that may indicate need for insulin or increased risk for diabetic ketoacidosis or other complications.
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration is up to 42 days plus the follow-up period up to Day 70.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: CPK, creatine phosphokinase; N, number of subjects in treatment arm; n, number of subjects meeting criteria; NA, not applicable; N_w, number of subjects with data; ULN, upper limit of normal

Renal Function

There were 6 subjects in the ceftobiprole arm who had a high creatinine of level 3 compared to 8 in the daptomycin arm. With exception of one subject in the ceftobiprole arm, (b) (6), discussed in Section 7.6.1.3, all others had a medical history of hemodialysis.

Table 54. Subjects With One or More Kidney Function Analyte Values Exceeding Specified Levels, Safety Population, Trial BPR-CS-009, Cohorts 1 and 2

Laboratory Parameter	Ceftobiprole N=191 n/N_w (%)	Daptomycin N=198 n/N_w (%)
Creatinine, high (mg/dL)		
Level 2 (≥2X baseline)	30/183 (16.4)	31/192 (16.1)
Level 3 (≥3X baseline)	6/183 (3.3)	8/192 (4.2)
eGFR, low (mL/min/1.73 m^2)		
Level 2 (≥50% decrease)	18/180 (10.0)	19/192 (9.9)
Level 3 (≥75% decrease)	2/180 (1.1)	1/192 (0.5)
CrCl, low (mL/min)		
Level 2 (≥50% decrease)	5/180 (2.8)	5/186 (2.7)
Level 3 (≥75% decrease)	0/180 (0)	1/186 (0.5)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration is up to 42 days plus the follow-up period up to Day 70.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
eGFR values are calculated from serum creatinine using chronic kidney disease epidemiology collaboration (CKD-EPI) equation.
Abbreviations: CrCl, creatinine clearance; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data

Hematology

There were 6 subjects (3.2%) in the ceftobiprole arm who had a low neutrophil count of level 3 (<0.5 x 10^3/µL) ((b) (6) (b) (6)) compared to the daptomycin arm which had 3 subjects (1.5%). When assessing the timing and concomitant medications, it appeared that in 4 of these 6 cases, the neutropenia could have been associated with ceftobiprole (b) (6) (b) (6)). In most cases, the AEs related to low WBC counts occurred later in the course of ceftobiprole (after Day 20). Of note, leukopenia has been proposed by the Applicant in section 6 of labeling.

- Subject (b) (6) was a 70-year-old female with a medical history of iron deficiency anaemia and hypertension who had a neutrophil count of 9 x 10^9 /L on Day 1. Her neutrophil count slowly declined until the end of her ceftobiprole therapy when it was 0.6 x 10^9 /L on Day 36. There was a reported AE of leukopenia on Day 35. She was not receiving any concomitant medications but was given filgrastim on Day 35. Her neutrophil count recovered back to Baseline on Day 42.

Three of these instances of ceftobiprole medocaril sodium for injection ((b) (6) (b) (6)) did not have any corresponding AEs related to low neutrophil counts

(e.g., neutropenia, leukopenia, lymphopenia, or white blood cell decreased), and these subjects are described below:

- Subject (b) (6) was a 63-year-old female with a medical history of hypertension, diabetes mellitus, and anemia who had a neutrophil count of 10.3 x 10^9 /L on Day 1. Her neutrophil count gradually decreased to 0.09 x 10^9 /L on Day 28 when she finished her course of ceftobiprole. Her neutrophil count recovered to 6.86 x 10^9 /L on Day 42. Because there were no concomitant medications and the neutrophil count improved after discontinuation of ceftobiprole, there is a possibility that ceftobiprole caused the neutropenia.
- Subject (b) (6) was a 64-year-old female with a medical history of diabetes mellitus type 2 who had a neutrophil count of 9.1 x 10^9 /L on Day 1. The subject finished a 27-day course of ceftobiprole and on Day 28, the neutrophil count was 0.03 x 10^9 /L. On Day 35, the neutrophil count recovered to 4.03 x 10^9 /L. Besides ceftobiprole, the subject was also on omeprazole from Day -2 to Day 18. However, because the neutrophil continued to decrease even after omeprazole was discontinued, it appeared to be more likely that ceftobiprole caused the neutropenia.
- Subject (b) (6) was a 47-year-old male with a medical history of chronic kidney disease requiring hemodialysis, myocardial infarction, chronic cardiac failure, and anaemia. The subject had a neutrophil count of 12.49 x 10^9 /L on Day 1. On Day 22, his neutrophil count was 0.49 x 10^9 /L. The subject also experienced cardiac failure on this day and died on the next day. Concomitant medications that were administered for more than 10 days included dexketoprofen from Day -2 to Day 23 and esomeprazole from Day 5 to Day 23. Although there are other confounding factors, it was possible that the neutropenia could have been related to ceftobiprole.

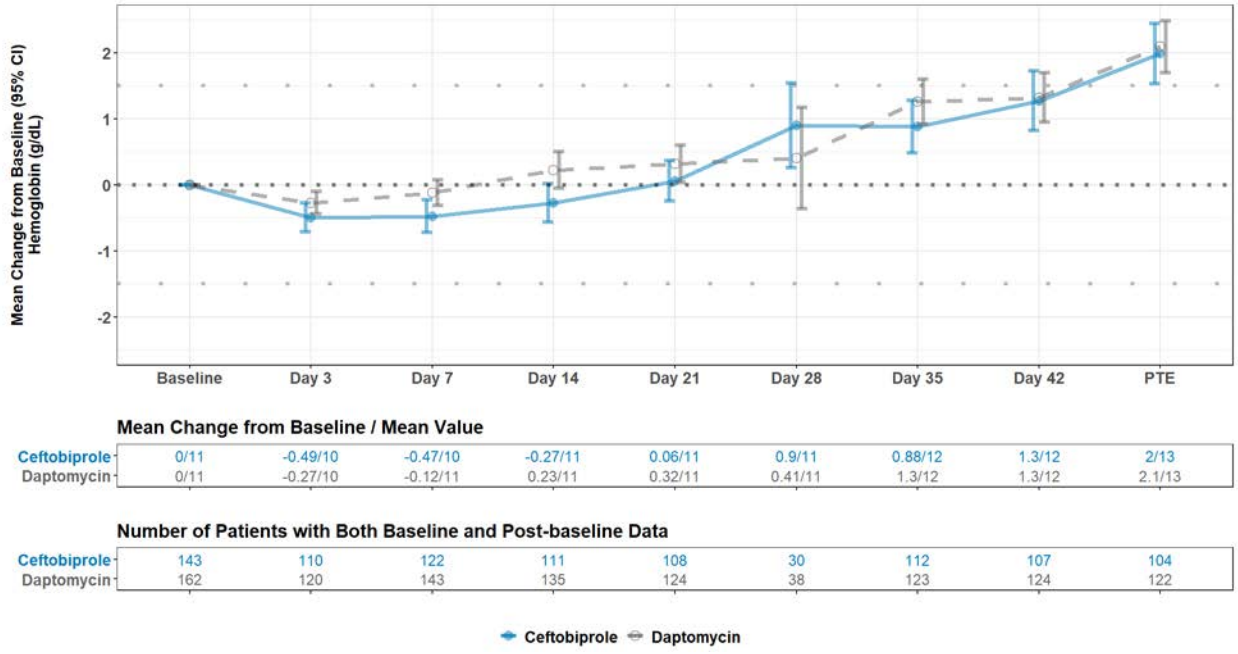
Subject profiles with AEs related to neutropenia were also reviewed. Of these, 3 subjects (b) (6) (b) (6) were not included in Table 55 below, laboratory values exceeding specified levels (i.e., with neutrophils < 0.5 x 10^3/µl):

- Subject (b) (6) was a 55-year-old male with a medical history of chronic hepatitis C, anaemia, chronic cardiac failure, and drug dependence found to have endocarditis and septic pulmonary embolism. On Day 3, the neutrophil count was 1.75x 10^9 /L (6.78x 10^9 /L on Day 1) and continued to stay at this level until ceftobiprole was stopped on Day 21 when the neutrophil count was 1.53x 10^9 /L. On Day 22, after ceftobiprole was discontinued, the investigator reported an AE of neutropenia as the neutrophil count had decreased to 0.37x 10^9 /L. There were no recorded labs after this day. Although the subject was not on any prolonged concomitant medications known to cause neutropenia, due to the quick onset and that there was no further decrease of the neutrophils while on ceftobiprole, it is unlikely that the neutropenia was associated with ceftobiprole, although it is not fully excluded.
- Subject (b) (6) was an 89-year-old female with a medical history of anaemia, and decreased creatinine renal clearance. On Day 7, the subject had a neutrophil count of 1.04x 10^9 /L (12.5x 10^9 /L on Day 1) while still on ceftobiprole therapy. The subject finished ceftobiprole therapy on Day 13. As there were no further measurements of neutrophil counts after Day 7, it could not be determined if there was a temporal association with ceftobiprole.
- Subject (b) (6) who developed an SAE of leukopenia and associated decreased in absolute neutrophil count is discussed in Section 7.6.1.3.

Subject profiles with a low lymphocyte level 3 (i.e., <0.5x 10^3 cell/µL) were examined as well as subjects with AEs of either lymphocyte count decreased or lymphopenia ([redacted]). No subjects had profiles suggesting ceftobiprole as the cause of isolated low lymphocyte counts.

Subject profiles with a low hemoglobin level 3 (i.e., decreased by >2 g/dL from Baseline) were examined for any possible signals of drug-induced hemolytic anemia which has been seen with other cephalosporins or other causes of drug related anaemia such as bone marrow suppression. No subjects had any significant patterns in hemoglobin values or laboratory abnormalities (increased lactate dehydrogenase, low haptoglobin, increased bilirubin) to suggest drug-induced hemolytic anemia; or chronology to suggest bone marrow suppression. In 11 of these subjects, the level 3 decrease in hemoglobin occurred after ceftobiprole was discontinued while 14 occurred within 7 days of starting ceftobiprole. Four subjects required transfusions. For most of the subjects, the hemoglobin initially decreased but increased while on ceftobiprole treatment without the need for transfusions. Overall, no subjects exhibited a decrease in hemoglobin to suggest ceftobiprole as a cause. Furthermore, when comparing subjects who experienced the AE of anaemia in the ceftobiprole arm compared to the daptomycin arm, both arms experienced the same number of AEs (13.1%). By the PTE, both arms had similar mean change from Baseline.

Figure 6. Mean Hemoglobin Data Change From Baseline Over Time, Safety Population, Trial BPR-CS-009



Source: adlb.xpt; Software: R
Figures do not include time points with data from fewer than 10% of randomized/enrolled subjects in all treatment groups.
Only central laboratory data are included in the analysis.
Abbreviations: CI, confidence interval, PTE, post-treatment evaluation

Table 55. Subjects With One or More Hematology Analyte Values Exceeding Specified Levels, Safety Population, Trial BPR-CS-009, Cohorts 1 and 2

Laboratory Parameter	Ceftobiprole N=191 n/N_w (%)	Daptomycin N=198 n/N_w (%)
Complete blood count		
WBC, low (10^3 cells/uL)		
Level 1 (<3.5)	43/188 (22.9)	19/194 (9.8)
Level 2 (<3)	23/188 (12.2)	12/194 (6.2)
Level 3 (<1)	3/188 (1.6)	1/194 (0.5)
WBC, high (10^3 cells/uL)		
Level 1 (>10.8)	94/188 (50.0)	99/194 (51.0)
Level 2 (>13)	58/188 (30.9)	65/194 (33.5)
Level 3 (>15)	35/188 (18.6)	40/194 (20.6)
Hemoglobin, low (g/dL)		
Level 2 (>1.5 g/dL dec. from baseline)	55/141 (39.0)	43/159 (27.0)
Level 3 (>2 g/dL dec. from baseline)	37/141 (26.2)	29/159 (18.2)
Hemoglobin, high (g/dL)		
Level 2 (>2 g/dL inc. from baseline)	62/141 (44.0)	80/159 (50.3)
Level 3 (>3 g/dL inc. from baseline)	42/141 (29.8)	45/159 (28.3)
Platelets, low (10^3 cells/uL)		
Level 1 (<140)	43/187 (23.0)	29/194 (14.9)
Level 2 (<125)	32/187 (17.1)	22/194 (11.3)
Level 3 (<100)	15/187 (8.0)	12/194 (6.2)
WBC differential		
Lymphocytes, low (10^3 cells/uL)		
Level 1 (<1)	105/188 (55.9)	72/193 (37.3)
Level 2 (<0.75)	61/188 (32.4)	42/193 (21.8)
Level 3 (<0.5)	25/188 (13.3)	12/193 (6.2)
Lymphocytes, high (10^3 cells/uL)		
Level 1 (>4)	10/188 (5.3)	8/193 (4.1)
Level 2 (>10)	0/188 (0)	0/193 (0)
Level 3 (>20)	0/188 (0)	0/193 (0)
Neutrophils, low (10^3 cells/uL)		
Level 1 (<2)	56/188 (29.8)	37/194 (19.1)
Level 2 (<1)	15/188 (8.0)	8/194 (4.1)
Level 3 (<0.5)	6/188 (3.2)	3/194 (1.5)
Eosinophils, high (10^3 cells/uL)		
Level 1 (>0.65)	25/188 (13.3)	24/193 (12.4)
Level 2 (>1.5)	2/188 (1.1)	5/193 (2.6)
Level 3 (>5)	1/188 (0.5)	0/193 (0)
Coagulation studies		
PT, high (sec)		
Level 1 (>1.1X ULN)	108/187 (57.8)	116/193 (60.1)
Level 2 (>1.3X ULN)	53/187 (28.3)	55/193 (28.5)
Level 3 (>1.5X ULN)	24/187 (12.8)	29/193 (15.0)
PTT, high (sec)		
Level 1 (>1X ULN)	104/187 (55.6)	99/193 (51.3)
Level 2 (>1.21X ULN)	45/187 (24.1)	46/193 (23.8)
Level 3 (>1.41X ULN)	34/187 (18.2)	30/193 (15.5)

Source: adlb.xpt; Software: R
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration of treatment is up to 42 days plus the follow-up period up to Day 70.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; PT, prothrombin time; PTT, partial thromboplastin time; ULN, upper limit of normal; WBC, white blood cells

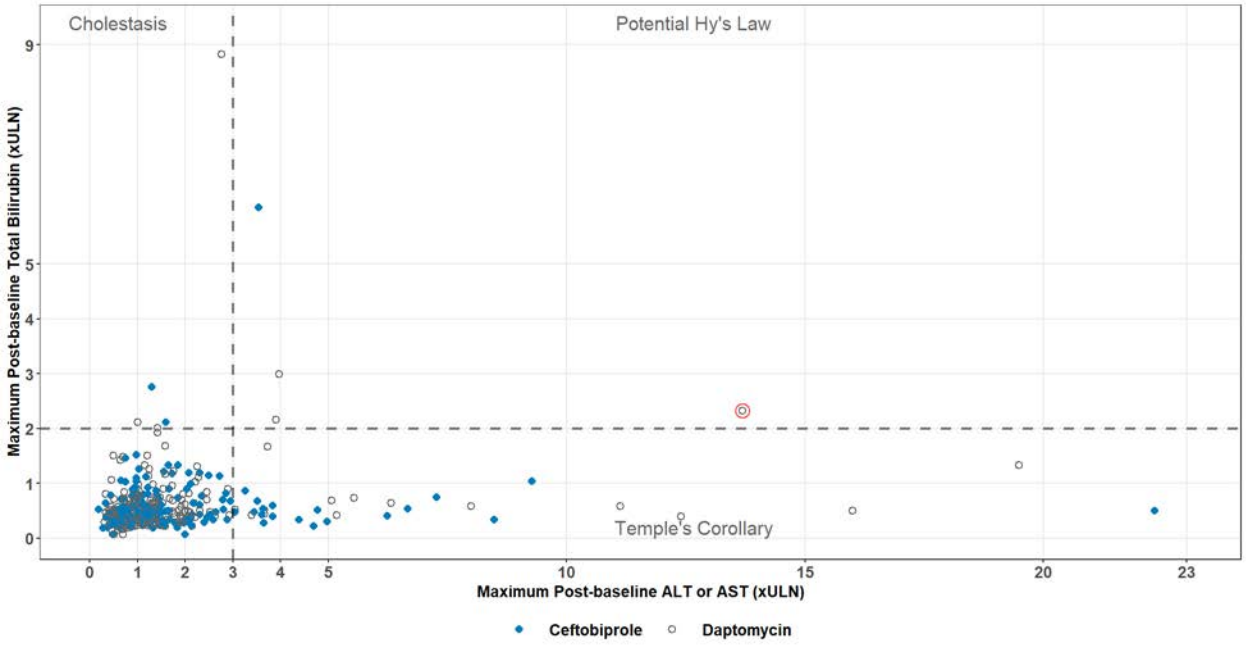
7.6.1.7. Assessment of Drug-Induced Liver Injury, Trial BPR-CS-009

Overall, the number of subjects in the four screening quadrants for drug-induced liver injury (DILI) were generally balanced between the two treatment arms. There were no identified cases of Hy's law in the ceftobiprole treatment arm.

One subject ([redacted] (b) (6)) in the ceftobiprole arm, represented by a blue dot in Figure 7, was in the potential Hy's Law quadrant but did not meet the criteria for Hy's Law as he did not have an alkaline phosphatase level of less than 2x the upper limit of normal. Also, prior to being randomized to ceftobiprole, the subject already had elevated liver enzymes (AST >3x upper limit of normal [ULN] and total bilirubin >5x ULN).

Graphical profiles of subjects noted in the cholestasis and temple's corollary quadrants were reviewed and elevated liver tests did not appear to be solely attributed to ceftobiprole.

Figure 7. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Trial BPR-CS-009, Cohorts 1 and 2



Source: adlb.xpt; Software: R
Each data point represents a subject plotted by their maximum ALT or AST versus their maximum total bilirubin values in the post-baseline period.
A potential Hy's Law case (red circle) was defined as having any post-baseline total bilirubin equal to or exceeding 2X ULN within 30 days after a post-baseline ALT or AST equal to or exceeding 3X ULN, and ALP less than 2X ULN (note ALP values are not circled). All subjects with at least one post-baseline ALT or AST and bilirubin are plotted.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal

Table 56. Subjects in Each Quadrant for Potential Hepatocellular DILI Screening Plot, Safety Population, Trial BPR-CS-009, Cohorts 1 and 2

Quadrant	Ceftobiprole N=191 n/N_w (%)	Daptomycin N=198 n/N_w (%)
Potential Hy's Law (right upper)	0/189 (0)	1/193 (0.5)
Cholestasis (left upper)	2/189 (1.1)	3/194 (1.5)
Temple's corollary (right lower)	19/189 (10.1)	14/194 (7.2)
Total	21/189 (11.1)	18/194 (9.3)

Source: adlb.xpt; Software: R
A potential Hy's Law case was defined as having any post-baseline total bilirubin equal to or exceeding 2X ULN within 30 days after a post-baseline ALT or AST equal to or exceeding 3X ULN, and ALP less than 2X ULN.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: DILI, drug-induced liver injury; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data

There were a few outliers with one or more liver test abnormality, as noted in Table 57 below. One subject had elevation in transaminases of > 10x ULN and one had an elevation in bilirubin >3 x ULN which are detailed below.

- Subject (b) (6) had a medical history significant for hypertension, chronic cardiac failure, chronic pancreatitis, stage 5 chronic kidney disease with an AV fistula, who developed ALT and AST ≥10x ULN. On Day 14, peak values of 755 U/L (baseline of 5 U/L) for ALT, 960 U/L for AST (baseline of 11U/L), 170 U/L for alkaline phosphatase (baseline of 59 U/L), and 64 U/L for gamma-glutamyl transferase (GGT) (baseline of 13 U/L). On Day 21, all liver related lab values decreased while on ceftobiprole (AST was 50 U/L and ALT 238 U/L). If the elevations were caused by ceftobiprole, it would be expected that there would be continued elevation or worsening of the liver enzymes. According to the investigator and FDA Reviewer, the transaminase elevation was less likely due to ceftobiprole. However, since there were no other apparent causes of the laboratory abnormalities, such as concomitant medications or other infection besides the primary infection, drug-induced transaminitis could not be fully excluded.
- Subject (b) (6) had a >3x ULN elevation in bilirubin on Day 8 (from 166 U/L on Day 1 to a peak of 708 U/L on Day 10). There were also increases in AST (20.5 U/L on Day 1 to 164.8 U/L on Day 10), ALT (19 U/L on Day 1 to 229.4 U/L on Day 10) and GGT (93 U/L on Day 1 to 528 U/L on Day 10). Ceftobiprole was discontinued on Day 9 and all values started to decrease on Day 13 and normalized by Day 41. The FDA reviewer agrees with the investigator that it is probable that ceftobiprole could have caused elevations of the liver enzymes given the temporal association.

Table 57. Subjects With One or More Liver Biochemistry Analyte Values Exceeding Level 2, Safety Population, Trial BPR-CS-009, Cohorts 1 and 2

Laboratory Parameter	Ceftobiprole N=191 n/N_w (%)	Daptomycin N=198 n/N_w (%)
Alkaline phosphatase, high (U/L)		
Level 2 (>2X ULN)	30/189 (15.9)	23/193 (11.9)
Level 3 (>3X ULN)	12/189 (6.3)	13/193 (6.7)
Alanine aminotransferase, high (U/L)		
Level 2 (>5X ULN)	5/189 (2.6)	9/194 (4.6)
Level 3 (>10X ULN)	1/189 (0.5)	1/194 (0.5)
Aspartate aminotransferase, high (U/L)		
Level 2 (>5X ULN)	5/189 (2.6)	6/194 (3.1)

Laboratory Parameter	Ceftobiprole N=191 n/N_w (%)	Daptomycin N=198 n/N_w (%)
Level 3 (>10X ULN)	1/189 (0.5)	5/194 (2.6)
Bilirubin, total, high (mg/dL)		
Level 2 (>2X ULN)	3/189 (1.6)	6/194 (3.1)
Level 3 (>3X ULN)	1/189 (0.5)	1/194 (0.5)

Source: adlb.xpt; Software: R
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration is up to 42 days plus the follow-up period up to Day 70.
For specific evaluation of drug-induced liver injury (DILI), see the figures "Hepatocellular Drug-Induced Liver Injury Screening Plot..." and "Cholestatic Drug-Induced Liver Injury Screening Plot..." and the tables "Subjects in Each Quadrant for Potential Hepatocellular DILI Screening Plot..." and "Subjects in Each Quadrant for Cholestatic DILI Screening Plot…"
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; ULN, upper limit of normal

All other subjects (n = 13) with a GQ related to liver enzyme increase (Table 52) were reviewed and no other cases could be solely attributed to ceftobiprole, although liver enzyme increased and hyperbilirubinemia cannot be fully ruled out. These adverse reactions have been proposed in labeling by the Applicant.

Overall, in both the ceftobiprole and daptomycin arms, there were no deaths associated with liver injury and the AEs relating to drug-induced liver injury Table 58 were similar in both arms.

Table 58. Adverse Events of Special Interest Assessment, Safety Population, Trial BPR-CS-009

Drug-Induced Liver Injury Assessment	Ceftobiprole N=191 n (%)	Daptomycin N=198 n (%)
AE grouping related to AESI	7 (3.7)	8 (4.0)
Alanine aminotransferase increased	5 (2.6)	6 (3.0)
Aspartate aminotransferase increased	5 (2.6)	5 (2.5)
Cholestasis	2 (1.0)	1 (0.5)
Hepatomegaly	0	1 (0.5)
Maximum severity		
Death	0	0
Life-threatening	0	0
Severe	0	1 (0.5)
Moderate	4 (2.1)	3 (1.5)
Mild	3 (1.6)	4 (2.0)
Serious	1 (0.5)	0
Deaths	0	0

Drug-Induced Liver Injury Assessment	Ceftobiprole N=191 n (%)	Daptomycin N=198 n (%)
Resulting in discontinuation	1 (0.5)	0
Relatedness	1 (0.5)	2 (1.0)
Number of subjects with adverse events with end dates on or before treatment end dates	0/7 (0)	3/8 (37.5)
Duration, days (from AE start date to AE end date)		
Mean (SD)	NA	11 (4.6)
Median (Q1, Q3)	NA	12 (9, 13.5)
Min, max	NA, NA	6, 15
Number of subjects with adverse events (occurred on or before treatment end date) with end dates missing (no end dates reported, assumed that AE continuing)	2/7 (28.6)	1/8 (12.5)
Number of subjects with adverse events (occurred on or before treatment end date) with end dates after treatment end dates	3/7 (42.9)	3/8 (37.5)
Mean (SD)	24.3 (9.6)	21 (19.5)
Median (Q1, Q3)	26 (20, 29.5)	14 (10, 28.5)
Min, max	14, 33	6, 43

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as adverse events which occurred between the start of the first dosing up to and including the scheduled post treatment evaluation visit.
Duration of treatment is up to 42 days plus the follow-up period up to Day 70.
Relatedness is determined by investigator.
Abbreviations: AE, adverse event; AESI, adverse events of special interest; N, number of subjects in treatment arm; n, number of subjects with adverse event; NA, not applicable; Q1, first quartile; Q3, third quartile; SD, standard deviation

7.6.1.8. Vital Signs' Analyses, Trial BPR-CS-009

The pulse and respiratory rate in both arms were similar throughout the trial, and decreased to more normal values as would be expected during improvement in infection. The mean body temperature change from Baseline over time was also similar in both arms.

SBP

Out of the 7 subjects with TEAEs of hypertension, 2 [redacted] (b) (6)) did not have past medical history of hypertension. These two had a maximum postbaseline SBP of 170 and 140 mm Hg, respectively. One subject [redacted] (b) (6)) required antihypertensive medications. The percentage of subjects with maximum SBP is shown below. Both arms appear to have similar distribution, with a slightly higher number of subjects in the ceftobiprole arm with SBP ≥140 mmHg. Adverse reaction of hypertension will be added to labeling.

Table 59. Percentage of Subjects With Maximum Systolic Blood Pressure by Category of Blood Pressure Post-Baseline, Safety Population, Trial BPR-CS-009

Systolic Blood Pressure (mm Hg)	Ceftobiprole N=191 n/Nw (%)	Daptomycin N=198 n/Nw (%)
<90	0/190 (0)	0/196 (0)
≥90	190/190 (100)	196/196 (100)
≥120	185/190 (97.4)	192/196 (98.0)
≥140	93/190 (48.9)	84/196 (42.9)
≥160	15/190 (7.9)	15/196 (7.7)
≥180	3/190 (1.6)	6/196 (3.1)

Source: advs.xpt; Software: R
Abbreviations: N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data

Diastolic Blood Pressure

A similar distribution can be seen in the percentage of subjects with maximum diastolic blood pressure; both arms appear to have similar distribution.

Table 60. Percentage of Subjects With Maximum Diastolic Blood Pressure by Category of Blood Pressure Post-Baseline, Safety Population, Trial BPR-CS-009, Cohorts 1 and 2

Diastolic Blood Pressure (mm Hg)	Ceftobiprole N=191 n/N_w (%)	Daptomycin N=198 n/N_w (%)
<60	1/190 (0.5)	0/196 (0)
≥60	189/190 (99.5)	196/196 (100)
≥90	66/190 (34.7)	60/196 (30.6)
≥110	2/190 (1.1)	0/196 (0)
≥120	1/190 (0.5)	0/196 (0)

Source: advs.xpt; Software: R
Abbreviations: N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data

7.6.1.9. Subgroup Analyses, Trial BPR-CS-009

Several subgroups were examined based on demographic variables. For most subgroups, the percent of AEs occurred at similar rates. However, there was a higher percentage of AEs in subjects ≥65 years old in the ceftobiprole arm as compared to the daptomycin arm. There was also a higher percentage of AEs seen in subjects ≥65 years old compared to subjects ≤65 years old within the group of subjects receiving ceftobiprole, however, the types of AEs seen were similar. A similar trend was seen among subjects ≥75 years old, however, the size of this subgroup was small. In the subgroup of subjects ≥75 years old, there was a similar frequency of SAEs (seven subjects in the ceftobiprole arm (41%) experienced 13 SAEs while 10 subjects in the daptomycin arm (48%) experienced 19 SAEs). In terms of mortality, there were 6 deaths in the ceftobiprole arm (35%) compared to 7 deaths in the daptomycin arm (33%). The FDA reviewer agrees with the investigator that none of these SAEs or deaths in the ceftobiprole arm could be attributed to the drug.

In addition, the majority of subjects were White, non-Hispanic or Latino, and from outside of the US. The frequency of AEs in these subgroups was similar to the frequency of AEs occurring in the entire safety population. The other demographic groups were too small to make any conclusions regarding safety, but no major differences are anticipated.

Table 61. Overview of Adverse Events by Demographic Subgroup, Safety Population, Trial BPR-CS-009

Characteristic	Ceftobiprole N=191 n/N_s (%)	Daptomycin N=198 n/N_s (%)
Sex		
Female	43/61 (70.5)	40/58 (69.0)
Male	78/130 (60.0)	77/140 (55.0)
Age group, years		
18 to 34	7/20 (35.0)	11/19 (57.9)
35 to 64	72/113 (63.7)	65/116 (56.0)
65 to 74	29/41 (70.7)	28/42 (66.7)
≥75	13/17 (76.5)	13/21 (61.9)
Age group ≥65, years		
≥65	42/58 (72.4)	41/63 (65.1)

Characteristic	Ceftobiprole N=191 n/N_s (%)	Daptomycin N=198 n/N_s (%)
Race		
White	113/181 (62.4)	112/192 (58.3)
Asian	1/1 (100)	1/1 (100)
Black or African American	3/4 (75.0)	4/5 (80.0)
Native Hawaiian or Other Pacific Islander	0/1 (0)	0/0 (NA)
Other	4/4 (100)	0/0 (NA)
Ethnicity		
Hispanic or Latino	11/14 (78.6)	14/15 (93.3)
Not Hispanic or Latino	109/176 (61.9)	102/182 (56.0)
Not reported	1/1 (100)	1/1 (100)
Geographic Region		
United States	3/5 (60.0)	4/5 (80.0)
Non-United States	118/186 (63.4)	113/193 (58.5)

Source: adae.xpt; Software: R
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with adverse event; NA, not applicable; N_s, total number of subjects for each specific subgroup and were assigned to that specific arm

7.6.2. Acute Bacterial Skin/Soft Tissue Infection, Trial BPR-CS-008

7.6.2.1. Overview of Treatment-Emergent Adverse Events Summary, Trial BPR-CS-008

The overall incidence of TEAEs was 44.3% in the ceftobiprole arm and 38.3% in the vancomycin and aztreonam arm. Most TEAEs in the ceftobiprole arm were mild or moderate, and there were fewer severe TEAEs as compared to the vancomycin and aztreonam arm (2.7% versus 7.0%). There was a lower incidence of SAEs in the ceftobiprole versus the vancomycin and aztreonam arm (1.8% and 3.5%, respectively). Treatment discontinuation due to TEAEs was also lower in the ceftobiprole arm compared to the vancomycin and aztreonam arm (1.8% versus 2.9%).

Five subjects in each arm had interruptions of their respective treatment. In the ceftobiprole arm, the AEs leading to interruption were blood creatinine increased in two subjects and the following in one subject each: pruritus, vomiting, and both headache and nausea. None were SAEs and all subjects recovered.

Table 62. Overview of Adverse Events, Safety Population, Trial BPR-CS-008

Event Category	Ceftobiprole N=334 n (%)	Vancomycin + Aztreonam N=342 n (%)
SAE	6 (1.8)	12 (3.5)
SAEs with fatal outcome	1 (0.3)	2 (0.6)
Life-threatening SAEs	0	1 (0.3)
AE leading to permanent discontinuation of study drug	6 (1.8)	10 (2.9)
AE leading to dose modification of study drug	5 (1.5)	5 (1.5)
AE leading to interruption of study drug	5 (1.5)	5 (1.5)
AE leading to reduction of study drug	0	0
AE leading to dose delay of study drug	0	0

Event Category	Ceftobiprole N=334 n (%)	Vancomycin + Aztreonam N=342 n (%)
Any AE	148 (44.3)	131 (38.3)
Severe and worse	9 (2.7)	24 (7.0)
Moderate	57 (17.1)	47 (13.7)
Mild	82 (24.6)	60 (17.5)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any adverse event which occurred between the start of the first dosing up to and including the scheduled last follow-up.
Duration of treatment is up to 14 days.
Severity as assessed by the Applicant.
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event

7.6.2.2. Deaths, Trial BPR-CS-008

In trial BPR-CS-008, both the ceftobiprole and vancomycin and aztreonam arm had a similar number of deaths [(0.3% versus 0.6%) respectively, as shown in Table 62].

The single death in the ceftobiprole arm occurred in subject (b) (6) who was a 36-year-old female with a medical history for illicit drug use (heroin) who completed 6 days of the study drug. On Day 31, the subject's father disclosed that the subject died due to a heroin overdose. The cause of death was not related to study drug per the investigator and the FDA reviewer.

Table 63. Deaths, Safety Population, Trial BPR-CS-008

Preferred Term	Ceftobiprole N=334 n (%)	Vancomycin + Aztreonam N=342 n (%)
Any AE leading to death	1 (0.3)	2 (0.6)
Accidental overdose	1 (0.3)	0
Cardiac arrest	0	1 (0.3)
Multiple organ dysfunction syndrome	0	1 (0.3)
Respiratory failure	0	1 (0.3)
Septic shock	0	1 (0.3)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any adverse event which occurred between the start of the first dosing up to and including the scheduled last follow-up.
Duration of treatment is up to 14 days.
For subject-level data, see the table "List of Adverse Events Leading to Death…"
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with adverse event

7.6.2.3. Serious Treatment-Emergent Adverse Events, Trial BPR-CS-008

The incidence of SAEs was lower in the ceftobiprole arm (1.8%) than in the vancomycin and aztreonam arm (3.5%) Of the 6 SAEs in the ceftobiprole arm, 5 had a non-fatal outcome. The SAE with a fatal outcome is discussed above in the Section 7.6.2.2. In the ceftobiprole arm, only the Infections and Infestations SOC contained more than one PT (i.e., pneumonia and skin bacterial infection), however, the overall risk difference in this SOC was greater in the vancomycin and aztreonam arm.

Table 64. Subjects With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Trial BPR-CS-008

System Organ Class Preferred Term	Ceftobiprole N=334 n (%)	Vancomycin + Aztreonam N=342 n (%)
Any SAE	6 (1.8)	12 (3.5)
Cardiac disorders (SOC)	0	1 (0.3)
Cardiac arrest	0	1 (0.3)
Gastrointestinal disorders (SOC)	0	1 (0.3)
Abdominal pain	0	1 (0.3)
Vomiting	0	1 (0.3)
General disorders and administration site conditions (SOC)	0	1 (0.3)
Multiple organ dysfunction syndrome	0	1 (0.3)
Immune system disorders (SOC)	0	1 (0.3)
Multiple allergies	0	1 (0.3)
Infections and infestations (SOC)	2 (0.6)	8 (2.3)
Pneumonia	1 (0.3)	0
Necrotising fasciitis	0	1 (0.3)
Sepsis	0	1 (0.3)
Septic shock	0	1 (0.3)
Skin bacterial infection	1 (0.3)	3 (0.9)
Cellulitis	0	2 (0.6)
Injury, poisoning and procedural complications (SOC)	1 (0.3)	0
Accidental overdose	1 (0.3)	0
Musculoskeletal and connective tissue disorders (SOC)	0	1 (0.3)
Rhabdomyolysis	0	1 (0.3)
Renal and urinary disorders (SOC)	0	1 (0.3)
Acute kidney injury	0	1 (0.3)
Respiratory, thoracic and mediastinal disorders (SOC)	1 (0.3)	2 (0.6)
Bronchial obstruction	1 (0.3)	0
Dyspnea	0	1 (0.3)
Respiratory failure	0	1 (0.3)
Skin and subcutaneous tissue disorders (SOC)	1 (0.3)	1 (0.3)
Pruritus	1 (0.3)	0
Rash	1 (0.3)	0
Angioedema	0	1 (0.3)
Vascular disorders (SOC)	1 (0.3)	1 (0.3)
Deep vein thrombosis	1 (0.3)	1 (0.3)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any adverse event which occurred between the start of the first dosing up to and including the scheduled last follow-up.
Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Duration of treatment is up to 14 days.
Abbreviations: interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; SAE, serious adverse event; SOC, system organ class

The following subjects in the ceftobiprole arm had SAEs. SAEs related to AEs of special interest such as pneumonia and thromboembolism are also discussed in this section. Of the six SAEs, rash and pruritis were probably related to ceftobiprole.

- Subject (b) (6) had a reported an SAE of rash and pruritis causing prolonged hospitalization. This was a 49-year-old male with no significant past medical history who developed an erythematous papular pruritic rash over his trunk and extremities 10 days after starting ceftobiprole for which ceftobiprole was discontinued. Concomitant medications included paracetamol, omeprazole, and enoxaparin. Two days after discontinuing ceftobiprole and receiving methylprednisolone and antihistamine therapy, the rash was completely resolved without sequelae. Due to the lack of other concomitant medications that have a high likelihood of causing the SAEs along with the temporal relationship, the FDA reviewer agrees with the investigator that the SAE was probably related to ceftobiprole.
- Subject (b) (6) had a reported an SAE of bronchial obstruction causing prolonged hospitalization. This was an 82-year-old female with a medical history of arterial hypertension who developed bronchospasms, cough, tachypnea, and scarce expectoration after 3 days of ceftobiprole treatment. She finished a 5-day regimen and ultimately, she recovered from the broncho-obstructive syndrome. The FDA reviewer agrees with the Applicant that the SAE was not related to ceftobiprole because despite the continuation of ceftobiprole, the broncho-obstructive symptom did not worsen.
- Subject (b) (6) had a reported an SAE of pneumonia causing hospitalization. This was a 64-year-old male with a medical history significant for alcohol use, methamphetamine abuse, IV heroin use, who was hospitalized for acute CAP approximately one month after ceftobiprole was discontinued (end of ceftobiprole treatment was Day 11 and hospitalization on Day 37). The FDA reviewer agrees with the investigator that the SAE was not related to ceftobiprole.
- Subject (b) (6) had a reported SAE of skin bacterial infection causing hospitalization. She was a 34-year-old female with a medical history of intravenous heroin use, tobacco use, and schizo-affective schizophrenia who, after 5 days of ceftobiprole, had worsening of primary ABSSSI with tenderness, warmth, erythema, and pain. A CT scan showed a well-defined area of fluid collection anterior to the deep fascia of the right thigh, slightly extending to the lateral aspect suggesting abscess formation. Incision and drainage were not done because the subject left before the procedure took place. While she was inpatient, she received two days of piperacillin-tazobactam, 1 day of meropenem, and 1 day of levofloxacin. By Day 35, the worsening of primary ABSSSI was considered resolved. The FDA reviewer agrees with the investigator that the SAE was not related to ceftobiprole as this could have been related to incomplete source control or worsening infection due to risk factors associated with intravenous drug use.

Reference ID: 5357793

- Subject (b) (6) had a reported SAE of deep vein thrombosis (DVT) causing hospitalization. This was a 39-year-old male with a medical history of intravenous heroin drug use, tobacco use, past tibial/fibula fractures who was randomized to ceftobiprole for right calf cellulitis. On the day of randomization, the subject complained of bilateral lower leg swelling with moderate pain and redness with the latter two symptoms starting 10 days prior. A DVT was found on ultrasound and the subject was admitted to the hospital 5 days after starting ceftobiprole; ceftobiprole was discontinued and switched to non-study antibacterial drugs. Because the subject had symptoms of a DVT prior to starting ceftobiprole, the FDA reviewer agrees with the investigator that the SAE is unlikely related to ceftobiprole.

7.6.2.4. Adverse Events and FDA Medical Queries Leading to Treatment Discontinuation, Trial BPR-CS-008

The incidence of AEs that led to treatment discontinuation was lower in the ceftobiprole arm compared to the vancomycin and aztreonam arm (1.8% versus 2.9%). The AEs that led to treatment discontinuation in the ceftobiprole arm included rash, pruritus, dysgeusia, deep vein thrombosis, wound infection, and skin bacterial infection. The subjects with AEs of rash, pruritis, and deep vein thrombosis leading to discontinuation are discussed in the Section 7.6.2.3.

The only AE that led to more than one discontinuation was skin bacterial infection (one is discussed in the SAE section, and one is noted below):

- Subject (b) (6) was a 36-year-old female with a medical history of intravenous heroin use, diabetes mellitus type II, and hepatitis C who, after 6 days of ceftobiprole, continued to have worsening of primary ABSSSI (started on Day 3). Ceftobiprole was discontinued on Day 6 and the AE resolved on Day 35. No other concomitant antibacterial drugs were given during Day 0 and Day 35 (when the subject was discontinued from the trial). The worsening of primary ABSSSI could be interpreted as the lack of efficacy of ceftobiprole in this subject rather than an AE per se; however, given that no additional antibacterial drugs were initiated, it is difficult to comment on the association of this event with ceftobiprole. The investigator considered it unrelated to trial drug.

Reference ID: 5357793

Table 65. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Trial BPR-CS-008

System Organ Class Preferred Term	Ceftobiprole N=334 n (%)	Vancomycin + Aztreonam N=342 n (%)
Any AE leading to discontinuation	6 (1.8)	10 (2.9)
Blood and lymphatic system disorders (SOC)	0	2 (0.6)
Anemia	0	1 (0.3)
Thrombocytopenia	0	1 (0.3)
Gastrointestinal disorders (SOC)	0	2 (0.6)
Abdominal pain	0	1 (0.3)
Nausea	0	1 (0.3)
Vomiting	0	2 (0.6)
Infections and infestations (SOC)	3 (0.9)	3 (0.9)
Wound infection	1 (0.3)	0
Skin bacterial infection	2 (0.6)	3 (0.9)
Nervous system disorders (SOC)	1 (0.3)	0
Dysgeusia	1 (0.3)	0
Psychiatric disorders (SOC)	0	1 (0.3)
Post-traumatic stress disorder	0	1 (0.3)
Skin and subcutaneous tissue disorders (SOC)	1 (0.3)	2 (0.6)
Pruritus	1 (0.3)	0
Rash	1 (0.3)	1 (0.3)
Urticaria	0	1 (0.3)
Vascular disorders (SOC)	1 (0.3)	0
Deep vein thrombosis	1 (0.3)	0

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any adverse event which occurred between the start of the first dosing up to and including the scheduled last follow-up.
Duration of treatment is up to 14 days.
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with adverse event; SOC, system organ class

7.6.2.5. Treatment-Emergent Adverse Events, Trial BPR-CS-008

AEs occurred in 148 of 334 subjects (44.3%) in the ceftobiprole arm and in 131 of 342 subjects (38.3%) in the comparator arm. The AEs that occurred with a risk difference of ≥1% in the ceftobiprole arm were gastrointestinal-related such as nausea (10.8% vs 5.6%), diarrhea (6.3% vs 4.7%), and dysgeusia (2.1% vs 0%). All AEs of nausea, vomiting or diarrhea were of mild to moderate severity and the majority had dose interruption or modification. More than half of these AEs were thought to be possibly/probably related to ceftobiprole by the investigator. As with the 009 trial, the GQ of bacterial infection was common in both arm but was not related to ceftobiprole and likely related to underlying medical conditions and was therefore, not included in the label.

There were no reports of diarrhea associated with *Clostridioides difficile*. Gastrointestinal symptoms such as nausea, vomiting, and diarrhea are often considered common adverse reactions associated with antibacterial drugs, and are proposed by the Applicant in labeling.

Leukopenia

The AEs related to leukopenia were reported in three subjects in the ceftobiprole arm (0.9%) and 2 subjects in the vancomycin and aztreonam arm (0.6%). The TEAEs in the ceftobiprole arm

were leukopenia and lymphopenia. None were considered serious. The subjects are discussed in the section discussing laboratory values.

Renal Impairment

There were 2 subjects in the ceftobiprole arm (0.6%) and 4 subjects in the vancomycin and aztreonam arm (1.2%) who experienced AEs related to the GQ of renal impairment (blood creatinine increased occurred in 2 subjects receiving ceftobiprole and acute kidney injury occurred in 4 subjects receiving vancomycin and aztreonam).The 2 subjects who experienced the AE of blood creatinine increased both had the decreasing creatinine while on ceftobiprole therapy, making it unlikely that ceftobiprole caused the AE.

Thrombosis

One subject (0.6%) in each arm experienced thrombosis (deep vein thrombosis in the GQ of thrombosis). The subject (b) (6)) with an AE of deep vein thrombosis in the ceftobiprole arm was previously discussed in the SAE section.

Rash/ Hypersensitivity

There were 7 (2.1%) in the ceftobiprole arm and 9 (2.6%) in the vancomycin and aztreonam arm who had AEs related to rash [rash (n=5), drug eruption (n=1), dermatitis (n=1)]. One subject (b) (6) had the drug withdrawn (due to an SAE of rash as discussed in Section 7.6.2.3). Adverse events related to rash in five other subjects were thought to be related to ceftobiprole (rash and dermatitis) by the investigator.

There were no subjects in the ceftobiprole arm who experienced any AEs related to hypersensitivity (GQ containing PTs: urticaria, drug hypersensitivity, angioedema).

Seizure

There were no AEs related to seizure in the ceftobiprole arm.

Liver enzyme Increase

These are discussed in Section 7.6.2.7.

Table 66. Grouped Queries by Preferred Term, Showing Terms Occurring in at Least 1% of Subjects in the Ceftobiprole Arm, Safety Population, Trial BPR-CS-008

Grouped Query Preferred Term	Ceftobiprole N=334 n (%)	Vancomycin N=342 n (%)
Nausea	36 (10.8)	19 (5.6)
Bacterial Infection[a]	25 (7.5)	32 (9.4)
Diarrhea	21 (6.3)	16 (4.7)
Headache[b]	21 (6.3)	24 (7.0)
Liver enzyme increased[c]	8 (2.4)	11 (3.2)
Nasopharyngitis[d]	8 (2.4)	4 (1.2)
Dysgeusia	7 (2.1)	0
Injection site reaction[e]	7 (2.1)	9 (2.6)
Rash[f]	7 (2.1)	9 (2.6)
Vomiting	7 (2.1)	7 (2.0)
Constipation	6 (1.8)	4 (1.2)
Drug withdrawal syndrome	4 (1.2)	6 (1.8)
Purulent material[g]	4 (1.2)	6 (1.8)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any adverse event which occurred between the start of the first dosing up to and including the scheduled last follow-up.
Duration of treatment is up to 14 days.
Recoded terms are defined based on the dictionary created in conjunction with the clinical team.
Adverse Events are sorted by prevalence in the Ceftobiprole arm.
[a] Bacterial infection includes skin bacterial infection, cellulitis, abscess limb, wound infection, device related infection, subcutaneous abscess, abdominal abscess, necrotizing fasciitis, pseudomonas infection, sepsis, urinary tract infection, wound abscess.
[b] Headache includes headache, migraine.
[c] Liver enzyme increased includes alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased, blood alkaline phosphatase increased.
[d] Nasopharyngitis includes upper respiratory tract infection, nasopharyngitis.
[e] Injection site reaction includes injection site reaction, infusion related reaction.
[f] Rash includes rash, dermatitis, drug eruption.
[g] Purulent material includes abscess limb, subcutaneous abscess, abdominal abscess, wound abscess.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with adverse event

7.6.2.6. Laboratory Findings, Trial BPR-CS-008

Chemistry findings between the two arms were similar with the exception of elevated blood urea nitrogen where level 3 elevations were greater in the vancomycin and aztreonam arm than in the ceftobiprole arm (3.6% vs 0.9%).

There were more subjects in the ceftobiprole arm with low potassium of level 2 and 3 compared to the vancomycin and aztreonam arm. Of the subjects who experienced a decrease in potassium of level 3 (b) (6), none experienced any cardiac related AEs.

Table 67. Subjects With Selected Chemistry Values Level 2 or Higher by Treatment Arm, Safety Population, Trial BPR-CS-008

Laboratory Parameter	Ceftobiprole N=334 n/N_w (%)	Vancomycin + Aztreonam N=342 n/N_w (%)
Sodium, low (mEq/L)		
Level 2 (<130)	3/329 (0.9)	0/336 (0)
Level 3 (<125)	2/329 (0.6)	0/336 (0)
Potassium, low (mEq/L)		
Level 2 (<3.4)	12/329 (3.6)	8/336 (2.4)
Level 3 (<3)	2/329 (0.6)	0/336 (0)

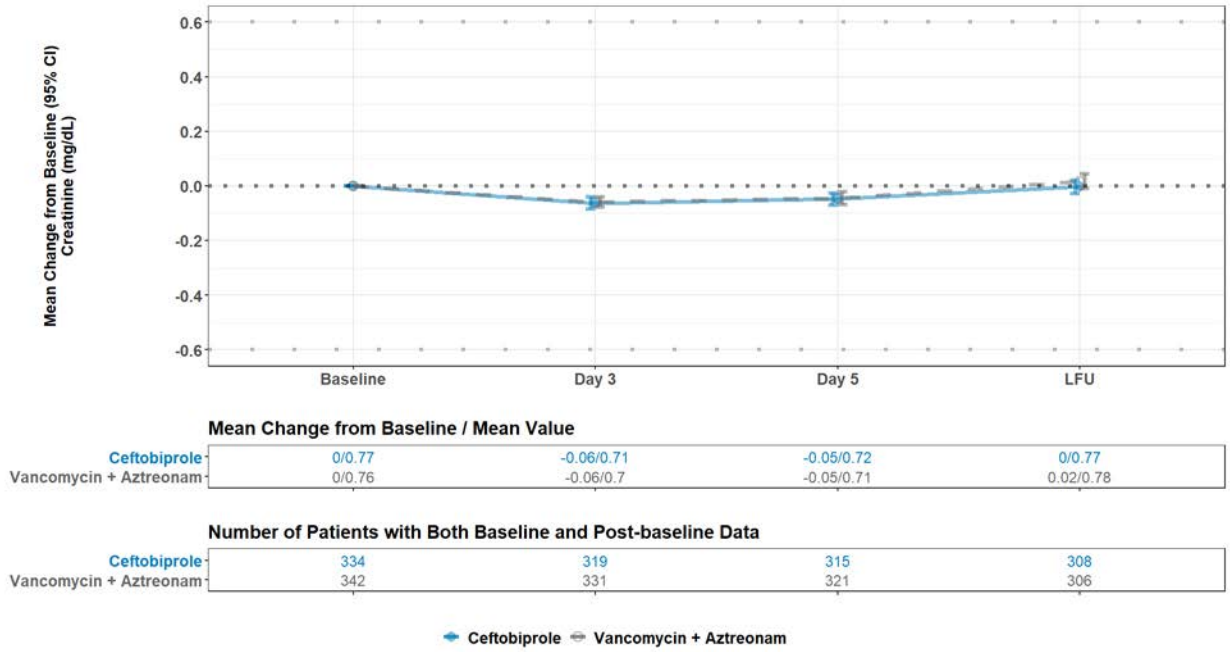
Potassium, high (mEq/L)		
Level 2 (>6)	4/329 (1.2)	2/336 (0.6)
Level 3 (>6.5)	3/329 (0.9)	0/336 (0)
Glucose, random, high (mg/dL)		
Level 2 (≥200)	33/329 (10.0)	35/336 (10.4)
Level 3 (>250)	24/329 (7.3)	20/336 (6.0)
Protein, total, low (g/dL)		
Level 2 (<5.4)	4/329 (1.2)	9/336 (2.7)
Level 3 (<5)	0/329 (0)	3/336 (0.9)
Blood urea nitrogen, high (mg/dL)		
Level 2 (>27)	11/329 (3.3)	13/336 (3.9)
Level 3 (>31)	3/329 (0.9)	12/336 (3.6)

Source: adlb.xpt; Software: R
Note that glucose values for hyperglycemia do not follow a nested format like the other labs. Level 1 corresponds to the diagnosis of prediabetes and is not inclusive of Level 2 and 3. Level 2 corresponds to the diagnosis of diabetes. Level 3 represents significant hyperglycemia that may indicate need for insulin or increased risk for diabetic ketoacidosis or other complications.
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration of treatment is up to 14 days.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects meeting criteria; NA, not applicable; N_w, number of subjects with data

While there was a higher incidence of level 2 decrease in creatinine clearance in the ceftobiprole arm (2.2% vs 0.6%), level 2 creatinine elevations were lower in the ceftobiprole arm (0.9% vs. vs 2.4%). Although one would expect a direct correlation between these two parameters, there were subjects with missing values where one subject had recorded values for one parameter but not the other, resulting in the discordance. Low estimated glomerular filtration rate values trended similarly with creatinine clearance, and were higher in the vancomycin and aztreonam arm. Both arms had similar mean changes in creatinine from baseline throughout the trial and returned to Baseline by the last follow-up.

Reference ID: 5357793

Figure 8. Mean Laboratory (Kidney Function) Data Change From Baseline Over Time, Safety Population, Trial BPR-CS-008



Source: adlb.xpt; Software: R
Figures do not include time points with data from fewer than 10% of randomized/enrolled patients in all treatment groups.
Only central laboratory data are included in the analysis.
eGFR values are calculated from serum creatinine using chronic kidney disease epidemiology collaboration (CKD-EPI) equation.
Abbreviations: CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; LFU, last follow-up (28-35 days after last treatment)

Table 68. Subjects With One or More Kidney Function Analyte Values Exceeding Level 2 or Higher, Safety Population, Trial BPR-CS-008

Laboratory Parameter	Ceftobiprole N=334 n/N_w (%)	Vancomycin + Aztreonam N=342 n/N_w (%)
Creatinine, high (mg/dL)		
Level 2 (≥2X baseline)	3/329 (0.9)	8/336 (2.4)
Level 3 (≥3X baseline)	0/329 (0)	1/336 (0.3)
eGFR, low (mL/min/1.73 m^2)		
Level 2 (≥50% decrease)	1/324 (0.3)	5/334 (1.5)
Level 3 (≥75% decrease)	0/324 (0)	1/334 (0.3)
CrCl, low (mL/min)		
Level 2 (≥50% decrease)	7/323 (2.2)	2/325 (0.6)
Level 3 (≥75% decrease)	0/323 (0)	0/325 (0)

Source: adlb.xpt; Software: R
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration of treatment is up to 14 days.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
eGFR values are calculated from serum creatinine using chronic kidney disease epidemiology collaboration (CKD-EPI) equation.
Abbreviations: CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data

There were no significant imbalances in hematological laboratory parameters between the ceftobiprole and vancomycin and aztreonam arm. However, subjects with a low WBC of level 3, a low lymphocyte of level 3, AEs of neutropenia, and lymphopenia were reviewed for an association between ceftobiprole and hematological abnormalities.

While there were no subjects in the ceftobiprole arm with a low WBC of level 3, there were 5 subjects in the ceftobiprole arm with a low lymphocyte count of level 3. All subjects, except for one subject (b) (6), had low lymphocyte counts prior to being randomized to ceftobiprole and this subject is discussed below:

- Subject (b) (6) was a 54-year-old male with a medical history of drug abuse and tobacco use and a lymphocyte count of 1.5 x 10^9/L on Day -1 who had an AE of lymphopenia with a lymphocyte count of 0.3 x 10^9/L on Day 5. The patient finished the course of treatment on Day 6 and the lymphocyte count normalized by Day 16. The only concomitant medication was lidocaine, which would not be expected to cause lymphopenia. Overall, it is unclear if ceftobiprole could have caused the lymphopenia as the decrease could have been related to the primary infection.

There was one subject in the ceftobiprole arm with a low neutrophil count of level 3:

- Subject (b) (6) is a 34-year-old male with a medical history of tobacco abuse, alcohol use, drug abuse, and seizure who had a neutrophil count of 10.9 x 10^9/L on Day -1. On Day 5, the neutrophil count decreased to 0.1 x 10^9/L and on Day 6, the subject finished his course of ceftobiprole, and neutrophil count increased to 5.2 x 10^9/L on Day 7. There was no reported AE of neutropenia. The decrease in neutrophils was unlikely to be related to ceftobiprole given the short course of the drug and likely decreased due to resolving infection.

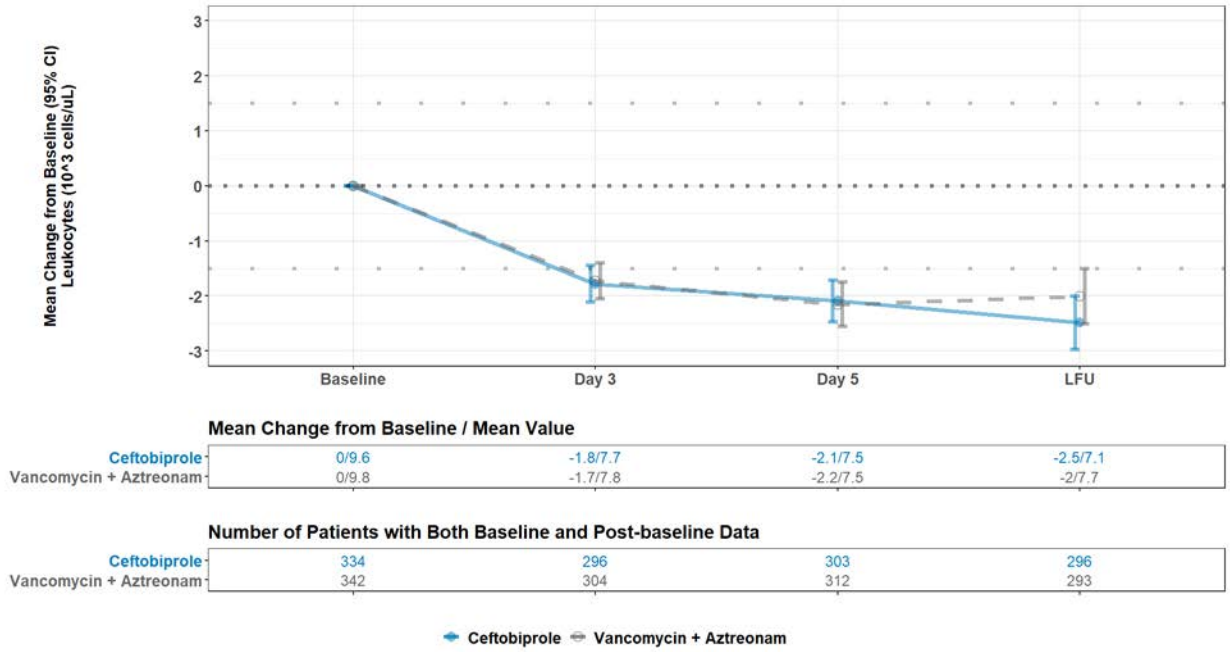
In addition, there were subjects with AEs related to hematological abnormalities. There were 2 subjects ((b) (6) with AEs of neutropenia and 1 subject (b) (6) (b) (6) with an AE of lymphopenia in the ceftobiprole arm.

Regarding subject (b) (6) the neutrophil count was 1 x 10^9/L on Day 2 and increased while on ceftobiprole. For subject (b) (6) the onset of neutropenia was 12 days after ceftobiprole was discontinued. There is no information regarding medications taken or other AEs around the time of treatment discontinuation. In both cases, onset of neutropenia does not suggest a strong correlation with ceftobiprole. For subject (b) (6) the lymphocyte count decreased daily from 1.4 x 10^9/L on Day 1 to a nadir of 0.3 x 10^9/L on Day 5. Ceftobiprole was discontinued on Day 6 and the lymphocyte count increased from the nadir on Day 7 and returned to baseline on Day 16 (next lab draw after Day 7). There were no other concomitant medications that could have caused this, but infection/sepsis could have contributed to the decrease.

Overall, the change in leukocytes from baseline through the last follow-up were similar between arms and decreased as expected as infection resolved.

Reference ID: 5357793

Figure 9. Mean Laboratory (Hematology) Data Change From Baseline Over Time, Safety Population, Trial BPR-CS-008



Source: Source: adlb.xpt; Software: R
Figures do not include time points with data from fewer than 10% of randomized/enrolled patients in all treatment groups.
Only central laboratory data are included in the analysis.
Abbreviations: CI, confidence interval; LFU, last follow-up (28-35 days after last treatment)

Table 69. Subjects With One or More Hematology Analyte Values Exceeding Level 2 or Higher, Safety Population, Trial BPR-CS-008

Laboratory Parameter	Ceftobiprole N=334 n/N_w (%)	Vancomycin + Aztreonam N=342 n/N_w (%)
Complete blood count		
WBC, low (10^3 cells/uL)		
Level 2 (<3)	11/334 (3.3)	11/339 (3.2)
Level 3 (<1)	0/334 (0)	0/339 (0)
WBC, high (10^3 cells/uL)		
Level 2 (>13)	43/334 (12.9)	53/339 (15.6)
Level 3 (>15)	29/334 (8.7)	35/339 (10.3)
Hemoglobin, low (g/dL)		
Level 2 (>1.5 g/dL dec. from Baseline)	77/334 (23.1)	81/339 (23.9)
Level 3 (>2 g/dL dec. from Baseline)	39/334 (11.7)	43/339 (12.7)
Hemoglobin, high (g/dL)		
Level 2 (>2 g/dL inc. from Baseline)	38/334 (11.4)	49/339 (14.5)
Level 3 (>3 g/dL inc. from Baseline)	16/334 (4.8)	11/339 (3.2)
Platelets, low (10^3 cells/uL)		
Level 2 (<125)	23/329 (7.0)	23/339 (6.8)
Level 3 (<100)	13/329 (4.0)	15/339 (4.4)

Laboratory Parameter	Ceftobiprole N=334 n/N_w (%)	Vancomycin + Aztreonam N=342 n/N_w (%)
WBC differential		
Lymphocytes, low (10^3 cells/uL)		
Level 2 (<0.75)	31/334 (9.3)	28/338 (8.3)
Level 3 (<0.5)	5/334 (1.5)	6/338 (1.8)
Lymphocytes, high (10^3 cells/uL)		
Level 2 (>10)	0/334 (0)	2/338 (0.6)
Level 3 (>20)	0/334 (0)	1/338 (0.3)
Neutrophils, low (10^3 cells/uL)		
Level 2 (<1)	7/334 (2.1)	4/338 (1.2)
Level 3 (<0.5)	1/334 (0.3)	2/338 (0.6)
Eosinophils, high (10^3 cells/uL)		
Level 2 (>1.5)	0/334 (0)	2/338 (0.6)
Level 3 (>5)	0/334 (0)	0/338 (0)
Coagulation studies		
PT, high (sec)		
Level 2 (>1.3x ULN)	9/329 (2.7)	14/335 (4.2)
Level 3 (>1.5x ULN)	4/329 (1.2)	7/335 (2.1)
PTT, high (sec)		
Level 2 (>1.21x ULN)	19/329 (5.8)	29/335 (8.7)
Level 3 (>1.41x ULN)	7/329 (2.1)	16/335 (4.8)

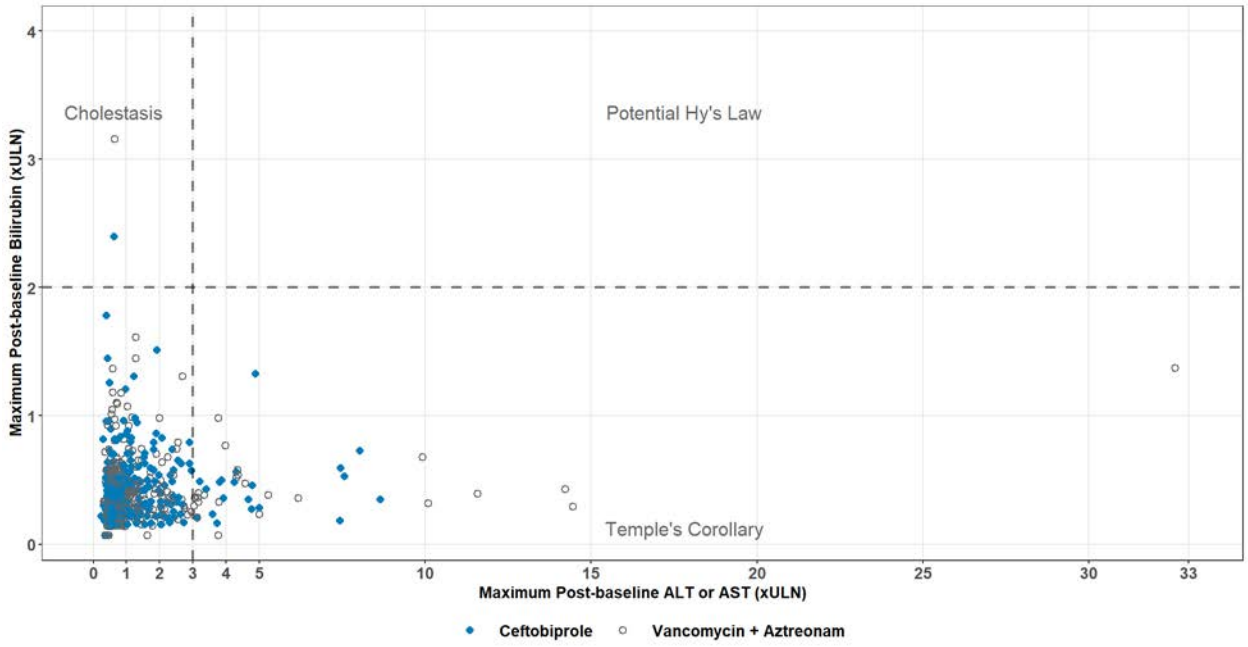
Source: adlb.xpt; Software: R
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration of treatment is up to 14 days.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects meeting criteria; Nw, number of subjects with data; PT, prothrombin time; PTT, partial thromboplastin time; ULN, upper limit of normal; WBC, white blood cells

7.6.2.7. Assessment of Drug-Induced Liver Injury, Trial BPR-CS-008

The analysis of drug-induced liver injury identified PTs related to liver injury in eight (2.4%) subjects treated with ceftobiprole and eleven (3.2%) subjects treated with the comparator (vancomycin and aztreonam). There were no Hy's law cases detected.

Reference ID: 5357793

Figure 10. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Trial BPR-CS-008



Source: adlb.xpt; Software: R
Each data point represents a subject plotted by their maximum ALT or AST versus their maximum total bilirubin values in the post-baseline period.
A potential Hy's Law case (red circle) was defined as having any post-baseline total bilirubin equal to or exceeding 2X ULN within 30 days after a post-baseline ALT or AST equal to or exceeding 3X ULN, and ALP less than 2X ULN (note ALP values are not circled). All subjects with at least one post-baseline ALT or AST and bilirubin are plotted.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal

AEs relating to hepatic injury:

The AEs reported in the ceftobiprole arm include gamma-glutamyl-transferase increased, alanine aminotransferase increased, aspartate aminotransferase increased, and blood alkaline phosphatase increased. None were categorized as severe TEAEs, SAEs, or TEAEs resulting in treatment discontinuation.

The investigator considered that ceftobiprole was a possible cause of the elevated liver enzymes in four subjects ((b) (6) in the ceftobiprole arm. The cases are described below:

- Subject (b) (6) is a 59-year-old male with a medical history of hepatitis C, and drug abuse who had reported AEs of AST and ALT increased on Day 5, which was the last day of ceftobiprole treatment. There were no concomitant medications and therefore it could have been possible that ceftobiprole caused the elevated liver enzymes. However, elevated liver enzymes secondary to infection cannot be ruled out.

In the other three cases involving increase in liver enzymes, alternative reasons for liver enzyme elevation were more likely or the timing of the AE was not well correlated with ceftobiprole treatment. These are noted below:

- Subject (b) (6), a 29-year-old female with a medical history of alcohol use and drug abuse, reported an AE of AST and ALT increased on Day 32. The subject received ceftobiprole only on Day 1 and liver enzymes obtained on Day 3 were within normal limits (ALT 19 U/L, AST 23 U/L). The limited exposure to ceftobiprole and the timing of the AE did not appear to correlate well with exposure to ceftobiprole.
- Subject (b) (6), a 31-year-old male with a medical history of drug abuse and alcohol use, began having elevated ALT and AST on Day 3. While still on ceftobiprole, the subject's AST decreased from 141 U/L on Day 3 to 87 U/L on Day 5. Furthermore, after stopping ceftobiprole on Day 5, the AST increased to 108 U/L on Day 16. Because of the inconsistent LFT changes, the reviewer found it unlikely that ceftobiprole caused the elevated liver enzymes, although it cannot be completely excluded.
- Subject (b) (6), a 40-year-old male with a medical history of hepatitis C and drug abuse, had an elevated AST of 208 U/L on Day 3 (from 68 U/L on Day 1). The AST decreased to 192 U/L while still on ceftobiprole and continued to decrease once discontinued. Furthermore, the bilirubin was 13.68 µmol/L on Day -1 and decreased while on ceftobiprole to 8 µmol/L on Day 5. Because of this, it was unlikely that ceftobiprole caused the elevated liver enzymes.

Table 70. Drug Induced Liver Injury Assessment, Safety Population, Trial BPR-CS-008

Drug-Induced Liver Injury Assessment	Ceftobiprole N=334 n (%)	Vancomycin + Aztreonam N=342 n (%)
AE grouping related to AESI	8 (2.4)	11 (3.2)
Alanine aminotransferase increased	8 (2.4)	10 (2.9)
Aspartate aminotransferase increased	7 (2.1)	10 (2.9)
Maximum severity		
Death	0	0
Life-threatening	0	0
Severe	0	0
Moderate	2 (0.6)	4 (1.2)
Mild	6 (1.8)	7 (2.0)
Serious	0	0
Deaths	0	0
Resulting in discontinuation	0	0
Relatedness	4 (1.2)	6 (1.8)
Number of subjects with adverse events with end dates on or before treatment end dates	0/8 (0)	2/11 (18.2)
Duration, days (from AE start date to AE end date)		
Mean (SD)	NA	2.5 (0.7)
Median (Q1, Q3)	NA	2.5 (2.2, 2.8)
Min, max	NA, NA	2, 3
Number of subjects with adverse events (occurred on or before treatment end date) with end dates missing (no end dates reported, assumed that AE continuing)	0/8 (0)	2/11 (18.2)

Drug-Induced Liver Injury Assessment	Ceftobiprole N=334 n (%)	Vancomycin + Aztreonam N=342 n (%)
Number of subjects with adverse events (occurred on or before treatment end date) with end dates after treatment end dates	5/8 (62.5)	6/11 (54.5)
Duration, days (from treatment end date to AE end date)		
Mean (SD)	25.8 (6.7)	22 (13)
Median (Q1, Q3)	29 (24, 29)	21 (11.2, 33)
Min, max	15, 32	8, 37

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any adverse event which occurred between the start of the first dosing up to and including the scheduled last follow-up.
Duration of treatment is up to 14 days.
Relatedness is determined by investigator.
Abbreviations: AE, adverse event; AESI, adverse events of special interest; N, number of subjects in treatment arm; n, number of subjects with adverse event; NA, not applicable; Q1, first quartile; Q3, third quartile; SD, standard deviation

No subjects experienced an AST or ALT >10x ULN. When comparing between the ceftobiprole and vancomycin and aztreonam arms, subjects in the ceftobiprole arm had fewer overall elevations in liver biochemistry tests. Profiles of subjects who had an AST and ALT of >5x ULN and >3x ULN were also examined for any potential safety signal of liver injury due to ceftobiprole. Given the short duration of ceftobiprole, there was no definitive evidence that ceftobiprole caused any of the elevations in LFTs, although it cannot be ruled out.

Table 71. Subjects With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels, Safety Population, Trial BPR-CS-008

Laboratory Parameter	Ceftobiprole N=334 n/N_w (%)	Vancomycin + Aztreonam N=342 n/N_w (%)
Alkaline phosphatase, high (U/L)		
Level 1 (>1.5x ULN)	15/329 (4.6)	31/336 (9.2)
Level 2 (>2x ULN)	9/329 (2.7)	11/336 (3.3)
Level 3 (>3x ULN)	3/329 (0.9)	4/336 (1.2)
Alanine aminotransferase, high (U/L)		
Level 1 (>3x ULN)	18/329 (5.5)	19/336 (5.7)
Level 2 (>5x ULN)	4/329 (1.2)	8/336 (2.4)
Level 3 (>10x ULN)	0/329 (0)	5/336 (1.5)
Aspartate aminotransferase, high (U/L)		
Level 1 (>3x ULN)	13/328 (4.0)	17/336 (5.1)
Level 2 (>5x ULN)	3/328 (0.9)	7/336 (2.1)
Level 3 (>10x ULN)	0/328 (0)	3/336 (0.9)
Bilirubin, total, high (mg/dL)		
Level 1 (>1.5x ULN)	3/329 (0.9)	2/336 (0.6)
Level 2 (>2x ULN)	1/329 (0.3)	1/336 (0.3)
Level 3 (>3x ULN)	0/329 (0)	1/336 (0.3)

Source: adlb.xpt; Software: R
.
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration of treatment is up to 14 days.
For specific evaluation of drug-induced liver injury (DILI), see the figures “Hepatocellular Drug-Induced Liver Injury Screening Plot...” and “Cholestatic Drug-Induced Liver Injury Screening Plot...” and the tables “Subjects in Each Quadrant for Potential Hepatocellular DILI Screening Plot...” and “Subjects in Each Quadrant for Cholestatic DILI Screening Plot…”
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; ULN, upper limit of normal

7.6.2.8. Vital Signs' Analyses, Trial BPR-CS-008

Heart Rate, Temperature, Respiratory Rate

The mean changes from Baseline to post-treatment in both arms were similar and within normal ranges.

Blood Pressure

Mean changes in systolic and diastolic blood pressure from baseline to last follow-up were small, with no clinically important differences observed among the treatment arms.

7.6.2.9. Subgroup Analyses, Trial BPR-CS-008

Table 72 shows the incidence of common TEAEs by demographic subgroups of sex, age, ethnicity, and race. The incidence of TEAEs in the ceftobiprole arm was higher in subjects between the age of 18 to 34 years and the most common TEAEs are discussed below. There were more TEAES in the subgroup of subjects ages 65-75 years in the ceftobiprole arm as compared to the vancomycin and aztreonam arm, but the number of subjects was too small to draw any meaningful conclusions. The majority of subjects were White, non-Hispanic or Latino, and from the US; the incidence of TEAEs appeared to be overall similar to the safety population. In addition, there did not appear to be imbalances in TEAEs by gender.

Age 18 to 34 years

In this age group, there was a higher percentage of subjects in the ceftobiprole arm (58.6%) who experienced AEs compared to the percentage of subjects in the vancomycin and aztreonam arm (40.3%). In addition, the percentage of TEAEs in the younger subgroup was higher than in the older subgroups receiving ceftobiprole. The most commonly reported AEs in the ceftobiprole arm were nausea (n = 14), headache (n = 5), diarrhea (n = 5), alanine aminotransferase increased (5 subjects), and aspartate aminotransferase increased (5 subjects). The most commonly reported AEs in the comparator arm were headache (6 subjects), diarrhea (5 subjects), nausea (4 subjects), abscess limb (4 subjects), and pyrexia (3). It appears that nausea and increased liver tests may have driven this difference between treatment arms in this subgroup of younger subjects. In this subgroup, there was one SAE each in the ceftobiprole arm (worsening of skin infection, (b) (6) (b) (6)) and vancomycin and aztreonam arm (cellulitis). There were no deaths in this subgroup.

Age 65-74 years

In this age group, there was a higher percentage of subjects in the ceftobiprole arm (48.1%) who experienced AEs compared to the percentage of subjects in the vancomycin and aztreonam arm (33.3%). The most commonly reported AEs in the ceftobiprole arm were blood creatinine increased (2 subjects), headache (2 subjects) and injection site reaction (2 subjects) while the most commonly reported AEs in the vancomycin and aztreonam arm were skin bacterial infection (3 subjects), nasopharyngitis (2 subjects) and oedema peripheral (2 subjects). There were 2 SAEs in the vancomycin and aztreonam arm (skin bacterial infection) and none in the ceftobiprole arm. There were no deaths in either treatment arm in this subgroup.

Reference ID: 5357793

Table 72. Overview of Adverse Events by Demographic Subgroup, Safety Population, Trial BPR-CS-008

Characteristic	Ceftobiprole N=334 n/N_s (%)	Vancomycin + Aztreonam N=342 n/N_s (%)
Sex		
Female	62/137 (45.3)	63/143 (44.1)
Male	86/197 (43.7)	68/199 (34.2)
Age group, years		
18 to 34	34/58 (58.6)	27/67 (40.3)
35 to 64	96/235 (40.9)	86/223 (38.6)
65 to 74	13/27 (48.1)	12/36 (33.3)
≥75	5/14 (35.7)	6/16 (37.5)
Age group ≥65, years		
≥65	18/41 (43.9)	18/52 (34.6)
Race		
White	140/317 (44.2)	122/328 (37.2)
American Indian or Alaska Native	2/4 (50.0)	1/3 (33.3)
Asian	0/0 (NA)	1/1 (100)
Black or African American	3/7 (42.9)	5/8 (62.5)
Native Hawaiian or Other Pacific Islander	1/1 (100)	0/0 (NA)
Other	2/5 (40.0)	2/2 (100)
Ethnicity		
Hispanic or Latino	52/103 (50.5)	44/114 (38.6)
Not Hispanic or Latino	96/231 (41.6)	87/228 (38.2)
Geographic Region		
United States	109/202 (54.0)	100/213 (46.9)
Non-United States	39/132 (29.5)	31/129 (24.0)

Source: adae.xpt; Software: R

Abbreviations: N, number of subjects in treatment arm; n, number of subjects with adverse event; NA, not applicable; N_s, total number of subjects for each specific subgroup and were assigned to that specific arm

7.6.3. Community-Acquired Bacterial Pneumonia, Trial CAP-3001

7.6.3.1. Overview of Treatment-Emergent Adverse Events Summary, Trial CAP-3001

Table 73 shows the overview of adverse events in Trial CAP-3001. SAEs were balanced between the two treatment arms. The ceftobiprole arm had more subjects with AEs leading to discontinuation of the study drug, dose modification, interruption, and reduction of the study drug compared to the ceftriaxone arm although the differences were not large. The ceftobiprole arm also had more subjects with AEs overall at 70% compared to 64.6% in the ceftriaxone arm. This difference was driven mostly by more moderate AEs seen in the ceftobiprole arm. Severe and mild AEs were balanced between the two arms.

Reference ID: 5357793

Table 73. Overview of Adverse Events, Safety Population, Trial CAP-3001

Event Category	Ceftobiprole N=310 n (%)	Ceftriaxone/ Linezolid N=322 n (%)
SAE	35 (11.3)	37 (11.5)
SAEs with fatal outcome	9 (2.9)	9 (2.8)
Life-threatening SAEs	2 (0.6)	5 (1.6)
SAEs requiring hospitalization	32 (10.3)	34 (10.6)
SAEs resulting in substantial disruption of normal life functions	6 (1.9)	9 (2.8)
AE leading to permanent discontinuation of study drug	18 (5.8)	12 (3.7)
AE leading to dose modification of study drug	8 (2.6)	2 (0.6)
AE leading to interruption of study drug	5 (1.6)	1 (0.3)
AE leading to reduction of study drug	3 (1.0)	1 (0.3)
AE leading to dose delay of study drug	0	0
Any AE	217 (70.0)	208 (64.6)
Severe and worse	28 (9.0)	29 (9.0)
Moderate	88 (28.4)	78 (24.2)
Mild	101 (32.6)	101 (31.4)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as an AE that is new in onset or aggravated in severity after the first dose treatment.
Duration of treatment up to 14 days.
Severity as assessed by the investigator.
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event

7.6.3.2. Deaths, Trial CAP-3001

The deaths between the ceftobiprole arm and the ceftriaxone arm were balanced with 9 deaths in each treatment arm (Table 74). There was one subject in the ceftobiprole arm and two subjects in the ceftriaxone arm that had more than one AE leading to death. The majority of AEs leading to death were different between the two arms. For the ceftobiprole arm, lung neoplasms and cardiac failure were more common whereas in the ceftriaxone arm, pneumonia and sudden death were most common. Cardiac and respiratory AEs were common AEs leading to death in the two treatment arms which is consistent with the hospitalized Trial population.

Review of the narratives of subjects who had died confirmed the investigator assessment that none of the deaths in the ceftobiprole treatment arm were related to the study treatment. For the ceftriaxone treatment arm, the investigator attributed subject (b) (6)'s death to be likely related to the treatment. Review of the narrative confirms this assessment as the subject's pneumonia course continued to worsen requiring intensive care management likely due to ineffective treatment. The remaining deaths appear to be unrelated to study treatment.

Table 74. Overview of Deaths, Safety Population, Trial CAP-3001

Preferred Term	Ceftobiprole N=310 n (%)	Ceftriaxone/ Linezolid N=322 n (%)
Any AE leading to death	9 (2.8)	9 (2.8)
Lung neoplasm malignant	2 (0.6)	0
Cardiac failure	2 (0.6)	0
Acute pulmonary edema	1 (0.3)	0
Circulatory collapse	1 (0.3)	0
Delirium	1 (0.3)	0

Urinary tract infection	1 (0.3)	0
Acute myocardial infarction	1 (0.3)	1 (0.3)
Respiratory failure	1 (0.3)	1 (0.3)
Acute respiratory distress syndrome	0	1 (0.3)
Arrhythmia	0	1 (0.3)
Coronary artery disease	0	1 (0.3)
Hypoxia	0	1 (0.3)
Septic shock	0	1 (0.3)
Sudden death	0	2 (0.6)
Pneumonia	0	3 (0.9)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as an AE that is new in onset or aggravated in severity after the first dose treatment.
Duration of treatment up to 14 days.
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with adverse event

7.6.3.3. Serious Treatment-Emergent Adverse Events, Trial CAP-3001

SAEs were overall balanced between the two arms (Table 75). In addition, there was not an appreciable difference between the two arms with regards to the SOC of the SAEs. Within the ceftobiprole treatment arm, infections and infestations represented the highest group of SAEs (3.9%) followed by respiratory, thoracic, and mediastinal disorders (2.9%). One subject in the ceftobiprole arm developed anaphylactic shock. Subject (b) (6) had received 2 doses of ceftobiprole and during her third ceftobiprole dose, 1 hour into the infusion, the subject was found to be unconscious, pulseless, and apneic. Trial medication was discontinued, and the subject later fully recovered after resuscitation. Concomitant medications were not reported, and the investigator believed this event was related to the study drug. The labeling will include a warning for hypersensitivity reactions, including anaphylaxis.

Table 75. Subjects With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Trial CAP-3001

System Organ Class Preferred Term	Ceftobiprole N=310 n (%)	Ceftriaxone/ Linezolid N=322 n (%)
Any SAE	35 (11.3)	37 (11.5)
Blood and lymphatic system disorders (SOC)	1 (0.3)	1 (0.3)
Anemia	1 (0.3)	0
Thrombocytopenia	0	1 (0.3)
Cardiac disorders (SOC)	7 (2.3)	5 (1.6)
Angina pectoris	1 (0.3)	0
Cardiac failure acute	1 (0.3)	0
Myocardial infarction	1 (0.3)	0
Pericarditis	1 (0.3)	0
Supraventricular tachycardia	1 (0.3)	0
Ventricular fibrillation	1 (0.3)	0
Acute myocardial infarction	1 (0.3)	1 (0.3)
Cardiac failure	1 (0.3)	1 (0.3)
Arrhythmia	0	1 (0.3)
Cardiac failure congestive	0	1 (0.3)
Coronary artery disease	0	1 (0.3)
Atrial fibrillation	0	2 (0.6)

System Organ Class Preferred Term	Ceftobiprole N=310 n (%)	Ceftriaxone/ Linezolid N=322 n (%)
Gastrointestinal disorders (SOC)	3 (1.0)	2 (0.6)
Gastrointestinal hemorrhage	1 (0.3)	0
Nausea	1 (0.3)	0
Small intestinal obstruction	1 (0.3)	0
Vomiting	1 (0.3)	0
Abdominal pain	1 (0.3)	1 (0.3)
Abdominal distension	0	1 (0.3)
General disorders and administration site conditions (SOC)	1 (0.3)	3 (0.9)
Pyrexia	1 (0.3)	0
Treatment failure	0	1 (0.3)
Sudden death	0	2 (0.6)
Hepatobiliary disorders (SOC)	1 (0.3)	0
Hepatic cirrhosis	1 (0.3)	0
Immune system disorders (SOC)	1 (0.3)	0
Anaphylactic shock	1 (0.3)	0
Infections and infestations (SOC)	12 (3.9)	15 (4.7)
Empyema	4 (1.3)	1 (0.3)
Gastroenteritis viral	1 (0.3)	0
Tuberculosis	1 (0.3)	0
Urinary tract infection	1 (0.3)	0
Appendicitis	0	1 (0.3)
Clostridium difficile colitis	0	1 (0.3)
Lung abscess	0	1 (0.3)
Septic shock	0	2 (0.6)
Pneumonia	6 (1.9)	10 (3.1)
Injury, poisoning and procedural complications (SOC)	0	1 (0.3)
Rib fracture	0	1 (0.3)
Investigations (SOC)	0	1 (0.3)
Blood gases abnormal	0	1 (0.3)
Metabolism and nutrition disorders (SOC)	3 (1.0)	0
Dehydration	1 (0.3)	0
Diabetes mellitus	1 (0.3)	0
Hypoglycemia	1 (0.3)	0
Musculoskeletal and connective tissue disorders (SOC)	0	2 (0.6)
Back pain	0	1 (0.3)
Neck pain	0	1 (0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	4 (1.3)	3 (0.9)
Lung neoplasm malignant	4 (1.3)	2 (0.6)
Neoplasm malignant	0	1 (0.3)
Nervous system disorders (SOC)	0	1 (0.3)
Mental impairment	0	1 (0.3)
Psychiatric disorders (SOC)	2 (0.6)	0
Delirium	1 (0.3)	0
Panic attack	1 (0.3)	0
Renal and urinary disorders (SOC)	0	1 (0.3)
Urinary incontinence	0	1 (0.3)

System Organ Class Preferred Term	Ceftobiprole N=310 n (%)	Ceftriaxone/ Linezolid N=322 n (%)
Respiratory, thoracic and mediastinal disorders (SOC)	9 (2.9)	12 (3.7)
Acute pulmonary oedema	1 (0.3)	0
Acute respiratory failure	1 (0.3)	0
Hemoptysis	1 (0.3)	0
Organizing pneumonia	1 (0.3)	0
Pleural effusion	1 (0.3)	0
Pleurisy	1 (0.3)	0
Respiratory failure	3 (1.0)	4 (1.2)
Asthma	0	1 (0.3)
Bronchiectasis	0	1 (0.3)
Bronchospasm	0	1 (0.3)
Chronic obstructive pulmonary disease	0	1 (0.3)
Pneumothorax	0	1 (0.3)
Pulmonary edema	0	1 (0.3)
Acute respiratory distress syndrome	0	2 (0.6)
Hypoxia	0	2 (0.6)
Vascular disorders (SOC)	1 (0.3)	1 (0.3)
Circulatory collapse	1 (0.3)	0
Deep vein thrombosis	0	1 (0.3)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as an AE that is new in onset or aggravated in severity after the first dose treatment.
Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Duration of treatment up to 14 days.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with adverse event; SAE, serious adverse event; SOC, system organ class

7.6.3.4. Adverse Events Leading to Treatment Discontinuation, Trial CAP-3001

The overall rate of AEs leading to discontinuation was low at less than 10% in each trial arm (Table 76). The ceftobiprole arm had a higher rate of AEs leading to discontinuation compared to ceftriaxone at 5.8% vs 3.7%. The higher rate of AEs leading to discontinuation in the ceftobiprole arm was mainly due to gastrointestinal disorders with subjects experiencing vomiting, abdominal pain, and nausea compared to 1 subject experiencing abdominal distension leading to discontinuation in the ceftriaxone arm. Similar to SAEs, infections and infestations disorders were also relatively common in both arms. These results suggest ceftobiprole is relatively well tolerated with the drug leading to discontinuation in a relatively small percentage of subjects. Of note, nausea, vomiting, and abdominal pain will be labeled as adverse reactions in Section 6 of labeling.

Table 76. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Trial CAP-3001

System Organ Class Preferred Term	Ceftobiprole 500 mg N=310 n (%)	Ceftriaxone/Linezolid 2 g N=322 n (%)
Any AE leading to Discontinuation	18 (5.8)	12 (3.7)
Cardiac disorders (SOC)	2 (0.6)	0
Cardiac failure	1 (0.3)	0
Myocardial infarction	1 (0.3)	0

System Organ Class Preferred Term	Ceftobiprole 500 mg N=310 n (%)	Ceftriaxone/Linezolid 2 g N=322 n (%)
Gastrointestinal disorders (SOC)	5 (1.6)	1 (0.3)
Vomiting	4 (1.3)	0
Nausea	3 (1.0)	0
Abdominal pain	2 (0.6)	0
Diarrhea	1 (0.3)	0
Abdominal distension	0	1 (0.3)
General disorders and administration site conditions (SOC)	0	1 (0.3)
Sudden death	0	1 (0.3)
Hepatobiliary disorders (SOC)	1 (0.3)	1 (0.3)
Jaundice	1 (0.3)	0
Cholecystitis	0	1 (0.3)
Immune system disorders (SOC)	2 (0.6)	0
Anaphylactic shock	1 (0.3)	0
Hypersensitivity	1 (0.3)	0
Infections and infestations (SOC)	5 (1.6)	4 (1.2)
Pneumonia	2 (0.6)	1 (0.3)
Pulmonary tuberculosis	2 (0.6)	1 (0.3)
Empyema	1 (0.3)	0
Tuberculosis	1 (0.3)	0
Appendicitis	0	1 (0.3)
Septic shock	0	1 (0.3)
Investigations (SOC)	1 (0.3)	0
Transaminases increased	1 (0.3)	0
Musculoskeletal and connective tissue disorders (SOC)	0	1 (0.3)
Neck pain	0	1 (0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	1 (0.3)	0
Lung neoplasm malignant	1 (0.3)	0
Respiratory, thoracic and mediastinal disorders (SOC)	1 (0.3)	3 (0.9)
Pleurisy	1 (0.3)	0
Pulmonary edema	0	1 (0.3)
Respiratory failure	0	2 (0.6)
Vascular disorders (SOC)	1 (0.3)	1 (0.3)
Hypertension	1 (0.3)	0
Hyperemia	0	1 (0.3)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as an AE that is new in onset or aggravated in severity after the first dose treatment.
Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Duration of treatment up to 14 days.
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with adverse event; SOC, system organ class.

7.6.3.5. Treatment-Emergent Adverse Events, Trial CAP-3001

There were slightly more TEAEs in the ceftobiprole arm (70%) compared to the ceftriaxone arm (64.6%; Table 77). However, there is a notable difference between the types of TEAEs in each treatment arm. The TEAEs that occurred at a greater frequency in the ceftobiprole arm compared to the ceftriaxone arm included nausea, vomiting, rash, phlebitis, and hemorrhage (≥2% risk difference). Gastrointestinal related AEs were the most common AEs associated with the use of ceftobiprole. In addition, there are TEAEs in both arms that were balanced (liver enzyme

increased, headache, abdominal pain, diarrhea, insomnia, dizziness), which may be due to both drugs being cephalosporins or due to underlying medical comorbidities. Pneumonia was also balanced in both arms occurring at a high frequency however this is likely due to the underlying illness of the subject. Please refer to Section 17.4 for the table of subjects with all AEs occurring in the safety population.

Given the higher frequency of hemorrhage in the ceftobiprole arm, these subjects were evaluated in greater detail. There were 4 cases of hemoptysis categorized under hemorrhage. Two of the subjects may have developed hemoptysis that did not have an obvious cause aside from their underlying pulmonary illness. Of the remaining two, one subject was on warfarin and aspirin and the other developed hemoptysis 12 days after receiving the last dose of ceftobiprole and was also diagnosed with lung cancer. For the other subjects who developed hemorrhage as an AE, three of the subjects were on anti-coagulant medications and 4 subjects developed their AE several days to weeks after receiving their last dose of ceftobiprole. There were two subjects that developed hematoma and ecchymoses without a clear inciting event, however one of the subjects had only received one day of treatment. Based on these evaluations, there does not appear to be a strong signal that would indicate ceftobiprole is associated with hemorrhage as several of the AEs were likely due to concomitant use of anti-coagulant medications or occurred after treatment.

Table 77. Subjects With Common Adverse Events, Recoded, Occurring at ≥2% Frequency in the Ceftobiprole Arm, Safety Population, Trial CAP-3001

Preferred Term	Ceftobiprole N=310 n (%)	Ceftriaxone/ Linezolid N=322 n (%)
Any AE	217 (70.0)	208 (64.6)
Liver enzyme increased[a]	30 (9.7)	34 (10.6)
Nausea	30 (9.7)	13 (4.0)
Vomiting	27 (8.7)	9 (2.8)
Diarrhea	22 (7.1)	28 (8.7)
Headache	21 (6.8)	23 (7.1)
Bacterial infection[b]	19 (6.1)	15 (4.7)
Hypokalaemia	14 (4.5)	19 (5.9)
Pneumonia[c]	14 (4.5)	14 (4.3)
Insomnia	14 (4.5)	13 (4.0)
Rash[d]	14 (4.5)	6 (1.9)
Hemorrhage[e]	13 (4.2)	7 (2.2)
Phlebitis[f]	13 (4.2)	7 (2.2)
Hypertension[g]	12 (3.9)	14 (4.3)
Abdominal pain[h]	11 (3.5)	10 (3.1)
Constipation	11 (3.5)	8 (2.5)
Dizziness[i]	10 (3.2)	8 (2.5)
Viral infection[j]	10 (3.2)	4 (1.2)
Hyperglycemia[k]	8 (2.6)	10 (3.1)
Cough[l]	7 (2.3)	6 (1.9)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as an AE that is new in onset or aggravated in severity after the first dose treatment. Duration of treatment up to 14 days.
Recoded terms are defined based on the dictionary created in conjunction with the clinical team.
Adverse Events are sorted by prevalence in the Ceftobiprole arm.
[a] Liver enzyme increased includes Aspartate aminotransferase increased, Gamma-glutamyltransferase increased, Blood alkaline phosphatase increased, Alanine aminotransferase increased, Hepatic enzyme increased, Transaminases increased, Alanine aminotransferase, Liver function test increased.
[b] Bacterial infection includes Pneumonia chlamydial, Abscess limb, Urethritis, Clostridium difficile colitis, Tuberculosis, Empyema, Pseudomonas infection, Borrelia test positive, Sepsis, Urinary tract infection, Lung abscess, Cellulitis, Cholecystitis, Hordeolum, Appendicitis, Pulmonary tuberculosis, Cholecystitis chronic. Infected Bite.
[c] Pneumonia includes Pneumonia, Pneumonia chlamydial, Pneumonia necrotizing, Tuberculosis, Empyema, Lung abscess, Pulmonary tuberculosis.
[d] Rash includes Rash, Rash pruritic, Dermatitis allergic, Dermatitis contact.
[e] Hemorrhage includes Conjunctival hemorrhage, Melaena, Blood urine present, Hemoptysis, Epistaxis, Gastrointestinal hemorrhage, Hematuria, Hematochezia, Hematoma, Rectal Hemorrhage, Ecchymoses.
[f] Phlebitis includes Phlebitis, Injection site phlebitis.
[g] Hypertension includes Hypertension, Blood pressure increased, Hypertensive crisis.
[h] Abdominal pain includes Abdominal pain, Abdominal discomfort, Abdominal pain upper.
[i] Dizziness includes Dizziness, Vertigo.
[j] Viral infection includes Viral Infection, Oral herpes, Hepatitis C, HIV infection, Herpes simplex, Influenza. Gastrointestinal viral, Genital herpes.
[k] Hyperglycemia includes Hyperglycemia, Diabetic foot, Diabetes mellitus, Type 2 diabetes mellitus, Diabetic complication.
[l] Cough includes Cough, Productive cough, Hemoptysis.
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with adverse event

7.6.3.6. Laboratory Findings, Trial CAP-3001

The number of subjects with either high or low chemistry analyte values were generally balanced between the two treatment arms (Table 78). There were slightly more abnormalities in the ceftriaxone arm with low sodium and elevated BUN. Elevated creatinine was also seen more frequently in the ceftriaxone arm at 4.1% compared to 1.1% in the ceftobiprole arm (Table 79). There were more cases of high potassium (6.5% vs 3.6%) and low glucose (5.5% vs 3%) in the ceftobiprole subjects. Of note, hyperkalemia and hypoglycemia were reported as AEs less commonly for ceftobiprole compared to ceftriaxone. The number of subjects with liver abnormalities were balanced with no major differences between the two arms (Table 80). Total cholesterol and triglycerides were also balanced between the two arms (Table 81). Regarding hematology laboratory values, leukocytosis was observed more in the ceftriaxone arm at 31% compared with 24% in the ceftobiprole arm (Table 82). The remainder of abnormal hematologic values were otherwise balanced.

Overall, there does not appear to be any major difference between ceftobiprole and ceftriaxone with respect to chemical, renal, cholesterol, hepatic, or hematologic laboratory values.

Table 78. Subjects With One or More Chemistry Analyte Values With Elevated or Low Values Meeting Specified Levels, Safety Population, Trial CAP-3001

Laboratory Parameter	Ceftobiprole N=310 n/N_w (%)	Ceftriaxone / Linezolid N=322 n/N_w (%)
Sodium, low (mEq/L)		
Level 1 (<132)	12/292 (4.1)	17/304 (5.6)
Level 2 (<130)	5/292 (1.7)	11/304 (3.6)
Level 3 (<125)	1/292 (0.3)	2/304 (0.7)
Sodium, high (mEq/L)		
Level 1 (>150)	0/292 (0)	1/304 (0.3)
Level 2 (>155)	0/292 (0)	1/304 (0.3)
Level 3 (>160)	0/292 (0)	0/304 (0)
Potassium, low (mEq/L)		
Level 1 (<3.6)	34/292 (11.6)	35/304 (11.5)
Level 2 (<3.4)	17/292 (5.8)	17/304 (5.6)
Level 3 (<3)	2/292 (0.7)	5/304 (1.6)
Potassium, high (mEq/L)		
Level 1 (>5.5)	19/292 (6.5)	11/304 (3.6)
Level 2 (>6)	3/292 (1.0)	3/304 (1.0)
Level 3 (>6.5)	0/292 (0)	1/304 (0.3)
Chloride, low (mEq/L)		
Level 1 (<95)	16/292 (5.5)	23/304 (7.6)
Level 2 (<88)	2/292 (0.7)	1/304 (0.3)
Level 3 (<80)	0/292 (0)	0/304 (0)
Chloride, high (mEq/L)		
Level 1 (>108)	9/292 (3.1)	12/304 (3.9)
Level 2 (>112)	1/292 (0.3)	3/304 (1.0)
Level 3 (>115)	0/292 (0)	0/304 (0)
Bicarbonate, low (mEq/L)		
Level 1 (<20)	21/292 (7.2)	22/302 (7.3)
Level 2 (<18)	7/292 (2.4)	9/302 (3.0)
Level 3 (<15)	1/292 (0.3)	3/302 (1.0)
Bicarbonate, high (mEq/L)		
Level 3 (>30)	42/292 (14.4)	43/302 (14.2)

Laboratory Parameter	Ceftobiprole N=310 n/N_w (%)	Ceftriaxone / Linezolid N=322 n/N_w (%)
Glucose, low (mg/dL)		
Level 1 (<70)	16/292 (5.5)	9/302 (3.0)
Level 2 (<54)	2/292 (0.7)	0/302 (0)
Level 3 (<40)	0/292 (0)	0/302 (0)
Glucose, random, high (mg/dL)		
Level 2 (≥200)	30/292 (10.3)	26/302 (8.6)
Level 3 (>250)	22/292 (7.5)	15/302 (5.0)
Calcium, low (mg/dL)		
Level 1 (<8.4)	35/292 (12.0)	37/304 (12.2)
Level 2 (<8)	7/292 (2.4)	14/304 (4.6)
Level 3 (<7.5)	2/292 (0.7)	7/304 (2.3)
Calcium, high (mg/dL)		
Level 1 (>10.5)	17/292 (5.8)	10/304 (3.3)
Level 2 (>11)	1/292 (0.3)	1/304 (0.3)
Level 3 (>12)	0/292 (0)	0/304 (0)
Protein, total, low (g/dL)		
Level 1 (<6)	28/292 (9.6)	28/304 (9.2)
Level 2 (<5.4)	7/292 (2.4)	3/304 (1.0)
Level 3 (<5)	2/292 (0.7)	2/304 (0.7)
Albumin, low (g/dL)		
Level 1 (<3.1)	76/292 (26.0)	93/302 (30.8)
Level 2 (<2.5)	24/292 (8.2)	26/302 (8.6)
Level 3 (<2)	5/292 (1.7)	8/302 (2.6)
CPK, high (U/L)		
Level 1 (>3X ULN)	6/292 (2.1)	4/302 (1.3)
Level 2 (>5X ULN)	3/292 (1.0)	2/302 (0.7)
Level 3 (>10X ULN)	1/292 (0.3)	0/302 (0)
Blood urea nitrogen, high (mg/dL)		
Level 1 (>23)	36/292 (12.3)	69/304 (22.7)
Level 2 (>27)	17/292 (5.8)	37/304 (12.2)
Level 3 (>31)	11/292 (3.8)	21/304 (6.9)

Source: adlb.xpt; Software: R
Note that glucose values for hyperglycemia do not follow a nested format like the other labs. Level 1 corresponds to the diagnosis of prediabetes and is not inclusive of Level 2 and 3. Level 2 corresponds to the diagnosis of diabetes. Level 3 represents significant hyperglycemia that may indicate need for insulin or increased risk for diabetic ketoacidosis or other complications.
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration of treatment up to 14 days.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: CPK, creatine phosphokinase; N, number of subjects in treatment arm; n, number of subjects meeting criteria; Nw, number of subjects with data; ULN, upper limit of normal

Table 79. Subjects With One or More Kidney Function Analyte Values Exceeding Specified Levels, Safety Population, Trial CAP-3001

Laboratory Parameter	Ceftobiprole N=310 n/N_w (%)	Ceftriaxone/ Linezolid N=322 n/N_w (%)
Creatinine, high (mg/dL)		
Level 1 (≥1.5X baseline)	3/283 (1.1)	12/291 (4.1)
Level 2 (≥2X baseline)	0/283 (0)	3/291 (1.0)
Level 3 (≥3X baseline)	0/283 (0)	1/291 (0.3)

Laboratory Parameter	Ceftobiprole N=310 n/N_w (%)	Ceftriaxone/ Linezolid N=322 n/N_w (%)
eGFR, low (ml/min/1.73 m^2)		
Level 1 (≥25% decrease)	14/252 (5.6)	20/267 (7.5)
Level 2 (≥50% decrease)	0/252 (0)	4/267 (1.5)
Level 3 (≥75% decrease)	0/252 (0)	1/267 (0.4)

Source: adlb.xpt; Software: R
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration of treatment up to 14 days.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
eGFR values are calculated from serum creatinine using chronic kidney disease epidemiology collaboration (CKD-EPI) equation.
Abbreviations: eGFR, estimated glomerular filtration rate; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data

Table 80. Subjects With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels, Safety Population, Trial CAP-3001

Laboratory Parameter	Ceftobiprole N=310 n/N_w (%)	Ceftriaxone / Linezolid N=322 n/N_w (%)
Alkaline phosphatase, high (U/L)		
Level 1 (>1.5X ULN)	17/292 (5.8)	17/304 (5.6)
Level 2 (>2X ULN)	8/292 (2.7)	6/304 (2.0)
Level 3 (>3X ULN)	3/292 (1.0)	2/304 (0.7)
Alanine aminotransferase, high (U/L)		
Level 1 (>3X ULN)	20/292 (6.8)	20/302 (6.6)
Level 2 (>5X ULN)	5/292 (1.7)	4/302 (1.3)
Level 3 (>10X ULN)	2/292 (0.7)	1/302 (0.3)
Aspartate aminotransferase, high (U/L)		
Level 1 (>3X ULN)	14/292 (4.8)	14/302 (4.6)
Level 2 (>5X ULN)	1/292 (0.3)	2/302 (0.7)
Level 3 (>10X ULN)	1/292 (0.3)	1/302 (0.3)
Bilirubin, total, high (mg/dL)		
Level 1 (>1.5X ULN)	4/292 (1.4)	3/302 (1.0)
Level 2 (>2X ULN)	3/292 (1.0)	2/302 (0.7)
Level 3 (>3X ULN)	1/292 (0.3)	1/302 (0.3)

Source: adlb.xpt; Software: R
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration of treatment up to 14 days.
For specific evaluation of drug-induced liver injury (DILI), see the figures “Hepatocellular Drug-Induced Liver Injury Screening Plot...” and “Cholestatic Drug-Induced Liver Injury Screening Plot...” and the tables “Subjects in Each Quadrant for Potential Hepatocellular DILI Screening Plot...” and “Subjects in Each Quadrant for Cholestatic DILI Screening Plot…”
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; ULN, upper limit of normal

Table 81. Subjects With One or More Lipids Analyte Values Exceeding Specified Levels, Safety Population, Trial CAP-3001

Laboratory Parameter	Ceftobiprole N=310 n/N_w (%)	Ceftriaxone/ Linezolid N=322 n/N_w (%)
Cholesterol, total, high (mg/dL)		
Level 1 (>200)	158/292 (54.1)	155/304 (51.0)
Level 2 (>210)	134/292 (45.9)	134/304 (44.1)
Level 3 (>225)	101/292 (34.6)	107/304 (35.2)

Laboratory Parameter	Ceftobiprole N=310 n/N_w (%)	Ceftriaxone/ Linezolid N=322 n/N_w (%)
Triglycerides, high (mg/dL)		
Level 1 (>150)	188/292 (64.4)	184/304 (60.5)
Level 2 (>300)	32/292 (11.0)	39/304 (12.8)
Level 3 (>500)	6/292 (2.1)	5/304 (1.6)

Source: adlb.xpt; Software: R
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration of treatment up to 14 days.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data

Table 82. Subjects With One or More Hematology Analyte Values Exceeding Specified Levels, Safety Population, Trial CAP-3001

Laboratory Parameter	Ceftobiprole N=310 n/N_w (%)	Ceftriaxone/ Linezolid N=322 n/N_w (%)
WBC, low (10^3 cells/uL)		
Level 1 (<3.5)	7/291 (2.4)	7/297 (2.4)
Level 2 (<3)	3/291 (1.0)	3/297 (1.0)
Level 3 (<1)	0/291 (0)	0/297 (0)
WBC, high (10^3 cells/uL)		
Level 1 (>10.8)	70/291 (24.1)	92/297 (31.0)
Level 2 (>13)	36/291 (12.4)	44/297 (14.8)
Level 3 (>15)	23/291 (7.9)	26/297 (8.8)
Hemoglobin, low (g/dL)		
Level 2 (>1.5 g/dL dec. from baseline)	21/247 (8.5)	13/237 (5.5)
Level 3 (>2 g/dL dec. from baseline)	15/247 (6.1)	3/237 (1.3)
Hemoglobin, high (g/dL)		
Level 2 (>2 g/dL inc. from baseline)	37/247 (15.0)	30/237 (12.7)
Level 3 (>3 g/dL inc. from baseline)	5/247 (2.0)	9/237 (3.8)
Platelets, low (10^3 cells/uL)		
Level 1 (<140)	16/291 (5.5)	10/296 (3.4)
Level 2 (<125)	11/291 (3.8)	4/296 (1.4)
Level 3 (<100)	3/291 (1.0)	1/296 (0.3)
Lymphocytes, low (10^3 cells/uL)		
Level 1 (<1)	40/291 (13.7)	29/297 (9.8)
Level 2 (<0.75)	18/291 (6.2)	15/297 (5.1)
Level 3 (<0.5)	4/291 (1.4)	3/297 (1.0)
Lymphocytes, high (10^3 cells/uL)		
Level 1 (>4)	8/291 (2.7)	12/297 (4.0)
Level 2 (>10)	2/291 (0.7)	0/297 (0)
Level 3 (>20)	1/291 (0.3)	0/297 (0)
Neutrophils, low (10^3 cells/uL)		
Level 1 (<2)	19/291 (6.5)	20/297 (6.7)
Level 2 (<1)	2/291 (0.7)	1/297 (0.3)
Level 3 (<0.5)	0/291 (0)	0/297 (0)
Eosinophils, high (10^3 cells/uL)		
Level 1 (>0.65)	10/291 (3.4)	11/297 (3.7)
Level 2 (>1.5)	1/291 (0.3)	4/297 (1.3)
Level 3 (>5)	0/291 (0)	0/297 (0)

Source: adlb.xpt; Software: R
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration of treatment up to 14 days.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; WBC, white blood cells

7.6.3.7. Assessment of Drug-Induced Liver Injury, Trial CAP-3001

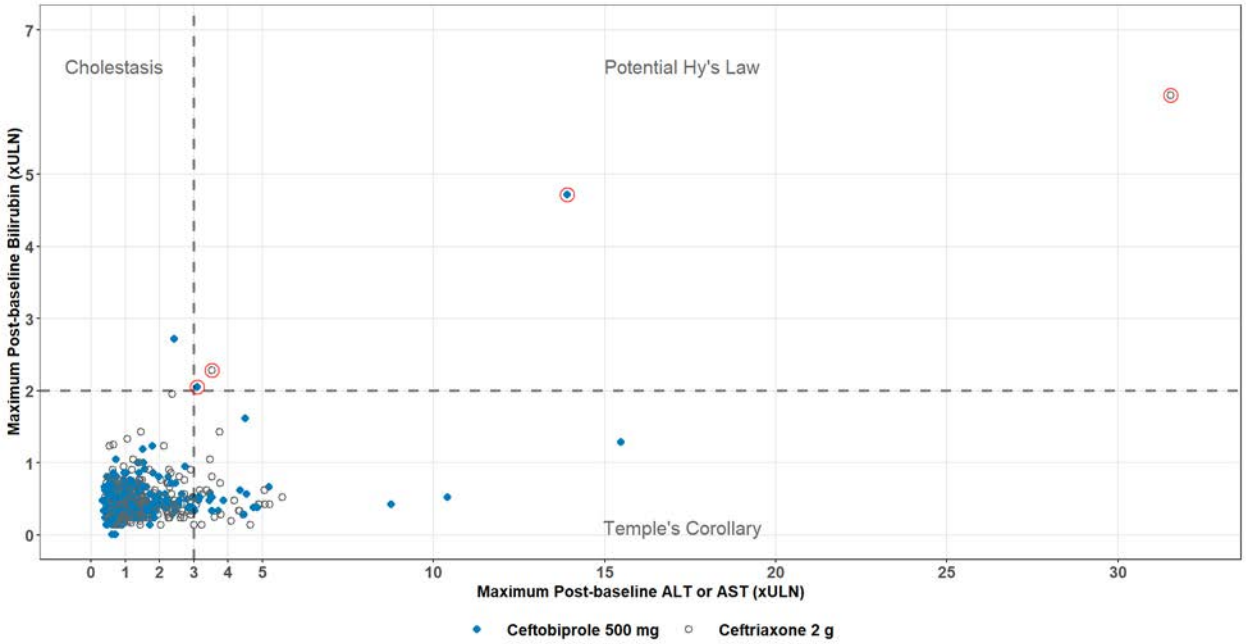
Figure 11 shows a screening assessment for potential cases of DILI. Overall, the number of subjects in the four quadrants were generally balanced between the two arms (Table 83). There were two subjects in each treatment arm – subjects (b) (6) in the ceftobiprole arm and subjects (b) (6) in the ceftriaxone arm – that fit the criteria for potential Hy's Law.

- In the ceftriaxone arm, subject (b) (6) was found to have elevated ALT at 45 U/L, AST at 114 U/L, and bilirubin at 2.22 mg/dL prior to receiving study medication for 3 days. Alkaline phosphatase and GGT were also elevated. Repeat blood work on the third day showed normalized ALT but increased alkaline phosphatase, AST at 127 U/L, and bilirubin at 2.81 mg/dL with a decrease in GGT. Repeat blood work to assess resolution of elevated liver function tests was not done. The subject had elevated values prior to receiving the study drug which may be due to initial illness and during treatment there was both improvement and worsening of lab values. In this subject, it is unclear if the study treatment is related to the liver dysfunction, but it is unlikely given the overall trend.
- Subject (b) (6) did not have liver function tests prior to receiving ceftriaxone. After receiving treatment for 9 days, liver function tests were obtained and the subject had normal levels of ALT, AST, alkaline phosphatase, and GGT. Bilirubin was elevated at 4.39 mg/dL. Study drug was stopped on day 11 and on day 13, subject had elevated ALT at 575 U/L, AST at 1072 U/L, and increased bilirubin levels that peaked at 6.02 mg/dL. GGT and alkaline phosphatase remained normal throughout the study. Lab work done at the end of the study showed resolution of all liver function tests except a persistent mildly increased bilirubin. Subject had developed a rib fracture on day 10 and cardiac failure on day 34. Subject had also received ranitidine concurrently with study treatment. While rare, ranitidine has been associated with liver injury with resolution upon stopping medication and it is possible that concurrent use of ranitidine and other medications may have caused the hepatic injury.

- In the ceftobiprole arm, subject (b) (6) was found to have elevated AST at 3861 U/L, ALT at 883 U/L, bilirubin at 2.81 mg/dL, and elevated GGT prior to receiving treatment for 4 days. While on treatment, ALT decreased while the alkaline phosphatase and GGT increased along with bilirubin which peaked at 5.79 mg/dL. AST was not done at the time. Repeat lab work done at the end of the trial showed resolution of elevated laboratory values except for GGT but that value of GGT had decreased to less than the initial elevated value. Given the elevated values prior to receiving the study drug with a subsequent decrease in some of the values while on treatment, it is less likely that the liver injury is due to the study drug. It is likely that the initial abnormal laboratory values were due to the initial illness.
- Subject (b) (6) had mildly elevated ALT, AST, and bilirubin prior to receiving ceftobiprole. Alkaline phosphatase and GGT were within normal range throughout the trial. Subject received 8 days of treatment and during treatment, ALT, AST, and bilirubin increased until the last day of treatment. ALT and AST levels peaked at 68 U/L and 105 U/L respectively. Repeat testing done days after stopping treatment showed decreasing ALT and AST however bilirubin continued to increase to a peak of 2.51 mg/dL. There was no repeat testing to trend resolution of the remaining elevated values. Approximately 47 days after last laboratory test, the subject was reported to have hepatic cirrhosis. Given the diagnosis of hepatic cirrhosis near the end of the trial, it is likely that the subject had underlying liver disease prior to enrollment. This is supported in the initial elevated lab values prior to starting treatment. Any association with ceftobiprole and DILI would be difficult to determine in this subject.

Based on these two subjects who met potential Hy's Law criteria, there is no signal associating ceftobiprole with DILI.

Figure 11. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Trial CAP-3001



Source: adlb.xpt; Software: R
Each data point represents a subject plotted by their maximum ALT or AST versus their maximum total bilirubin values in the post-baseline period.
A potential Hy's Law case (red circle) was defined as having any post-baseline total bilirubin equal to or exceeding 2X ULN within 30 days after a post-baseline ALT or AST equal to or exceeding 3X ULN, and ALP less than 2X ULN (note ALP values are not circled).

All subjects with at least one post-baseline ALT or AST and bilirubin are plotted. The within 30 days analysis window rule does not apply to cholestatic DILI and temple's corollary cases.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced livery injury; ULN, upper limit of normal

Table 83. Subjects in Each Quadrant for Potential Hepatocellular DILI Screening Plot, Safety Population, Trial CAP-3001

Quadrant	Ceftobiprole N=310 n/N_w (%)	Ceftriaxone/Linezolid N=322 n/N_w (%)
Potential Hy's law (right upper)	2/292 (0.7)	2/302 (0.7)
Cholestasis (left upper)	1/292 (0.3)	0/302 (0)
Temple's corollary (right lower)	21/292 (7.2)	25/302 (8.3)
Total	24/292 (8.2)	27/302 (8.9)

Source: adlb.xpt; Software: R
A potential Hy's Law case was defined as having any post-baseline total bilirubin equal to or exceeding 2X ULN within 30 days after a post-baseline ALT or AST equal to or exceeding 3X ULN, and ALP less than 2X ULN. The within 30 days analysis window rule does not apply to cholestatic DILI and temple's corollary cases.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: DILI, drug-induced liver injury; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data

7.6.3.8. Vital Signs' Analyses, Trial CAP-3001

Review of the vital signs data showed no clinical differences between the treatment arms. Over the course of the trial there were changes in both arms consistent with resolution of bacterial pneumonia including decreased heart rate, temperature, and respiratory rate along with increased blood pressure.

7.6.3.9. Subgroup Analyses, Trial CAP-3001

Based on the sub-group analysis (Table 84), there were more subjects with reported AEs in the ceftobiprole arm reported in each sex, race, ethnicity, and geographic subgroup which is consistent with the higher rate of AEs in the general population. Of note, there were fewer ceftobiprole subjects with AEs in the older age groups (>65 and >75 years). Overall, there does not appear to be major differences in the incidence of AEs by subgroup beyond what was observed in the general trial population. Some of the differences in AEs between the two treatment arms may be due to low enrollment within that subgroup. For example, there were only 33 total subjects in the Black or African American subgroup.

Table 84. Overview of Adverse Events by Demographic Subgroup, IV Treatment Period, Safety Population, Trial CAP-3001

Characteristic	Ceftobiprole N=310 n/N_s (%)	Ceftriaxone/ Linezolid N=322 n/N_s (%)
Sex, n (%)		
Female	101/133 (75.9)	92/136 (67.6)
Male	116/177 (65.5)	116/186 (62.4)
Age group ≥65, years, n (%)		
≥65	78/111 (70.3)	90/126 (71.4)
Age group ≥75, years, n (%)		
≥75	36/54 (66.7)	46/62 (74.2)

Characteristic	Ceftobiprole N=310 n/N_s (%)	Ceftriaxone/ Linezolid N=322 n/N_s (%)
Race, n (%)		
Asian	50/68 (73.5)	47/72 (65.3)
Black or African American	15/16 (93.8)	14/17 (82.4)
Other	24/33 (72.7)	19/30 (63.3)
White	128/193 (66.3)	128/203 (63.1)
Ethnicity, n (%)		
Hispanic or Latino	57/71 (80.3)	65/83 (78.3)
Not Hispanic or Latino	160/239 (66.9)	141/237 (59.5)
Missing	0/0 (NA)	2/2 (100)
Geographic region, n (%)		
USA	36/40 (90.0)	33/40 (82.5)
Non-USA	181/270 (67.0)	175/282 (62.1)

Source: adae.xpt; Software: R
Abbreviations: IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; N_s, total number of subjects for each specific subgroup and were assigned to that specific arm

7.6.4. Community-Acquired Bacterial Pneumonia, Trial BPR-PIP-002 (Pediatric)

7.6.4.1. Overview of Treatment-Emergent Adverse Events Summary, Trial BPR-PIP-002

The proportion of subjects with TEAEs was similar in the ceftobiprole arm and the comparator cephalosporin arm (31.9% vs. 29.5% respectively). The majority of TEAEs were mild in both arms of the trial. The incidence of AEs leading to permanent discontinuation of the trial drug was higher in the ceftobiprole arm than in the comparator arm (4.3% vs. 0) and is discussed in further detail in Section 7.6.4.4. There was one subject with an AE leading to interruption of the study drug, and one subject with a severe AE, both of which occurred in ceftobiprole arm. There were seven SAEs in the ceftobiprole arm vs. two SAEs in the comparator arm during the study period which are discussed below in Section 7.6.4.3

Table 85. Overview of Adverse Events, Safety Population, Trial BPR-PIP-002

Event Category	Ceftobiprole N=94 n (%)	Cephalosporin ± Vancomycin N=44 n (%)
Any AE	30 (31.9)	13 (29.5)
Severe and worse	3 (3.2)	0
Moderate	11 (11.7)	2 (4.5)
Mild	16 (17)	11 (25)
AEs leading to permanent discontinuation of study drug	4 (4.3)	0
AEs leading to dose modification of study drug	1 (1.1)	0
AEs leading to interruption of study drug	1 (1.1)	0
AEs leading to reduction of study drug	0	0
AEs leading to dose delay of study drug	0	0

Event Category	Ceftobiprole N=94 n (%)	Cephalosporin ± Vancomycin N=44 n (%)
SAEs	7 (7.4)	2 (4.5)
SAEs with fatal outcome	0	0
Life-threatening SAEs	0	0
SAEs requiring hospitalization	6 (6.4)	2 (4.5)
Other	2 (2.1)	0

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any adverse event that began after treatment began.
Duration of treatment is 7-14 days including a minimum of 3 days of study drug treatment and subsequent switch to defined age-appropriate oral antibacterial drug.
Severity as assessed by the investigator.
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event

7.6.4.2. Deaths, Trial BPR-PIP-002

There were no deaths in Trial BPR-PIP-002.

7.6.4.3. Serious Treatment-Emergent Adverse Events, Pediatric Trial BPR-PIP-002

In the trial, seven subjects experienced SAEs in the ceftobiprole arm, and two subjects experienced one SAE each in the comparator cephalosporin arm.

Table 86. Subjects With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Trial BPR-PIP-002

System Organ Class Preferred Term	Ceftobiprole N=94 n (%)	Cephalosporin ± Vancomycin N=44 n (%)
Any SAE	7 (7.4)	2 (4.5)
Gastrointestinal disorders (SOC)	1 (1.1)	0
Vomiting	1 (1.1)	0
Immune system disorders (SOC)	1 (1.1)	0
Hypersensitivity	1 (1.1)	0
Infections and infestations (SOC)	4 (4.3)	1 (2.3)
Pneumonia	3 (3.2)	0
Pharyngitis streptococcal	1 (1.1)	0
Tonsillitis streptococcal	1 (1.1)	0
Bronchitis	0	1 (2.3)
Nervous system disorders (SOC)	0	1 (2.3)
Seizure like phenomena	0	1 (2.3)

System Organ Class Preferred Term	Ceftobiprole N=94 n (%)	Cephalosporin ± Vancomycin N=44 n (%)
Respiratory, thoracic and mediastinal disorders (SOC)	2 (2.1)	0
Pleural effusion	1 (1.1)	0
Pleurisy	1 (1.1)	0

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any adverse event that began after treatment began.
Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Duration of treatment is 7-14 days including a minimum of 3 days of study drug treatment and subsequent switch to defined age-appropriate oral antibacterial drug
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with adverse event; SAE, serious adverse event; SOC, system organ class

The narratives for the SAEs that occurred in the ceftobiprole arm are provided below. Two of these SAEs - hypersensitivity and pneumonia - occurred during the IV treatment period and the remainder (pleuropneumonia, pneumonia (2 events), tonsillitis streptococcal, pharyngitis streptococcal, pleural effusion, and vomiting) occurred following transition to oral antibacterial drugs:

- Subject (b) (6) experienced two SAEs of hypersensitivity and pleural effusion. This 17-year-old female with no significant medical history was admitted for treatment of CABP. On Day 3 of ceftobiprole administration, during the infusion, she experienced facial and extremity edema, a diffuse itchy rash, high fever and sweating. There was no associated hypotension or bronchospasm. Ceftobiprole was discontinued and the subject was treated with IV dexamethasone and oral chloropyramine. Symptoms resolved in an hour, and she was transitioned to treatment with cefuroxime and levofloxacin. Two days later, a chest x-ray demonstrated bilateral pneumonia and right-sided pleural effusion and her antibacterial regimen was adjusted to cefuroxime and clindamycin. A follow-up chest x-ray 2 days later revealed progression of pneumonia at which time vancomycin was initiated. CT chest showed bilateral hydrothoraces which were categorized as an SAE due to prolongation of hospitalization. Bilateral chest tubes were placed. Amikacin and amoxicillin/clavulanate were started for persistent fever. She improved clinically, her chest tubes were removed and she was transitioned to oral levofloxacin. The FDA reviewer's evaluation supports the relatedness of the SAE of hypersensitivity to ceftobiprole because it occurred during the IV infusion. However, this reviewer agrees with the investigator that the SAE of pleural effusion is likely due to complications of pneumonia and unrelated to study drug.
- Subject (b) (6) was a 1-year-old male with no significant medical history who was hospitalized for CABP. He had an SAE of pneumonia on Day 1. He was noted to have tachypnea during initial screening for the trial. On the same day, the subject received the first dose of ceftobiprole but was transferred to the intensive care unit for worsening tachypnea and was placed on mechanical ventilation later that day. Due to persistent fever following the second dose of ceftobiprole, the study drug was discontinued, and the subject was started on ceftriaxone and clarithromycin. Because his therapy was switched prior to Day 4, this subject did not have a clinical response assigned on that day and was judged to have a category of "worsened" at EOT. His clinical outcome was failure at the TOC visit. This reviewer agrees with the investigator that the pneumonia is unlikely to be related to the study drug, given that symptoms were present prior to his receiving the first dose of ceftobiprole and subsequent clinical worsening occurred within 24 hours of the start of treatment. The narrative is

compatible with worsening of underlying infection and occurred too soon after ceftobiprole initiation to support relatedness to the drug.

- Subject (b) (6) was a 6-year-old female with a history of atrial septal defect and asthma, who had an SAE of pleuropneumonia. She was treated with ceftobiprole for CABP and appeared well at EOT. No information was provided regarding the anatomical location of the original CABP. Two weeks later, she developed fever and was diagnosed with an upper respiratory infection and subsequently with left-sided pleuropneumonia necessitating hospitalization. She was treated with ceftriaxone for a week with improvement. She was discharged home but returned again the following day - imaging showed left sided pneumonia with an effusion measuring 5.5 cm. She was hospitalized again and treated with ceftriaxone and azithromycin for another week. This subject had a clinical response of improved assigned at Day 4 and at EOT but was judged to have a clinical outcome of failure at the TOC visit. The occurrence of pleuropneumonia and a large effusion two weeks after initial treatment for CABP may be compatible with the development of a complicated pleural effusion or empyema; this reviewer agrees with the investigator that it is unlikely to be related to administration of ceftobiprole.
- Subject (b) (6) was a 2-year-old male who experienced an SAE of pneumonia. He was originally hospitalized for CABP and treated with ceftobiprole for 5 days, followed by 5 days of oral amoxicillin clavulanate. The location of his pneumonia was not specified. His clinical response at Day 4 was judged to be improved and cured at the EOT visit. Twelve days after the EOT visit, he developed low grade fever and was diagnosed with a new left lobar pneumonia for which he was hospitalized and transferred to the intensive care unit within two hours of admission due to worsening tachypnea, dyspnea and persistent fever. He was treated with ceftriaxone, meropenem, and clarithromycin during this hospitalization and improved with treatment. Because the new pneumonia was diagnosed 12 days after his first EOT visit, it could have represented failure of treatment of the initial pneumonia. His overall clinical outcome was judged by the investigator to be failure at the TOC visit. This reviewer agrees with the Applicant that it is likely not related to administration of the study drug.
- Subject (b) (6) was a 3-year-old female treated for CABP with ceftobiprole for 3 days followed by amoxicillin clavulanate for 7 days. Fourteen days after the TOC visit, she developed fever and cough and was diagnosed with the SAEs of streptococcal pharyngitis and tonsillitis streptococcal for which she was hospitalized and treated with amoxicillin-clavulanate. Because there was approximately 3 weeks between completion of ceftobiprole treatment for CABP and the onset of her tonsillopharyngitis, these SAEs were not judged to be related to ceftobiprole.

- Subject (b) (6) was a 2-year-old male who was treated for 4 days with ceftobiprole for CABP and then transitioned to oral cefuroxime for 7 days. He experienced 4 episodes of vomiting after the second dose of cefuroxime but vomiting resolved later that same day after treatment with IV glucose, granisetron, ranitidine, and normal saline. This was considered an SAE as it prolonged hospitalization for one day, but this reviewer agrees with the Applicant that the vomiting was unlikely to be related to ceftobiprole given that it was temporally related to administration of cefuroxime.
- Subject (b) (6) was a 4-year-old male with no significant medical history who was admitted with CABP and initiated on ceftobiprole. No details were provided regarding findings on initial imaging. He exhibited cough, persistent fever and hypoxemia continuing into Day 4 of study treatment and was diagnosed with pleuritis. Chest x-ray on Day 4 found a new blunted right costophrenic angle and chest ultrasound noted free fluid. The subject had a thoracostomy tube placed the same day with drainage of 250 mL of yellow fluid. Analysis of the pleural fluid showed polymorphonuclear leukocytes (>25 per low-powered field) and 2+ gram-positive cocci on smear but was negative on culture. A chest tube was placed the following day, ceftobiprole was discontinued, and amikacin, meropenem, and vancomycin were started. Pleuritis was classified as an SAE as it resulted in prolongation of hospitalization. In this reviewer's opinion, the SAE is not a safety event per se, but rather appears to represent worsening infection which may have been the result of failure of treatment with ceftobiprole.

7.6.4.4. Adverse Events and FDA Medical Queries Leading to Treatment Discontinuation, Trial BPR-PIP-002

The incidence of AEs leading to treatment discontinuation was higher in the ceftobiprole arm than in the comparator cephalosporin arm (4.3% versus 0), as seen in Table 87 The four AEs that led to discontinuation in the ceftobiprole arm included hypersensitivity, pneumonia, pleurisy, and urticaria; the first three were SAEs and are described in Section 7.6.4.3. The narrative for the remaining subject with urticaria leading to treatment discontinuation is provided below Table 87.

Table 87. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Trial BPR-PIP-002

System Organ Class Preferred Term	Ceftobiprole N=94 n (%)	Cephalosporin ± Vancomycin N=44 n (%)
Any AE leading to discontinuation	4 (4.3)	0
Immune system disorders (SOC)	1 (1.1)	0
Hypersensitivity	1 (1.1)	0
Infections and infestations (SOC)	1 (1.1)	0
Pneumonia	1 (1.1)	0
Respiratory, thoracic and mediastinal disorders (SOC)	1 (1.1)	0
Pleurisy	1 (1.1)	0
Skin and subcutaneous tissue disorders (SOC)	1 (1.1)	0
Urticaria	1 (1.1)	0

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any adverse event that began after treatment began.
Duration of treatment is 7-14 days including a minimum of 3 days of study drug treatment and subsequent switch to defined age-appropriate oral antibacterial drug.
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with adverse event; SOC, system organ class

Subject [redacted] was an 11-year-old male with medical history of hydatid cysts of the lung and liver which were surgically resected in [redacted] respectively. In [redacted], he was admitted to a hospital with CABP and randomized to ceftobiprole treatment. Prior to trial entry, he received two days of oral cefuroxime and two days of IV cefepime. The subject experienced urticaria while receiving his 4th infusion of ceftobiprole on Day 2. No other symptoms or signs were recorded, but the subject was treated with epinephrine and methylprednisolone with resolution of symptoms. Ceftobiprole was discontinued. Although hypersensitivity has been described secondary to hydatid cyst content spillage during surgical resection, the timing of this subject's urticaria was not temporally related to cyst removal. This AE is considered more likely related to the study drug given that it occurred during ceftobiprole infusion.

7.6.4.5. Treatment-Emergent Adverse Events, Trial BPR-PIP-002

TEAEs occurred with similar frequency in both treatment arms – 31.9% of subjects in the ceftobiprole arm and 29.5% of subjects in the comparator cephalosporin arm (Table 88). The most common TEAEs in the ceftobiprole arm were vomiting (7.4% of subjects), viral infection (4.3%), headache (3.2%), pneumonia (3.2%), and alanine aminotransferase increased (3.2%), all with a risk difference of >3.0 compared to the comparator arm while the most common AE in the comparator cephalosporin arm was diarrhea (9.1% of subjects, risk difference -7.0). The ceftobiprole arm had more AEs related to hypersensitivity, phlebitis, urticaria, and infusion site reactions (6 subjects compared to 1 in comparator cephalosporin arm). The ceftobiprole arm also had more AEs related to the lower respiratory tract including pleurisy, pleural effusion and pneumonia (3 subjects compared to 0 in comparator cephalosporin arm) which are likely reflective of the infection under study and the 2:1 enrollment in the ceftobiprole versus comparator arms.

There were only 5 subjects in the ceftobiprole arm with HABP included in the trial. Among these subjects, there were two AEs, chromaturia and pyrexia, neither of which were considered SAEs.

Reference ID: 5357793

Table 88. Subjects with Adverse Events, Safety Population, Trial BPR-PIP-002

Preferred Term	Ceftobiprole N=94 n (%)	Cephalosporin ± Vancomycin N=44 n (%)
Any AE	30 (31.9)	13 (29.5)
Vomiting	7 (7.4)	1 (2.3)
Viral infection	4 (4.3)	0
Headache	3 (3.2)	0
Pneumonia	3 (3.2)	0
Alanine aminotransferase increased	3 (3.2)	0
Infusion site reaction	2 (2.1)	0
Aphthous ulcer	1 (1.1)	0
Aspartate aminotransferase increased	1 (1.1)	0
Dehydration	1 (1.1)	0
Dermatitis allergic	1 (1.1)	0
Functional gastrointestinal disorder	1 (1.1)	0
Hyperkalemia	1 (1.1)	0
Hypersensitivity	1 (1.1)	0
Laryngitis	1 (1.1)	0
Nasopharyngitis	1 (1.1)	0
Pharyngitis streptococcal	1 (1.1)	0
Phlebitis	2 (2.1)	0
Pleural effusion	1 (1.1)	0
Pleurisy	1 (1.1)	0
Pyrexia	2 (2.1)	0
Tonsillitis streptococcal	1 (1.1)	0
Upper respiratory tract infection	1 (1.1)	0
Wheezing	1 (1.1)	0
Chromaturia	1 (1.1)	0
Neutropenia	1 (1.1)	1 (2.3)
Otitis media	1 (1.1)	1 (2.3)
Urticaria	1 (1.1)	1 (2.3)
Abdominal pain	0	1 (2.3)
Gastroenteritis	0	1 (2.3)
Pain in extremity	0	1 (2.3)
Rhinitis	0	1 (2.3)
Seizure like phenomena	0	1 (2.3)
Thrombocytopenia	0	1 (2.3)
Bronchitis	0	2 (4.5)
Diarrhea	2 (2.1)	4 (9.1)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any adverse event that began after treatment began.
Duration of treatment is 7-14 days including a minimum of 3 days of study drug treatment and subsequent switch to defined age-appropriate oral antibacterial drug.
Coded as MedDRA preferred terms.
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with adverse event

7.6.4.6. Laboratory Findings, Trial BPR-PIP-002

Chemistry analyte values between the ceftobiprole and comparator arms were generally similar in this trial. Alterations in sodium levels were minor and balanced between treatment arms. Hypokalemia occurred with a frequency of approximately 4-5.4% in both treatment arms, however, there was an imbalance in favor of ceftobiprole in the occurrence of hyperkalemia with a lower percentage occurring in the ceftobiprole arm versus the comparator cephalosporin arm (4.3% versus 9.1% respectively, risk difference -4.7).

Reference ID: 5357793

Table 89. Subjects With One or More Chemistry Analyte Values With Elevated or Low Values Meeting Specified Levels, Safety Population, Trial BPR-PIP-002

Laboratory Parameter	Ceftobiprole N=94 n/N_w (%)	Cephalosporin ± Vancomycin N=44 n/N_w (%)
Sodium, low (mEq/L)		
Level 1 (<132)	1/92 (1.1)	0/44 (0)
Level 2 (<130)	0/92 (0)	0/44 (0)
Level 3 (<125)	0/92 (0)	0/44 (0)
Sodium, high (mEq/L)		
Level 1 (>150)	1/92 (1.1)	0/44 (0)
Level 2 (>155)	0/92 (0)	0/44 (0)
Level 3 (>160)	0/92 (0)	0/44 (0)
Potassium, low (mEq/L)		
Level 1 (<3.6)	5/92 (5.4)	2/44 (4.5)
Level 2 (<3.4)	4/92 (4.3)	2/44 (4.5)
Level 3 (<3)	0/92 (0)	0/44 (0)
Potassium, high (mEq/L)		
Level 1 (>5.5)	4/92 (4.3)	4/44 (9.1)
Level 2 (>6)	2/92 (2.2)	2/44 (4.5)
Level 3 (>6.5)	2/92 (2.2)	1/44 (2.3)

Source: adlb.xpt; Software: R
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration of treatment is 7-14 days including a minimum of 3 days of study drug treatment and subsequent switch to defined age-appropriate oral antibacterial drug.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data

Analysis of renal function indicates that 10.3% of subjects in the ceftobiprole arm and 7.7% of subjects in the comparator cephalosporin arm had a creatinine level rise to ≥1.5x baseline. There were two subjects in the trial who had elevations in creatinine to ≥2x baseline, both in the ceftobiprole arm. There was also a large percentage of subjects in both arms of the trial in whom creatinine clearance decreased by ≥25% (23% in ceftobiprole arm and 14.0% in the comparator cephalosporin arm, risk difference 9.0), likely reflective of severity of disease, fluid shifts and possibly non-antibacterial medication effects.

Table 90. Subjects With One or More Kidney Function Analyte Values Exceeding Specified Levels, Safety Population, Trial BPR-PIP-002

Laboratory Parameter	Ceftobiprole N=94 n/N_w (%)	Cephalosporin ± Vancomycin N=44 n/N_w (%)
Creatinine, high (mg/dL)		
Level 1 (≥1.5X baseline)	9/87 (10.3)	3/39 (7.7)
Level 2 (≥2X baseline)	2/87 (2.3)	0/39 (0)
Level 3 (≥3X baseline)	0/87 (0)	0/39 (0)
eGFR, low (mL/min/1.73 m^2)		
Level 1 (≥25% decrease)	2/87 (2.3)	0/39 (0)
Level 2 (≥50% decrease)	0/87 (0)	0/39 (0)
Level 3 (≥75% decrease)	0/87 (0)	0/39 (0)

Laboratory Parameter	Ceftobiprole N=94 n/N_w (%)	Cephalosporin ± Vancomycin N=44 n/N_w (%)
CrCl, low (mL/min)		
Level 1 (≥25% decrease)	20/87 (23.0)	6/43 (14.0)
Level 2 (≥50% decrease)	0/87 (0)	0/43 (0)
Level 3 (≥75% decrease)	0/87 (0)	0/43 (0)

Source: adlb.xpt; Software: R
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration of treatment is 7-14 days including a minimum of 3 days of study drug treatment and subsequent switch to defined age-appropriate oral antibacterial drug.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
eGFR values are calculated from serum creatinine using chronic kidney disease epidemiology collaboration (CKD-EPI) equation.
Abbreviations: CrCl, creatinine clearance; eGFR, estimated glomerular filtration rate; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data

Hematology test values indicated similar trends in ceftobiprole and comparator cephalosporin arms respectively in WBC counts, both Level 1 elevated (63% versus 54.5% respectively were greater than 10,800 cells/mL) and Level 1 decreased (9.8% versus 9.1 % respectively were less than 3,500 cells/mL). However, 41.3% vs. 25% of subjects in the ceftobiprole vs. comparator arms respectively had Level 3 elevations in WBC counts. In keeping with the expected physiological response to infection, WBC measurements were in general, abnormal at the start of the trial and trended toward normal by the time of TOC visit. Clinically relevant Levels 2 and 3 neutropenia and thrombocytopenia were reasonably balanced between treatment arms. Other hematology analytes including hemoglobin, lymphocyte, and eosinophil counts all had similar changes in both treatment arms. Although pancytopenia is described in association with the cephalosporin class of medications, pneumonia, severity of illness as well as the duration of treatment may have contributed to changes in the hematology values seen in this trial.

Table 91. Subjects With One or More Hematology Analyte Values Exceeding Specified Levels, Safety Population, Trial BPR-PIP-002

Laboratory Parameter	Ceftobiprole N=94 n/Nw (%)	Cephalosporin ± Vancomycin N=44 n/Nw (%)
WBC, low (10^3 cells/uL)		
Level 1 (<3.5)	9/92 (9.8)	4/44 (9.1)
Level 2 (<3)	5/92 (5.4)	3/44 (6.8)
Level 3 (<1)	0/92 (0)	0/44 (0)
WBC, high (10^3 cells/uL)		
Level 1 (>10.8)	58/92 (63.0)	24/44 (54.5)
Level 2 (>13)	45/92 (48.9)	16/44 (36.4)
Level 3 (>15)	38/92 (41.3)	11/44 (25.0)
Hemoglobin, low (g/dL)		
Level 2 (>1.5 g/dL dec. from baseline)	4/81 (4.9)	3/34 (8.8)
Level 3 (>2 g/dL dec. from baseline)	2/81 (2.5)	1/34 (2.9)
Hemoglobin, high (g/dL)		
Level 2 (>2 g/dL inc. from baseline)	10/81 (12.3)	5/34 (14.7)
Level 3 (>3 g/dL inc. from baseline)	3/81 (3.7)	1/34 (2.9)
Platelets, low (10^3 cells/uL)		
Level 1 (<140)	5/92 (5.4)	3/44 (6.8)
Level 2 (<125)	3/92 (3.3)	2/44 (4.5)
Level 3 (<100)	1/92 (1.1)	1/44 (2.3)

Laboratory Parameter	Ceftobiprole N=94 n/Nw (%)	Cephalosporin ± Vancomycin N=44 n/Nw (%)
Lymphocytes, low (10^3 cells/uL)		
Level 1 (<1)	5/91 (5.5)	0/44 (0)
Level 2 (<0.75)	1/91 (1.1)	0/44 (0)
Level 3 (<0.5)	0/91 (0)	0/44 (0)
Lymphocytes, high (10^3 cells/uL)		
Level 1 (>4)	42/91 (46.2)	16/44 (36.4)
Level 2 (>10)	4/91 (4.4)	2/44 (4.5)
Level 3 (>20)	0/91 (0)	0/44 (0)
Neutrophils, low (10^3 cells/uL)		
Level 1 (<2)	32/92 (34.8)	22/44 (50.0)
Level 2 (<1)	6/92 (6.5)	3/44 (6.8)
Level 3 (<0.5)	1/92 (1.1)	1/44 (2.3)
Eosinophils, high (10^3 cells/uL)		
Level 1 (>0.65)	16/91 (17.6)	11/44 (25.0)
Level 2 (>1.5)	2/91 (2.2)	1/44 (2.3)
Level 3 (>5)	0/91 (0)	0/44 (0)

Source: adlb.xpt; Software: R
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration of treatment is 7-14 days including a minimum of 3 days of study drug treatment and subsequent switch to defined age-appropriate oral antibacterial drug.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; WBC, white blood cells

7.6.4.7. Assessment of Drug-Induced Liver Injury, Trial BPR-PIP-002

There were no Hy's Law cases. In the ceftobiprole arm, three subjects with CABP experienced transaminase elevation. One subject, [redacted] (b) (6) had both ALT and AST elevation. The remaining two subjects, [redacted] (b) (6) had ALT elevation alone.

- Subject [redacted] (b) (6) was a 6-year-old male with no significant medical history who had elevation in both ALT and AST. Bilirubin remained normal throughout the trial. The subject's concomitant medications included antipyretics (paracetamol on Days 1-3 and ibuprofen) and IV fluids and he was transitioned to oral cefuroxime axetil on study Day 13. Discrepancies were noted in the ADLB dataset for this subject with varying ULN values for ALT and AST at different time points during the study period. Thus, the fold-elevation from ULN could not be accurately determined and instead, the maximum fold-elevation from baseline value is depicted for this subject in Table 92. Because the maximum values of AST and ALT occurred at EOT after a 13-day course of ceftobiprole, and there was minimal use of concomitant medications, relatedness to ceftobiprole is possible. However, the etiology of this subject's pneumonia was not determined and may have been contributory as well to the rise in liver enzymes.

Table 92.Hepatic Enzyme Abnormalities Over Time in Subject (b) (6)

(b) (6)	Baseline	Treatment Day 4	EOT (Study Day 16)	TOC (Study Day 28)	Maximum Fold-Elevation From Baseline Value
ALT (U/L)	56	27	219	63	3.9x (at EOT)
AST (U/L)	46	21	228	31	5x (at EOT)
Bilirubin (mg/dL)	0.4	0.16	0.16	0.26	-

Source: ADLB dataset, created by the clinical reviewer
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; EOT, end of treatment; TOC, test-of-cure

- Subject (b) (6) was a 9-year-old male with a history of acute laryngitis who experienced ALT elevation to >5 x ULN. There was a mild elevation in AST as well to >2 x ULN. For this subject, the ULNs for ALT (30 U/L) and AST (38 U/L) remained consistent in testing over time. There was no associated rise in bilirubin. The subject's concomitant medications included ambroxol, diclofenac, and sodium chloride and he was transitioned to oral amoxicillin on study day 7. Diclofenac can cause hepatotoxicity that may start as early as one week into use, and the subject received at least 14 days from 7 days prior to the start of the trial to study Day 7. The mildly elevated ALT and AST at baseline in addition to the upward trend of both during the study period may be somewhat attributable to diclofenac use or possibly the etiology of pneumonia, but both returned to within normal limits by TOC.

Table 93, Hepatic Enzyme Abnormalities Over Time in Subject (b) (6)

(b) (6)	Baseline (Fold-Elevation From ULN)	Study Day 4 (Fold-Elevation From ULN)	EOT (Study Day 10) (Fold-Elevation From ULN)	TOC (Study Day 21) (Fold-Elevation From ULN)
ALT (U/L)	64 (2.1x)	49 (1.6x)	151 (5x)	26 (0.9x)
AST (U/L)	54 (1.4x)	30 (0.8x)	78 (2.1x)	29 (0.8x)
Bilirubin (mg/dL)	0.075 (0.1x)	0.16 (0.2x)	0.44 (0.4x)	0.21 (0.2x)

Source: ADLB dataset, created by the clinical reviewer
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; EOT, end of treatment; TOC, Test of Cure; ULN, upper limit of normal

- Subject (b) (6) was a 16-year-old female with a history of measles and varicella infection (both >1 year prior to study enrollment) who experienced ALT elevation to >3 x ULN at EOT. For this subject, the ULNs for ALT (20 U/L) and AST (30 U/L) remained consistent in testing over time. The subject's concomitant medications included antipyretics (paracetamol and ibuprofen) and IV fluids, and the subject was transitioned to oral cefuroxime axetil on study Day 8. Paracetamol was administered for one day so was unlikely to have contributed to the elevation in ALT. The subject's AST remained relatively stable. There was no associated rise in bilirubin during the trial.

Table 94. Hepatic Enzyme Abnormalities Over Time in Subject (b) (6)

(b) (6)	Baseline (Fold-elevation from ULN)	Study Day 4 (Fold-Elevation From ULN)	EOT (Study Day 12) (Fold-Elevation From ULN)	TOC (Study Day 22) (Fold-Elevation From ULN)
ALT (U/L)	7 (0.4x)	15 (0.8x)	78 (3.9x)	15 (0.8x)
AST (U/L)	10 (0.3x)	16 (0.5x)	36 (1.2x)	12 (0.4x)
Bilirubin (mg/dL)	0.21 (0.2x)	0.12 (0.1x)	0.14 (0.1x)	0.19 (0.2x)

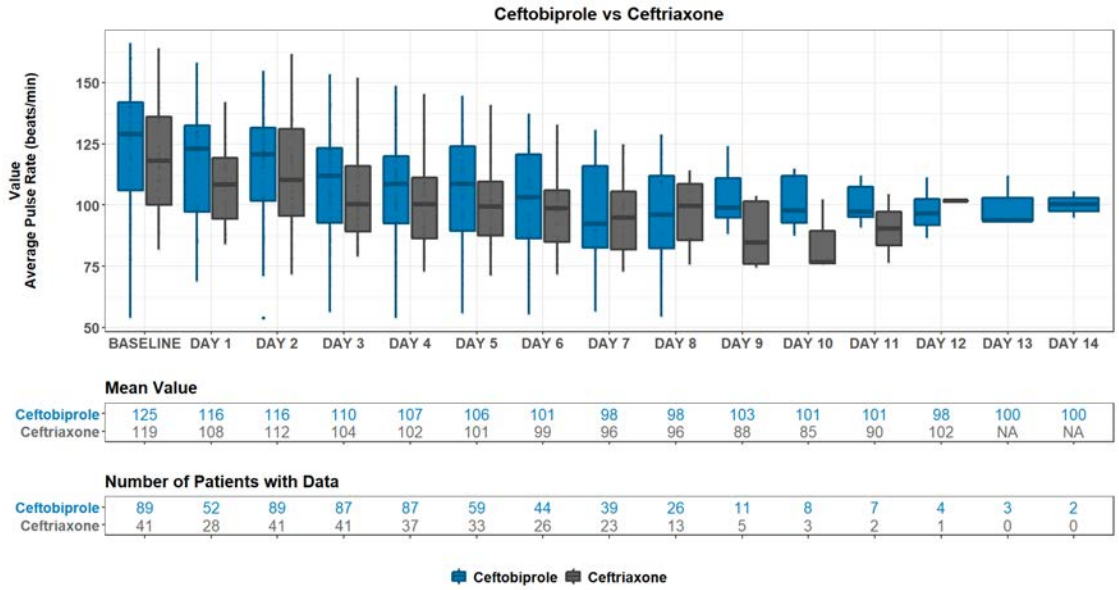
Source: ADLB dataset, created by the clinical reviewer.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; EOT, end of treatment; TOC, test-of-cure; ULN, upper limit of normal

Due to the discrepancies in the normal ranges for AST, ALT and bilirubin values among Trial subjects, a four-quadrant e-DISH plot could not be formulated.

7.6.4.8. Vital Signs' Analyses, Trial BPR-PIP-002

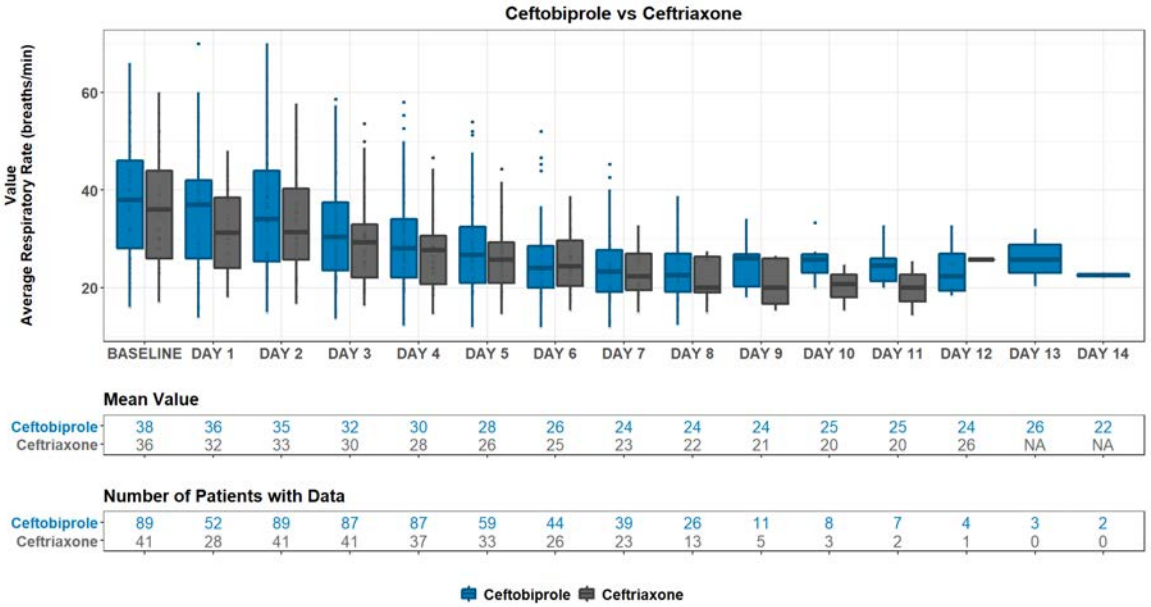
Subjects in both treatment arms experienced tachycardia, tachypnea and higher body temperature at Trial entry, which trended toward normal during the course of the Trial. These changes at trial enrollment likely reflected appropriate physiological responses to pneumonia, and improvement during the course of the trial is to be expected as pneumonia resolves. The trends in heart rate, respiratory rate and body temperature are displayed in Figure 12 through Figure 14 below.

Figure 12. Median and Interquartile Range of Pulse Rate Over Time by Treatment Arm, IV Treatment Period, Safety Population, Trial BPR-PIP-002



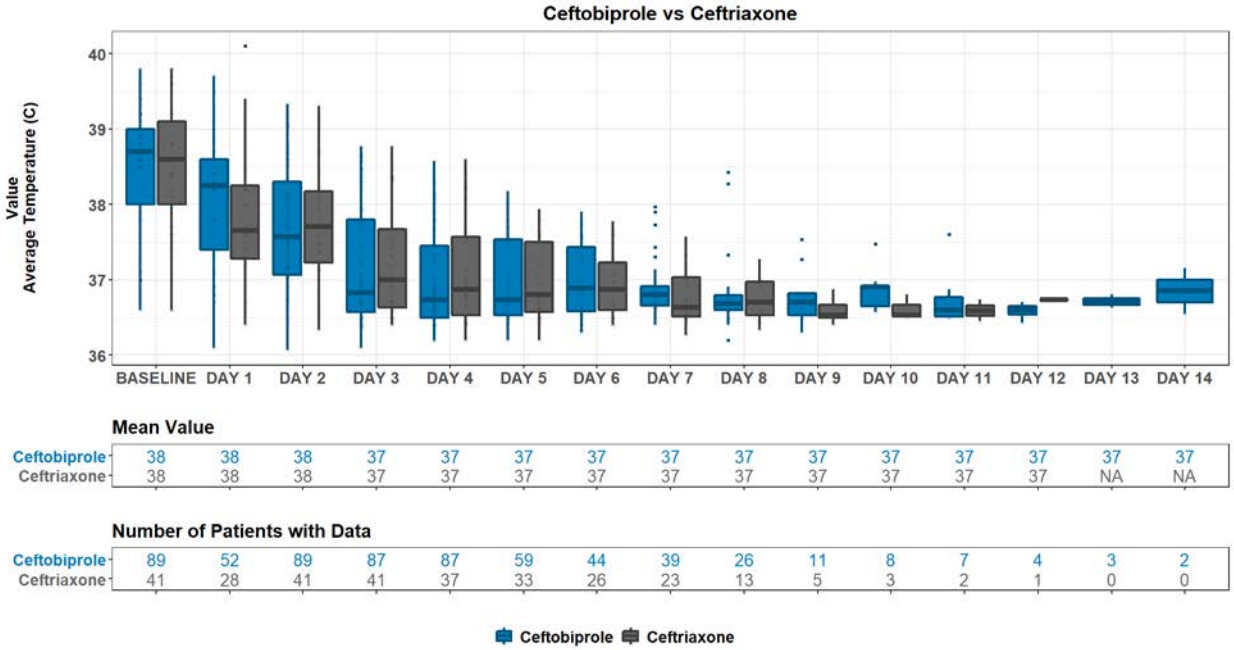
Source: advs.xpt; Software: R
Boxes span the interquartile range (25th to 75th percentile); horizontal lines indicate median; whiskers indicate 1.5X the interquartile range; individual outliers are those beyond this range.
Abbreviations: IV, intravenous; NA, not applicable

Figure 13. Median and Interquartile Range of Respiratory Rate Over Time by Treatment Arm, IV Treatment Period, Safety Population, Trial BPR-PIP-002



Source: advs.xpt; Software: R
Boxes span the interquartile range (25th to 75th percentile); horizontal lines indicate median; whiskers indicate 1.5X the interquartile range; individual outliers are those beyond this range.
Abbreviations: IV, intravenous; NA, not applicable

Figure 14. Median and Interquartile Range of Body Temperature Over Time by Treatment Arm, IV Treatment Period, Safety Population, Trial BPR-PIP-002



Source: advs.xpt; Software: R
Boxes span the interquartile range (25th to 75th percentile); horizontal lines indicate median; whiskers indicate 1.5X the interquartile range; individual outliers are those beyond this range.
Abbreviations: IV, intravenous; NA, not applicable

Subjects in the ceftobiprole arm experienced both systolic and diastolic hypotension more frequently than those in the comparator cephalosporin arm (systolic 13.8% versus 9.1% respectively, risk difference 4.7; diastolic 54.3% and 43.2% respectively, risk difference 11.1) as

seen in Table 95. It is possible that these differences were reflective of differences in severity of infection or ages of the subjects in each treatment arm as it does not appear biologically plausible for the Trial drug to be associated with hypotension per se.

Table 95. Percentage of Subjects Meeting Specific Hypotension Levels Post-Baseline, Safety Population, Trial BPR-PIP-002

Blood Pressure (mm Hg)	Ceftobiprole N=94 n/N_w (%)	Cephalosporin ± Vancomycin N=44 n/N_w (%)
SBP <90	13/94 (13.8)	4/44 (9.1)
DBP <60	51/94 (54.3)	19/44 (43.2)

Source: advs.xpt; Software: R
Abbreviations: DBP, diastolic blood pressure; N, number of subjects in treatment arm; n, number of subjects meeting criteria; Nw, number of subjects with data; SBP, systolic blood pressure

7.6.4.9. Subgroup Analyses, Trial BPR-PIP-002

Table 96 shows the incidence of AEs by demographic subgroups of sex and age. The incidence of AEs in female subjects was higher in the ceftobiprole arm compared to the comparator cephalosporin arm (29.3% and 17.4% respectively). Information from Dr. Ines Pagan, the pharmacology/toxicology reviewer indicates that although there were no specific juveniles included in the animal studies for ceftobiprole, there were no significant differences in the toxicity profiles of females compared to males in these studies.

Fewer subjects in the 3 months to <2 years and the 2 years to <6 years age groups in the ceftobiprole arm had TEAEs (35.1% and 25% respectively) compared to the same age groups in the cephalosporin ± vancomycin arm (47.4% and 50% respectively). Conversely, more subjects in the 12 years to <18 years age group in the ceftobiprole arm had TEAEs compared to the comparator arm (33% versus 0). However, the number of subjects in each of these categories was too small to draw any meaningful conclusions. There were no subgroup analyses performed for ethnicity or race given that all but one subject enrolled in the trial were White. This lack of ethnic diversity in the trial may limit generalizability of results to populations in the U.S.

Table 96. Overview of Adverse Events by Demographic Subgroup, IV Treatment Period, Safety Population, Trial BPR-PIP-002

Characteristic	Ceftobiprole N=94 n/N_s (%)	Cephalosporin ± Vancomycin N=44 n/N_s (%)
Sex		
Female	12/41 (29.3)	4/23 (17.4)
Male	18/53 (34.0)	9/21 (42.9)
Age group, years		
3 months to <2 years	13/37 (35.1)	9/19 (47.4)
2 years to <6 years	3/12 (25.0)	1/2 (50.0)
6 years to <12 years	8/27 (29.6)	3/12 (25.0)
12 years to <18 years	6/18 (33.3)	0/11 (0)

Source: adae.xpt; Software: R
Abbreviations: IV, intravenous; N, number of subjects in treatment arm; n, number of subjects with adverse event; N_s, total number of subjects for each specific subgroup and were assigned to that specific arm

7.6.5. Hospital-Acquired Bacterial Pneumonia and Ventilator-Associated Bacterial Pneumonia, Trial BAP 248/307

The BAP 248/307 Trial was submitted to augment the safety database of ceftobiprole. The Applicant is not seeking an indication for HABP/VABP. This trial will be briefly described below followed by a discussion of safety results.

BAP 248/307 was a phase 3, randomized, double-blind, active-control, prospective, multicenter trial evaluating the safety and efficacy of ceftobiprole compared to linezolid/ceftazidime in adult subjects diagnosed with HABP and VABP. Pertinent inclusion criteria included subjects clinically diagnosed with pneumonia after a minimum of 72 hours of hospitalization or residence in a chronic care facility and who had clinical signs/symptoms of pneumonia. Subjects who were pregnant or lactating, had renal impairment, hepatic dysfunction, who were HIV positive, or had a known or suspected condition that may have jeopardized adherence to protocol requirements were excluded from the trial. A total of 781 subjects were randomly assigned to the two study arms with a total of 772 subjects included in the safety analysis, 386 subjects in each arm. There were 567 subjects in the non-VABP subgroup (283 in the ceftobiprole arm and 284 in the linezolid/ceftazidime arm) and 205 subjects in the VABP subgroup (103 in the ceftobiprole arm and 102 in the linezolid/ceftazidime arm).

7.6.5.1. Overview of Treatment-Emergent Adverse Events Summary, Trial BAP 248/307

Table 97 summarizes the AEs in Trial BAP 248/307. SAEs occurred in slightly more subjects in the ceftobiprole arm at 36% compared to the linezolid/ceftazidime arm at 32%. More subjects developed AEs leading to discontinuation of study drug with 14% of the ceftobiprole subjects compared to 10% of the linezolid/ceftazidime subjects. There were also more subjects experiencing AEs leading to dose modification in the ceftobiprole arm. Overall AEs were balanced between the treatment arms at 78%. There were slightly more severe AEs in the ceftobiprole arm at 38% compared to 35% of the comparator arm.

Table 97. Overview of Adverse Events, Safety Population, Trial BAP248/307

Event Category	Ceftobiprole N=386 n (%)	Linezolid/ Ceftazidime N=386 n (%)
SAE	140 (36.3)	123 (31.9)
SAEs with fatal outcome	86 (22.3)	84 (21.8)
Life-threatening SAEs	0	0
AE leading to permanent discontinuation of study drug	54 (14.0)	40 (10.4)
AE leading to dose modification of study drug	7 (1.8)	2 (0.5)
AE leading to interruption of study drug	3 (0.8)	0
AE leading to reduction of study drug	4 (1.0)	2 (0.5)
AE leading to dose delay of study drug	0	0

Reference ID: 5357793

Event Category	Ceftobiprole N=386 n (%)	Linezolid/ Ceftazidime N=386 n (%)
Any AE	299 (77.5)	300 (77.7)
Severe and worse	148 (38.3)	136 (35.2)
Moderate	86 (22.3)	101 (26.2)
Mild	65 (16.8)	63 (16.3)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as an AE that is new in onset or aggravated in severity after the first dose treatment.
Duration of treatment up to 14 days.
Severity as assessed by the investigator.
Table 65 of the CSR reports 88 deaths in the ceftobiprole arm. The discrepancies are because subject BAP248307-(b) (6) died but did not report any AE, and because subject BAP248307(b) (6) had an AE (cardio-respiratory arrest) that had a fatal outcome but is not marked as a serious AE.
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event

7.6.5.2. Deaths, Trial BAP 248/307

Refer to Section 7.7.1 regarding deaths in Trial BAP 248/307.

7.6.5.3. Serious Treatment-Emergent Adverse Events, Trial BAP 248/307

There were slightly more subjects with SAEs in the ceftobiprole arm compared to the linezolid/ceftazidime (Table 98). For ceftobiprole, the largest number of SAEs were noted in the following SOC: infection/infestations at 13.5% followed by respiratory, thoracic, and mediastinal disorders at 10.4% and cardiac disorders at 9.1%. Specific SAEs that were >1% in the ceftobiprole arm included cardiac failure, cardiac arrest, sepsis, septic shock, multiorgan dysfunction, pneumonia, respiratory failure and distress, hyponatremia, and brain edema. A significant portion of the SAEs were related to respiratory or infectious etiologies in both treatment arms. This likely reflects underlying pulmonary disease and the disease process of nosocomial pneumonia.

Table 98. Subjects With Serious Adverse Events Occurring at ≥0.5% Frequency by System Organ Class and Preferred Term, Safety Population, Trial BAP248/307

System Organ Class Preferred Term	Ceftobiprole N=386 n (%)	Linezolid/ Ceftazidime N=386 n (%)
Any SAE	140 (36.3)	123 (31.9)
Blood and lymphatic system disorders (SOC)	3 (0.8)	5 (1.3)
Anemia	1 (0.3)	2 (0.5)
Neutropenia	0	2 (0.5)

System Organ Class Preferred Term	Ceftobiprole N=386 n (%)	Linezolid/ Ceftazidime N=386 n (%)
Cardiac disorders (SOC)	35 (9.1)	33 (8.5)
Cardiac failure congestive	4 (1.0)	0
Bradycardia	4 (1.0)	1 (0.3)
Myocardial infarction	4 (1.0)	1 (0.3)
Cardiac failure	8 (2.1)	6 (1.6)
Ventricular fibrillation	2 (0.5)	1 (0.3)
Cardiac arrest	7 (1.8)	8 (2.1)
Cardiopulmonary failure	1 (0.3)	2 (0.5)
Cardiac failure acute	0	2 (0.5)
Cardio-respiratory arrest	1 (0.3)	3 (0.8)
Cardiogenic shock	1 (0.3)	3 (0.8)
Myocardial ischemia	0	2 (0.5)
Arrhythmia	0	4 (1.0)
Gastrointestinal disorders (SOC)	10 (2.6)	11 (2.8)
Nausea	2 (0.5)	0
Vomiting	2 (0.5)	1 (0.3)
Pancreatitis necrotizing	0	2 (0.5)
General disorders and administration site conditions (SOC)	13 (3.4)	14 (3.6)
Therapy non-responder	2 (0.5)	0
Pyrexia	4 (1.0)	3 (0.8)
Multiple organ dysfunction syndrome	6 (1.6)	7 (1.8)
Death	0	2 (0.5)
General physical health deterioration	0	2 (0.5)
Hepatobiliary disorders (SOC)	4 (1.0)	5 (1.3)
Cholecystitis	2 (0.5)	0
Hepatic failure	0	2 (0.5)
Infections and infestations (SOC)	52 (13.5)	39 (10.1)
Septic shock	13 (3.4)	6 (1.6)
Sepsis	11 (2.8)	9 (2.3)
Lung abscess	2 (0.5)	1 (0.3)
Pneumonia	15 (3.9)	14 (3.6)
Empyema	1 (0.3)	2 (0.5)
Staphylococcal sepsis	0	2 (0.5)
Bacteremia	0	3 (0.8)
Injury, poisoning and procedural complications (SOC)	6 (1.6)	2 (0.5)
Craniocerebral injury	2 (0.5)	0
Brain herniation	2 (0.5)	1 (0.3)
Metabolism and nutrition disorders (SOC)	9 (2.3)	5 (1.3)
Hyponatremia	5 (1.3)	2 (0.5)
Metabolic acidosis	2 (0.5)	0
Nervous system disorders (SOC)	21 (5.4)	15 (3.9)
Coma	3 (0.8)	0
Brain edema	5 (1.3)	3 (0.8)
Cerebral infarction	2 (0.5)	0
Cerebral vasoconstriction	2 (0.5)	0
Intracranial pressure increased	3 (0.8)	1 (0.3)
Ischemic stroke	3 (0.8)	1 (0.3)
Seizure	3 (0.8)	1 (0.3)
Stroke in evolution	0	2 (0.5)
Renal and urinary disorders (SOC)	6 (1.6)	7 (1.8)
Renal failure	3 (0.8)	3 (0.8)
Acute kidney injury	2 (0.5)	3 (0.8)

System Organ Class Preferred Term	Ceftobiprole N=386 n (%)	Linezolid/ Ceftazidime N=386 n (%)
Respiratory, thoracic and mediastinal disorders (SOC)	40 (10.4)	42 (10.9)
Respiratory distress	6 (1.6)	1 (0.3)
Respiratory acidosis	3 (0.8)	1 (0.3)
Respiratory arrest	2 (0.5)	0
Respiratory failure	16 (4.1)	14 (3.6)
Dyspnea	2 (0.5)	1 (0.3)
Pneumothorax	2 (0.5)	2 (0.5)
Pulmonary edema	3 (0.8)	3 (0.8)
Acute respiratory distress syndrome	4 (1.0)	5 (1.3)
Asphyxia	1 (0.3)	2 (0.5)
Emphysema	0	2 (0.5)
Acute respiratory failure	1 (0.3)	4 (1.0)
Pulmonary embolism	2 (0.5)	6 (1.6)
Vascular disorders (SOC)	16 (4.1)	9 (2.3)
Circulatory collapse	3 (0.8)	1 (0.3)
Hypertension	2 (0.5)	0
Hypotension	4 (1.0)	3 (0.8)
Shock	4 (1.0)	3 (0.8)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as an AE that is new in onset or aggravated in severity after the first dose treatment.
Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.
Duration of treatment up to 14 days.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects with adverse event; SAE, serious adverse event; SOC, system organ class

7.6.5.4. Adverse Events Leading to Treatment Discontinuation, Trial BAP 248/307

The number of subjects with AEs leading to discontinuation is listed in Table 99. While the ceftobiprole arm had more subjects with AEs leading to discontinuation (14%) compared to linezolid/ceftazidime (10.4%), the difference was not driven by one particular SOC. The respiratory, thoracic, and mediastinal disorders SOC had the highest number of subjects with AEs leading to discontinuation in both treatment arms followed by infections and infestations and nervous system disorders. Upon review of the AEs listed, many of the AEs appear to be related to the underlying condition of the subjects. For example, pneumonia, sepsis, and acute respiratory distress syndrome are expected conditions in this subject population. Of note, hyponatremia was found to be associated with discontinuation of ceftobiprole in 4 subjects (1%) compared to 1 subject in the comparator arm (0.3%). Low sodium values are discussed in the "Laboratory Findings" subsection below.

Table 99. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Trial BAP248/307

System Organ Class Preferred Term	Ceftobiprole N=386 n (%)	Linezolid/ Ceftazidime N=386 n (%)
Any AE leading to Discontinuation	54 (14.0)	40 (10.4)
Blood and lymphatic system disorders (SOC)	3 (0.8)	1 (0.3)
Leukocytosis	1 (0.3)	0
Normocytic anemia	1 (0.3)	0
Anemia	1 (0.3)	1 (0.3)
Cardiac disorders (SOC)	8 (2.1)	7 (1.8)
Cardiac arrest	3 (0.8)	0
Bradycardia	2 (0.5)	0
Cardiac failure	1 (0.3)	0
Cor pulmonale acute	1 (0.3)	0
Pulseless electrical activity	1 (0.3)	0
Acute myocardial infarction	1 (0.3)	1 (0.3)
Arrhythmia	0	1 (0.3)
Cardio-respiratory arrest	0	1 (0.3)
Cardiomyopathy	0	1 (0.3)
Sinus tachycardia	0	1 (0.3)
Cardiogenic shock	0	2 (0.5)
Congenital, familial and genetic disorders (SOC)	0	1 (0.3)
Color blindness	0	1 (0.3)
Gastrointestinal disorders (SOC)	4 (1.0)	4 (1.0)
Dysbiosis	1 (0.3)	0
Upper gastrointestinal hemorrhage	1 (0.3)	0
Vomiting	2 (0.5)	1 (0.3)
Diarrhea	0	1 (0.3)
Ileus	0	1 (0.3)
Intestinal perforation	0	1 (0.3)
Nausea	1 (0.3)	2 (0.5)
General disorders and administration site conditions (SOC)	5 (1.3)	2 (0.5)
Multiple organ dysfunction syndrome	2 (0.5)	0
Adverse drug reaction	1 (0.3)	0
Generalized edema	1 (0.3)	0
Pyrexia	1 (0.3)	1 (0.3)
Death	0	1 (0.3)
Hepatobiliary disorders (SOC)	0	5 (1.3)
Acute hepatic failure	0	1 (0.3)
Cholecystitis acute	0	1 (0.3)
Hepatic failure	0	1 (0.3)
Hepatitis	0	1 (0.3)
Liver disorder	0	1 (0.3)
Immune system disorders (SOC)	1 (0.3)	1 (0.3)
Hypersensitivity	1 (0.3)	1 (0.3)
Infections and infestations (SOC)	10 (2.6)	8 (2.1)
Pneumonia	5 (1.3)	2 (0.5)
Sepsis	2 (0.5)	0
Candida infection	1 (0.3)	0
Oral candidiasis	1 (0.3)	0
Meningitis	1 (0.3)	1 (0.3)
Septic shock	2 (0.5)	2 (0.5)
Abdominal abscess	0	1 (0.3)
Urinary tract candidiasis	0	1 (0.3)
Bacteremia	0	2 (0.5)

System Organ Class Preferred Term	Ceftobiprole N=386 n (%)	Linezolid/ Ceftazidime N=386 n (%)
Injury, poisoning and procedural complications (SOC)	1 (0.3)	0
Craniocerebral injury	1 (0.3)	0
Investigations (SOC)	4 (1.0)	1 (0.3)
Creatinine renal clearance decreased	1 (0.3)	0
Hepatic enzyme increased	1 (0.3)	0
Laboratory test abnormal	1 (0.3)	0
Liver function test abnormal	1 (0.3)	0
Alanine aminotransferase increased	0	1 (0.3)
Aspartate aminotransferase increased	0	1 (0.3)
Blood urea increased	0	1 (0.3)
Metabolism and nutrition disorders (SOC)	6 (1.6)	2 (0.5)
Hyponatremia	4 (1.0)	1 (0.3)
Metabolic acidosis	1 (0.3)	0
Metabolic disorder	1 (0.3)	0
Hypocalcemia	1 (0.3)	1 (0.3)
Hypokalemia	0	1 (0.3)
Hypomagnesaemia	0	1 (0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	0	1 (0.3)
Mediastinum neoplasm	0	1 (0.3)
Nervous system disorders (SOC)	9 (2.3)	7 (1.8)
Seizure	2 (0.5)	0
Brain edema	3 (0.8)	2 (0.5)
Cerebral infarction	1 (0.3)	0
Cerebral vasoconstriction	1 (0.3)	0
Epilepsy	1 (0.3)	0
Meningism	1 (0.3)	0
Cerebral hemorrhage	0	1 (0.3)
Clonus	0	1 (0.3)
Headache	0	1 (0.3)
Psychomotor hyperactivity	0	1 (0.3)
Stroke in evolution	0	1 (0.3)
Psychiatric disorders (SOC)	1 (0.3)	1 (0.3)
Delirium	1 (0.3)	1 (0.3)
Renal and urinary disorders (SOC)	6 (1.6)	2 (0.5)
Renal failure	2 (0.5)	0
Acute kidney injury	2 (0.5)	1 (0.3)
Polyuria	1 (0.3)	0
Renal impairment	1 (0.3)	0
Oliguria	1 (0.3)	1 (0.3)

System Organ Class Preferred Term	Ceftobiprole N=386 n (%)	Linezolid/ Ceftazidime N=386 n (%)
Respiratory, thoracic and mediastinal disorders (SOC)	12 (3.1)	8 (2.1)
Acute respiratory distress syndrome	3 (0.8)	0
Asphyxia	1 (0.3)	0
Dyspnea	1 (0.3)	0
Pleural effusion	1 (0.3)	0
Pneumothorax	1 (0.3)	0
Respiratory acidosis	2 (0.5)	1 (0.3)
Respiratory arrest	1 (0.3)	0
Respiratory distress	1 (0.3)	0
Bronchospasm	1 (0.3)	1 (0.3)
Pulmonary embolism	1 (0.3)	1 (0.3)
Tachypnea	1 (0.3)	1 (0.3)
Respiratory failure	1 (0.3)	2 (0.5)
Pulmonary edema	0	2 (0.5)
Skin and subcutaneous tissue disorders (SOC)	4 (1.0)	2 (0.5)
Dermatitis allergic	1 (0.3)	0
Pruritus	1 (0.3)	0
Rash	1 (0.3)	0
Rash vesicular	1 (0.3)	0
Urticaria	1 (0.3)	1 (0.3)
Hyperhidrosis	0	1 (0.3)
Surgical and medical procedures (SOC)	0	1 (0.3)
Therapeutic procedure	0	1 (0.3)
Vascular disorders (SOC)	2 (0.5)	1 (0.3)
Phlebitis	1 (0.3)	0
Vascular fragility	1 (0.3)	0
Shock	0	1 (0.3)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as an AE that is new in onset or aggravated in severity after the first dose treatment. Duration of treatment up to 14 days.
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with adverse event; SOC, system organ class

7.6.5.5. Treatment-Emergent Adverse Events, Trial BAP 248/307

TEAEs occurred in a similar proportion of subjects in the two treatment arms at 77.5% for ceftobiprole and 77.7% for linezolid/ceftazidime (Table 100). The TEAEs that had the highest incidence in the ceftobiprole arm were bacterial infection, diarrhea, respiratory failure, pyrexia, hypokalemia, hyponatremia, and vomiting. Of these TEAEs, vomiting, bacterial infection, pyrexia, and hyponatremia had a >2% risk difference in the ceftobiprole arm compared to the linezolid/ceftazidime arm. There was also an imbalance in renal impairment and cardiac failure in the ceftobiprole arm compared to the linezolid/ceftazidime arm. The high incidence of overall TEAEs is likely due to the significant comorbidities of the subjects and their complicated disease course. A significant portion of subjects in this trial required intensive care management with extensive medical histories contributing to their illness. Of the TEAEs with an imbalance, bacterial infection and cardiac failure were likely related to underlying medical conditions. Hyponatremia was also noted in the laboratory findings (see section below). Vomiting was noted in the other clinical studies as associated with ceftobiprole. Renal impairment was not observed when examining the laboratory data (see Laboratory Findings section below). Please refer to Section 0 for the table of subjects with all AEs occurring in the safety population.

Table 100. Subjects With Common Adverse Events, Recoded, Occurring at ≥4% Frequency in the Ceftobiprole Arm, Safety Population, Trial BAP248/307

Preferred Term	Ceftobiprole N=386 n (%)	Linezolid/Ceftazidime N=386 n (%)
Any AE	299 (77.5)	300 (77.7)
Bacterial infection[a]	70 (18.1)	55 (14.2)
Diarrhea	43 (11.1)	60 (15.5)
Respiratory failure[b]	42 (10.9)	37 (9.6)
Pyrexia[c]	41 (10.6)	33 (8.5)
Hypokalemia	40 (10.4)	33 (8.5)
Hyponatremia	38 (9.8)	26 (6.7)
Vomiting	28 (7.3)	12 (3.1)
Arrhythmia[d]	27 (7.0)	29 (7.5)
Hemorrhage[e]	26 (6.7)	30 (7.8)
Anemia[f]	26 (6.7)	24 (6.2)
Liver enzyme increased[g]	25 (6.5)	23 (6.0)
Pneumonia[h]	25 (6.5)	21 (5.4)
Fungal infection[i]	22 (5.7)	29 (7.5)
Renal & urinary tract infection[j]	22 (5.7)	24 (6.2)
Renal impairment[k]	21 (5.4)	13 (3.4)
Cardiac failure[l]	19 (4.9)	10 (2.6)
Hypertension[m]	18 (4.7)	20 (5.2)
Phlebitis[n]	18 (4.7)	16 (4.1)
Hypotension	17 (4.4)	14 (3.6)
Hyperglycemia	16 (4.1)	24 (6.2)
Constipation	16 (4.1)	24 (6.2)
Dyspnea[o]	16 (4.1)	11 (2.8)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as an AE that is new in onset or aggravated in severity after the first dose treatment.
Duration of treatment up to 14 days.
Recoded terms are defined based on the dictionary created in conjunction with the clinical team.
Adverse Events are sorted by prevalence in the Ceftobiprole arm.
[a] Bacterial infection includes Urinary tract infection, Sepsis, Bacteremia, Clostridium difficile colitis, Cholecystitis, Device related sepsis, Postoperative wound infection, Empyema, Lung abscess, Pyelonephritis, Staphylococcal bacteremia, Abdominal abscess, Abscess, Cholecystitis acute, Conjunctivitis bacterial, Device related infection, Fournier's gangrene, Implant site infection, Incision

site cellulitis, Meningitis tuberculous, Pneumonia legionella, Pseudomonas infection, Psoas abscess, Pulmonary tuberculosis, Pustule, Staphylococcal infection, Subdiaphragmatic abscess, Wound abscess, Wound infection, Abdominal sepsis, Breast abscess, Bronchitis bacterial, Cholangitis, Clostridial infection, Cystitis, Endocarditis bacterial, Erysipelas, Pyopneumothorax, Staphylococcal sepsis, Stenotrophomonas infection, Urethritis.
[b] Respiratory failure includes Respiratory failure, Asphyxia, Sleep apnea syndrome, Hypoxia, Tracheostomy, Acute respiratory failure, Respiratory arrest, Respiratory acidosis, Endotracheal intubation, Mechanical ventilation, Cardiopulmonary failure, Acute respiratory distress syndrome, Cyanosis, Carbon dioxide increased, Hypoventilation.
[c] Pyrexia includes Pyrexia, Hyperthermia.
[d] Arrhythmia includes Arrhythmia, Bradycardia, Sinus tachycardia, Atrial fibrillation, Tachycardia, Supraventricular tachycardia, Supraventricular extrasystoles, Tachyarrhythmia, Ventricular tachycardia, Ventricular extrasystoles, Ventricular fibrillation.
[e] Hemorrhage includes Hematoma evacuation, Splenic hemorrhage, Epistaxis, Hematuria, Hematochezia, Gastric hemorrhage, Petechiae, Gastrointestinal hemorrhage, Ecchymosis, Hemothorax, Hemoptysis, Hematoma, Hemorrhage, Ear hemorrhage, Vaginal hemorrhage, Melaena, Cerebral hemorrhage, Duodenal ulcer hemorrhage, Post procedural hemorrhage, Gastric ulcer hemorrhage, Gastritis hemorrhagic, Intraventricular hemorrhage, Small intestinal hemorrhage, Hemorrhage subcutaneous.
[f] Anemia includes Anemia, Hemoglobin decreased, Normocytic anemia.
[g] Liver enzyme increase includes Alanine aminotransferase increased, Aspartate aminotransferase increased, Gamma-glutamyltransferase increased, Liver function test abnormal, Hepatic enzyme abnormal, Transaminases increased, Hepatic enzyme increased, Gamma-glutamyltransferase abnormal, Blood alkaline phosphatase increased, Hyperbilirubinemia, Blood bilirubin increased.
[h] Pneumonia includes Pneumonia, Empyema, Pneumonia aspiration, Lung abscess, Pulmonary tuberculosis, Pneumonia legionella
[i] Fungal infection includes Fungal infection, Fungal skin infection, Candida infection, Oropharyngeal candidiasis, Oral candidiasis, Systemic candida, Urinary tract candidiasis, Fungaemia, Fungal test positive, Vulvovaginal candidiasis.
[j] Renal & urinary tract infection includes Urinary tract infection, Cystitis, Urinary tract candidiasis, Pyelonephritis, Urethritis, Culture Urine Positive.
[k] Renal impairment includes Renal impairment, Renal failure, Acute kidney injury, Blood creatinine increased, Creatinine renal clearance decreased.
[l] Cardiac failure includes Cardiac failure, Cardiac failure acute, Cardiac failure chronic, Cardiac failure congestive, Right ventricular failure.
[m] Hypertension includes Hypertension, Hypertensive crisis, Blood pressure increased.
[n] Phlebitis includes Phlebitis, Infusion site phlebitis, Thrombophlebitis, Injection site phlebitis.
[o] Dyspnea includes Respiratory distress, Dyspnea.
Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with adverse event

7.6.5.6. Laboratory Findings, Trial BAP 248/307

The tables below summarize the laboratory data from Trial 248/307 (Table 101,Table 102,Table 103,Table 104,and Table 105). In the ceftobiprole treatment arm, there were more cases of hyponatremia (19.4%) compared to the linezolid/ceftazidime treatment arm (14%). It appears this difference in cases of hyponatremia was largely driven by mild cases (between 130 and 132 mEq/L). The remainder of the chemistry values were relatively balanced between the two treatment arms. Of note, hyponatremia will be listed as an adverse reaction in section 6 of labeling. Evidence of renal dysfunction in each arm was also overall balanced with elevated creatinine occurring in 8.4% of subjects in the ceftobiprole arm vs. 7.5% in the linezolid/ceftazidime arms. While in the ceftobiprole arm there were more cases of elevated alkaline phosphatase at 24.1% compared to linezolid/ceftazidime at 15.5%, elevations in AST, ALT, and bilirubin levels were overall balanced between the two arms and did not exceed more than 10% of all subjects. Elevations in cholesterol levels were also balanced between the two arms, however there were more cases of hypertriglyceridemia in the ceftobiprole arm (52.2%) compared to the linezolid/ceftazidime arm (43.3%). Outliers in hematology values were also overall balanced between the two arms, but lymphopenia occurred more in the ceftobiprole arm (33.1%) than linezolid/ceftazidime (27.7%).

Overall, there does not appear to be major differences in the laboratory values between the treatment arms. The subject population in the Trial was fairly ill with multiple medical comorbidities that may be contributing to certain laboratory value outliers.

Reference ID: 5357793

Table 101. Subjects With One or More Chemistry Analyte Values With Elevated or Low Values Meeting Specified Levels, Safety Population, Trial BAP248/307

Laboratory Parameter	Ceftobiprole N=386 n/N_w (%)	Linezolid/Ceftazidime N=386 n/N_w (%)
Sodium, low (mEq/L)		
Level 1 (<132)	63/324 (19.4)	47/335 (14.0)
Level 2 (<130)	37/324 (11.4)	31/335 (9.3)
Level 3 (<125)	14/324 (4.3)	11/335 (3.3)
Sodium, high (mEq/L)		
Level 1 (>150)	6/324 (1.9)	8/335 (2.4)
Level 2 (>155)	4/324 (1.2)	4/335 (1.2)
Level 3 (>160)	1/324 (0.3)	2/335 (0.6)
Potassium, low (mEq/L)		
Level 1 (<3.6)	65/322 (20.2)	67/334 (20.1)
Level 2 (<3.4)	44/322 (13.7)	45/334 (13.5)
Level 3 (<3)	13/322 (4.0)	14/334 (4.2)
Potassium, high (mEq/L)		
Level 1 (>5.5)	15/322 (4.7)	16/334 (4.8)
Level 2 (>6)	6/322 (1.9)	3/334 (0.9)
Level 3 (>6.5)	2/322 (0.6)	1/334 (0.3)
Bicarbonate, low (mEq/L)		
Level 1 (<20)	51/312 (16.3)	56/319 (17.6)
Level 2 (<18)	18/312 (5.8)	23/319 (7.2)
Level 3 (<15)	4/312 (1.3)	5/319 (1.6)
Bicarbonate, high (mEq/L)		
Level 3 (>30)	28/312 (9.0)	51/319 (16.0)
Glucose, low (mg/dL)		
Level 1 (<70)	8/316 (2.5)	3/324 (0.9)
Level 2 (<54)	5/316 (1.6)	1/324 (0.3)
Level 3 (<40)	0/316 (0)	1/324 (0.3)
Glucose, random, high (mg/dL)		
Level 2 (≥200)	50/316 (15.8)	44/324 (13.6)
Level 3 (>250)	20/316 (6.3)	21/324 (6.5)
Calcium, low (mg/dL)		
Level 1 (<8.4)	117/324 (36.1)	114/335 (34.0)
Level 2 (<8)	70/324 (21.6)	74/335 (22.1)
Level 3 (<7.5)	28/324 (8.6)	27/335 (8.1)
Calcium, high (mg/dL)		
Level 1 (>10.5)	8/324 (2.5)	4/335 (1.2)
Level 2 (>11)	1/324 (0.3)	1/335 (0.3)
Level 3 (>12)	1/324 (0.3)	0/335 (0)
Protein, total, low (g/dL)		
Level 1 (<6)	124/324 (38.3)	131/335 (39.1)
Level 2 (<5.4)	70/324 (21.6)	71/335 (21.2)
Level 3 (<5)	41/324 (12.7)	39/335 (11.6)
Albumin, low (g/dL)		
Level 1 (<3.1)	228/317 (71.9)	237/326 (72.7)
Level 2 (<2.5)	131/317 (41.3)	144/326 (44.2)
Level 3 (<2)	66/317 (20.8)	78/326 (23.9)

Reference ID: 5357793

Laboratory Parameter	Ceftobiprole N=386 n/N_w (%)	Linezolid/Ceftazidime N=386 n/N_w (%)
Blood urea nitrogen, high (mg/dL)		
Level 1 (>23)	93/324 (28.7)	80/335 (23.9)
Level 2 (>27)	54/324 (16.7)	51/335 (15.2)
Level 3 (>31)	46/324 (14.2)	40/335 (11.9)

Source: adlb.xpt; Software: R
Note that glucose values for hyperglycemia do not follow a nested format like the other labs. Level 1 corresponds to the diagnosis of prediabetes and is not inclusive of Level 2 and 3. Level 2 corresponds to the diagnosis of diabetes. Level 3 represents significant hyperglycemia that may indicate need for insulin or increased risk for diabetic ketoacidosis or other complications.
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration of treatment up to 14 days.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data

Table 102. Subjects With One or More Kidney Function Analyte Values Exceeding Specified Levels, Safety Population, Trial BAP248/307

Laboratory Parameter	Ceftobiprole N=386 n/N_w (%)	Linezolid/Ceftazidime N=386 n/N_w (%)
Creatinine, high (mg/dL)		
Level 1 (≥1.5X baseline)	26/308 (8.4)	23/307 (7.5)
Level 2 (≥2X baseline)	8/308 (2.6)	6/307 (2.0)
Level 3 (≥3X baseline)	2/308 (0.6)	4/307 (1.3)
eGFR, low (ml/min/1.73 m^2)		
Level 1 (≥25% decrease)	23/299 (7.7)	22/295 (7.5)
Level 2 (≥50% decrease)	6/299 (2.0)	7/295 (2.4)
Level 3 (≥75% decrease)	2/299 (0.7)	3/295 (1.0)
CrCl, low (ml/min)		
Level 1 (≥25% decrease)	40/292 (13.7)	44/289 (15.2)
Level 2 (≥50% decrease)	9/292 (3.1)	7/289 (2.4)
Level 3 (≥75% decrease)	1/292 (0.3)	3/289 (1.0)

Source: adlb.xpt; Software: R
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration of treatment up to 14 days.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
eGFR values are calculated from serum creatinine using chronic kidney disease epidemiology collaboration (CKD-EPI) equation.
Abbreviations: CRCL, creatinine clearance; eGFR, estimated glomerular filtration rate; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data

Table 103. Subjects With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels, Safety Population, Trial BAP248/307

Laboratory Parameter	Ceftobiprole N=386 n/N_w (%)	Linezolid/Ceftazidime N=386 n/N_w (%)
Alkaline phosphatase, high (U/L)		
Level 1 (>1.5X ULN)	78/323 (24.1)	52/335 (15.5)
Level 2 (>2X ULN)	48/323 (14.9)	26/335 (7.8)
Level 3 (>3X ULN)	11/323 (3.4)	6/335 (1.8)
Alanine aminotransferase, high (U/L)		
Level 1 (>3X ULN)	22/316 (7.0)	24/326 (7.4)
Level 2 (>5X ULN)	9/316 (2.8)	10/326 (3.1)
Level 3 (>10X ULN)	5/316 (1.6)	4/326 (1.2)
Aspartate aminotransferase, high (U/L)		
Level 1 (>3X ULN)	15/311 (4.8)	17/320 (5.3)
Level 2 (>5X ULN)	7/311 (2.3)	4/320 (1.2)
Level 3 (>10X ULN)	3/311 (1.0)	2/320 (0.6)

Laboratory Parameter	Ceftobiprole N=386 n/N_w (%)	Linezolid/Ceftazidime N=386 n/N_w (%)
Bilirubin, total, high (mg/dL)		
Level 1 (>1.5X ULN)	12/317 (3.8)	11/326 (3.4)
Level 2 (>2X ULN)	6/317 (1.9)	3/326 (0.9)
Level 3 (>3X ULN)	4/317 (1.3)	0/326 (0)

Source: adlb.xpt; Software: R
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration of treatment up to 14 days.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; ULN, upper limit of normal

Table 104. Subjects With One or More Lipids Analyte Values Exceeding Specified Levels, Safety Population, Trial BAP248/307

Laboratory Parameter	Ceftobiprole N=386 n/N_w (%)	Linezolid/Ceftazidime N=386 n/N_w (%)
Cholesterol, total, high (mg/dL)		
Level 1 (>200)	67/324 (20.7)	69/335 (20.6)
Level 2 (>210)	52/324 (16.0)	57/335 (17.0)
Level 3 (>225)	39/324 (12.0)	38/335 (11.3)
Triglycerides, high (mg/dL)		
Level 1 (>150)	169/324 (52.2)	145/335 (43.3)
Level 2 (>300)	27/324 (8.3)	28/335 (8.4)
Level 3 (>500)	3/324 (0.9)	3/335 (0.9)

Source: adlb.xpt; Software: R
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration of treatment up to 14 days.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data

Table 105. Subjects With One or More Hematology Analyte Values Exceeding Specified Levels, Safety Population, Trial BAP248/307

Laboratory Parameter	Ceftobiprole N=386 n/N_w (%)	Linezolid/Ceftazidime N=386 n/N_w (%)
Complete Blood Count		
WBC, low (10^3 cells/uL)		
Level 1 (<3.5)	4/309 (1.3)	12/312 (3.8)
Level 2 (<3)	3/309 (1.0)	9/312 (2.9)
Level 3 (<1)	0/309 (0)	1/312 (0.3)
WBC, high (10^3 cells/uL)		
Level 1 (>10.8)	127/309 (41.1)	120/312 (38.5)
Level 2 (>13)	80/309 (25.9)	69/312 (22.1)
Level 3 (>15)	53/309 (17.2)	49/312 (15.7)
Hemoglobin, low (g/dL)		
Level 2 (>1.5 g/dL dec. from baseline)	36/241 (14.9)	44/245 (18.0)
Level 3 (>2 g/dL dec. from baseline)	18/241 (7.5)	26/245 (10.6)
Hemoglobin, high (g/dL)		
Level 2 (>2 g/dL inc. from baseline)	43/241 (17.8)	39/245 (15.9)
Level 3 (>3 g/dL inc. from baseline)	17/241 (7.1)	20/245 (8.2)
Platelets, low (10^3 cells/uL)		
Level 1 (<140)	17/300 (5.7)	25/301 (8.3)
Level 2 (<125)	14/300 (4.7)	20/301 (6.6)
Level 3 (<100)	7/300 (2.3)	9/301 (3.0)

Laboratory Parameter	Ceftobiprole N=386 n/N_w (%)	Linezolid/Ceftazidime N=386 n/N_w (%)
WBC Differential		
Lymphocytes, low (10^3 cells/uL)		
Level 1 (<1)	102/308 (33.1)	86/310 (27.7)
Level 2 (<0.75)	51/308 (16.6)	41/310 (13.2)
Level 3 (<0.5)	19/308 (6.2)	19/310 (6.1)
Lymphocytes, high (10^3 cells/uL)		
Level 1 (>4)	2/308 (0.6)	6/310 (1.9)
Level 2 (>10)	1/308 (0.3)	0/310 (0)
Level 3 (>20)	1/308 (0.3)	0/310 (0)
Neutrophils, low (10^3 cells/uL)		
Level 1 (<2)	6/308 (1.9)	16/311 (5.1)
Level 2 (<1)	1/308 (0.3)	5/311 (1.6)
Level 3 (<0.5)	0/308 (0)	3/311 (1.0)
Eosinophils, high (10^3 cells/uL)		
Level 1 (>0.65)	19/308 (6.2)	21/311 (6.8)
Level 2 (>1.5)	1/308 (0.3)	2/311 (0.6)
Level 3 (>5)	0/308 (0)	0/311 (0)

Source: adlb.xpt; Software: R
Threshold levels 1, 2, and 3 as defined by the Standard Safety Tables & Figures Integrated Guide.
Duration of treatment up to 14 days.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; ULN, upper limit of normal; WBC, white blood cells

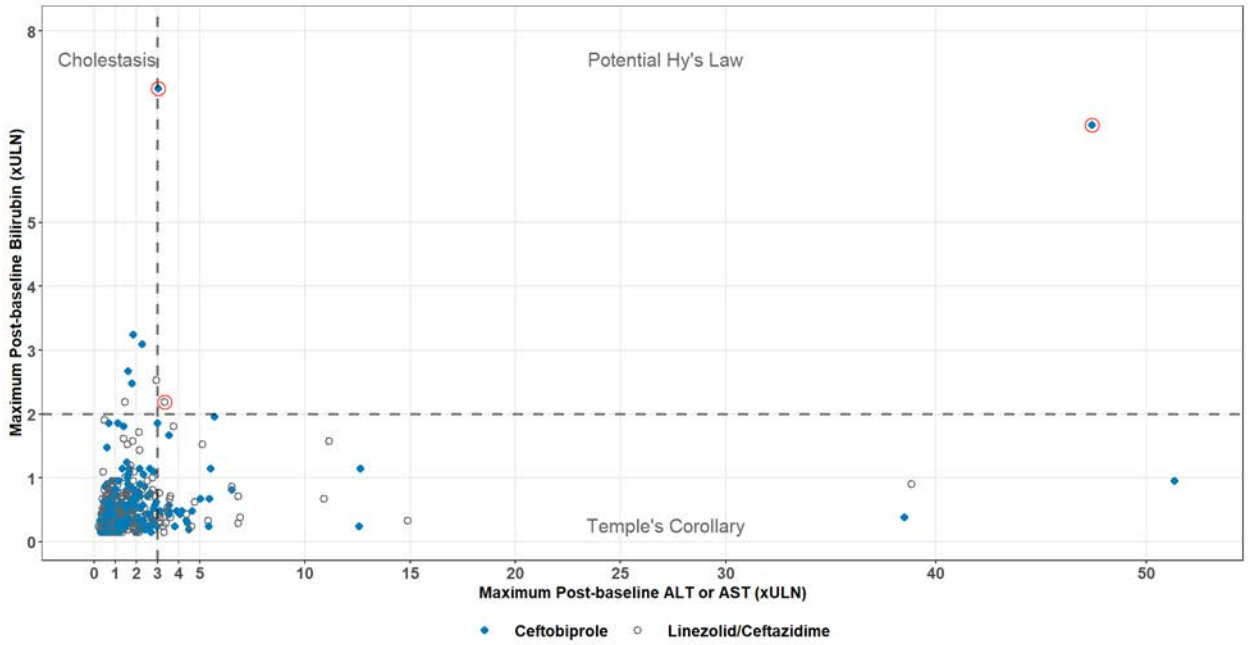
7.6.5.7. Assessment of Drug-Induced Liver Injury, Trial BAP 248/307

Figure 15 shows a screening assessment for potential cases of DILI. Overall, the number of subjects in the four quadrants were generally balanced between the two arms (Table 106). There were two subjects in the ceftobiprole arm – subjects (b) (6) – that fit the criteria for potential Hy's Law.

- Subject (b) (6) had normal levels of ALT, AST, and alkaline phosphatase and mildly elevated bilirubin and GGT prior to enrollment. The subject received 7 days of ceftobiprole, and lab work done on Day 7 showed increasing levels of all liver enzymes and bilirubin values with ALT and AST peaking at 784 U/L and 1612 U/L, respectively, and with a bilirubin at 8 mg/dL. The subject was also progressing to multi-organ system failure and expired on day 7. The subject's worsening trajectory of illness confounds the association between ceftobiprole and DILI as the elevated liver enzymes could also be attributed to the multi-organ system failure.
- Subject (b) (6) had elevated ALT at 49 U/L and bilirubin at 5.2 mg/dL prior to receiving treatment. On Day 4, repeat lab work was obtained which showed increasing ALT at 103 U/L, AST at 78 U/L, bilirubin at 8.71 mg/dL. Alkaline phosphatase and GGT were also elevated. Ceftobiprole was stopped at this time. Repeat blood work was done again on Day 8 which showed ALT, AST, and bilirubin down-trending while alkaline phosphatase and GGT were shown to be increased. No further blood work was performed. Upon enrollment, subject had also received multiple other antibacterial drugs including piperacillin-tazobactam and gentamicin for 1 day. Concurrent administration of these drugs may have contributed to an increase in all of the liver enzymes as piperacillin-tazobactam can cause elevated ALT, AST, and bilirubin.

The association between DILI and ceftobiprole is unlikely based on the results of this trial. The severity of illness in the subjects with concurrent use of hepatotoxic medications likely caused the elevated liver enzymes.

Figure 15. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Trial BAP248/307



Source: adlb.xpt; Software: R
Each data point represents a subject plotted by their maximum ALT or AST versus their maximum total bilirubin values in the post-baseline period.
A potential Hy's Law case (red circle) was defined as having any post-baseline total bilirubin equal to or exceeding 2X ULN within 30 days after a post-baseline ALT or AST equal to or exceeding 3X ULN, and ALP less than 2X ULN (note ALP values are not circled). All subjects with at least one post-baseline ALT or AST and bilirubin are plotted. The within 30 days analysis window rule does not apply to cholestatic DILI and temple's corollary cases.
The applicant reports only 2 potential Hy's Law cases in the clinical study report due to a difference in definition. The applicant did not include a post-baseline AST equal to or exceeding 3X ULN as meeting part of the criteria for a potential Hy's Law case. Because the CDS definition does include that criterion, subject BAP248307-[redacted] (b) (6) was additionally identified as a potential Hy's Law case.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; ULN, upper limit of normal

Table 106. Subjects in Each Quadrant for Potential Hepatocellular DILI Screening Plot, Safety Population, Trial BAP248/307

Quadrant	Ceftobiprole N=386 n/N_w (%)	Linezolid/Ceftazidime N=386 n/N_w (%)
Potential Hy's law (right upper)	2/316 (0.6)	1/326 (0.3)
Cholestasis (left upper)	4/316 (1.3)	2/326 (0.6)
Temple's corollary (right lower)	24/316 (7.6)	27/326 (8.3)
Total	30/316 (9.5)	30/326 (9.2)

Source: adlb.xpt; Software: R
A potential Hy's Law case was defined as having any post-baseline total bilirubin equal to or exceeding 2X ULN within 30 days after a post-baseline ALT or AST equal to or exceeding 3X ULN, and ALP less than 2X ULN. The within 30 days analysis window rule does not apply to cholestatic DILI and temple's corollary cases.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: DILI, drug-induced liver injury; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data

7.6.5.8. Vital Signs' Analyses, Trial BAP 248/307

Review of the vital signs data showed no clinical differences between the treatment arms. Over the course of the Trial, there were changes in both arms consistent with resolution of bacterial pneumonia including decreased heart rate, temperature, and respiratory rate along with increased blood pressure.

7.6.5.9. Subgroup Analyses, Trial BAP 248/307

In the subgroup analysis, the incidence of overall AEs within each subgroup appears to be balanced (Table 107). The differences in the Black or African American and other race subgroups are likely due to the small number of subjects within each group.

Table 107. Overview of Adverse Events by Demographic and Diagnosis Subgroup, Safety Population, Trial BAP248/307

Characteristic	Ceftobiprole N=386 n/N_s (%)	Linezolid/Ceftazidime N=386 n/N_s (%)
Sex, n (%)		
F	83/110 (75.5)	115/145 (79.3)
M	216/276 (78.3)	185/241 (76.8)
Age group ≥75, years, n (%)		
≥75	75/89 (84.3)	93/107 (86.9)
Race, n (%)		
Asian	38/45 (84.4)	38/45 (84.4)
Black or African American	11/11 (100)	6/8 (75.0)
Other	10/16 (62.5)	15/19 (78.9)
White	240/314 (76.4)	241/314 (76.8)
Geographic region, n (%)		
USA	45/47 (95.7)	41/44 (93.2)
Non-USA	254/339 (74.9)	259/342 (75.7)
Infection type, n (%)		
HABP	214/283 (75.6)	219/284 (77.1)
VABP	85/103 (82.5)	81/102 (79.4)

Source: adae.xpt; Software: R
Abbreviations: HABP, hospital-acquired bacterial pneumonia, N, number of subjects in treatment arm; n, number of subjects with adverse event; N_s, total number of subjects for each specific subgroup and were assigned to that specific arm; VABP, ventilator-associated bacterial pneumonia

7.7. Key Safety Review Issues

7.7.1. Higher Mortality for Ceftobiprole Patients With VABP in Trial BAP 248/307

Issue

Increased deaths were observed in the VABP subgroup of Trial BAP 248/307 in subjects in the ceftobiprole arm compared to the linezolid/ceftazidime arm.

Background

In Trial BAP 248/307, a subgroup analysis was done on the safety population based on their pneumonia diagnosis. Of the total 772 subjects, there were 205 VABP subjects with 103 subjects in the ceftobiprole arm and 102 in the linezolid/ceftazidime arm. It was noted that VABP subjects in the ceftobiprole arm had a higher rate of death compared to the subjects in the linezolid/ceftazidime arm. Although the trial was not submitted for an evaluation of efficacy, the increased deaths may have represented a safety issue in this subgroup of subjects. An in-depth analysis of the data was conducted to evaluate potential causes and reasons for the increased deaths in the VABP subgroup.

Assessment

The total deaths in Trial BAP 248/307 were overall balanced between both arms (23% ceftobiprole vs. 22% linezolid/ceftazidime). In the HABP (non-VABP) subgroup however, there were fewer deaths in the ceftobiprole arm at 18.7% compared to 21.1% in the linezolid/ceftazidime arm. This is contrasted by more deaths in the VABP subgroup among ceftobiprole subjects (33%) compared to the linezolid/ceftazidime arm (23.5%). Given this higher rate of death, the narratives for all the deaths in the BAP 248/307 trial were reviewed to determine whether the study drug was related to death. The study drug and death were considered unrelated by the FDA reviewer if the death occurred within 48 hours of receiving the first dose of treatment, the death occurred after receiving the last dose of treatment, or another cause of death was established in the narrative. If a subject who was diagnosed with VABP, initiated treatment, and subsequently expired within a day, the study drug likely would have not made a difference in the subject's trajectory and the death was deemed unrelated to the treatment. In addition, if a subject completed treatment of study drug with resolution of their illness but expired afterwards, this was also considered unrelated as clinical cure was documented and the death was not considered treatment failure. Study drug and death were considered related if there was treatment failure characterized by worsening of VABP that led to death after 48 hours of initiating treatment or if the subject's death was due to an AE related to the study treatment. There was one death related to an allergic reaction, presumably from the trial treatment in the HABP subgroup in a subject receiving linezolid/ceftazidime.

Based on the narrative reviews, the death and study drug relatedness were balanced between the two trial arms in the overall trial population with 12.6% of the deaths in the ceftobiprole arm and 14.3% of the deaths in the linezolid/ceftazidime arm deemed related to the study drug (Table 108). This balance in study drug relatedness is also seen within the subgroups. HABP subject deaths related to the trial treatment was seen in 17% of the ceftobiprole deaths and 16.7% linezolid/ceftazidime deaths. In the VABP subject subgroup, both treatment arms had 5.9% of the deaths deemed related to the Trial drug.

Table 108. Deaths and Drug Relatedness Determined by FDA Reviewer

Event Category	Ceftobiprole n (%)	Linezolid/Ceftazidime n (%)
Total deaths	87*	84
Unrelated	76 (87.4)	71 (84.5)
Related	11 (12.6)	12 (14.3)
Allergy	0	1 (1.2)

Reference ID: 5357793

Event Category	Ceftobiprole n (%)	Linezolid/Ceftazidime n (%)
VABP deaths total	34	24
Unrelated	32 (94.1)	22 (91.7)
Related	2 (5.9)	2 (5.9)
HABP (non-VABP) deaths total	53	60
Unrelated	44 (83)	49 (81.7)
Related	9 (17)	10 (16.7)
Allergy	0	1 (1.7)

Source: FDA Reviewer
*: Total deaths were 88 patients with one patient who died but did not report an AE.
Abbreviations: HABP, hospital-acquired bacterial pneumonia; n, number of subjects meeting criteria; VABP, ventilator-associated bacterial pneumonia

Conclusion

Despite the increased deaths in the VABP subgroup who received ceftobiprole compared to those who received linezolid/ceftazidime, most of the deaths do not appear to be related to the study treatment itself. The increased deaths in the VABP subgroup may have been due to chance, as there was a small number of subjects in the VABP subgroup relative to the entire trial. In addition, the acuity and severity of illness in this subgroup may have led to increased deaths overall, thereby confounding the association between deaths and trial treatment. However, information on increased mortality in VABP subjects treated with ceftobiprole will be included in the ceftobiprole labeling as a warning, emphasizing that ceftobiprole is not approved for the treatment of VABP.

7.7.2. Imbalance in Adverse Events Related to Thrombosis in Trial BPR-CS-009

Issue

An increased frequency of thrombosis was observed in the ceftobiprole arm as compared to daptomycin arm in the BPR-CS-009 trial. This was evaluated further as a key safety issue due to nonclinical signals of thromboembolic events discussed in Section 7.1 and summarized below.

Background

In the nonclinical/toxicology studies, there were findings of thrombi observed across species (at the injection site in the rat, marmoset, and dog) and emboli noted in marmosets in the heart, lung, kidney, mostly with administration of ceftobiprole for a duration of over 1 month. The Applicant stated that in the 13-week studies in rats and marmosets, the thrombus formation was around the tip of the infusion catheter. When examining the histological changes, it was consistent with mechanical irritation by the infusion catheter, subsequently causing vascular-wall irritation and subsequent thrombus formation. The mechanical irritation was attributed to the small size of the veins relative to the large size of the implanted catheter. Ultimately, it was thought that the thrombus formation was caused by local irritation and injury along with the higher concentrations of ceftobiprole as compared with the clinical studies.

Assessment

When grouping the PTs using the narrow FMQ, there was a slightly higher incidence of thrombosis in the ceftobiprole vs. the comparator arm.

Reference ID: 5357793

Table 109. Adverse Events Assessment of Thrombosis FDA Medical Query (Narrow), Safety Population, Trial BPR-CS-009, Cohorts 1 and 2

FMQ (Narrow) Preferred Term	Ceftobiprole N=191 n (%)	Daptomycin N=198 n (%)
Thrombosis (FMQ)	10 (5.2)	4 (2.0)
Acute myocardial infarction	1 (0.5)	0
Angina unstable	0	1 (0.5)
Arteriovenous fistula thrombosis	1 (0.5)	0
Atrial thrombosis	1 (0.5)	0
Deep vein thrombosis	1 (0.5)	1 (0.5)
Ischaemic stroke	0	1 (0.5)
Myocardial infarction	1 (0.5)	1 (0.5)
Portal vein thrombosis	1 (0.5)	0
Splenic infarction	0	1 (0.5)
Thrombophlebitis	1 (0.5)	0
Thrombosis	1 (0.5)	0
Venous thrombosis limb	2 (1.0)	0
Maximum severity		
Death	2 (1.0)	1 (0.5)
Life-threatening	0	0
Severe	1 (0.5)	2 (1.0)
Moderate	2 (1.0)	1 (0.5)
Mild	5 (2.6)	0
Serious	4 (2.1)	3 (1.5)
Deaths	2 (1.0)	1 (0.5)
Resulting in discontinuation	0	0
Relatedness	0	0
Number of subjects with adverse events with end dates on or before treatment end dates	4/10 (40.0)	0/4 (0)
Duration, days (from AE start date to AE end date)		
Mean (SD)	14 (9.6)	NA
Median (Q1, Q3)	15.5 (10.8, 18.8)	NA
Min, max	1, 24	NA, NA
Number of subjects with adverse events (occurred on or before treatment end date) with end dates missing (no end dates reported, assumed that AE continuing)	1/10 (10.0)	0/4 (0)
Number of subjects with adverse events (occurred on or before treatment end date) with end dates after treatment end dates	4/10 (40.0)	1/4 (25.0)
Duration, days (from treatment end date to AE end date)		
Mean (SD)	9 (5.7)	54 (NA)
Median (Q1, Q3)	9.5 (5.8, 12.8)	54 (54, 54)
Min, max	2, 15	54, 54

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as adverse events which occurred between the start of the first dosing up to and including the scheduled post treatment evaluation visit.
Duration of treatment is 42 days plus the follow-up period up to Day 70.
Relatedness is determined by the investigator.
Abbreviations: AE, adverse event; FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; NA, not applicable; Q1, first quartile; Q3, third quartile; SD, standard deviation
Abbreviations: AE, adverse event; FMQ, FDA medical query; N, number of subjects in treatment arm; n, number of subjects with adverse event; NA, not applicable; Q1, first quartile; Q3, third quartile; SD, standard deviation

A grouped query for thrombosis was created encompassing the following PTs: thrombosis, DVT, atrial thrombosis, venous thrombosis limb, portal vein thrombosis, splenic infarction, and

arteriovenous fistula thrombosis. As myocardial infarction is often due to a different pathophysiology, PTs related to myocardial infarction/acute myocardial infarction were not included in the grouped query. In addition, the PT 'thrombophlebitis' (for subject (b) (6)) was combined in another grouped query termed 'phlebitis' given similar pathophysiology; the description of the AE is noted in Table 110 below. Using the thrombosis grouped query, there was still an imbalance with the ceftobiprole group experiencing 7 (3.5%) cases of thrombosis compared to 2 (1%) in the daptomycin arm. Of note, all AEs in the thrombosis grouped query in both treatment arms were considered 'not related' to trial drug by the investigator. The AEs in the daptomycin arm included splenic infarction and DVT; the DVT was an SAE and occurred 9 days after the last dose of daptomycin.

To obtain more information about the context of the thrombosis events, an information request was sent to the Applicant on November 2, 2023. The Applicant's response as well as subject narratives and profiles were evaluated to determine if there was any definitive relationship between ceftobiprole and thrombi formation (i.e., the formation of a thrombus in the presence of ceftobiprole without alternative cause). The 7 subjects with the grouped query of thrombosis are described below. None led to death or treatment discontinuations, and two were SAEs ((b) (6) (b) (6)).

Another information request was sent to the Applicant on February 23, 2024, requesting further clarification for subjects with AEs of DVT, venous thrombosis limb, thrombosis and thrombophlebitis who had a history of thrombotic events prior to enrollment in the trial, and that information is included in Table 1 as well as in the narratives below.

- (b) (6) was a 58-year-old female with a medical history of recently diagnosed DVT, osteomyelitis and epidural abscess in T8-9, abscess drainage eight days prior to enrollment and spinal decompression six days prior enrollment, who had a reported AE of thrombosis on Day 11. The verbatim term was post-thrombotic disease of the lower extremities and in the information request response, the Applicant clarified that the subject was diagnosed with DVT 6 days prior to starting ceftobiprole and experienced a mild post-thrombotic syndrome of the lower extremities on Day 11. The Applicant stated that these events were clearly linked as the post-thrombotic syndrome (i.e., the chronic condition) was seen as favorable progress of the pre-study deep vein thrombosis (i.e., the acute condition).
- (b) (6) was a 65-year-old female with a medical history of thrombophlebitis (diagnosed 46 days prior to enrollment), aortic arteriosclerosis, and hypertension who had a reported AE of DVT on Day 15. During the same time as the thrombophlebitis, the subject also had a chronic wound on the right calf for which she had a necrectomy two days prior to enrollment. The exact location of the initial acute thrombophlebitis on the right lower extremity was not recorded, and the location of the DVT was at the right medial gastrocnemius. The Applicant noted that it is possible that the exact location could have been different and the two events were distinct, however, the chronic wound and necrectomy may have predisposed for the development of a DVT. Additional risk factors for thrombosis included not receiving DVT prophylaxis and the presence of an immobilization bandage. Immobilization is a known risk factor for DVT (Samama 2000).
- (b) (6) was a 45-year-old female with a medical history of hemodialysis, chronic kidney disease, diabetes mellitus, nontunneled central venous catheter placement 12 days prior to enrollment who had an SAE of atrial thrombosis on Day 5 which was found on transesophageal echocardiography. She was placed on heparin and a repeat echocardiography

Reference ID: 5357793

showed reduced size of the thrombosis while she was still on ceftobiprole treatment. It is unlikely that ceftobiprole contributed to the formation of atrial thrombosis as the thrombosis improved during treatment.

- (b) (6) was a 48-year-old male with a medical history of diabetes mellitus, multiple surgeries two months prior to enrollment (pancreatectomy 64 days prior, colectomy 62 days prior, splenectomy 3 days prior), who had an AE of venous thrombosis limb on Day 8. The verbatim term was right leg phlebothrombosis and the Applicant noted that the subject had been diagnosed with a right lower extremity DVT 21 days prior to starting ceftobiprole. The Applicant also noted that it is unclear whether the pre-study DVT and the AE of venous thrombosis limb occurred at the exact same location and it is uncertain whether these were related events.
- (b) (6) was a 34-year-old female with a medical history of intravenous drug abuse who had an AE of venous thrombosis limb and a reported term of right basilic vein thrombosis on Day 13. Prior to the AE, she had not been receiving any DVT prophylaxis, had a peripherally inserted central catheter placed in the right basilic vein on Day 3 which was removed once the DVT was diagnosed, and had a history of intravenous drug abuse which are all associated with a risk of thrombi formation (McColl et al. 2001). The association with ceftobiprole is unlikely, but not fully excluded.
- (b) (6) was a 45-year-old male with a medical history of chronic pancreatitis, distal pancreatomy 11 days prior to enrollment, who had an AE of portal vein thrombosis on Day 8. In a study involving 991 subjects who underwent distal pancreatomy, 2.1% were diagnosed with portal vein thrombosis (Kamath et al. 2014). As portal vein thrombosis is a very specific type of thrombosis and may have been due to prior surgery, it is less likely that there was an association with ceftobiprole.
- (b) (6) is a 58-year-old female with a medical history of arteriovenous fistula, hemodialysis, and type 2 diabetes mellitus experienced an SAE of arteriovenous fistula thrombosis on Day 45 which was 23 days after ceftobiprole was discontinued. Because of the prolonged time between the onset of the thrombosis and the last dose of ceftobiprole, an association between the thrombosis and ceftobiprole is unlikely.

Conclusion

Out of the 7 subjects discussed above, 4 had events that appeared to be unrelated to ceftobiprole (one had pre-existing DVT and post-thrombotic syndrome, one had portal vein thrombosis in the setting of pancreatic surgery, and 2 had no clear temporal association with ceftobiprole). However, in 2 subjects, it was not clear if the DVT or venous thrombosis was the same as the episode occurring several days before treatment with ceftobiprole (b) (6) (b) (6)). Another subject had an upper extremity DVT in the setting of a peripherally inserted central catheter line (b) (6)). The remaining 3 subjects in the ceftobiprole arm who experienced venous thrombosis had other risk factors for venous thrombosis such as immobilization, multiple surgeries, or IV lines, however, the contribution of ceftobiprole could not be fully excluded. Given the nonclinical findings of thromboemboli in multiple animal species, a similar finding in humans may be possible, but overall less likely given confounding factors in the study population (e.g., multiple comorbidities, prolonged hospitalization, prior surgical procedures, and inconsistent DVT prophylaxis).

Notably, no significant imbalance in thrombosis events was noted in the other clinical trials discussed in this review. Additionally, thromboembolic disease has not been reported with ceftobiprole in the post market setting (from countries where it is approved for indications of HABP and CABP). However, ceftobiprole will be administered to subjects with SAB who may be prone to valvular insufficiency, peripheral vascular disease, and potentially prolonged hospitalization predisposing them to venous thrombosis. Therefore, thrombosis will be included in section 6 of the labeling under the subsection “Selected Adverse Reactions of ZEVTERA in Adult Patients” occurring at a rate < 2% in the clinical trials and will be further monitored by routine surveillance in the post-market setting.

Reference ID: 5357793

Table 110. Case Overview (b) (6)

Patient	(b) (6)			
Pre-study medical history verbatim term	• Varicose vein disease of the lower limbs (unknown start date) • Acute thrombophlebitis of the right leg (Day −46)	• Right-sided deep vein thrombosis of the leg (Day −21)	• Deep vein thrombosis (lower extremities) (Day −6)	• Thrombophlebitis of the right small saphenous vein (Day −35) • Acute thrombosis of the sural veins of the right lower extremity (Day −7)
Pre-study clinical context	Chronic wound infection requiring necrectomy on Day −2	Long-term ICU stay due to severe abdominal infection with destructive pancreatitis and spleen abscess with multiple surgeries and periods of immobilisation	Spondylodiscitis, epidural abscess and compression myelopathy with lower paraplegia. Microsurgical decompression of the spinal canal	Complicated open fracture of the right leg, requiring external fixation, with subsequent extensive wound infection and phlegmon,
Adverse event term	• Deep vein thrombosis of the right leg (Day 15) (per discharge report: located in the medial gastrocnemius sinus of the right leg)	• Right leg phlebothrombosis (Day 8)	• Post-thrombotic syndrome of the lower extremities (Day 11)	• Postthrombophlebitis syndrome (Day 11) Note: on Day 26, an adverse event of 'lymphostasis of the right leg' was reported
Sponsor interpretation				
- Location of the pre-study event	Same area (right calf) but possibly different location	Same area (right leg) but limited information	Same location (lower extremities), but different syndromes	Likely same location (right leg), but different syndromes
- Reporting as an adverse event	Pre-study event and adverse event are considered different events. Pre-study event of a thrombophlebitis in the area of a chronic wound of the right calf. Adverse event described as deep vein thrombosis in a calf vein, with surgical intervention of necrectomy, lavage and drainage as predisposing factor.	Pre-study event and adverse event are not clearly discernible. Both the pre-study event and the adverse event were located in the right leg, but a conclusion cannot be made on the exact location and whether the pre-study event and the reported adverse event were clearly distinct events.	The AE of mild post-thrombotic disease of the lower extremities was described as favorable progress of the previous deep vein thrombosis based on a review of queries in the EDC. These events are therefore clearly linked, but in the Applicant's view represent different disease conditions/syndromes (i.e. acute vs chronic), so that reporting post-thrombotic disease as an AE seems justified.	Pre-study events of thrombophlebitis of the saphenous vein and a deep vein thrombosis of the sural veins in the context of a complicated open fracture of the right leg. The AE of postthrombophlebitis syndrome (right lower limb) and the subsequently reported AE of a lymphostasis (right leg), suggests that both AEs describe a sequela of the pre-study medical history events, but represent different disease conditions/syndromes (i.e. acute vs chronic), so that reporting postthrombophlebitis syndrome as an AE seems justified.

Source: Response to Information request, submitted by Applicant
Abbreviations: AE, adverse event; EDC, electronic data capture

8. Therapeutic Individualization

8.1. Intrinsic Factors

8.1.1. Renal Impairment

Renal impairment had a significant effect on ceftobiprole exposure. Following a single infusion of ceftobiprole 250 mg over 30 minutes, systemic exposure (area under the concentration-time curve $[AUC]_{last}$) was 29% higher in subjects with mild renal impairment, and 2.5-fold, and 3.3-fold higher in subjects with moderate and severe renal impairment, respectively, compared to subjects with normal renal function. Urinary recovery was approximately 74% to 32% in subjects with mild to severe renal impairment, respectively (see Section 14.2.3.
Dose adjustment for renal impairment is recommended as depicted in Table 111 based on 1) FDA analyses and PK simulations 2) the Applicant's population PK analyses 3) evaluation of target attainment rates for the proposed doses in subjects with moderate and severe renal impairment and 4) safety and efficacy data from the pivotal phase 3 efficacy trials using the proposed dose adjustments.

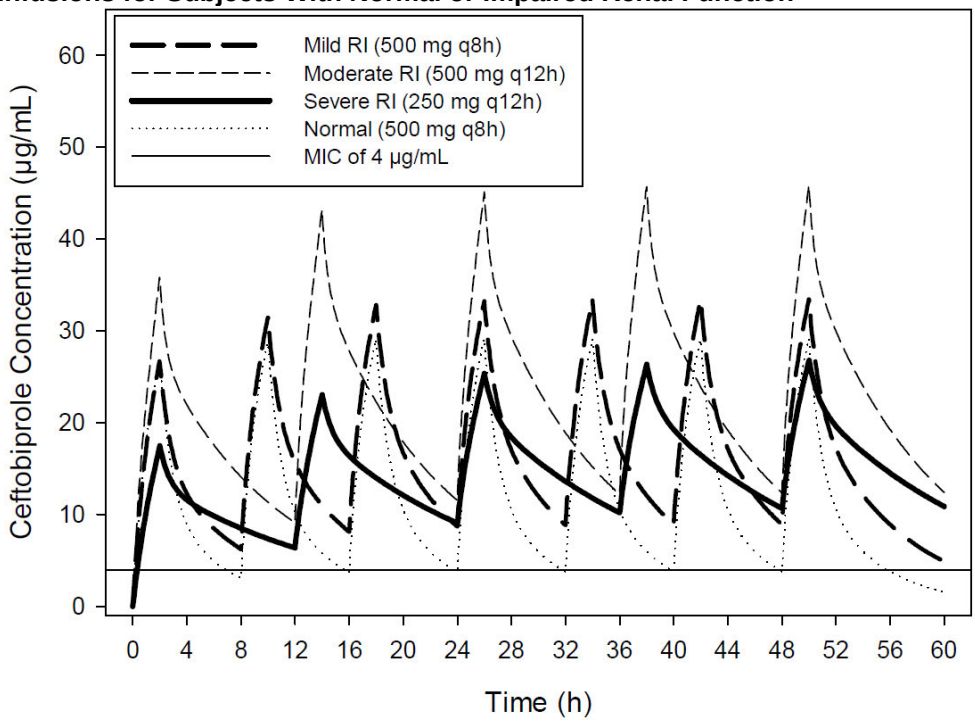
Table 111. Ceftobiprole Dosage for Adult Patients With Renal Impairment

Indication	Creatinine Clearance (mL/min)	Dosage Regimen	Duration of Treatment
SAB	30 to <50	500 mg every 8 hours on Days 1 to 8 500 mg every 12 hours from Day 9	Up to 42 days
	15 to <30	250 mg every 8 hours on Days 1 to 8 250 mg every 12 hours from Day 9	
ABSSSI or CABP	30 to <50	500 mg every 12 hours	5 to 14 days
	15 to <30	250 mg every 12 hours	

Source: Study BAP00018; Study BPR-CS-008; Study BPR-CS-009; Study CAP-3001
Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; CABP, community-acquired bacterial pneumonia; SAB, *Staphylococcus aureus* bacteremia
500 mg ceftobiprole is equivalent to 667 mg ceftobiprole medocaril sodium

These dosage adjustments are supported by simulations of concentration-time profiles using the data from BAP00018, as displayed in Figure 16. Predicted maximum plasma concentration (C_{max}) and AUC values and corresponding ratios in comparison to values for subjects with normal renal function following 500 mg q8h over 120 minutes are presented in Table 112. The greatest difference in exposure compared to normal subjects was observed with the recommended dose for moderate renal impairment (500 mg q12h). The proposed dosage adjustment in moderate renal impairment results in steady-state exposure ratios of 1.5 and 1.9 for C_{max} and AUC, respectively.

Figure 16. Simulated Plasma Concentration-Time Profiles of Ceftobiprole Administered as 2-Hour Infusions for Subjects With Normal or Impaired Renal Function



Source: Study BAP00018 errata
Abbreviations: h, hour; MIC, minimum inhibitory concentration; RI, renal impairment

Table 112. Predicted Ceftobiprole C_{max} and AUC in Subjects With Normal and Impaired Renal Function Following the Proposed Dosage Adjustment in Adult Patients with Renal Impairment

	Day 1		Day 3	
Renal Function	**C_{max} (µg/mL)**	**AUC_{0-8} (µg·hr/mL)**	**C_{max} (µg/mL)**	**AUC_{0-8} (µg·hr/mL)**
Normal	26.6	84.6	29.1	99.0
Mild	26.7	102	33.4	143
Moderate	35.8	211	45.1	288
Severe	17.5	116	25.4	189
Ratios to Normal (calculated over 24 hours for AUC)				
Mild	1.0	1.2	1.2	1.4
Moderate	1.3	1.7	1.5	1.9
Severe	0.66	0.91	0.87	1.3

Source: Study Report BAP00018 Errata and Clinical Pharmacology Review by Kim Bergman (2007)
Simulated doses: Normal, 500 mg q8h; Mild, 500 mg q8h; Moderate, 500 mg q12h; Severe, 250 mg q12h
Abbreviations: AUC, area under the concentration-time curve; AUC0-8, area under the concentration-time curve from time 0 to 8 hours; C_{max}, maximum plasma concentration

The evaluation of PK/PD target attainment at the proposed dosage, with adjustment for renal function, was performed for each indication in simulated subjects with varying renal function and in a population representative of each respective clinical trial population. Overall, the percent probabilities of PK/PD target attainment among simulated subjects based on median and randomly assigned free-drug plasma %fT>MIC targets associated with net bacterial stasis and a 1-log10 CFU reduction from baseline, weighted over the MIC distributions for the isolate collections evaluated, were >90% for each indication and relevant bacterial isolate (See Section 14.5 for more information).

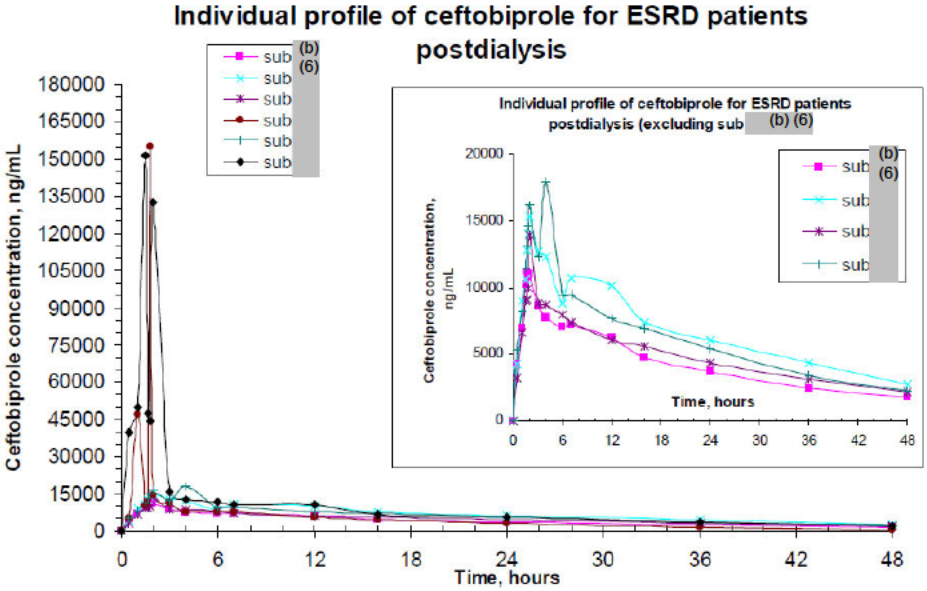
8.1.2. End-Stage Renal Disease and Patients Receiving Intermittent Hemodialysis

Dosage in subjects with end-stage renal disease (ESRD) (defined as a CrCL < 15 mL/min) and subjects receiving intermittent hemodialysis (iHD) is supported by simulated ceftobiprole exposures derived using a population PK model fit with data from nine phase 1 studies and three phase 3 studies, including 20 subjects with SAB who received ceftobiprole after iHD (see Section 14.5.2.3). These simulations, in combination with adequate target attainment, support a ceftobiprole dosage of 250 mg every 24 hours in subjects with CrCL <15 mL/min and subjects receiving iHD, when dosed after the iHD session (see Section 14.5.2.3). The Applicant conducted a PK study in subjects with ESRD requiring hemodialysis, where six ESRD subjects requiring hemodialysis were matched by age and weight with six healthy subjects. The PK of ceftobiprole was compared between healthy subjects and ESRD subjects dosed after dialysis (post-dialysis) or dosed before dialysis (pre-dialysis). In ESRD subjects receiving a 4-hour dialysis session after a 2-hour 250 mg ceftobiprole intravenous infusion, 28% of the dose was removed by hemodialysis.

The clinical pharmacology reviewer noted that plasma data used for PK analysis by the Applicant was not consistent with the raw data provided in the assay report. Specifically, the plasma concentrations at 30 min for ceftobiprole medocaril sodium, ceftobiprole, and the open-ring metabolite from all the ESRD subjects during the period 2 (i.e., postdialysis) of the study were switched with their respective concentrations at 90 min in the Applicant's report.

Upon further analysis the reviewer also noted questionable concentration-time profiles for four out of six ESRD subjects when dosed after hemodialysis. As illustrated in Figure 17, ceftobiprole concentrations approximately ten-fold higher than expected were observed in Subjects (b) (6) during the infusion phase. Furthermore, the plasma concentration time profiles were considered abnormal for Subjects (b) (6) as well due to unexpected additional peaks after the infusion was over. Taken together, the questionable data in 4 out of the 6 ESRD subjects studied precluded reliable estimation on ceftobiprole PK characteristics in the ESRD subjects dosed after hemodialysis.

Figure 17. Individual Ceftobiprole Concentration-Time Profiles in the Plasma Following a 2-Hour Intravenous Infusion of Ceftobiprole 250 mg to Subjects With ESRD Dosed After Hemodialysis.



Source: Study CSI-1007, reviewer analysis
Subjects (b) (6) Were Excluded in the Insert
Abbreviations: ESRD, end-stage renal disease

In the phase 3 Trial, BPR-CS-009, 20 subjects with SAB received ceftobiprole while on intermittent hemodialysis. Ceftobiprole 250 mg was administered as 2-hour IV infusion every 24 hours. On the days of hemodialysis, ceftobiprole was administered after the hemodialysis session was completed.

Of these 20 subjects, 8 had confirmed ceftobiprole administration and PK samplings post-dialysis. All 8 subjects had CrCL <30 mL/min, six of whom had a CrCL <15 mL/min. A total of 6 subjects with CrCL <30 mL/min were not on iHD , one of which had a CrCL <15 mL/min.

These data were included in the Applicant's population PK model and additional simulations were conducted to support the proposed dosage of 250 mg IV q24h (infused over 2 hours) in ESRD patients. The simulated exposures (AUC and C_{max}) were compared to simulated exposures in patients with normal renal function (90 – 150 mL/min). Mean AUC and C_{max} values for Day 1 and Day 5 (SAB) or Day 7 (ABSSSI or CABP) are shown in Table 113. These data were included in the Applicant's population PK model and additional simulations were conducted to support the proposed dosage of 250 mg IV q24h (infused over 2 hours) in ESRD subjects. The simulated exposures (AUC and C_{max}) were compared to simulated exposures in subjects with normal renal function (90 – 150 mL/min). Mean AUC and C_{max} values for Day 1 and Day 5 (SAB) or Day 7 (ABSSSI or CABP) are shown in Table 113.

Table 113. Summary of Ceftobiprole Exposures by Indication and Renal Function

	Day 1		Day 5 (SAB) or Day 7 (ABSSSI or CABP)	
Indication and Variable	**>0 to <15 mL/min 250 mg q24h**	**>90 to <150 mL/min 500 mg q6/q8h**	**>0 to <15 mL/min 250 mg q24h**	**>90 to <150 mL/min 500 mg q6/q8h**
SAB				
Mean AUC	120	209	253	237
Mean C_{max}	10.9	20.2	19.1	20.2

Indication and Variable	Day 1		Day 5 (SAB) or Day 7 (ABSSSI or CABP)	
	>0 to <15 mL/min 250 mg q24h	>90 to <150 mL/min 500 mg q6/q8h	>0 to <15 mL/min 250 mg q24h	>90 to <150 mL/min 500 mg q6/q8h
ABSSSI				
Mean AUC	121	159	271	174
Mean C_{max}	10.7	17.4	19.7	17.7
CABP				
Mean AUC	158	199	343	215
Mean C_{max}	12	18.8	21.2	19

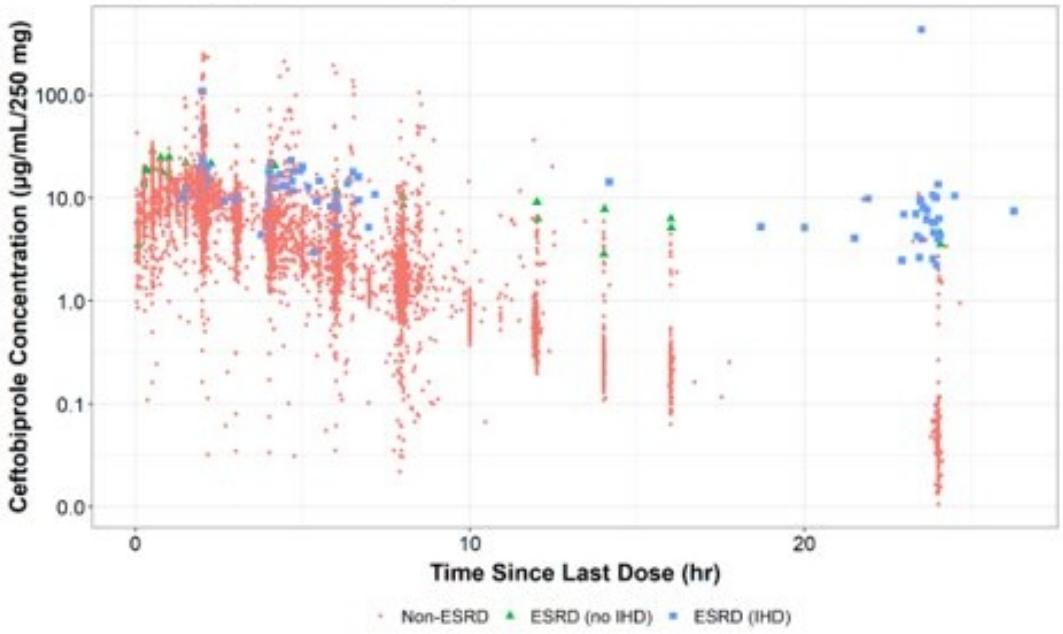
Source: Study BPR-CS-009
Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; AUC, area under the concentration-time curve; CABP, community-acquired bacterial pneumonia; C_{max}, maximum plasma concentration; q6h, every 6 hours; q8h, every 8 hours; q24h, every 24 hours; SAB, *Staphylococcus aureus* bacteremia

The model-based simulations outlined in Table 113 did not incorporate removal by iHD due to the preclusion of a reliable extraction ratio from the Applicant's phase 1 ESRD study. Therefore, Day 1 exposures were used as a conservative estimate to assume 100% ceftobiprole removal during iHD. For the SAB indication, Day 1 AUC and C_{max} values were 1.7- and 1.9-fold lower in ESRD subjects compared to subjects with normal renal function, respectively. For ABSSSI and CABP, the Day 1 AUC and C_{max} values were approximately 1.3- and 1.6-fold lower than subjects with normal renal function.

Based on the lower exposures observed on Day 1 in ESRD subjects, PK/PD target attainment analyses were conducted for each indication to support the proposed dosage. The overall percentage probabilities of PK/PD target attainment on Days 1 in subjects with SAB was > 99.9% for *S. aureus*. In ABSSSI subjects, overall target attainment on Day 1 was >99.9% for *S. aureus*, 100% for *Streptococcus* species, and 87.2% for *Enterobacterales*. In CABP subjects, overall target attainment on Day 1 was 100% for S. *pneumoniae*, >99.9% for *S. aureus*, and were 87.0% or 87.1% for *Enterobacterales*.

An additional analysis for visual inspection revealed similar plasma concentrations in phase 3 subjects on and off iHD based on pooled PK data of phase 3 ABSSI, CAP, SAB subjects (Figure 18). In addition, a subgroup analysis conducted by the Agency suggests that hemodialysis did not impact overall success or ACM in SAB subjects with a CrCL <15 mL/min enrolled in Trial BPR-CS-009 compared to subjects receiving daptomycin at the PTE visit (Table 114 and Table 115, respectively). Taken together, the proposed dosage of 250 mg IV q24h for ESRD subjects is acceptable given the similar steady state exposures compared to subjects with normal renal function, high rates of target attainment on Day 1 and similar efficacy noted in the phase 3 SAB Trial.

Figure 18. Dose-Normalized Plasma Concentrations vs. Time From Last Dose for all Subjects/Patients Used in the Model Fit Stratified by Sampling Time and Colored by ESRD With and Without Intermittent Hemodialysis



Source: Applicant's response to Information Request [request dated 2NOVEMBER2023; EDR link: *IR_SEQ026*]
Abbreviations: ESRD, end-stage renal disease; hr, hour; IHD, intermittent hemodialysis

Table 114. Subgroup Results for Overall Success at the PTE Visit in the Modified Intent-to-Treat Population by Baseline Creatinine Clearance and Dialysis

CrCL (mL/min)	Dialysis	Ceftobiprole	Daptomycin
<15	Y	7/13 (53.8%)	8/13 (61.5%)
<15	N	0/0	0/0
15-30	Y	3/6 (50.0%)	4/8 (50.0%)
15-30	N	3/5 (60.0%)	2/8 (25.0%)
Not available	Y	3/5 (60.0%)	3/4 (75.0%)

Source: Study BPR-CS-009, statistical reviewer internal analysis
Abbreviations: CrCL, creatinine clearance; N, no; PTE, post-treatment evaluation; Y, yes

Table 115. Subgroup Results for All-Cause Mortality at the PTE Visit in the Modified Intent-to-Treat Population by Baseline Creatinine Clearance and Dialysis

CrCL (mL/min)	Dialysis	Ceftobiprole	Daptomycin
<15	Y	2/13 (15.4%)	1/13 (7.7%)
<15	N	0/0	0/0
15-30	Y	0/6 (0.0%)	2/8 (25.0%)
15-30	N	1/5 (20.0%)	4/8 (50.0%)
Not available	Y	1/5 (20.0%)	0/4 (0.0%)

Source: Study BPR-CS-009, statistical reviewer internal analysis
Abbreviations: CrCL, creatinine clearance; N, no; PTE, post-treatment evaluation; Y, yes

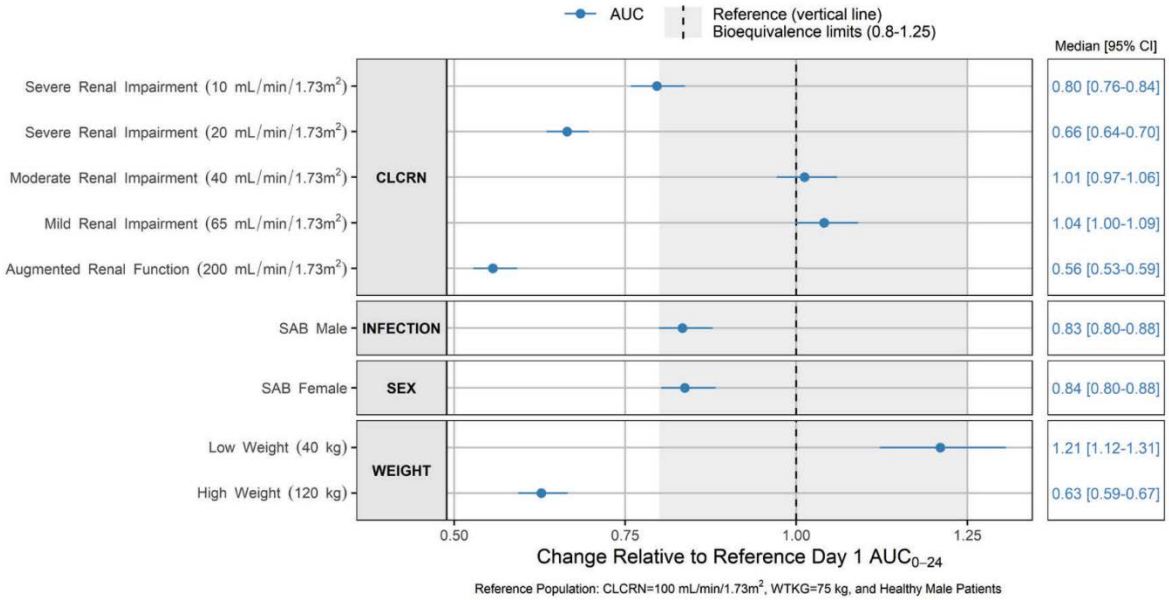
8.1.3. Patients With Augmented Renal Clearance

In a covariate analysis conducted by the Applicant, the subgroup with the greatest difference in predicted ceftobiprole exposures was subjects with augmented renal function. The Applicant simulated ceftobiprole $AUC_{0\text{-}24h}$ on Day 1 in subjects with various degrees of renal impairment

relative to a population of healthy male subjects who have a body weight of 75 kg and normal renal function (BSA-indexed CL_{CR} of 100 mL/min/1.73 m^2) using the final population PK model. In subjects with CL_{CR} above 150 mL/min/1.73 m^2, a point estimate of 44% reduction in exposures (i.e., 24-hour AUC) compared to subjects with normal renal function Figure 19. These results suggest a ceftobiprole dosage of 500 mg (equivalent to 667 mg of ceftobiprole medocaril sodium) every 6 hours in subjects with increased renal clearance is likely to achieve approximately the same exposures achieved with a dosage of 500 mg every 8 hours in subjects with normal renal function in SAB.

For ABSSSI and CAP, a dosage adjustment to 500 mg every 6 hours also demonstrated adequate target attainment in subjects with CL_{CR} of 150 mL/min to ≤240 mL/min (see Section 14.5). Hence, this dosage adjustment is recommended in adult subjects with a CL_{CR} >150 mL/min. Despite incorporating BSA-indexed CL_{CR} in the final population PK analysis for ABSSSI, CAP, and SAB in adults, the renal dose adjustment described in the ceftobiprole labeling is based on CL_{CR} without indexing to BSA. This is because the model-predicted exposure comparisons and PTA analyses across renal function groups were conducted using subject level CL_{CR} without BSA indexing. The effect of augmented renal clearance (CL_{CR} >150 mL/min) on ceftobiprole PK in pediatric subjects is unknown.

Figure 19. Forest Plots Showing Impact of Statistically Significant Covariate-Parameter Relationships on Ceftobiprole



Source: Applicant's Population PK Report 00594-2
Abbreviations: AUC, area under the concentration-time curve; AUC_{0-24}, area under the concentration-time curve from time 0 to 24 hours; CI, confidence interval; CLCRN, Normalized Creatinine Clearance; SAB; *Staphylococcus aureus* bacteremia

8.1.4. Pediatric Patients with Renal Impairment

The Applicant conducted population PK modeling and simulation using a model fit with pooled pediatric and adult data to support dosing in pediatric patients with renal impairment (b) (4) (b) (4). Renal function for the observed pediatric data in this model was determined using the Schwartz formula (Schwartz et al. 2009) Ceftobiprole CL was modeled as a function of

glomerular filtration rate estimated using the Rhodin formula based on fat-free mass (Rhodin et al. 2009). While there are several pediatric formulas are available for estimating glomerular filtration rate, clinical selection of an estimating equation should be based on current therapeutic area guidelines and the practice of medicine.

Based on 1) exposures in children with renal impairment being similar to that observed in adults and 2) adequate target attainment rates, dose adjustments for pediatric patients down to 2 years of age with moderate and severe renal impairment are recommended as outlined in Table 116. For patients aged <2 years, there remains insufficient information to recommend dosage adjustments in the setting of renal impairment due to the complexity of renal maturation and the lack of PK data in this subpopulation.

Table 116. Ceftobiprole Recommended Dosage Regimens for Pediatric Patients With CABP and with Renal Impairment

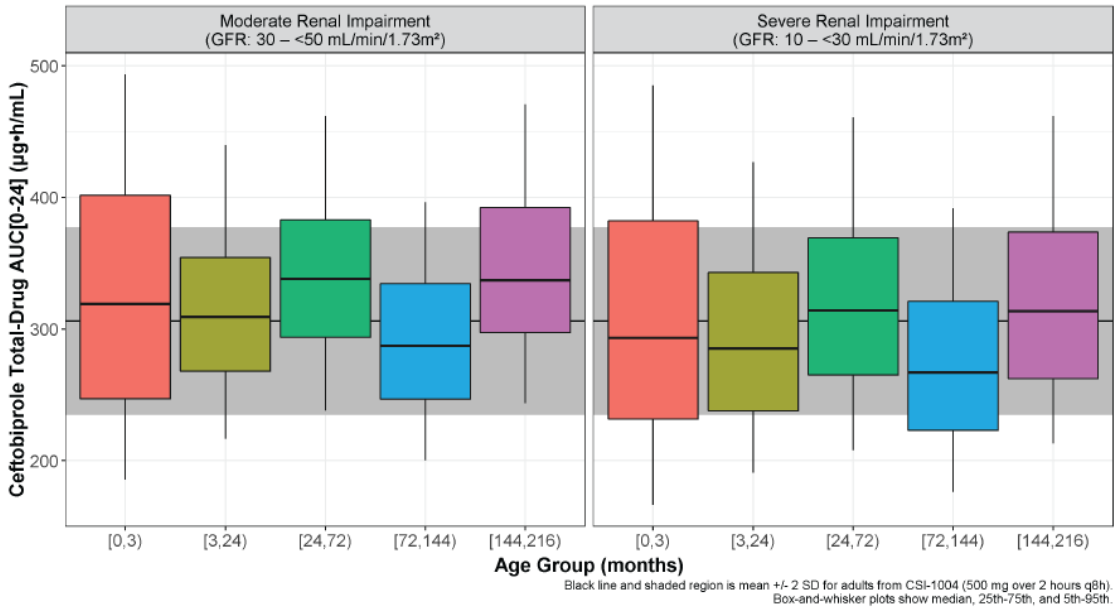
Age Group	eGFR (mL/min/1.73^2)	Dosage	Infusion Solution Concentration and Duration
12 years to <18 years	30 to <50	7.5 mg/kg (up to 500 mg) every 12 hours	2 mg/mL over 2 hours
	15 to <30	7.5 mg/kg (up to 250 mg) every 12 hours	
6 years to <12 years	30 to <50	7.5 mg/kg (up to 500 mg) every 12 hours	4 mg/mL over 2 hours
	15 to <30	7.5 mg/kg (up to 250 mg) every 24 hours	
≥2 years to <6 years	30 to <50	10 mg/kg every 12 hours	
	15 to <30	10 mg/kg every 24 hours	

Source: Applicant's Population PK Report 00616-3A
Renal function should be closely monitored, and the dose adjusted accordingly.
Abbreviations: CABP, community-acquired bacterial pneumonia; eGFR, estimated glomerular filtration rate

The Applicant used a population PK model, including the assumption of proportional effects of renal impairment in adults and pediatric subjects, to predict exposures associated with the recommended dose adjustments for pediatric subjects with renal impairment. A pediatric population PK model was fit to a pooled dataset of pediatric and phase 1 healthy adult subjects, including adults with renal impairment, to assess the ability of the model to capture the impact of renal impairment previously shown for adults. Of note, the observed pediatric data included in this model does not include pediatric subjects with moderate or severe renal impairment as these subjects were excluded from the clinical studies (see Section 6.2.4).

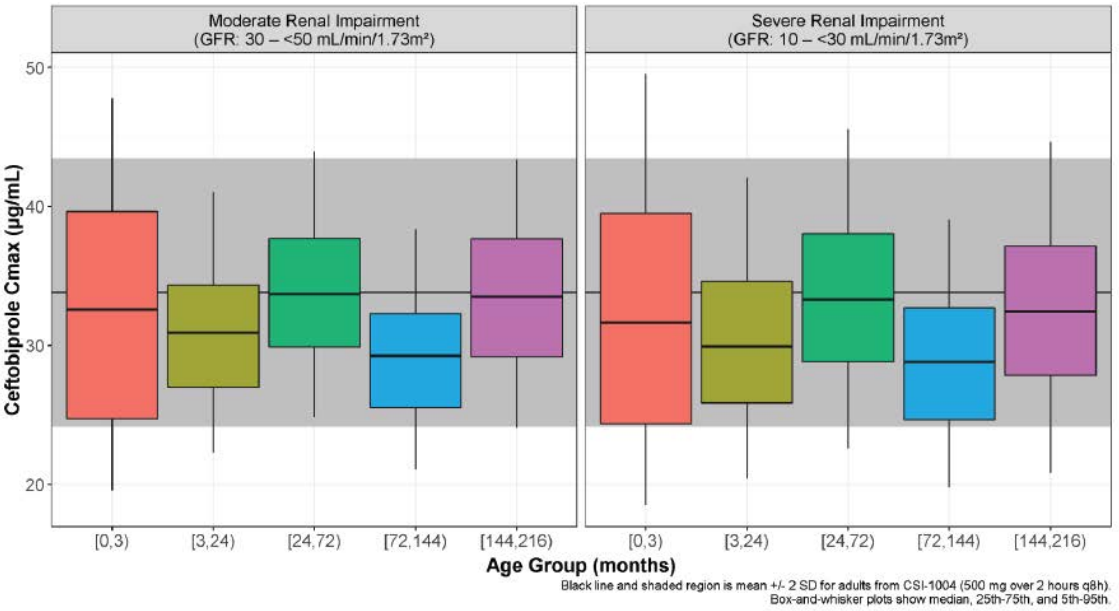
The predicted ceftobiprole exposure associated with these doses are in the range of those observed in adults (Figure 20 and Figure 21) and result in robust PK/PD target attainment Table 117). (b) (4) (b) (4) (b) (4) In pediatric subjects with renal impairment who are at least 2 years of age, several aspects of renal function, including renal ontogeny and glomerular filtration, are expected to be comparable to adult values. Thus, exposure matching and target attainment can be used to support the dosage in this population under the assumption of proportional effects of renal impairment in adults and pediatric subjects.

Figure 20. Distribution of Predicted Ceftobiprole AUC0-24 by Age Group in Renally Impaired Patients Using the Population PK Model Fit to Pooled Pediatric/Adult Data



Source: Applicant's Population PK Report 00616-3A
Abbreviations: AUC_{0-24}, area under the concentration-time curve from time 0 to 24 hours; GFR, glomerular filtration rate; PK, pharmacokinetic

Figure 21. Distribution of Predicted Ceftobiprole C_{max} by Age Group in Renally Impaired Patients Using the Population PK Model Fit to Pooled Pediatric/Adult Data



Source: Applicant's Population PK Report 00616-3A
Abbreviations: C_{max}, maximum plasma concentration; GFR, glomerular filtration rate; PK, pharmacokinetic

Table 117. Predicted PK-PD Target Attainment by Age Group in Patients With Renal Impairment Using the Population PK Model Fit to the Pooled Pediatric/Adult Data

Target (%fT>MIC)	Birth to <30 mo 15 mg/kg q12h	3 mo to <2 yr 10 mg/kg q12h	2 to <6 yr 10 mg/kg q12h	6 to <12 yr 7.5 mg/kg q12h	12 to <18yr 7.5 mg/kg q12h
Moderate Renal Impairment (GFR: 30 to <50 mL/min/1.73m^2)					
30%	100	100	100	100	100
40%	99.9	99.9	100	99.9	100
50%	98.7	99.5	99.9	98.9	100
60%	93.8	97.6	98.0	95.6	99.3
Severe Renal Impairment (GFR: 10 to < 30 mL/min/1.73m^2)					
30%	100	99.9	100	100	100
40%	99.2	99.6	100	99.5	100
50%	94.3	97.2	97.7	95.8	99.3
60%	87.2	91.0	92.4	86.9	96.0

Source: Applicant's Population PK Report 00616-3A
Note: All regimens administered as a 2-h infusion with a maximum allowable dose of 500 mg regardless of subject's weight
Patients with a body weight <4 kg given 10 mg/kg instead of 15 mg/kg
Abbreviations: GFR, glomerular filtration rate; MIC, minimum inhibitory concentration; PD, pharmacodynamic; PK, pharmacokinetic; q12h, every 12 hours

Reference ID: 5357793

8.1.5. Hepatic Impairment

The effects of hepatic impairment on the PK of ceftobiprole have not been evaluated. Ceftobiprole does not undergo significant hepatic metabolism and has low plasma protein binding. As such, hepatic impairment is not expected to alter the elimination of ceftobiprole. Dosage adjustments are not necessary in patients with impaired hepatic function.

8.1.6. Body Weight

A single-dose study was conducted to investigate the PK of ceftobiprole in subjects with morbid obesity in comparison to non-obese subjects. Exposure to ceftobiprole was lower in morbidly obese subjects attributed to a larger volume of distribution and a higher CL, resulting in ~17% lower exposure which is unlikely to be clinically relevant. No doses adjustment based on body weight were made in the phase 3 studies.

The effect of weight was also evaluated in the adult population PK (PopPK) analysis and in the PK/PD target attainment analysis. Although body weight was a statistically significant predictor of interindividual variability in CL, central and peripheral volumes of distribution in the PopPK analysis, ceftobiprole dose adjustments based on body weight are not required to ensure sufficient PK/PD target attainment.

8.1.7. Gender

The effects of gender on ceftobiprole PK were evaluated in two phase 1 studies, as a primary objective of study BAP00036 and a secondary objective of Study CSI-1004. Systemic exposure to ceftobiprole was higher in females, with 21% higher C_{max} and 15% higher AUC_{last} in BAP00036 and 24% higher C_{max} and 14% higher AUC0-inf in CSI-1004, compared to males. The higher systemic exposure in females observed in these studies was attributed to a lower body weight in females.

The effect of gender was also evaluated in the PopPK analysis. In the adult PopPK model, gender identified as statistically significant predictor of the interindividual variability observed in the peripheral volume of distribution but was not found to be clinically relevant. Dose adjustment is not indicated based on gender.

8.1.8. Other Intrinsic Factors

The effects of adult age and race were evaluated in the PopPK analysis and were not identified as statistically significant covariates. Accordingly, dose adjustments based on age or race are not indicated.

Reference ID: 5357793

8.2. Extrinsic Factors

8.2.1. Pharmacokinetics Based Drug-Drug Interactions

Ceftobiprole as a Victim of Drug-Drug Interactions

In hepatocytes, ceftobiprole was slowly metabolized to the open-ring hydrolysis product BAL1029 and does not appear to undergo significant hepatic metabolism.

In vitro studies showed that ceftobiprole is not a substrate of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), multidrug resistance protein 2 (MRP2), bile salt export pump, organic anion-transporting polypeptide (OATP) 1B1, OATP1B3, or OCT1 in vitro. Ceftobiprole was a substrate of the renal uptake transporters organic anion transporter 1 (OAT1) and organic cation transporter 2 (OCT2) but not OAT3 in vitro. Ceftobiprole was not evaluated as a substrate of multidrug and toxin extrusion protein 1 (MATE1), or MATE2-K as active secretion does not contribute to ceftobiprole elimination.

Ceftobiprole as a Perpetrator of Drug-Drug Interactions

In vitro studies showed that ceftobiprole did not inhibit or induce cytochrome P450 (CYP) 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5 at therapeutic plasma concentrations. Hence, ceftobiprole is unlikely to result in clinically relevant CYP-mediated DDIs.

In vitro studies showed ceftobiprole was an inhibitor of OATP1B1 and OATP1B3 but was not an inhibitor of P-gp, BCRP, OAT1, OAT3, OCT1, or OCT2.

The in vitro transporter inhibition assessment based on calculated R values is outlined in Table 118. A drug has the potential to inhibit a transporter in vivo if the R value is >1.1. Since the in vitro studies indicate that a drug is an OATP1B1 or OATP1B3 inhibitor, we recommend the Applicant conduct an in vivo drug interaction study evaluating ceftobiprole as an inhibitor of OATP1B1 and OATB1B3 transporters as a post-marketing requirement (see Section 14.1.5).

Table 118. In Vitro Transporter Inhibition Assessment Based on Calculated R Values

Transporter	IC_{50} (µM)*	R value ($I_{max,u}$[a]/IC_{50}) Cut off: 0.1	R value ($1+[I_{in,max,u}$[a]/IC_{50}]) Cut off: 1.1
P-gp	> 200; > 84	< 0.1672; < 0.3984	-
BCRP	> 200; > 84	< 0.1672; < 0.3984	-
OATP1B1	67.6; > 84	-	1.4951; < 1.3984
OATP1B3	44.1; > 84	-	1.7591; < 1.3984
OAT1	> 200; > 84	< 0.1672; < 0.3984	-
OAT3	> 200; > 84	< 0.1672; < 0.3984	-
OCT1	> 200; > 84	< 0.1672; < 0.3984	-
OCT2	> 200; > 84	< 0.1672; < 0.3984	-
MATE1	> 200; > 84	< 0.1672; < 0.3984	-
MATE2K[b]	-	-	-

BCRP = Breast cancer resistance protein, IC_{50} = Concentration required to inhibit 50% of the activity, $I_{in,max,u}$ = estimated maximal unbound plasma inhibitor concentration at the inlet to the liver, Imax,u = maximal unbound plasma concentration of the interacting drug at steady state, MATE1 = Multidrug and toxin extrusion protein 1, MATE2K = multidrug and toxin extrusion protein 2, OAT = Organic anion transporter, OATP1B1 = Organic anion-transporting polypeptide 1B1, OATP1B1 = Organic anion-transporting polypeptide 1B3, OCT = Organic cation transporter, P-gp = P glycoprotein.
* Data from two studies
[a] $I_{max,u}$, $I_{in,max,u}$ = unbound maximum plasma concentration, assuming 84% unbound; R values calculated using population PK C_{max} of 21.3 µg/mL (highest value simulated for CABP indication) and molecular weight of 534.57 g/mol.
[b] It was not possible to assess MATE2K inhibition due to solvent interaction.

Source: Study FK5942; Study XT138008; Study XT228043Abbreviations: IC50, half-maximal inhibitory concentration; Imax, maximum inhibition

8.3. Plans for Pediatric Drug Development

In their Agreed Initial Pediatric Study Plan (iPSP) dated September 30, 2022, the Applicant detailed plans for two phase 3 clinical studies. The first is a trial to assess the safety, tolerability and efficacy of ceftobiprole medocaril sodium for treatment of ABSSSI in pediatric subjects aged less than 18 years. (b) (4)

(b) (4)

Based on information provided in the Agreed iPSP, the Applicant plans to meet the following milestones: the final protocol submission by June 2024, study completion by June 2027, and final report submission by December 2027.

The second proposed trial in the Agreed iPSP will assess the safety, tolerability and efficacy of ceftobiprole medocaril sodium for treatment of SAB in pediatric subjects aged less than 18 years.

(b) (4)

(b) (4). Per the Agreed iPSP, the Applicant planned to meet the following milestones: final protocol submission by December 2024, study completion by June 2028, and final report submission by December 2028.

(b) (4)

The current formulation (powder for reconstitution for IV administration) was used in the completed adult and pediatric phase 3 trials, and there are no plans for additional formulation development.

The Applicant's Agreed iPSP does not discuss the need for a partial waiver for CABP in subjects less than 3 months of age. Because community-acquired pneumonia in neonates and infants under 3 months of age is often of viral etiology and its presentation can overlap with neonatal sepsis, the Division, after discussion with the Pediatric Review Committee, granted a partial waiver for CABP in pediatric subjects less than 3 months of age.

8.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential

Nonclinical Reproductive and Developmental Toxicology and Lactation Data

Intravenous administration of ceftobiprole medocaril sodium to pregnant rats and monkeys during organogenesis showed no evidence of adverse fetal developmental outcomes at doses approximately 1.4 times and 0.9 times the MRHD, respectively, based on BSA comparison. Intravenous administration of ceftobiprole medocaril sodium to rats 2-weeks prior to mating, during organogenesis, and through lactation resulted in no significant adverse fertility or fetal development effects in offspring at doses approximately 1.4 times the MRHD, based on BSA comparison. Slight reductions in number of pups born per litter and decreased postnatal survival up to day 4 after birth were associated with maternal toxicity (mortality, reduced food consumption and body weight gain in surviving females during gestation). No offspring adverse effects were observed in surviving pups during the postnatal postweaning development period (Days 5 through 22) at doses up to 360 mg/kg.

Pregnant rats were administered ceftobiprole at doses of 175, 250, and 360 mg/kg/day from 14-days pre-mating through lactation/postpartum day 21. Ceftobiprole was excreted in rat milk at levels of approximately 20% of the corresponding maternal plasma ceftobiprole levels. The concentration of ceftobiprole in animal milk does not necessarily predict the concentration of drug in human milk.

9. Product Quality

Approval With a Postmarketing Commitment

The Office of Pharmaceutical Quality (OPQ) review team assessed NDA 218275 with respect to chemistry, manufacturing, and controls (CMC). The proposed drug product, ceftobiprole medocaril sodium for injection, is a sterile lyophilized powder filled into single-dose glass vials, which need to be reconstituted and further diluted for intravenous infusion. Each drug product vial contains 667 mg ceftobiprole medocaril sodium (equivalent to 500 mg of ceftobiprole) and is supplied in a carton containing 10 single-dose vials. The majority of CMC information provided in the NDA to assure and demonstrate the identity, strength, purity, and quality of the proposed drug product, ceftobiprole medocaril sodium for injection, was found to be adequate. However, since the proposed drug product is an injectable powder for reconstitution, it needs to comply with applicable guidances and regulations to ensure that the excess solid in a vial is sufficient to allow for withdrawal and administration of the net container content of the drug product. Therefore, additional finished drug product and in-process controls are needed. In addition, the currently established drug product assay and impurity limits are considered acceptable on an interim basis and should be reassessed based on the stability testing results for three new drug product batches manufactured using a revised drug substance assay calculation. These issues will be addressed through two PMC studies (the PMC descriptions and draft timelines are included in Section 24, below). All manufacturing and testing facilities were found acceptable. An exception to the FDA/USP salt policy guidance was made for the drug name, strength and equivalency statement in consultation with OND.

9.1. Device or Combination Product Considerations

Not applicable.

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review

The Applicant has provided attestation that all trials submitted for this NDA were conducted in accordance with good clinical practice and all applicable regulatory requirements. The trial protocols were reviewed by independent ethics committees and institutional review boards. The Applicant has also provided a letter certifying and disclosing that all the investigators do not have any financial interests or arrangements and there are no concerns that this has any impact on the interpretation of the safety and efficacy of the trials.

A review of the clinical sites was conducted by OSI to ensure data quality and protocol safety. Seven clinical sites were chosen for inspection based upon their high enrollment in their respective pivotal trials (6 clinical investigators and the Applicant). Two sites (Site 044 in Bulgaria and 067 in California, USA) were selected for BPR-CS-008, two sites (Site 203 and 205 both in Bulgaria) were selected for BPR-CS-009, and two sites (886005 in Taiwan and 001003 in Georgia, USA) were selected for CAP-3001. The seventh site inspected was Basilea Pharmaceutical International LTD in Switzerland and this was directed to investigate specific concerns about good clinical practice regarding the three trials. Of note, under NDA 22132,

Reference ID: 5357793

ceftobiprole was not approved for an indication of complicated skin and skin structure infections (cSSSI) given concerns about data integrity in prior trials which were not submitted in this NDA. In addition, as overall efficacy for the sites in Ukraine was greater than for any country and with fewer AEs in Trial BPR-CS-009, an applicant inspection was requested by the Division because of the inability to inspect sites in Ukraine due to travel restrictions.

For all three audited trials, OSI did not find evidence of unblinding or biased data collection. The trial monitoring for both the studies sponsored by Basilea and the internal audit of the legacy study done by Basilea appeared adequate. Overall, the trials appear to be conducted adequately and the data was consistent with the Applicant's records for the efficacy and safety data. No major issues were identified. For details, refer to clinical inspection summary written by Dr. John Lee from OSI, dated February 7, 2024, in DAARTs.

11. Advisory Committee Summary

The application was not presented at an advisory committee meeting. There were no review issues identified for which Advisory Committee advice was needed.

Reference ID: 5357793

III. Additional Analyses and Information

12. Summary of Regulatory History

Basilea Pharmaceutica, Ltd., (Applicant) submitted a Pre-Investigational New Drug Application for BAL 5788 for injection on July 24, 2002, for the treatment of Complicated Skin and Skin Structure Infections (cSSSI).

On September 16, 2002, the Division held a meeting with the Applicant to discuss the drug development program, leading into phase 2 studies. The Division recommended that the Applicant provide data from repeat dose toxicity studies and full reports for toxicology, nonclinical, and pharmacokinetic (PK) metabolic studies, along with full assay validation data from plasma samples obtained, as part of their forthcoming investigational new drug (IND) submission.

On November 7, 2002, the Applicant submitted their investigational new drug application (IND 064407) which was deemed safe to proceed by the Division on December 9, 2002.

On June 30, 2005, the ownership of the IND was transferred to Johnson and Johnson Pharmaceutical Research & Development, L.L.C. On January 24, 2011, IND ownership was transferred back to Basilea Pharmaceutica, Ltd.

On June 24, 2014, a type C, Guidance meeting was held to discuss the drug development program for the CABP indication.

The Applicant submitted requests for Qualified Infectious Disease Product (QIDP) designations under the GAIN Act, on April 09, 2015, for CABP and ABSSSI. These indications were granted QIDP designation on July 20, 2015, and August 7, 2015, respectively.

On November 17, 2015, a type B, End of Phase 2 meeting was held to discuss the phase 3 drug development program for the indications ABSSSI, CABP, and *Staphylococcus aureus* bacteremia (SAB). Issues discussed included the NI margin, primary efficacy endpoint, concomitant antibiotic use, number of studies, and treatment duration.

Reference ID: 5357793

The Applicant submitted special protocol assessments (SPA), Clinical SPA-6 and Clinical SPA-7, to the IND as follows:

- March 31, 2016: SPA-6 was submitted titled: "A randomized, double-blind, multicenter study to establish the safety and efficacy of ceftobiprole medocaril sodium compared with vancomycin plus aztreonam in the treatment of acute bacterial skin and skin structure infections (ABSSSI)." The Division issued a Special Protocol-Agreement letter for SPA-6 on May 12, 2016. This SPA was amended on May 5, 2017, and a Special Protocol-Agreement Modification letter was issued on July 13, 2017. The protocol was further amended on July 23, 2018, to refine the inclusion/exclusion criteria, use of aztreonam in the study, and the addition of a pre-specified subgroup (illicit drug users) in the trial. A Special Protocol-Agreement Modification letter was issued on September 25, 2018.
- May 17, 2016: SPA-7 was submitted titled: "A randomized, open-label, multi-center study to establish the efficacy and safety of ceftobiprole medocaril sodium compared to standard-of-care therapy in the treatment of complicated bacteremia, including infective endocarditis, caused by *Staphylococcus aureus*". The FDA issued a Special Protocol-No Agreement letter for SPA-7 on June 16, 2016. On September 27, 2016, a type A SPA meeting was held and on March 24, 2017, FDA issued a SPA letter following the Applicant's submission addressing outstanding issues. Several additional requests for protocol modifications were received and agreements reached between May 2017 and February 2020. The last SPA Modification letter issued on May 20, 2020.

On May 13, 2016, FDA issued type C, Guidance, Written Response Only meeting comments to the Applicant to address the proposed treatment duration of ceftobiprole medocaril sodium in the planned complicated SAB study.

On October 26, 2017, the Applicant submitted a request for QIDP designation for the indication of SAB. QIDP designation was granted for this indication on December 8, 2017.

Basilea Pharmaceutica International Ltd. completed the following pivotal trials under IND 064407: "A randomized, double-blind, multicenter study to establish the safety and efficacy of ceftobiprole medocaril sodium compared with vancomycin plus aztreonam in the treatment of acute bacterial skin and skin structure infections" (BPR-CS-008) and "A randomized, double-blind, multicenter study to establish the efficacy and safety of ceftobiprole medocaril sodium compared to daptomycin in the treatment of *Staphylococcus aureus* bacteremia, including infective endocarditis" (BPR-CS-009). In addition, the Applicant completed a trial in pediatric subjects (aged 3 months to < 18 years) with hospital-acquired bacterial pneumonia (HABP) or CABP requiring hospitalization (BPR-PIP-002) as part of the marketing application.

On March 28, 2019, FDA issued Written Responses Only comments as a type B Guidance meeting to provide information related to recruitment issues with clinical trial (BPR-CS-009) for SAB.

Reference ID: 5357793

On June 03, 2020, a Chemistry, Manufacturing, and Controls (CMC) Pre-new drug application (NDA) meeting was held to discuss the contents of the CMC section for the planned NDA submission and to address questions related to the quality of the commercial ceftobiprole medocaril sodium drug substance and drug product. Topics discussed included the acceptability of the proposed regulatory starting materials, the planned strategy to control mutagenic impurities, and the proposed specifications for the drug substance and the drug product. The Division commented that the acceptability of the proposed specifications would be a review issue. The Division agreed that the Applicant's proposal for submitting a comparability protocol to demonstrate the equivalence of the manufacturing processes at both sites appeared reasonable.

On June 30, 2021, following the review of the FDA Preliminary Meeting Comments the Applicant cancelled a type C guidance meeting scheduled for July 06, 2021. This meeting was to discuss the planned safety analysis and breakpoints. The Division stated that the later issues would be evaluated during the NDA review.

On May 31, 2022, the Applicant informed FDA effective June 01, 2022, their corporate name, and address, had changed from Basilea Pharmaceutica International Ltd. to Basilea Pharmaceutica International Ltd., Allschwil.

The Applicant submitted a type B Pre-NDA meeting request on August 15, 2022, and the teleconference was held on October 13, 2022. Several product quality aspects of the planned NDA were discussed including the schedule for submitting stability data and methods validation templates. The Applicant updated the Division on the GMP status of the manufacturing facility and stated that the facility would be ready for inspection at the time of submission. It was agreed that a late submission of 9-month real-time stability data could be submitted within 30 days of the NDA receipt date. Additionally, clinical aspects of the submission were discussed and agreed to as they pertain to adverse events of special interest (AESI), the integrated summary of safety, statistical analysis plan, and information on case report forms for serious adverse events (SAEs) and discontinuations.

To address the requirements of the Pediatric Requirements Equity Act, an initial Pediatric Study Plan was submitted on December 21, 2021. On November 1, 2022, FDA issued an Agreed Initial Pediatric Study Plan-Agreement letter, in response to the Applicant's submission of an Initial Pediatric Study (iPSP). The Agreed iPSP was included in the NDA submission.

On August 3, 2023, Basilea Pharmaceutica International Ltd., Allschwil, submitted NDA 218275 for ceftobiprole medocaril sodium for injection for the indications of SAB and ABSSSI in adult subjects and CABP in adult and pediatric subjects. The NDA received priority review designation on September 28, 2023, and was filed on October 02, 2023. The requested proprietary name, Zevtera, was found conditionally acceptable by the Division of Medication Error and Prevention Analysis on October 30, 2023.

NDA 218275 for ceftobiprole medocaril sodium for injection has a PDUFA goal date of April 3, 2024.

Reference ID: 5357793

13. Pharmacology Toxicology

13.1. Summary Review of Studies Submitted With the Investigational New Drug Application

13.1.1. Pharmacology

Ceftobiprole medocaril sodium is a 5th generation cephalosporin antibacterial with bactericidal activity against gram-positive and gram-negative pathogens.

Further details regarding in vitro and in vivo efficacy of ceftobiprole medocaril sodium can be found in Section 19, Clinical Microbiology.

13.1.1.1. Safety Pharmacology

For reference, the following compound identifiers have been used for ceftobiprole medocaril sodium (pro-drug): BAL5788-001, BAL0005788-001, BAL5788, JNJ-30982081, JNJ-30982081-(b) (4), Ro 65-5788, Ro 65-5788/001 and for its active metabolite ceftobiprole (Ro 63-9141/000, 63-9141, BAL9141).

Table 119. In Vivo Cardiovascular Safety Study in Marmosets and Rats

Study Feature and Methods	Details
Applicant Study Number	100431
Contract Lab Study Number	100431
Study Title	Cardiovascular Safety Studies in Marmosets and Rats with Ro 65-5788/001 (Prodrug of Ro 63-9141/000)
Species/Strain	Rat/Sprague Dawley Monkey/Marmoset
Number/dose group	Hypertensive rats (n=4) or normotensive marmosets (n=3) sex not identified
Doses	Ro 65-5788/001 (ceftobiprole medocaril sodium) 30 and 100 mg/kg
Route of Administration	IV
Dosing Frequency	Single bolus injection
Parameters Measured	Mean arterial pressure (MAP) and heart rate (HR) from 5 hours before up to 24 hours after drug administration (at 10-minute intervals)
Findings	Mean arterial pressure (MAP) increased during the first nine hours and for almost 24 hours following 100 mg/kg bolus in rats and marmosets, respectively (approximately 20%). Lower doses of 30 or 35 mg/kg or longer 1-hour infusions of 50 or 100 mg/kg did not appreciably affect blood pressure. With the 1-hour infusion of 100 mg/kg, plasma levels at two and six hours were 54 and 3.5 mcg/mL, respectively. The results suggest a clinically significant effect on blood pressure and monitoring was recommended in humans.
Validity	Valid

Source: Reviewer generated table.
Abbreviations: HR, heart rate; IV, intravenous; MAP, mean arterial pressure; n, number of subjects in treatment arm

Table 120. In Vivo Cardiovascular Safety Study in Dogs

Study Feature and Methods	Details
Applicant Study Number	B-165'433
Contract Lab Study Number	(b) (4)
Study Title	Ro 65-5788 (Prodrug of Ro 63-9141): Cardiovascular Study in Conscious Dogs
Species/Strain	Dog/Beagle (~9 months of age)
Number/Sex/dose group	(1/sex, total 2 animals)
Doses	0, 25, 75, 250 mg/kg
Route of Administration	4-hour intravenous infusion
Dosing Frequency	Once weekly (2 doses)
Parameters measured	Blood pressure, heart rate and electrocardiogram parameters (P-wave duration and amplitude, P-Q interval, QRS complex and Q-T interval) were measured at 20-minute intervals during infusion at 5- and 6- hours post initiation of infusion. Plasma levels were measured at the end of infusion (1-2 hours post infusion).
Findings	No significant findings on blood pressure, heart rate, or ECG profile observed.
Validity	This study was not considered valid due to the low number of animals.

Source: Reviewer generated table.
Abbreviations: ECG, electrocardiogram

Table 121. In Vitro Cardiovascular Safety

Study Feature and Methods	Details
Applicant Study Number	TOX7518
Contract Lab Study Number	(b) (4)
Study Title	Effect of BAL9141 on HERG tail current recorded from stably transfected HEK293 cells
Methods	BAL9141 (batch# 05R0002) in DMSO was sonicated prior to use in the test system. Cells (cultured HEK293 cells transfected with HERG cDNA) were plated on glass coverslips in 35 mm^2 dishes for electrophysiology studies at a density of 0.5 x 10^5 cells per dish, placed in patch clamping (-80 mvolts) recording chambers. Cells systems (n=4) were then treated with either BAL9141 (5mM), vehicle (0.2% DMSO) or reference substance (100nM E-4031) and test system allowed to equilibrate for 15 minutes prior to HERG tail current recording.
Findings	There were no differences in HERG tail current between the BAL9141 and control vehicle. The reference substance E-4031 induced a 96.7% inhibition of HERG tail currents, consistent with known activity.
Validity	Test was considered valid.

Source: Reviewer generated table.
Abbreviations: DMSO, dimethyl sulfoxide

Table 122. Central Nervous System

Study Feature and Methods	Details
Applicant Study Number	1006581
Contract Lab Study Number	(b) (4)
Study Title	Ro 63-9141: CNS Safety Study in Mice (i.c.v. and i.v. Application)

Study Feature and Methods	Details
Species/Strain	Mice/Ibm:MORO
Number/Sex/dose group	8 males/group
Doses	Intracerebral (ICV): Ro 63-9141 (ceftobiprole) batch# 19936B001) in 7.5% gelatin/0.62% sodium chloride: 0-30 mcg/mouse; Comparators: imipenem and meropenem in PBS at 0.3-30 and 10-1000 mcg/mouse, respectively. Intravenous (IV): Ro 65-5788 (ceftobiprole medocaril sodium, batch# 18116B58) at 0, 62.5, 125, 250, 500 and 1000 mg/kg (bolus injection)
Route of Administration	ICV and IV
Dosing Frequency	Single dose
Parameters measured	• Clinical signs and convulsant activity: observed for 30 continuous minutes or up to 8-hour observation period • Plasma/ brain levels: 0.5, 1, 1.5, 2, 4 and 6 hours post dose • BUN/creatinine and kidney histopathology
Findings	• ED50 for convulsions with Ro 63-9141 ICV was 2.55 mcg/mouse. Convulsions occurred within minutes of injection, death within an hour. Brain levels of Ro 63-9141 were variable with peak levels at 250 mg/kg and were 2.5 mcg/head and 4.7 mcg/head with 500 mg/kg. BUN levels at 250 and 500 mg/kg were elevated approximately 5-fold above controls. ED50 for imipenem and meropenem were 3.16 and 548 mcg/mouse, respectively. • All mice injected IV with 1000 mg/kg Ro 65-5788 exhibited clonic and tonic convulsions within 30 minutes of injection and 4/8 died within the first 30 minutes. At doses of 250 and 500 mg/kg IV, clonic and tonic convulsions, vocalization, straub tail, and death (8/12 at 500 mg/kg) were noted. In the kidneys, moderate to marked deposits, dilation congestion, degeneration of distal tubules, necrosis and detritus in distal tubules were seen at 250 and 500 mg/kg (increasing in severity and incidence with dose) • Rat CSF levels after IV administration were less than 1% and 5% of plasma levels up to 6 hours post administration at 20 mg/kg and 500 mg/kg, respectively. BUN doubled between 5 minutes and four hours. Creatinine levels were minimally affected. • Ro 63-9141-induced convulsion appears to be a primary effect and not secondary to kidney damage as convulsions were seen with direct injection into the brain.

Source: Reviewer generated table.
Abbreviations: BUN, blood urea nitrogen; CSF, cerebrospinal fluids; ED50, median effective dose; ICV, intracerebral; IV, intravenous

Table 123. In Vivo Pulmonary Function Study in Rats

Study Feature and Methods	Details
Applicant Study Number	TOX7593
Contract Lab Study Number	(b) (4)
Study Title	Effects of BAL5788 on Pulmonary Function in the Anaesthetized, Ventilated Sprague-Dawley Rat
Species/Strain	Rat/Sprague Dawley
Number/Sex/dose group	8 males/group

Doses	0, 125, 250, 500 mg/kg (expressed as BAL9141 which is approximately 25% lower than the pro-drug BAL5788; batch 30-4EXP)
Route of Administration	Intravenous
Dosing Frequency	Single dose (4-hour infusion)
Parameters measured	Airway resistance and dynamic lung compliance measured over 255 minutes
Positive control	Acetylcholine hydrochloride
Findings	The airway resistance and dynamic lung compliance did not differ significantly across groups.
Validity	Positive control (Acetylcholine) increased resistance by three to four-fold.

Source: Reviewer generated table

Absorption, Distribution, Metabolism, Excretion, Pharmacokinetics

The absorption, distribution, metabolism, and excretion of ceftobiprole medocaril (BAL5788) and ceftobiprole (active metabolite, BAL9141) was investigated in multiple species. Pharmacokinetics were assessed in the mouse, rat, rabbit, cynomolgus monkey, marmoset and dog. Excretion was primarily investigated in the rat.

Absorption

Nearly all studies have been conducted via the intravenous route, except for juvenile toxicology study conducted in rats by the subcutaneous route.

Distribution

Low-to-moderate plasma protein binding (18 to 40%) was detected in mouse, rabbit, dog, monkey, and human plasma, across a concentration range of 30-300µM. A comparative study of mouse and human showed that protein binding in both species is low.

In a rat exploratory quantitative whole body autoradiography study following a single intravenous administration of ^{14}C radiolabeled ceftobiprole medocaril sodium (20 mg/kg), quantifiable levels of radioactivity (>0.29 mcg-equiv/g) were detected in all tissues with a low overall distribution into most organs and tissues. The highest concentrations of radioactivity 15 minutes post-dose were found in the kidney (34.2 and 32.3 mcg-equiv/g in the cortex and medulla, respectively), skin (19.63 mcg-equiv/g), tooth pulp (19.17), liver (18.96 mcg-equiv/g), lung (17.3 mcg-equiv/g), blood (17.04 mcg-equiv/g), connective tissue (15.73 mcg-equiv/g), aorta (11.61 mcg-equiv/g) and stomach mucosa (11.98 mcg-equiv/g). Lower levels (below 10 mcg-equiv/g) were detected in mandibular and mesenteric lymph nodes, adrenal gland, thyroid, adrenal gland, pituitary gland, salivary glands, lacrimal gland, harderian gland, pineal body and muscle with lowest levels detected in the brain and spinal cord (0.38 and 0.58 mcg-equiv/g, respectively). Elimination of radioactivity was rapid (declining over 10-fold in 7 hours) except for the kidney with an estimated half-life of over 24 hours. Elimination of radioactivity was predominantly by the renal route (82% of the dose within 48 hours). In a similar distribution study in mice, the highest concentrations of radioactivity across tissues were found in the coagulating gland (78.29 mcg-equiv./g), the excretory organs kidney (30.43 and 24.24 mcg-equiv./g in cortex and medulla, respectively) and liver (26.26 mcg-equiv./g), as well as in skin and aorta. Elimination from tissues was rapid (declining concentrations by 10fold in 2 hours) with detectable levels only in the kidney cortex and liver by 24 hours.

Reference ID: 5357793

Metabolism

The parent pro-drug compound BAL5788 is rapidly metabolized to BAL9141. BAL941 is further metabolized to the open lactam ring form (BAL2070, up to 10% of the urinary compounds in this form). Further metabolism of BAL9141 into open ring forms were seen in multiple species (up to 4 other metabolites, ~5%).

The metabolism of BAL5788 (ceftobiprole medocaril sodium) was investigated in vitro using primary cultures of hepatocytes from livers of humans, rats, mouse, dog, marmoset, and cynomolgus monkeys and rat and mouse brain homogenates and rat liver and kidney homogenates. Ceftobiprole medocaril sodium (pro-drug) was rapidly metabolized to Ro 63-9141, which in turn metabolized to the open beta-lactam ring form, BAL 65-2070. The percentage of metabolism at 48 hours is shown below.

Table 124. Metabolism of BAL5788 (Ceftobiprole Medocaril Sodium)

Species/Organ	Ro 63-9141 (ceftobiprole) metabolized (%)
Mouse	69
Rat	48
Dog	43
Marmoset	64
Human	51
Mouse brain	50 (Ro 65-2070 + 2 peaks)
Rat brain	50 (Ro 65-2070 + 4 peaks)
Rat kidney	100 (Ro 65-2070 + 4 peaks)

Source: Reviewer generated table

- In an Applicant report (BAP00069), the comparative metabolism of ceftobiprole medocaril sodium was investigated in vivo after administration of a single dose of radiolabeled (14C) ceftobiprole medocaril sodium (13.3 mg/kg). The report included the metabolic profiles in rat plasma, urine, bile and kidney, rat brain and marmoset urine. The majority of the drug was shown to be eliminated in the urine. Within 5 to 10 minutes, the majority of the drug was converted from ceftobiprole medocaril sodium (pro-drug to ceftobiprole). Approximately 10% of the compound detected in urine was the open ring form (Ro 65-2070) with other 4 metabolites detected (below 5%). Small amounts of ceftobiprole were detected in the cerebrospinal fluid (CSF) of rats (1 to 2%). There did not appear to be significant differences in the metabolic profiles of males and females.

Table 125. Comparative Metabolism of Ceftobiprole Medocaril Sodium Summary

Source	Timepoint	Total radioactivity (%)	Metabolites
Rat plasma	10 minutes	---	>50% as 9141 (ceftobiprole)
Rat plasma	2 hr	---	88% as ceftobiprole, 3% as ceftobiprole medocaril, 5-8% as other
Rat urine	0-4 hr	74.2	>50% as 9141 (ceftobiprole), <1% ceftobiprole medocaril sodium, ~10% as metabolite 2070, 3 other peaks about 5%
Rat urine	0-24 hr	87.2	---
Marmoset urine	2 weeks	---	90% as ceftobiprole, 5% as metabolite 2070, 1% as ceftobiprole medocaril sodium
Rat bile	0-24 hr	17.8	---
Rat brain	10 minutes	---	Ceftobiprole as “predominant”, 5% other
Rat CFS	2 hr	1-2.4	Ceftobiprole only
Rat kidney	4 hr	---	Ceftobiprole as “predominant”, 10% as metabolite 2070

Source: Reviewer generated table
Abbreviations: hr, hour

Excretion

Urinary excretion accounted for the majority of BAL5788 elimination in all species. Excretion was primarily investigated in the rat with 95% of the dose administered recovered in the urine after four days post dose. Cumulative excretion in rat showed 73% eliminated in the urine, 17% in the feces, 3% in the cage wash and 1% left in the carcass.

Table 126. Urinary Excretion of BAL9141 (% Dose Administered That is Recovered in 24 Hours)

Species	Range of % of dose	Mean % dose
Rat	52-74%	65%
Rabbit	2-32%	Unstable
Monkey	13-42%	---
Rat	16-71%	47%
Marmoset	27-52%	39%

Source: Reviewer generated table

Interactions

In vitro studies ceftobiprole (active metabolite) did not appear to be a substrate or cause inhibition of several human proteins that may have a role in drug-drug interactions including human efflux transporters (P-glycoprotein, BCRP, bile salt export pump [BSEP] and MRP2) or human uptake transporters (organic anion-transporting polypeptide [OATP]1B1, OATP1B3, OCT1, OCT2, OAT1 and OAT3).

Reference ID: 5357793

Toxicokinetics

The following studies are summarized in Table 127 below.

1. Pharmacokinetics of a novel cephalosporin, Ro 63-9141, in mice following single intravenous bolus administration (B-166-154)
2. Ro 65-5788 (5th Generation Cephalosporin): Pharmacokinetics of the Active Entity Ro 63-9141 Following Single Intravenous Bolus Administration of Ro 65-5788 to Marmosets (Study No. ST_99_194.1)
3. Non-Clinical Research Report – BAL5788 (5th Generation Cephalosporin): Pharmacokinetics of the Prodrug BAL5788 and the Active Entity BAL9141 Following Single Intravenous Bolus Administration of BAL5788 to Rats (Study No. ST_99_237.1) /(Upgrade of Roche Report NO. B-170'764, March 17, 2000)
4. Non-Clinical Research Report – BAL5788 (5th Generation Cephalosporin): Pharmacokinetics of the Prodrug BAL5788 and Active Entity BAL9141 Following Single Intravenous Bolus Administration of BAL5788 to Cynomolgus Monkeys (Study No. ST_99_330.1) / Upgrade of Roche Report No. B-170'765, March 24, 2000)
5. Non-Clinical Research Report – Pharmacokinetics of BAL9141 in Rats Following Single Intravenous Bolus Administration of BAL9141 or BAL5788 in Comedication with Probenecid / (Upgrade of Roche Report No. B-166'157, November 13, 1997)
6. Non-Clinical Research Report – Pharmacokinetics of BAL9141 in Rats Following Single intravenous Bolus Administration (Upgrade of Roche Report No. B-166'151, June 16, 1997)
7. Non-Clinical Research Report – Exploratory Pharmacokinetics of BAL9141 in Female Rabbits Following Single Intravenous Bolus Administration (Upgrade of Roche Report No. B-166'152, June 16, 1997)
8. Non-Clinical Research Report – Pharmacokinetics of BAL9141 in Cynomolgus Monkey Following Single Intravenous Infusion Administration ((b) (4) Study No. 161-299) / (Upgrade of Roche Report No. B-166'153, July 07, 1997)

Table 127. Toxicokinetic Studies Summary

Study #	Test Article	Vehicle	Species	Route	Dose	Method LOQ	Timepoint (hr)	AUC mcg/hr/mL	C_{max} mcg/mL	Clearance mL/min/kg	$T_{1/2}$ (h)
1	Ro 63-9141	25% DMSO/75% NaCl	Male mouse (moro) 2/pt	IV bolus	10 mg/kg	HPLC/ 10 ng/mL	0.08, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4	13.8	33.1 At 5 min	12.0	0.48
1	Ro 63-9141	25% DMSO/75% NaCl	Male mouse (moro) 2/pt	IV bolus	10 mg/kg	Bioassay / 0.25 Mcg/mL	0.08, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4	16.8	37.5 At 5 min	9.93	0.27
2	Ro 65-5788	Citrate buffered saline	Male marmosets N=3	IV bolus	20 mg/kg	HPLC/ 10 ng/mL	0, 0.083, 0.33, 1, 2, 4, 6, 8	No 5788 at 5 min 9141: 74.93	83.2 At 5mim	5.05	0.95
3	BAL5788	Citrate buffered saline	Male Wistar Rats	IV bolus	20 mg/kg	HPLC/ 10 ng/mL	0, 0.08, 0.25, 0.5, 1, 2, 3, 4	5788: 3.03 9141: 25.9	5788:9.61 T 5 min, 0 at 2h 9141:44 at 5 min	9141: 13 5788: not calculated	5788: 0.21 9141: 0.58
4	BAL5788	Citrate buffered saline	Male cyno monkeys	IV bolus	20 mg/kg	HPLC/ 100 ng/mL	0, 0.083, 0.17, 0.33, 0.5, 0.75, 1, 2, 3, 6, 7	5788: not detectable at 20 min 9141: 132	5788: 10.2 @ 5 min 9141: 146	5788: not calculated 9141: 2.59 ± 0.37	5788: <5 min 9141: 1.34
5	Ro 65-5587	Citrate buffered saline	Male marmosets N=4	IV bolus	20 mg/kg	HPLC/ 10 ng/mL	0, 0.083, 0.33, 1, 2, 4, 6, 8	5788: not detected at 5 min 9141: 74.93	83.2 at 5 min	5.05	0.95

Reference ID: 5357793

Study #	Test Article	Vehicle	Species	Route	Dose	Method LOQ	Timepoint (hr)	AUC mcg/hr/mL	C_{max} mcg/mL	Clearance mL/min/kg	$T_{1/2}$ (h)
6	BAL9141	10% DMSO 90% NaCl	Male Rats (RoRo) 2/point	IV bolus	7.3 mg/kg	HPLC 8 ng/mL	0.07, 0.17, 0.25, 0.5, 1, 1.5, 2, 4, 6, 8	19	23	8.75	0.5
7	BAL9141	10% DMSO 90% NaCl	Female rabbits n=4	IV bolus	3.5 mg/kg	HPLC 30 ng/mL	0.07, 0.25 0.5, 1, 2, 3, 4, 5, 6, 7, 8	20.0	16.4 at 0.7 h	4.2	0.82
8	BAL9141	20% DMSO 80% NaCl	Male cyno monkeys	IV over 30 min	7.3 mg/kg	HPLC 16 mcg/mL	0, 0.25, 0.5, 0.75, 1, 2, 3, 4, 5, 6, 7, 8	59.9	123 at 5 min	2.83	1.7

Source: Reviewer generated table
Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum plasma concentration; DMSO, dimethyl sulfoxide; HPLC, high performance liquid chromatology; hr, hour; IV, intravenous; LOQ, limits of quantification; $T_{½}$, half-life

Reference ID: 5357793

13.1.2. Toxicology

13.1.2.1. General Toxicology

13.1.2.1.1. Repeated Dose Toxicology/Toxicokinetic Studies

For reference, the following compound identifiers have been used for ceftobiprole medocaril sodium (pro-drug): BAL5788-001, BAL0005788-001, BAL5788, JNJ-30982081, JNJ-30982081-(b) (4), Ro 65-5788, Ro 65-5788/001 and for its active metabolite ceftobiprole (Ro 63-9141/000, 63-9141, BAL9141)

BAP00230. A Two-Week Toxicity Study of BAL5788 (Prodrug of BAL9141) Via Intravenous Infusion in Dogs Followed by a Two-Week Recovery Period

Key Study Findings

- Histaminergic reaction (reddening of the skin, face edema, injection of the oral mucosa, vomiting and salivation) primarily associated with the shorter infusion time (30 minutes). Findings significantly decreased with a longer infusion time for the high and medium dosed animals (2 hours). These finding correlated with a dose dependent increase in plasma levels of histamine that returned to control levels after infusion (approximately 4 hours from start of infusion).
- Injection site hemorrhage (slight) of the subcutis observed in all animals, hyperplasia of the tunica intima was observed at 50 and 100 mg/kg/day in males and females.
- No observed adverse effect level (NOAEL) considered at 100 mg/kg/day (1.2-fold the MHRD based on body surface area [BSA] comparisons).

Table 128. Study Information

Study Features and Methods	Details
GLP Compliance:	Yes
Dose and frequency of dosing:	0, 25, 50 and 100 mg/kg/day (calculated as BAL9141)
Route of administration:	IV infusion (over 30-minute period, initially, changed to 2 hours due to severe toxicity at the mid and high dose groups) once daily
Formulation/vehicle:	BAL5788 (batch PO103)/ 5% dextrose
Species/strain:	Dog/ Beagle
Number/sex/group:	2-3/sex/group
Age:	5-7 months (males: 7.2-10 kg; females: 7.1-9.3 kg)
Satellite groups/unique design:	Infusion time changed from 30 minutes to 2 hours for the 50 and 100 mg/kg groups
Deviation from study protocol affecting interpretation of results:	None that had an impact on the outcome of the study.

Source: Reviewer generated table.
Abbreviations: GLP, good laboratory practice; IV, intravenous

Table 129. Observations and Results

Parameters	Major Findings
Mortality	No unscheduled deaths
Clinical signs	In nearly all treated animals: On first day of dosing (Day 0) vomiting, reddening of the auricles, conjunctiva, oral mucosa were observed for approximately 30 minutes after the end of infusion. In 4/5 males and 3/5 females, facial edema, reddening of the skin (i.e., extremities) or erythema were observed over the whole-body during infusion. Sedation, scratching, prone or sitting position, spontaneous defecation, decreased activity, somnolence, vomiting, and or retching and salivation were also observed in some animals during infusion. After extension of the infusion time to 2 hours, the incidence of vomiting was reduced (about 3/5 males and females vomited during infusion), reddening of auricles was still observed in some animals but the reddening of the conjunctiva and oral mucosa were no longer observed. Although occasional vomiting and reddening of the auricles and conjunctiva were observed, incidence and severity of findings decreased over time.
Body weights	No treatment-related changes
Ophthalmoscopy	No treatment-related changes
Hematology	No treatment-related changes
Clinical chemistry	Histamine levels evaluated in 25 and 100 mg/kg/day groups on days 0 and 1 were slightly elevated (~ 2-fold) in one animal at 25 mg/kg at 0.5 hours after start of infusion (back to control levels within an hour) and greatly elevated in all animals at 100 mg/kg/day (up to 160-fold) at 0.25 and 0.5 hours after start of infusion (back to control levels at approximately 4 hours). This correlated with observations of reddening of the skin and facial edema (primarily at the high dose).
Urinalysis	No treatment related changes
Gross pathology	Red foci at the site of injection observed across all groups, including controls
Organ weights	No treatment-related changes
Histopathology Adequate battery: Yes	Slight kidney eosinophilic droplets in the proximal tubules of the kidney at 50 mg/kg/day (1-2/3 males and females) and in all animals at the 100 mg/kg/day (persistent at the end of the recovery period). Injection site hemorrhage (slight) of the subcutis observed in all animals, hyperplasia of the tunica intima was observed at 50 and 100 mg/kg/day in males and females.

Source: Reviewer generated table.

Table 130. Plasma Histamine Concentrations (nm/L) in Dogs

Dose of BAL5788 (mg/kg)	Animal No.	Day 0				Day 1				
		0.25h	0.5h	1h	4h	pre	0.25h	0.5h	2h	4h
0	1	-	13.3	-	-	-	-	-	-	-
	7	-	16.3	-	-	-	-	-	-	-
	Mean	-	14.8	-	-	-	-	-	-	-
	SD	-	NC	-	-	-	-	-	-	-
25	12	6.9	8.8	6.6	6.4	-	-	-	-	-
	14	15.9	44.6	16.8	21.1	-	-	-	-	-
	Mean	11.4	26.7	11.7	13.8	-	-	-	-	-
	SD	NC	NC	NC	NC	-	-	-	-	-
100	23	>2400	>2400	133.9	14.7	17.2	16.0	37.2	70.2	17.6
	25	737.6	491.2	32.3	10.0	16.3	10.8	11.6	14.7	11.6
	29	>2400	1549.5	78.8	12.5	12.3	10.7	15.2	23.9	12.5
	32	1084.1	1640.4	61.9	14.9	15.6	16.9	33.7	39.7	14.4
	Mean	910.9	1227.0	76.7	13.0	15.4	13.6	24.4	37.1	14.0
	SD	NC	638.9	42.7	2.3	2.1	3.3	12.9	24.3	2.7

>2400 was not calculated
- : No sample, NC : Not calculated

Source: Reviewer generated table

BAP00346. A Two-Week Bridging Toxicity Study of BAL5788 (Prodrug of BAL9141) Via Intravenous Infusion in Rats Followed by a Two-Week Recovery Period

Key Study Findings

- There were no significant differences between formulations BAL5788 A and B
- NOAEL considered at 360 mg/kg (approximately 1.4 the maximum recommended human dose [MRHD] based on BSA comparisons)

Table 131. Study Information

Study Features and Methods	Details
GLP Compliance:	Yes (Japanese)
Dose and frequency of dosing:	0, 175, 360 mg/kg/day (BAL5788 A and BAL5788 B, six experimental groups in total)
Route of administration:	IV infusion
Formulation/vehicle:	BAL5788 (PL-289, 92.9% purity)/ 5% dextrose
Species/strain:	Rat/ Sprague Dawley
Number/sex/group:	3-5/sex/group
Age:	8 weeks (males: 235-265 g; females: 171-205 g)
Satellite groups/unique design:	Catheter implanted into the femoral vein into the post-cava under anesthesia 13-14 days prior to dosing. A tube for continuous infusion was placed subcutaneously from implantation site to an exit site on the back tied to a fixed point and attached to a syringe and extension tube. Animals were fitted to a jacket to hold the system and physiological saline was run through the system continuously using an infusion pump to prevent blockage in the catheter.
Deviation from study protocol affecting interpretation of results:	None that had an impact on the outcome of the study.

Source: Reviewer generated table
Abbreviations: GLP, good laboratory practice; IV, intravenous

Table 132. Observations and Results

Parameters	Major Findings
Mortality	No unscheduled deaths

Clinical signs	Soft or mucous stools were observed in some animals at 175 or 360 mg/kg/day. Abnormal colored urine (yellowish-brown.
Body weights	No treatment-related changes
Ophthalmoscopy	No treatment-related changes
Hematology	No treatment-related changes
Clinical chemistry	No treatment-related changes
Urinalysis	No treatment-related changes
Gross pathology	Injection site: thickening and yellowish-brown material in almost all animals (including controls)
Organ weights	No treatment-related changes
Histopathology Adequate battery: Yes	Injection site: mononuclear cell infiltration in all groups including controls, vascular wall necrosis and thrombus observed primarily at the high dose in males and females Kidney pigments in proximal tubules (all treated animals), however, no other findings observed indicative of kidney toxicity.

Source: Reviewer generated table

Toxicokinetics

BAL5587 and BAL9141 were evaluated in plasma (Once on Days 0 and 13 within the last 10 minutes of infusion) and in urine (at 0-2, 2-4, and 4 to 6 hours after initiation of infusion Days 0 and 13.

Reference ID: 5357793

Table 133. Plasma Concentrations of BAL5587 and BAL9141 10 Minutes Before the End of 4-Hour Intravenous Infusion of BAL5788 on Days 0 and 13

Analyte	Test Article	Dose (mg/kg/day)	Concentration Day 0 (mcg/mL)				Concentration Day 13 (mcg/mL)			
			Sex	Concentration	Sex	Concentration	Sex	Concentration	Sex	Concentration
BAL9141	BAL5788-A	175	M	54.12	F	67.5	M	65.36	F	60.79
	BAL5788-A	360	M	124	F	119	M	110	F	130
	BAL5788-B	175	M	57	F	78.74	M	59.44	F	72.60
	BAL5788-B	360	M	129	F	134.15	M	131.11	F	128.33
BAL5788	BAL5788-A	175	M	7.18	F	14.7	M	14.77	F	6.9
	BAL5788-A	360	M	28.06	F	22.78	M	10.12	F	18.59
	BAL5788-B	175	M	14.61	F	7.91	M	11.94	F	11.01
	BAL5788-B	360	M	34.25	F	22.02	M	18.89	F	11.15

Source: Reviewer generated table

Table 134. Concentrations of BAL5587 and BAL9141 in Urine for 0 to 2, 2 to 4 and 4 to 6 Hours After Initiation of a 4-Hour Intravenous Infusion of BAL5788 to Rats on Days 0 and 13

Analyte	Test Articles	Dose (mg/kg/day)	Sex		Day 0						Day 13					
					0-2 hours		2-4 hours		4-6 hours		0-2 hours		2-4 hours		4-6 hours	
					Concentration (µg/mL)	Excretion (µg)	Concentration (µg/mL)	Excretion (µg)	Concentration (µg/mL)	Excretion (µg)	Concentration (µg/mL)	Excretion (µg)	Concentration (µg/mL)	Excretion (µg)	Concentration (µg/mL)	Excretion (µg)
BAL9141	BAL5788-A	175	Male	Mean	6360.296	7031.8	5358.646	19053.0	6841.242	4933.8	1714.058	2553.4	9873.830	18152.1	N.C.	N.C.
				SD	3805.845	3761.7	1443.642	3108.1	1738.426	2557.9	N.C.	N.C.	6003.701	4100.4	N.C.	N.C.
			Female	Mean	5860.191	7675.5	9218.610	9638.6	N.C.	N.C.	4107.652	3502.1	6808.299	10262.0	7014.636	2567.4
				SD	2034.669	5093.3	N.C.	N.C.	N.C.	N.C.	N.C.	N.C.	2405.713	8305.2	2556.972	2037.7
	BAL5788-A	360	Male	Mean	10013.072	8855.6	12325.901	21548.1	10559.863	6278.7	8991.536	6796.8	15064.758	18463.6	19698.868	9390.9
				SD	2874.392	6233.6	6367.632	10166.6	N.C.	N.C.	6927.762	4822.9	7476.483	4931.0	7212.949	4210.1
			Female	Mean	14583.368	5870.1	9897.499	13928.6	15251.496	2246.7	6470.083	13265.4	7327.005	10733.2	14342.574	7979.4
				SD	3287.398	1958.2	8899.457	1794.7	N.C.	N.C.	3162.010	1308.0	3607.653	529.7	3679.323	8488.2
	BAL5788-B	175	Male	Mean	4155.610	4520.6	5948.831	14612.3	7653.540	6926.0	3579.129	2505.4	9230.966	11481.6	10582.205	7730.3
				SD	3824.961	6903.0	3462.504	13104.1	4597.146	7951.7	N.C.	N.C.	1460.441	3322.2	3290.378	2126.3
			Female	Mean	7641.770	5018.9	16461.806	4801.4	N.C.	N.C.	5292.586	5356.2	8101.010	8134.0	12936.140	7092.8
				SD	3874.584	3050.4	N.C.	N.C.	N.C.	N.C.	N.C.	N.C.	4294.189	3003.5	N.C.	N.C.
	BAL5788-B	360	Male	Mean	9288.620	10465.3	8229.493	21579.0	11606.980	4542.5	2716.053	7213.0	6880.478	15885.5	N.C.	N.C.
				SD	1745.518	5053.9	1336.890	3265.5	2013.271	777.9	N.C.	N.C.	1573.159	3722.7	N.C.	N.C.
			Female	Mean	18204.142	6904.3	16576.603	12231.8	23455.478	2345.6	3979.188	3462.7	11029.610	14188.8	12924.026	6726.7
				SD	4707.671	4330.8	4551.821	6883.3	N.C.	N.C.	1896.551	2999.2	5564.982	12249.4	2021.360	1205.8
BAL5788	BAL5788-A	175	Male	Mean	0.000	0.0	0.000	0.0	0.000	0.0	0.000	0.0	0.000	0.0	N.C.	N.C.
				SD	0.000	0.0	0.000	0.0	0.000	0.0	N.C.	N.C.	0.000	0.0	N.C.	N.C.
			Female	Mean	135.451	166.1	125.237	125.3	N.C.	N.C.	68.418	54.8	131.721	75.5	33.421	20.1
				SD	3.911	92.0	N.C.	N.C.	N.C.	N.C.	N.C.	N.C.	130.173	74.2	57.887	34.8
	BAL5788-A	360	Male	Mean	0.000	0.0	0.000	0.0	0.000	0.0	87.870	83.6	97.602	93.4	70.790	35.4
				SD	0.000	0.0	0.000	0.0	N.C.	N.C.	77.925	99.2	88.983	106.3	122.612	61.3
			Female	Mean	530.106	257.8	148.831	149.5	275.539	38.0	125.837	225.6	295.467	559.0	228.525	143.6
				SD	242.747	177.6	158.766	132.6	N.C.	N.C.	118.147	198.3	266.355	700.4	48.947	168.5
	BAL5788-B	175	Male	Mean	0.000	0.0	0.000	0.0	0.000	0.0	0.000	0.0	0.000	0.0	0.000	0.0
				SD	0.000	0.0	0.000	0.0	0.000	0.0	N.C.	N.C.	0.000	0.0	0.000	0.0
			Female	Mean	87.423	69.9	146.246	58.5	N.C.	N.C.	86.628	95.3	93.219	134.1	134.197	80.5
				SD	151.421	121.1	N.C.	N.C.	N.C.	N.C.	N.C.	N.C.	81.994	131.8	N.C.	N.C.
	BAL5788-B	360	Male	Mean	99.054	148.6	0.000	0.0	0.000	0.0	51.059	137.9	66.905	127.1	N.C.	N.C.
				SD	90.837	136.3	0.000	0.0	0.000	0.0	N.C.	N.C.	115.883	220.2	N.C.	N.C.
			Female	Mean	595.739	239.8	250.271	192.0	446.125	44.6	118.491	103.0	195.268	180.9	170.314	73.4
				SD	271.042	183.3	273.252	170.3	N.C.	N.C.	107.174	131.0	224.227	300.8	176.953	70.8

Data are the mean with SD of the results from 2 or 3 animals.
N.C.: Not calculated (n<3)

Source: Applicant report table

TOX7586. A Two-Week Bridging Toxicity Study of BAL5788 (Prodrug of BAL9141) Via Intravenous Infusion in Rats

Key Study Findings

- Injection site reaction (inflammatory cells, thrombi)
- There were no significant differences between the toxicological profile of the 2 formulations tested
- NOAEL was considered at 360 mg/kg/day (1.4 times the MRHD based on BSA comparison)

Reference ID: 5357793

Table 135. Study Information

Study Features and Methods	Details
GLP Compliance:	Yes (Japanese)
Dose and frequency of dosing:	0, 75, 360 mg/kg/day (calculated as BAL9141) of BAL5788-A and BAL5788-B (total of 6 dose groups)
Route of administration:	IV infusion (over 4 hours) once daily
Formulation/vehicle:	BAL5788-A (batch 30-4EXP, 91.6% purity, older formula); BAL5788-B (batch I050605, 100% purity)/ 5% dextrose
Species/strain:	Rat/ Sprague Dawley
Number/sex/group:	5/sex/group
Age:	10 weeks (males: 325-427 g; females: 210-258 g)
Satellite groups/unique design:	
Deviation from study protocol affecting interpretation of results:	None that had an impact on the outcome of the study.

Source: Reviewer generated table
Abbreviations: GLP, good laboratory practice; IV, intravenous

Table 136. Observations and Results

Parameters	Major Findings
Mortality	No unscheduled deaths
Clinical signs	Abnormal urine color in all treated animals. Soft stools and vomiting observed a few times during dosing at 100 and 200 mg/kg
Body weights	No treatment-related changes
Ophthalmoscopy	No treatment-related changes
Hematology	No treatment-related changes
Clinical chemistry	No treatment-related changes
Urinalysis	Abnormally colored urine
Gross pathology	Injection site effects including thickening of the tissue and yellowish-brown material in nearly all treated animals
Organ weights	No treatment-related changes
Histopathology Adequate battery: Yes	Injection site findings included perivascular edema and fibrosis (slight to moderate), inflammatory cell infiltration (slight to marked , vascular wall necrosis (moderate to marked) and thrombus (slight to marked). Thrombus formation in the controls was noted in 1 animal.

Source: Reviewer generated table

BAP00046. A Four-Week Toxicity Study of BAL5788 (Prodrug of BAL9141) Via Intravenous Infusion in Rats Followed by a Four-Week Recovery Period

Key Study Findings

- Injection site brown material (gross observations) which correlated with granulomas and muscle necrosis in all animal groups with higher incidence in treated animals showing a trend to persistent damage with dose
- Study NOAEL considered at 360 mg/kg/day corresponding to plasma levels of BAL5788 at 19.25 mcg/mL and BAL9141 at 92.5 mcg/mL (day 27, 10 minutes prior to end of infusion, male and female combined)

Table 137. Study Information #BAP00046

Study Features and Methods	Details
GLP Compliance:	Yes (Japanese GLP)
Dose and frequency of dosing:	0, 175, 250, 360 mg/kg/day, once daily
Route of administration:	IV
Formulation/vehicle:	BAL5788: PHA0109120/P, PHA0109121/P, PHA0109122/P, PHA0109123/P and PHA0109130/P (purity not specified)
Species/strain:	Rat/ SPF Crj: CD (SD) IGS
Number/sex/group:	Main: 5/sex/group; Interim (2 weeks) and recovery: 3/sex for control and HD
Age:	Approximately 8 weeks
Satellite groups/unique design:	Number/sex/group low (versus commonly used 10/sex/group for main). Animals catheterized approximately 10 days prior to initiation of the study.
Deviation from study protocol affecting interpretation of results:	None

Source: Reviewer generated table
Abbreviations: GLP, good laboratory practice; HD, high dose; IV, intravenous

Table 138. Observations and Results #BAP00046

Parameters	Major Findings
GLP Compliance	Yes
Mortality	No unscheduled deaths
Clinical signs	Abnormal urine color (yellow/orange) throughout dosing period for all treated animals (extending to the first day of recovery for the 360 mg/kg/day group)
Body weights	No test article related findings
Ophthalmoscopy	No test article related findings
Hematology	No test article related findings
Clinical chemistry	No test article related findings
Urinalysis	Increased urinary specific gravity and N-Acetyl-β-d-glucosaminidase (NAG) at 360 mg/kg/day in males at weeks 2 and 4 (approximately 30%). Findings not observed at recovery.
Gross pathology	Injection site (brown material) across all groups
Organ weights	No test article related findings
Histopathology Adequate battery: Yes	Injection site consisting of slight to marked granuloma or muscle necrosis observed at week 4 (some treated animals) and at recovery (primarily at the high dose males and females and 1 control female). Kidney hyaline droplets observed in the proximal tubules at 250 and 360 mg/kg/day, reversible at recovery.

Source: Reviewer generated table.
Abbreviations: GLP, good laboratory practice; NAG, N-Acetyl-β-d-glucosaminidase

Table 139. Incidence of Microscopic Observations in Rat

Incidence of microscopic observations in rat					
Observation	**Week 2 n=3**	**Week 4 (n=5)**		**Week 4 Recovery (n=3)**	
	Males	**Males**	**Females**	**Males**	**Females**
Injection site—granuloma (G1-2)	---	2 L, 3 M(G3)	3 L, 3 M, 3 H	2 H	1 C, 1 H
Injection site—muscle necrosis (G2)	---	1L	2 L, 2 M, 4 H	2 H (G2/G4)	1 H

G1= very slight, G2 = slight, G3 = moderate, G4 = marked
Source: Reviewer generated table

Toxicokinetic parameters

Toxicokinetics

- Blood plasma levels (2/sex/group) of BAL5788 and BAL9141 (mcg/mL) were evaluated on Days 0 and 27 at 10 minutes prior the end of infusion and 2 hours post infusion. Overall, there did not appear to be significant differences of exposure between males and females, dose proportional increases or significant exposure accumulation when comparing Days 1 to 27 of either BAL5788 or BA L9141.

Table 140. Toxicokinetics Analysis

Plasma levels of BAL5788 and BAL9141 in rats (ug/mL)									
Dose mg/kg	Sex	BAL5788				BAL9141			
		Day 0		Day 27		Day 0		Day 27	
		-10 min	2 h	-10 min	2 h	-10 min	2 h	-10 min	2 h
175	M	27.2	0	12.7	0	39.2	5.3	55.2	12.4
	F	18.5	0	7.1	0	45.0	4.5	55.1	5.3
250	M	13.8	0	14.5	0.8	50.0	7.6	85.1	37.1
	F	26.1	0	29.3	0	58.7	13.5	72.2	24.9
360	M	18.9	0	19.9	1.9	72.4	8.2	90.0	20.2
	F	9.6	1.0	18.6	1.2	88.4	22.8	95.5	33.3

Source: Reviewer generated table

- Urine levels of BAL5788 and BAL9141 were evaluated on days 0 and 13 [high dose only], at 0-2, 2-4, 4-6 h after the start of infusion. The urinary levels of BAL5788 were highly variable and ranged from 0-277 mcg/mL. Levels of BAL9141 were slightly less variable and showed some dose dependence. On Study Day 0, the highest measured urinary concentrations of BAL9141 were 15170 mcg/ml (male, 360 mg/kg, 0-2h) and 17280 mcg/ml (female, 250 mg/kg, 4-6 h). On day 13, the highest urinary concentration of BAL9141 was 23160 mcg/mL (male, 360 mg/kg, 4-6 h). On day 27, the highest urinary concentrations of BAL9141 were 15070 mcg/mL (male, 175 mg/kg, 2-4h) and 16330 mcg/mL (female, 360 mg/kg, 4-6 h). There was no indication of drug precipitation in the distal tubules or collecting tubules.

BAP00045. A Four-Week Toxicity Study of BAL5788 (Prodrug of BAL9141) Via Intravenous Infusion in Common Marmosets Followed by a Four-Week Recovery Period

Key Study Findings

- Injection site granuloma, muscle necrosis, and subcutaneous tissue edema/fibrosis/vascularization at the injection site
- NOAEL considered at 200 mg/kg (0.75 times the MRHD, corresponding to plasma levels of 153.5 and 136.3 mcg/mL, respectively during the last 10 minutes of infusion)

Table 141. Study Information

Study Features and Methods	Details
GLP Compliance:	Yes (Japanese)
Dose and frequency of dosing:	0, 50, 100, 200 mg/kg/day, once daily
Route of administration:	IV infusion (over 4 hours)
Formulation/vehicle:	BAL5788 (lot LSE 01-0016-9); Batches: PHA0109126/P, PHA0109127/P, PHA0109128/P, PHA0109129/P (purity not specified)/Vehicle: Citrate buffered saline (assumed). Saline administrated in between dosing to keep catheter patent.
Species/strain:	Monkey/ Common marmosets
Number/sex/group:	Main: 3/sex/group Recovery: 3/sex/group
Age:	12-15 months
Satellite groups/unique design:	Animals catheterized approximately 10 days prior to beginning of dosing
Deviation from study protocol affecting interpretation of results:	None

Source: Reviewer generated table
Abbreviations: GLP, good laboratory practice; IV, intravenous

Table 142. Observations and Results

Parameters	Major Findings
Mortality	No unscheduled deaths
Clinical signs	Abnormal urine color in all treated animals. Soft stools and vomiting observed a few times during dosing at 100 and 200 mg/kg
Body weights	No significant differences in body weights of treated animals compared to controls.
Ophthalmoscopy	No treatment-related changes
Hematology	No treatment-related changes
Clinical chemistry	Increases in total protein (15-20%, not observed at recovery) and albumin (25-35%, not observed at recovery) at the mid and high dose in males and at all doses tested in females (not observed at recovery).
Urinalysis	Abnormally colored urine
Gross pathology	Injection site catheter related damage in the females including inferior vena cava wall thickening and dilatation with extravasation, adhesions of the colon/liver/kidney.
Organ weights	None
Histopathology Adequate battery: Yes	Injection site granuloma, muscle necrosis, and subcutaneous tissue edema/fibrosis/vascularization at the injection site.

Source: Reviewer generated table

Toxicokinetics

Toxicokinetics (urine collected 0-2, 2-4, 4-6 hours post initiation of infusion Day 0 and Day 28; plasma collected during last 10 minutes of first and last infusions 2 hours after end of infusion): The individual animal data was not included but summary data is included below. The values for BAL5788 at 2 hours post-infusion were all below the limit of quantitation except for the females at 200 mg/kg/day on Day 27 (0.31 µg/mL). Plasma levels of BAL5788 were independent of dose administered. There were no discernible gender differences. There was a relatively linear dose response for BAL9141 both prior to the end of infusion and at 2 hours.

Reference ID: 5357793

Table 143. Toxicokinetic Parameters

Plasma levels of BAL5788 and BAL9141 (ug/mL)							
Dose mg/kg	Sex	BAL5788		BAL9141			
		Day 0	Day 27	Day 0		Day 27	
		-10 min	-10 min	-10 min	+ 2 h	-10 min	+2 h
50	M	0.6	3.8	38.5	8.2	40.1	16.8
	F	0.4	0.9	30.8	6.8	38.2	11.6
100	M	2.7	1.6	100.7	24.8	92.9	31.5
	F	1.4	0.3	66.8	10.7	96.6	28.8
200	M	1.5	3.4	163.7	33.9	152.1	37.6
	F	1.0	1.5	153.5	29.4	136.3	54.6

Source: Reviewer generated table

TOX-7154/ A Thirteen-Week Toxicity Study of BAL5788 (Prodrug of BAL9141) Via Intravenous Infusion in Common Marmosets Followed by a Four-Week Recovery Period

Key Study Findings

- Mortality was observed at all doses tested (≥50 mg/kg). The cause of death was attributed to thrombosis/emboli in the lung and heart, potentially originating from the injection site thrombi.
- Clinical signs in early death animals included clonic/tonic seizures, decreased activity, vomit and hind leg paralysis. Lymphoid depletion and atrophy were observed in the spleen, thymus and lymph nodes.
- Liver findings (only in males) included hepatocellular vacuolization and hypertrophy.
- Lung findings included fibrosis and thrombosis.
- No NOAEL was established in this study due to mortality observed at all doses tested.

Table 144. Study Information

Study Features and Methods	Details
GLP Compliance:	Yes
Dose and frequency of dosing:	0, 50, 100, 200 mg/kg/day (once daily, 4-hour infusion, 8 mL/kg)
Route of administration:	IV infusion
Formulation/vehicle:	BAL5788: 30-4EXP (% purity not specified) / 5% dextrose
Species/strain:	Monkey/Common marmoset
Number/sex/group:	Main: 5/sex/group Recovery: 6/sex/group, control and high dose group only TK: 3/sex/group (control and high dose)
Age:	Age not provided (Weight: males 220 to 349 g, females 241 to 334 g)
Satellite groups/unique design:	TK and recovery (due to unscheduled deaths recovery had 2/sex/group). Low dose group treatment was terminated at 10 weeks.
Deviation from study protocol affecting interpretation of results:	None

Source: Reviewer generated table
Abbreviations: GLP, good laboratory practice; IV, intravenous; TK, toxicokinetic

Reference ID: 5357793

Table 145. Observations and Results

Parameters	Major Findings
Mortality	Death or euthanasia prior to scheduled sacrifice at all doses tested (low dose: 2/4 males and 1/5 females; mid-dose: 2/5 males and 1/5 females; high dose: 2/8 males and 3/9 females). Prior to death or euthanasia, animals showed similar clinical signs including decreased activity with lateral recumbency, clonic or tonic convulsions, edema, hind limb paralysis and vomiting. Unscheduled death animals: One high dose animal died one day after the first dose; however, the rest of animals were found dead between days 27-62 or euthanized due to signs of overt toxicity between days 48-64. One animal was euthanized on day 64 due to lack of patency in the catheter.
Clinical signs	Animals surviving to scheduled sacrifice: High dose males and females showed abnormal urine color (5/6) and occasional vomiting (2-3/6 males and females, 1 to 23 times) and low incidence soft stools in females (2/6, 1 to 2 time; most findings observed after week 4 of the study (not significant findings observed at recovery).
Body weights	No remarkable changes observed
Feed consumption	No remarkable changes observed
Ophthalmoscopy	No remarkable changes observed
Hematology	No remarkable changes observed
Clinical chemistry	Early death males: increased BUN (2 to 3-fold) and creatinine (1 to 3-fold).
Urinalysis	No remarkable changes observed
Gross pathology	Early death animals: thickening of the vascular wall and yellowish/white material at the injection site (drug material suspected but not confirmed by testing). Sporadic observations included edema/ascites/hydrothorax, hydropericardium and lymph node enlargement. Scheduled sacrifice: nearly all animals (including control) had injection site thickening of the vascular wall and deposition of yellowish white material at the tip of the catheter and in the vena cava and femoral/ iliac veins. Only injection site damage persisted through recovery.
Organ weights	In the 200 mg/kg/day males at the end of dosing, kidney weights were increased relative to body (11.8%) and brain weights (14%).
Histopathology Adequate battery: Yes	In the early death animals, liver findings (seen only in males) were Grade 1-2 in severity and consisted of hepatocellular vacuolization and hypertrophy; extramedullary hematopoiesis reached Grade 3 severity in 1 of 2 low dose males and was Grade 1-2 in the remaining males and all females. Lymphoid depletion and atrophy were seen (G1-3) in the spleen, thymus, and lymph nodes along with extramedullary hematopoiesis (spleen only) in all of the early death males. The Applicant attributed these changes to stress. The cause of death was likely due to thrombo-embolic events in 5/6 males and all of the females. Scheduled sacrifice: Vascular: injection site and iliac vein thrombosis, with emboli in the heart and lung. Kidney: pigmentation (mid and high dose males and females).

Source: Reviewer generated table.
Abbreviations: BUN, blood urea nitrogen

Toxicokinetics

BAL9141 plasma levels were similar in males and females and showed a relatively linear dose response. The urinary excretion of BAL 9141 and BAL5788 after intravenous (IV) infusion on Days 0 and 91 showed large standard errors, however, the main product excreted was BAL9141, with low detectable levels of BAL5788 (barely above the limit of detection during and after infusion).

Table 146. Plasma Concentrations of BAL5788 and BAL9141 in Marmosets (mcg/mL)

Dose	Time	Males				Females			
		BAL5788		BAL9141		BAL5788		BAL9141	
		Day 1	Day 90	Day 1	Day 90	Day 1	Day 90	Day 1	Day 90
0	-10 m	0±0	0±0	0±0	0±0	0±0	0±0	0±0	0±0
	+ 2 h	0±0	0±0	0±0	0±0	0±0	0±0	0±0	0±0
50	-10 m	0±0	0±0	28±7	33	0±0	0±0	32±5	30±14
	+ 2 h	0±0	0±0	9±6	15	0±0	0±0	9±2	8±2
100	-10 m	0.8±0.8	0.2±0.3	71±9	63±11	0.2±0.5	0±0	72±15	72±17
	+2 h	0±0	0±0	19±10	24±3	0±0	0±0	17±10	17±7
200	-10 m	0.5±0.5	0.2±0.4	132±7	109±50	0.2±0.4	0±0	124±16	101±20
	+2 h	0±0	0±0	29±5	40±31	0±0	0±0	35±25	41±23

Source: Applicant's table from study report

BAP00728. A Thirteen-Week Toxicity Study of BAL5788 (Prodrug of BAL9141) Via Intravenous Infusion in Rats Followed by a Four-Week Recovery Period

Key Study Findings

- Mortality observed in males ≥250 mg/kg/day. Prior to death/euthanasia, no unusual signs (6/11 males) or decreased activity, emaciation, hypothermia and/or clonic/ tonic convulsions (5/11 males) were observed.
- Primary findings of surviving animals were thrombi and necrosis at the injection site which was more prevalent and severe in treated animals compared to controls. Kidney findings included eosinophilic tubules and the presence of foreign material in the tubules/ducts, likely due to drug precipitate.
- NOAEL was considered at 125 mg/kg/day (equivalent to 0.5-fold the maximum human dose of 2.84 g/day based on body surface area comparisons).

Table 147. Study Information

Study Features and Methods	Details
GLP Compliance:	Yes
Dose and frequency of dosing:	Males: 0, 125, 250, mg/kg/day once daily and 750 mg/kg/day administered as 375 mg/kg twice daily. Females: 0, 125, 250 mg/kg once daily with a high dose of 376 mg/kg/day administered as 188 mg/kg twice daily
Route of administration:	IV infusion (2.0 mL/kg/hr)
Formulation/vehicle:	BAL5788 (30-4EXP)/ 5% dextrose
Species/strain:	Rat/CD(SD) ISG
Number/sex/group:	Main study: 15/sex/group control and high dose; 10/sex/group for TK and recovery (5/sex/group control and high dose)
Age:	8 weeks/ Weight M: 222-286 g; F: 180-208 g
Satellite groups/unique design:	5/sex/group
Deviation from study protocol affecting interpretation of results:	None that had an impact on the outcome of the study.

Source: Reviewer generated table
Abbreviations: GLP, good laboratory practice; IV, intravenous; TK, toxicokinetic

Reference ID: 5357793

Table 148. Observations and Results

Parameters	Major Findings
Mortality	Male deaths at ≥ 250 mg/kg (2/10), 500 mg/kg (5/10) and 750 mg/kg (4/15), observed at scattered timepoints, however, the majority observed after 1 month of treatment (death of 3 males on days 1-13, deaths of 8 males starting on day 34 up to day 87). No unscheduled deaths in females.
Clinical signs	Prior to death/euthanasia either no unusual signs (6/11 males) or decreased activity, emaciation, hypothermia and clonic/ tonic convulsions (5/11 males).
Body weights	Decreased (more than 10%) in surviving males at 750 mg/kg beginning at week 5 and persisted through recovery.
Ophthalmoscopy	No test article related effects.
Hematology	Males: decreased RBC at mid- (13%) and high (15%) dose. Compensatory increase in reticulocytes (maximum of 59% increase at mid dose). Platelets decreased by 11% in high dose males. No significant changes observed in females.
Clinical chemistry	Males: increased BUN at 500 mg/kg and 750 mg/kg (up to 2X, continued through recovery) and increased creatinine by 50% at 500 mg/kg, not observed at recovery. No significant changes observed in females.
Urinalysis	Increased N-acetyl-β-glucosaminidase (NAG, 2X, may indicate tubular damage) in all treated males (at 4 weeks), not at 13 weeks or recovery. Females: pH shift towards acidic at weeks 4 and 13.
Gross pathology	Major findings at injection site (induration, thickening, yellow brown material, all treated animals, of higher incidence at the mid- and high dose) and kidneys (discoloration, enlarged, dilation of low incidence primarily at mid and high dose in males and females, not fully recovered).
Organ weights	Increased adrenal and kidney weights (around 20%) in mid- and high dose males and females.
Histopathology Adequate battery: Yes	Early death animals Injection site: thrombus formation at the injection site (along with inflammatory cells, necrosis, thickening) Kidney: foreign material, eosinophilic bodies in tubules and ducts Spleen, thymus, lymph nodes cellular depletion in at least 1-2 animals/dose Surviving animals Injection site: in both control and treated animals including abscess, inflammatory cells thickening; necrosis and thrombi more prevalent and severe in treated animals and continued to recovery. Kidney: eosinophilic bodies in the tubules, foreign material in tubules/ducts in all but 1 treated animals and kidney interstitial fibrosis in males at the high dose (moderate) Injection site: observed at all doses and some control animals in both males and females, injection site necrosis and thrombus

Source: Reviewer generated table
Abbreviations: BUN, blood urea nitrogen; RBC, red blood cell

Toxicokinetics

Table 149. Plasma Toxicokinetic Parameters in Rats Treated IV With BAL5788

Dose mg/kg	Sex	BAL5788		BAL9141	
		Day 0	Week 13	Week 0	Week 13
125	M	9.77	4.79	60.86	69.03
	F	22.98	3.51	59.40	73.41
250	M	3.71	13.61	58.36	83.69
	F	15.01	11.85	70.54	72.88
188 X2	F	6.14	3.02	69.15	76.14
500	M	40.11	17.95	235.51	112.08
375 X2	M	1.51	24.42	125.50	139.70

Source: Reviewer generated table
Abbreviations: IV, intravenous

TOX7918. BAL5788 (Cephalosporin Prodrug) Toxicity Study by Intravenous Infusion to Beagle Dogs for 13 Weeks

Key Study Findings

- Five animals (out of 6) were euthanized (from day 30 to day 76) due to lack of patency of the dosing catheter (inability to continue dosing)
- Injection site brown material (gross observations) which correlated with granulomas, inflammation and subcutaneous necrosis in all animal groups
- Sporadically, reddening of the gums was observed in high dose animals (primarily the first 3 weeks of dosing)
- Study NOAEL was considered at 8 mg/kg/day (approximately 0.1-fold of the maximum human dose)

Table 150. Study Information TOX7918

Study Features and Methods	Details
GLP Compliance:	Yes
Dose and frequency of dosing:	0, 8, 32 mg/kg/day, once daily
Route of administration:	IV
Formulation/vehicle:	BAL5788 (batch 30-4EXP and 10-5EXP, 94.9% purity)/ 5% dextrose
Species/strain:	Dog/Beagle
Number/sex/group:	3/sex/group
Age:	29-32 weeks (Males: 10.2-14.2 kg; Females: 8.7 -12.4 kg)
Satellite groups/unique design:	3/sex/group (used for interim euthanasia, dose: 8 mg/kg)
Deviation from study protocol affecting interpretation of results:	Beginning at week 2-3, the 2 hours test article infusion was followed by a 22-hour 5% dextrose infusion to keep the veins open. Animals were sacrificed (5/6 animals in the high dose when they were unable to receive the full 10 mL over 2 hours on 3 consecutive occasions (< 25% of dose).

Source: Reviewer generated table
Abbreviations: GLP, good laboratory practice; IV, intravenous

Table 151. Observations and Results TOX7918

Parameters	Major Findings
GLP Compliance	Yes
Mortality	There were 5 unscheduled deaths at the high dose at weeks 4 and 11 (animals were euthanized due to lack of patency in dosing catheter which impeded animal dosing). Interim euthanasia animals survived to scheduled date.
Clinical signs	Reddening of the pinnae and/or gums was observed sporadically in the high dose during the first 3 weeks. Prior to stopping dosing, 1 high dose male had pain/lameness in leg with catheter.
Body weights	No findings observed
Ophthalmoscopy	No findings observed
Hematology	No findings observed
Clinical chemistry	Increases in histamine in high dose males and females (1 of 2 males 2-fold, 1 of 3 females 3-fold), with no relevant increases at the end of the 13-week study.
Urinalysis	No findings observed
Gross pathology	Increased incidence of abnormal contents of cannula observed in the high dose animals. The contents included fibrin, erythrocytes (in clumps), and inflammatory cells.
Organ weights	No findings observed
Histopathology Adequate battery: Yes	Examination of animal catheters showed presence of erythrocytes, fibrin and inflammatory cells or at examination “vena cava adhesion, distal cannula to intimal aspect, encapsulating cannula”. Focal thrombi were frequently found in the high dose unscheduled death animals. Other damage at the vessel walls and at the actual catheter site included subcutaneous fibrosis/hemorrhage/inflammation and subcutaneous necrosis, that did not change significantly in incidence or severity between the control high dose animals.

Source: Reviewer generated table
Abbreviations: GLP, good laboratory practice

Toxicokinetics

Plasma levels of BAL5788 and BAL9141 were evaluated on day 1, weeks 4 and 13 at pre-dose, 10 minutes and 2 hours post-dose.

Table 152. Plasma Levels in 13-Week Dog Study (mcg/mL)

Time	Dose mg/kg	Sex	BAL5788			BAL9141		
			Day 1	Week 4	Week 13	Day 1	Week 4	Week 13
10 min	8	M	12.3±5.3	9.8±6.4	7.2±4.1	12.9±2.0	13.6±1.6	18.8±1.8
		F	13.5±4.5	11.9±6.7	9.7±7.1	14.4±1.9	16.7±1.7	15.4±3.7
	32	M	74.8±12.2	6.1	29.6	49.2±2.3	24.9±21.2	48.1
		F	22.3±31.4	26.5±38.7	---	53.9±4.4	62.8±5.1	---
2 h	8	M	---	---	---	5.6±0.9	5.8±1.6	6.4±1.0
		F	---	---	---	6.0±1.2	6.6±0.9	5.7±1.9
	32	M	---	---	---	21.0±5.3	10.2	37.0
		F	---	---	---	16.9±0.7	18.2±0.8	---

Source: Reviewer generated table

Local Tolerance

TOX7588. A Local Irritation Study of BAL5788 by Intravenous Injection to Rabbits

Methods

The purpose of this study was to test the irritation potential of 2 ceftobiprole medocaril sodium formulations made from slightly different synthesis routes (BAL5788 A, intended for dilution in saline and B intended for dilution in 5% dextrose). BAL5788-A (drug product [DP] formula, batch # 30-4EXP, 91.6% purity); BAL-5788-B (New DP formula, batch # I050605, 100.9% purity) in 5 % dextrose was administered by IV injection to male Kbt rabbits (2.9-3.4 kg, 15 weeks old, 3/group) into the ear vein (0.05 mL/site/day) once daily for 8 consecutive days. Positive control bromosulfalein (BSP) diluted into saline. Clinical signs (daily), body weight (prior to administration), observations of the injection site, and histopathology of the injection site (Day 8) were conducted/observed.

Results

There were no clinical signs. Body weights did not change significantly from controls. At 10 mg/mL very slight to slight inflammation was observed in most rabbits (including controls) around the injection site between Days 3 and 5. Positive control rabbits showed slight or moderate inflammation along with thrombi throughout the dosing period. With the exception of the positive control animals where cell infiltration, desquamation edema, fibrosis, hemorrhage and thrombus were noted, there were no noteworthy findings. There were no significant differences in local irritation between the BAL5788 formulations A and B; BAL5788 was no more irritating than normal saline this 8- day study in rabbits.

TOX7904. A Local Irritation Study of BAL5788 by Intravenous Injection to Rabbits-2

Methods

BAL-5788-B (formula, batch # I050605, 100.9% purity), vehicle (5% dextrose) or positive control BSP were administered intravenously into the ear vein at 0, 2 and 10 mg/mL either as fresh solution or aged for 30-hour period to male Kbt:JW rabbits (2.9-3.3 kg, 16 weeks old, 3/group) for 8 consecutive days.

Clinical signs (daily), body weight (prior to administration), observations of the injection site, and histopathology of the injection site (Day 8) were conducted/observed.

Results

There were no abnormal clinical signs or changes in body weight. There were no dose dependent changes in inflammation as compared to physiological saline at the injection site. The BSP animals showed slight to moderate inflammation and small thrombi. No significant differences in microscopic observations were made with BAL5788 or physiological saline. The positive controls showed cell infiltration, desquamation edema, fibrosis, hemorrhage and thrombi. Aging BAL5788 did not result in greater local irritation potential.

Reference ID: 5357793

13.1.2.2. Genetic Toxicology

For reference, the following compound identifiers have been used for ceftobiprole medocaril sodium (pro-drug): BAL5788-001, BAL0005788-001, BAL5788, JNJ-30982081, JNJ-30982081-(b) (4), Ro 65-5788, Ro 65-5788/001 and for its active metabolite ceftobiprole (Ro 63-9141/000, 63-9141, BAL9141)

Table 153. B167'797: Mutagenicity Evaluation of Ro 655788/001 in the Ames Test

Study Features and Methods	Details
Study No	B167'797
Study Title	Mutagenicity Evaluation of Ro 655788/001 in the Ames Test
Conducting laboratory	(b) (4)
GLP Compliance	Yes
Drug, lot #, % purity	90301B217101, 89.47% purity
Strains:	*Salmonella typhimurium* (TA97, TA98, TA100, TA102 and TA1535) *Escherichia coli* (WP2 *uvrA*)
Concentrations in the definitive study/method	0, 1, 3.16, 10, 31.6 and 100 mcg/plate (standard) and 0, 0.5, 1.58 and 50 mcg/ plate (pre-incubation assay) with or without metabolic activation (+/- S9).
Basis of concentration selection	Based on preliminary tests and observed toxicity in the test system.
Negative control	Vehicle (DMSO)
Positive control	Sodium azide, ICR 191, 2-nitrofluorene, mitomycin C, 2-aminoanthracene.
Formulation/vehicle	DMSO
Results	There were no remarkable increases in the number of revertants above controls in two replicate experiments, therefore Ro 655788/001 (pro-drug) was considered negative for mutagenicity under the conditions of this test.
Validity	No precipitation noted at up to 5000 mcg/mL. Doses at or above 166 mcg/plate were overtly toxic to the test system (obliteration of background lawn growth). The test article was significantly more toxic for some bacterial strains including TA1535 as low as 1 mcg/plate (a repeat test was conducted at concentrations of 0.01-1 mcg/plate, not considered interpretable). Positive controls increased the number of revertants by approximately 10-fold. The study was considered valid under the conditions tested, however, unable to draw definite conclusions on the mutagenic potential based on the high level of cytotoxicity in the test system.

Source: Reviewer generated table.
Abbreviations: GLP, good laboratory practice

Table 154. TOX8637 CHO/HPRT Forward Mutation Assay of JNJ-30982081

Study Features and Methods	Details
Study No	TOX8637
Study Title	CHO/HPRT forward mutation assay of JNJ-30982081 in duplicate cultures with a confirmatory assay
Conducting laboratory	(b) (4)
GLP Compliance	Yes
Drug, lot #, % purity	JNJ-30982081 (also known as Ro 65-5788/001, batch 6004DR027Z, 88.1% purity)

Reference ID: 5357793

Cell line	CHO-K1-BH4 Chinese hamster ovary (CHO)
Concentrations in the definitive study	0, 100, 300, 600, 700, 800, 900, 1000, 1100, 1200, and 1300 mcg/mL with S9, and 0, 100, 300, 600, 1000, 1250, 1500, 1750, 2000, 2500, and 3000 mcg/mL without S9.
Basis of dose selection	Preliminary dose range finding assay, evaluation of cytotoxicity. Relative survival at concentrations of 1250 mcg/mL with S9 and 2500 mcg/mL without S9 were 1.7 and 29.4%, respectively (no colony growth was observed at higher concentrations). The test article was found to be freely soluble at all concentrations evaluated with and without S9.
Formulation/vehicle	
Negative control	Culture medium (Ham's Nutrient Mixture)
Positive control	Ethylmethanesulfonate (200mcg/mL), without S9; Methylcholanthrene (5 mcg/mL) with S9
Experimental conditions	Initial test: Initial test (duplicate samples) 100, 300, 600, 700, 800, 900, 1000, 1100, 1200, and 1300 mcg/mL with S9, and 100, 300, 600, 1000, 1500, 2000, 2500, 3000, 3500, and 4000 mcg/mL without S9. cultures treated at concentrations ≥1100 mcg/mL with S9 and ≥2500 mcg/mL without S9 were discarded prior to selection due to excessive cytotoxicity. The average relative survival at concentrations of 1000 mcg/mL with S9 and 2000 mcg/mL without S9 were 15.7 and 23.7%, respectively. Test error (cloning efficiencies at the time of selection that were >300% in all cultures with S9). Confirmatory test: Concentrations of 100, 300, 600, 700, 800, 900, 1000, 1100, 1200, and 1300 mcg/mL with S9, and 100, 300, 600, 1000, 1250, 1500, 1750, 2000, 2500, and 3000 mcg/mL without S9. Cultures treated at concentrations ≥1000 mcg/mL with S9, and at 100 and 1000 mcg/mL without S9, were discarded prior to selection due to excessive cytotoxicity. Re-test: Due to an error in the initial test a re-test was conducted with similar conditions as above but only using S9. Concentrations of 700, 1100 and 1200 were discarded. The average relative survival at a concentration of 1300 mcg/mL was 20.3% (the average relative survival reached a minimum of 19.2% at a concentration of 1000 mcg/mL).
Results	Initial test: Average mutant frequencies of the vehicle control cultures were 1.8 TGr mutants/10^6 clonable cells with S9 and 5.9 TGr mutants/10^6 clonable cells without S9, cultures treated with JNJ-30982081 ranged from 0.3 to 1.9 TGr mutants/10^6 clonable cells with S9, and 1.9 to 4.6 TGr mutants/10^6 clonable cells without S9. No differences in mutant frequencies observed between test article and controls. Confirmatory test: Average mutant frequencies of the vehicle control cultures were 1.1 TGr mutants/10^6 clonable cells with and without S9, while those of the remaining cultures treated with JNJ-30982081 ranged from 2.1 to 8.0 TGr mutants/106 clonable cells with S9, and <0.6 to 6.5 TGr mutants/10^6 clonable cells without S9. Although the assay criteria for positive response was not exceeded, several test article concentrations (600, 700, 800, 900, 1250, 1500, 2500 and 2000 mcg/mL) showed mutant frequencies that were statistically significantly higher than concurrent and historical controls. Re-test: The average mutant frequency of the vehicle control cultures was 4.3 TGr mutants/10^6 clonable cells, cultures treated with JNJ-30982081 ranged from 2.7 to 4.6 TGr mutants/10^6 clonable cells. No differences observed between test article and controls.
Validity	Assay criteria for positive response: ≥15 TGr mutants/10^6 clonable cells over the concurrent vehicle controls (spontaneous mutant frequency of the vehicle controls must be <15 TGr mutants/10^6 clonable cells). Concurrent positive and negative controls performed as expected.

Source: Reviewer generated table
Abbreviations: CHO, Chinese hamster ovary; GLP, good laboratory practice; HPRT, hypoxantine phosphoribosyl transferase

Reference ID: 5357793

Table 155. Ro 9141/001 Mouse Lymphoma Cell Mutation Test (ML/TK) Research Report # B-167'775

Study Features and Methods	Details
Study No	Ro 9141/001
Study Title	Ro 9141/001 Mouse lymphoma cell mutation test (ML/TK). Research report # B-167'775
Conducting laboratory	(b) (4)
GLP Compliance	Yes
Drug, lot #, % purity	Ro 63-9141/001, batch # 18116B018, A/2191/31/1, 99.4%
Cell line	Mouse lymphoma L5178Y tk+/- cells
Concentrations in the definitive study	0, 39.06, 78.13, 156.25, 312.50, 625, 1250, 2500 and 5000 mcg/mL (39.06 to 5000 mcg/mL equivalent to 0.07-8.3 mmol/L)
Basis of concentration selection	Preliminary range finding (full range of doses up to 5000 mcg/mL tested, toxicity observed at 3000 mcg/mL with 26% reduction of survival)
Negative control	RPMI media
Positive control	4-nitroguinoline 1 oxide, benzo[a]-pyrene
Formulation/vehicle	Ro 63-9141/001/ culture media (RPMI 5 with 20mM Hepes)
Incubation and sampling time	3-hour incubation time, 2-day plating
Results	Ro 63-9141/001 (ceftobiprole) was considered positive for mammalian mutation. No precipitates observed, decreased survival approximately 50% observed starting at 3040 mcg/mL. The number of small colonies increased by 3-fold and a minimal increase in the number of large colonies. Positive controls increased 3-fold for large colonies and 8-fold for small colonies.
Validity	Acceptance criteria for normal range mutant in negative control was 80-250 per 10^6 viable cells and reference substance induced a clear increase in TK-mutant clones. Results from vehicle control and positive control articles behaved as expected, and the test was considered valid. The test was considered positive for mutagenicity and clastogenicity.

Source: Reviewer generated table.
Abbreviations: GLP, good laboratory practice; ML, mouse lymphoma; TK, toxicokinetic

Table 156. Ro 65-5700/001: Mouse Lymphoma Cell Mutation Test (ML/TK) Research Report # B-169'336

Study Features and Methods	Details
Study No	B-169'336
Study Title	VNRX-5133: In Vitro Flow Cytometric Micronucleus Assay in CHO Cells in 96-well Plates
Conducting laboratory	(b) (4)
GLP Compliance	Yes
Drug, lot #, % purity	Ro 65-5788/001, batch 90301B217101, 90%
Cell line	Mouse lymphoma L5178Y tk+/- cells
Concentrations in the definitive study	Without metabolic activation: 0, 125, 250, 375, 500 mcg/mL and 50, 100, 150, 200, 225 mcg/mL; with metabolic activation 0, 125, 250, 500, 750, 1000 and 1250 mcg/mL
Basis of concentration selection	Based on precipitation, cell viability, pH/osmolality
Negative control	RPMI media
Positive control	4-nitroguinoline 1 oxide, benzo[a]-pyrene, methyl methanesulfonate
Formulation/vehicle	Ro 65-5788/001/RPMI media
Incubation and sampling time	3 or 24 hours
Results	A dose dependent increase in small colonies was seen beginning at 375 mcg/mL, increasing approximately 10-fold without metabolic activation. Increases in small colonies began at 500 mcg/mL at 6-fold increase. Similar results were seen in the second study at 150 mcg/mL without activation and at 750 mcg/mL with activation, both with three hours of drug incubation. The study considered positive for mutagenicity and clastogenicity.
Validity	Study was considered valid. At concentrations at or above 4000 mcg/mL, precipitates were formed. Cell survival at 1000 mcg/mL was decreased to 3% after a 3-hour incubation period without S9 and 17% with S9. With 24 hours of treatment at 1000 mcg/mL cell survival was 1% of control. Positive and negative controls behaved as expected.

Source: Reviewer generated table.
Abbreviations: CHO, Chinese hamster ovary; GLP, good laboratory practice; ML, mouse lymphoma; TK, toxicokinetic

Table 157. Chromosome Aberration Test With Human Peripheral Blood Lymphocytes. Research Report # B-169'918

Study Features and Methods	Details
Study No	B-169'918
Study Title	Chromosome aberration test with human peripheral blood lymphocytes. Research report # B-169'918
Basis of dose selection	Up to 50% reduction in mitotic index
Cell line	Human peripheral lymphocytes
Conducting laboratory	(b) (4)
Doses in the definitive study	0-5000 mcg/mL for Ro compounds, up to 860 mcg/mL for butanedione
Drug, lot #, % purity	Ro 65-57700/001, batch 90301B217101, 90% Ro 63-9141 batch 18116B2 2,3 butanedione 99%
Formulation/vehicle	Ham's F10 media, DMSO for butenedione
GLP Compliance	Yes
Incubation time	3 hours with 21-hour recovery, 24 hours
Negative control	Media, DMSO
Positive control	Bleomycin sulfate, cyclophosphamide
Results	Ro 65-5788 (pro-drug) increased cells with structural chromosomal aberrations by approximately 4-fold at 1000 mcg/mL after 3- and 21- hour treatment in the first experiment. In a replicate test, structural aberrations were increased at 393 mcg/mL. With 24-hour incubations Ro 65-5788 increased structural aberrations at 500 mcg/mL by 4.7-fold. Effects were similar in the presence or absence of metabolic activation. Ro 65-5788 and the breakdown component butanedione were both positive for chromosomal aberrations.
Study Validity	Study considered valid. Positive controls showed approximately 10-fold increases.

Source: Reviewer generated table
Abbreviations: GLP, good laboratory practice

Reference ID: 5357793

Table 158. Ro 65-5788/001: Micronucleus Test in Mouse Bone Marrow and Toxicokinetic Monitoring – Intravenous Administration Research Report # B-169'919

Study Features and Methods	Details
Study title	Ro 65-5788/001: micronucleus test in mouse bone marrow and toxicokinetic monitoring – intravenous administration research report # B-169'919
Study No	B-169'919
Basis of dose selection	Non-lethality
Species/strain	Mice/ Fullinsdorf Moro Albino
Conducting laboratory	(b) (4)
Doses	0, 72, 180, 450 mg/kg (5 animals/sex/group); parallel group for TK (n=4) for sampling at 5, 20, 120 minutes post-dose
Drug, lot #, % purity	Ro 65-5788, batch 90301B217101 90%
Formulation/vehicle	Citrate buffered saline
GLP Compliance	Yes. OECD and US-FDA
Incubation time	Marrows obtained at 24, 48 hours post-dose
Positive control	Cyclophosphamide
Results	Study considered negative. At least 4000 PCEs/animal counted. Two animals died at the high dose and were replaced. Three additional animals died at the high dose at 48 hours. There were no statistically significant increases in the number of micronucleated PCEs with Ro 65-5788 treatment for 24 or 48 hours.
Study Validity	Study considered valid (cyclophosphamide increased the number of micronucleated PCEs approximately 8-fold
Toxicokinetics	At 5 minutes post=dose levels of Ro 65-5788 were undetectable in all but the high dose

Source: Reviewer generated table
Abbreviations: GLP, good laboratory practice; n, number of subjects in treatment arm; PCE, polychromatic erythrocytes; TK, toxicokinetic

Table 159. Toxicokinetic Parameters of R0 63-9141 After Single Intravenous Administration of Ro 65-5788/001 to Mice in a Micronucleus Test

Dose * [mg/kg]	Gender	Toxicokinetic parameter			
		Cmax [µg/mL]	AUClast [h·µg/mL]	AUC(0-inf) [h·µg/mL]	CL/F [mL/min/kg]
72	female	132	83.7	83.9	10.7
	male	109	52.8	53.2	16.9
180	female	312	212	212	10.6
	male	285	228	228	9.87
450	female	808	733	not reported **	not reported **
	male	1000	950	not reported **	not reported **

* as Ro 65-5788/001

** not reported due to very large extrapolated part of the AUC(0-inf)

Source: Applicant's table in the study report
Abbreviations: AUClast, area under the concentration-time curve from the time of dosing to the time of the last measurable (positive) concentration; AUC0-inf, area under the concentration-time curve from time 0 to infinity; CL, clearance; C_{max}, maximum plasma concentration

Table 160. Ro 65-5788/001: Measurement of Unscheduled DNA Synthesis in Rat Liver Using an in Vivo/in Vitro Procedure. Report # 1003801

Study Features and Methods	Details
Study No	1003801
Study Title	Ro 65-5788/001: Measurement of unscheduled DNA synthesis in rat liver using an in vivo/in vitro procedure.
Conducting laboratory	(b) (4)
GLP Compliance	Yes. OECD and UK-GLP
Drug, lot #, % purity	Ro 65-5788/001, batch 90901B217103, 89.83%
Species/strain	Rat/ Han Wistar males (5/group, 8 weeks old, 186-250 g; TK: 4/group, sampling 0.08, 0.5, 2, 4 hours post-dose)
Concentrations in the definitive study	0, 200, 500 mg/kg as IV bolus
Basis of dose selection	Lethality in range finding study (500 and 750 mg/kg tested, lethality observed at 750 mg/kg)
Formulation/vehicle	Citric acid acidified saline solution (pH 5)
Negative control	Vehicle
Positive control	2-acetamidofluorene (2-AAF)
Experimental conditions	Incubations in sampling times 2 to 4 or 12 to 14 hours with primary hepatocyte cultures which were then 3H-thymidine labeled for 4 hours. After an overnight incubation, cells were mixed for autoradiography over 2 weeks. At least 100 cells/animals were analyzed
Results	Study considered negative. There were no statistically significant increases in unscheduled DNA synthesis with Ro 65-5788
Validity	Valid based on concurrence with historical controls and positive control increases in unscheduled DNA synthesis (approximately increased 4-fold in counts and % of cells in repair above 50-fold)

Source: Reviewer generated table
Abbreviations: GLP, good laboratory practice; TK, toxicokinetic

13.1.2.3. Carcinogenicity

No studies were available and none are warranted for this relatively short treatment duration.

13.1.2.4. Reproductive Toxicology

For reference, the following compound identifiers have been used for ceftobiprole medocaril sodium (pro-drug): BAL5788-001, BAL0005788-001, BAL5788, JNJ-30982081, JNJ-30982081-(b) (4), Ro 65-5788, Ro 65-5788/001 and for its active metabolite ceftobiprole (Ro 63-9141/000, 63-9141, BAL9141)

BAP00232/ Study for Effects of BAL5788 (Prodrug of BAL914) on Fertility and Early Embryonic Development to Implantation by Intravenous Infusion in Female Rats

Key Study Findings

- In the male and female rat with a maximal dose of 360 mg/kg infused over 4 hours, no effects on male or female fertility or early gestation were noted.
- NOAEL considered at 360 mg/kg/day (1.4 MHD based on body surface area comparisons)

Table 161. Methods, BAP00232

Parameter	Method Details
Dose and frequency of dosing:	0, 175, 250, 360 mg/kg/day, once daily (4 h infusion)
Dosing days	14 consecutive days prior to mating, during mating (no longer than 2 consecutive weeks, until implantation (7 consecutive days during gestation period)
Route of administration:	IV
Formulation/vehicle:	BAL5788 (PO103, 93.7% purity)/ 5% dextrose
Species/strain:	Rats/Crj:CD (SD) IGS
GLP compliance	Yes
Number/sex/group:	20
Study design:	IV administration, catheter implanted to femoral vein to postcava; dose levels selected based on previous 2-week and 4-week studies. Animals observed twice daily during dosing and once daily during no dosing period. Evaluated: estrous cycle, mating (copulation and pregnancy indices), TK, complete gross and histopathology. Pregnancies terminated on Day 15 of gestation (embryos examined)
Deviation from study protocol affecting interpretation of results:	Males euthanized after mating period (and not at confirmation of pregnancy) and were considered to have no adverse effects on the results of the study because fertility index was sufficiently high for evaluation.

Source: Reviewer generated table
Abbreviations: GLP, good laboratory practice; IV, intravenous; TK, toxicokinetic

Table 162. Observations and Results, BAP00232

Parameters	Major Findings
Mortality	No unscheduled deaths.
Clinical signs	Abnormal urine color on treated rats (golden yellow to orange)
Body weights	Body weight (twice weekly during premating, daily on GD1,8, then GD10, 13, and 15). There were no significant differences in body weight or body weight gain between treated and control females.
Fertility parameters	No treatment-related effects.
Necropsy findings	No treatment-related findings.
Cesarean section data	Not treatment related findings.

Source: Reviewer generated table
Abbreviations: GD, gestation day

Table 163. Plasma Concentration (mcg/mL) of BAL5788 and BAL9141 in Female Rats, BAP00232

Dose	BAL9141		BAL5788	
mg/kg	Day 0	Day 13	Day 0	Day 13
175	48.3±19.1	70.0±27.8	2.5±1.4	4.2±3.3
250	55.0±34.4	109.9±44.1	2.0±1.7	6.5±9.8
360	106.8±43.4	177.6±34.6	9.8±9.0	7.3±10.1

Source: Reviewer generated table

BAP000231/ Study for Effects of BAL5788 (Prodrug of BAL9141) on Fertility and Early Embryonic Development to Implantation by Intravenous Infusion in Male Rats

Key Study Findings

- There were no treatment related effects on male or female fertility or mating performance
- There were no treatment related effects in early embryonic development (number of embryonic deaths, post-implantation loss index, number of live embryos or embryonic viability)
- NOAEL dose was 360 mg/kg/day.

Table 164. Methods, BAP000231

Parameter	Method Details
Dose and frequency of dosing:	0, 175, 250, 360 mg/kg/day, once daily (4 h infusion)
Route of administration:	IV
Formulation/vehicle:	BAL5788 (PO103, 93.7 % purity)/ 5% dextrose
Species/strain:	Rat/Crj: CD (SD) IGS
GLP compliant	Yes
Number/sex/group:	20/sex/group
Satellite groups:	
Study design:	Animals treated for 14 days prior to mating, during mating period (no longer than 2 consecutive weeks)
Deviation from study protocol	None that affected interpretation of results

Source: Reviewer generated table
Abbreviations: GLP, good laboratory practice; IV, intravenous

Table 165. Observations and Results, BAP000231

Parameters	Major Findings
Mortality	No unscheduled deaths.
Clinical signs	Abnormal urine color on treated rats (golden yellow to orange)
Body weights	No treatment related body weight changes observed
Fertility parameters	No treatment-related fertility effects observed (males: copulatory or fertility index, sperm count, viability, activity, morphology or weight of caudal epididymis; females)
Necropsy findings	No treatment-related findings.

Source: Reviewer generated table

BAP00173/ Study for Effects of BAL5788 (Prodrug of BAL9141) on Embryo-Fetal Development by Intravenous Infusion in Rats

Key Findings

- There were no adverse fetal development effects observed.
- Maternal NOAEL and fetal NOAEL was considered at 360 mg/kg with an associated plasma concentration of 20.7 mcg/mL (BAL5788) and 126.2 mcg/mL (BAL9141) within the last 10 minutes of the slow infusion.

Reference ID: 5357793

Table 166**. Method of Embryo-Fetal Developmental Study in Rats, BAP00173**

Parameter	Method Details
Dose and frequency of dosing:	0, 175,250 and 360 mg/kg/day
Route of administration:	IV
Formulation/vehicle:	BAL5788 (Batch: HOP 020401, 92.3% purity)/ 5% dextrose
Species/strain:	Rat/Sprague Dawley
GLP compliant	Yes
Number/sex/group:	24 pregnant females/group main study; 5 females/group TK
Satellite groups:	4 pregnant females/group in the toxicokinetic study
Study design:	BAL5788 administered from implantation to closure of the cleft palate (GD 6-17)
Deviation from study protocol affecting interpretation of results:	None

Source: Reviewer generated table
Abbreviations: GD, gestation day; GLP, good laboratory practice; IV, intravenous; TK, toxicokinetic

Table 167**. Observations and Results, BAP00173**

Parameters	Major Findings
Mortality	No unscheduled deaths.
Clinical signs	Soft stools in one animal at 175 mg/kg/day and one in the 360 mg/kg/day.
Body weights	No treatment related effects
Feed consumption	Slightly higher at 360 mg/kg/day (GD 18-19), slightly decreased at 250 mg/kg/day GD 9-10
Necropsy findings Cesarean section data	No treatment related effects
Necropsy findings Offspring	No treatment related effects

Source: Reviewer generated table
Abbreviations: GD, gestation day

Toxicokinetics

BAL5788 was not detectable at any dose on gestation day (GD) 6 at 2 hours post-infusion. On GD 17, plasma BAL5788 concentrations were minimal at 0.603 mcg/mL at 2 hours post-infusion. Plasma concentrations of BAL9141 increased with dose and were approximately 5 times higher in the final ten minutes of infusion at all doses on GD 17 compared to GD6, but were minimal and not significantly different between the two gestation days at two hours post-infusion. The plasma levels at 10 min before end of infusion and 2-hour post-infusion on gestation days 6 and 17 are shown below. High inter-subject variability in plasma concentrations precluded a determination of a clear dose related exposure, but there was no evidence of plasma accumulation in all dose groups. Area under the concentration-time curve (AUC) and maximum plasma concentration (C_{max}) values were not calculated.

Reference ID: 5357793

Table 168. Plasma Levels of BAL5788 and BAL9141 in Pregnant Rats (mcg/mL on Gestation Day 6), BAP00173

Plasma levels of BAL5788 and BAL9141 in pregnant rats (mcg/mL) on Gestation Day 6				
Dose (mg/kg)	BAL5788		BAL9141	
	10 min	2 h	10 min	2 h
175	13.9±3.7	---	83.1±10.1	3.9±0.8
250	7.7±4.6	---	82.3±15.2	4.4±3.1
360	20.7±18.3	---	126.2±126.3	30.5±45.3

Source: Reviewer generated table

Table 169. Plasma Levels of BAL5788 and BAL9141 in Pregnant Rats (mcg/mL on Gestation Day 17), BAP00173

Plasma levels of BAL5788 and BAL9141 in pregnant rats (mcg/mL) on Gestration Day 17				
Dose (mg/kg)	BAL5788		BAL9141	
	10 min	2 h	10 min	2 h
175	6.6±6.1	---	50.8±44.1	5.3±5.3
250	19.5±15.8	---	101.5±15.3	11.8±6.8
360	15.2±13.1	---	73.8±64.0	6.6±4.5

Source: Reviewer generated table

BAP00051. Study for Effects of BAL5788 (Prodrug of BAL9141) on Embryo-Fetal Development by Intravenous Infusion in Cynomolgus Monkeys

Key Findings

Abortions were observed in 2 dams in the control group and 3 dams in the high dose group. There were no significant visceral variations or fetal abnormalities observed Maternal NOAEL was considered at 60 mg/kg and fetal NOAEL at 120 mg/kg.

Table 170. Method of Embryo-Fetal Developmental Study in Cynomolgus Monkeys, BAP00051

Parameter	Method Details
Dose and frequency of dosing:	0, 30, 60 and 120 mg/kg/day (calculated doses of BAL9141)
Route of administration:	IV
Formulation/vehicle:	BAL5788 (Batch: HOP 020401, 92.3% purity)/ 5% dextrose
Species/strain:	Monkey/Cynomolgus
GLP compliant	Yes, Japanese
Number/sex/group:	10 pregnant females/group (4-7 years old, 2.75-4.08 kg)
Satellite groups:	N/A
Study design:	BAL5788 administered during gestation (GD 20-50); dams e-sectioned on day 100
Deviation from study protocol affecting interpretation of results:	None that affected interpretation of results

Source: Reviewer table
Abbreviations: GD, gestation day; GLP, good laboratory practice; IV, intravenous

Table 171. Observations and Results, BAP00051

Parameters	Major Findings
Mortality	No unscheduled deaths of dams. Two control (day 60) and 3 high dose (GD 20- to 40) dams had abortions/embryonic deaths
Clinical signs	No test article related clinical signs
Body weights	In dams, -10% decrease in body weight **at the high dose at the end of pregnancy (representing a -33% decrease in body weight gain).** Organ weights in the fetuses (brain, thymus, heart, lungs spleen, liver, kidney, adrenals, uterus, ovaries, testes) were unaffected, except for the absolute and relative weights of the spleen and kidneys were decreased by approximately -20%.
Feed consumption	No appreciable decrease in food consumption
Necropsy findings Cesarean section data	No treatment related effects
Necropsy findings fetus	No treatment related findings
Other findings	All dams were pregnant with a single fetus. Gender ratios, fetal weights, crown-rump lengths, amniotic fluid and other parameters did not differ significantly between treated and control monkeys. Gender ratios, fetal weights, crown-rump lengths, amniotic fluid and other parameters did not differ significantly between treated and control monkeys

Source: Reviewer generated table
Abbreviations: GD, gestation day

Toxicokinetics

BAL5788 was not detectable at any dose at 2 hours post-infusion. Values on Day 20 and Day 50 did not differ to a significant extent. The C_{max} (10 minutes) and 2-hour post-infusion levels at GD 50 are shown below.

Table 172. Plasma levels of BAL5788 and BAL9141 in Pregnant Monkeys (mcg/mL), BAP00051

	BAL5788		BAL9141	
Dose (mg/kg)	**10 min**	**2 hr**	**10 min**	**2 hr**
30	4.5 ± 3.1	---	50.6 ± 8.9	10.2 ± 2.8
60	4.4 ± 2.5	---	105.9 ± 15.3	16.9 ± 5.9
120	13.9 ± 8.4	---	205.2 ± 29.1	41.9 ± 8.6

Source: Reviewer generated table

BAP00640/ Study for Effects of BAL5788 (Prodrug of BAL9141) on Pre- and Postnatal Development Including Maternal Function by Intravenous Infusion in Rats

Key Study Findings

- Live birth index and number of live pups was decreased at the high dose (maternally toxic dose), however, there were no post-natal findings (basic maturation milestones were unaffected)
- No findings observed on mating, fertility and pregnancy parameters
- The NOAEL was 250 mg/kg/day (0.9-fold MHD based on body surface area comparisons)

Table 173. Pre- and Post-Natal Development Study in Rats, BAP00640

Parameter	Method Details
Dose and frequency of dosing:	0, 175, 250, 360 mg/kg/day
Route of administration:	IV
Formulation/vehicle:	BAL5578 (30-4EXP, 100% purity)/ 5% dextrose
Species/strain:	Rat/Sprague-Dawley
GLP compliant	Yes (OECD and Japanese)
Number/sex/group:	F0: 24 dams/dose; pups culled to 4/sex/litter at lactation day 4 and 2/sex/litter at lactation day 22. 5 dams/dose
Study design:	Animals dosed once daily from day gestation day 6 to day 21 of lactation
Deviation from study protocol affecting interpretation of results:	Several protocol deviations were reported, none that would affect interpretations of results.

Source: Reviewer generated table
Abbreviations: GLP, good laboratory practice; IV, intravenous

Table 174. Study Findings (F0 Generation), BAP00640

Parameters	Major Findings
Mortality	Two F0 high dose dams died during gestation (days 12 and 18, attributed to thromboembolic events). Total litter losses in 2 dams at the high dose (days 2 and 5 of lactation), in one dam at mid dose (day 5 of lactation) and in three dams at the low dose (days 1, 2 and 10 of lactation).
Clinical signs	Abnormally colored urine in treated animals
Body weights	Evaluated every 2-3 days during organogenesis and lactation on dams, post-natal Days 7, 14, 22, 28, 42, 56, and 70. At day 20 of gestation, body weights were decreased by 7% in the high dose dams compared to controls (body weight gains were diminished by 21% during the gestation period). No significant differences between groups were noted during lactation.
Feed Consumption	There was a decrease in feed consumption at the high dose (-8%).
Gross pathology	Cecal enlargement in 8/19 low dose, 12/19 mid-dose and 11/21high dose dams
Fertility parameters	The gestation period, male/female ratio, and number of implantation sites did not differ significantly. Total litter resorption was observed in 1 high dose and 2 mid-dose dams. The live birth index and number of live pups decreased with dose. This may be associated with maternal toxicity at the HD. Total litter loss was noted in 2 control dams (Day 7 of lactation), 3 LD (Days 1, 2, and 10), 1 mg (Day 5), and 2 HD dams (day 2 and 5).

Source: Reviewer generated table
Abbreviations: HD, high dose; LD, low dose

Table 175. Study Findings (F1 Generation), BAP00640

Parameters	Major **Findings**
Mortality	Lower number of live pups and number of pups born at 360 mg/kg when compared to control
Clinical signs	No test article related findings
Body weights	No body weight differences observed
Behavior and activity	There were no significant differences in reaching basic maturation milestones (righting/papillary reflex, negative geotaxis, pain response, pinna detachment, incisor eruption or eyelid opening). Enlargement of the colon was noted in a mean of 6, 12, and 18 pups in the LD, MD, and HD groups. No significant differences were noted in skeletal abnormalities, external genitalia or body weights with dose.
Necropsy findings Visceral, skeletal exam	Enlargement of cecum in all treatment groups (8/61, 10/74 and 3/63 in the low, mid and high dose, respectively).
Mating, fertility, and pregnancy parameters	The copulation index with the F1 generation animals did not differ significantly with dose. While not statistically significant, the mean copulatory interval was 1 day shorter at the HD. Fertility index was 95% in the controls, 77% in the LD, 94% in the HD and 88% in the HD. A single litter was totally lost in the control and LD groups. Gestational weights did not differ significantly in the dams. There were no gross findings. There were no remarkable differences between doses in the gestation period, number of implantation sites, number of animals born live/dead, sex ratios or survival through day 7.

Source: Reviewer generated table
Abbreviations: HD, high dose; LD, low dose; MD, mid dose

Table 176. Study Findings (F2 Generation), BAP00640

Parameters	**Major Findings**
Mortality	No unscheduled deaths
Clinical signs	No findings
Body weights	No changes in body weight
Behavior and activity	No findings
Necropsy findings Visceral, skeletal exam	A slight increase was observed in the number of ossified sacral and caudal vertebras (attributed to higher body weight)

Source: Reviewer generated table

Toxicokinetics

Plasma levels of BAL5788 and BAL 4041 were evaluated in female rats on gestation day (GD) 6 and lactation day 20 during the last 10 minutes of infusion and 2 hours post dose. Milk was sampled on lactation day 20 1-2 hours post-dose.

Reference ID: 5357793

Table 177. Concentration of BAL9141 and BAL5788 in Plasma of Female Rats (mcg/mL), BAP00640

	Plasma, GD6		Plasma, LD20		Milk, LD20
	Infusion	2 h. post	Infusion	2 h post	
BAL9141					
175	106.0 ± 19.7	10.1 ± 5.4	87.2 ± 28.1	10.5 ± 1.9	16.7 ± 9.6
250	151.0 ± 9.7	10.6 ± 2.1	88.5 ± 10.9	18.5 ± 7.4	15.8 ± 10.2
360	194.4 ± 24.7	26.8 ± 17.5	93.3 ± 64.9	26.3 ± 19.5	20.3 ± 15.0
BAL5788					
175	21.8 ± 10.0	1.5 ± 1.2	18.8 ± 6.0	6.1 ± 6.4	BLQ
250	21.7 ± 9.5	3.3 ± 3.2	19.2 ± 6.1	6.3 ± 3.1	BLQ
360	34.2 ± 17.2	7.5 ± 9.9	17.5 ± 13.2	19.7 ± 38.9	1.8 ± 4.1

Source: Reviewer generated table
Abbreviations: BLQ, below limit of quantification; GD, gestation day; LD, low dose

TOX8611. Ceftobiprole Medocaril Sodium (BAL5788): A Subcutaneous Toxicity Study in Neonatal and Juvenile Albino Rats

Key Study Findings

- Mortality observed at the high dose (animals showed decreased or increased activity, pallor, vocalization and convulsions)
- Transient increased or decreased activity, increased muscle tone, vocalization and incoordination observed in some male and females post-dosing at the high dose (Days 14-17, not observed after Day 18)
- Injection site reaction (inflammation and hemorrhage) observed in all animals (higher incidence in treated animals)
- NOAEL considered at 100 mg/kg/day (AUC: 4.4 mcg/mL, C_{max} 9 mcg/mL at Day 49)

Reference ID: 5357793

Table 178. Methods, TOX8611. Ceftobiprole Medocaril Sodium (BAL5788)

Parameter	Method Details
Dose and frequency of dosing:	0, 50, 100 and 250 mg/kg/day
Dosing days	Pups were dosed for 49 consecutive days (starting on Day 1 post-partum)
Route of administration:	Subcutaneous
Formulation/vehicle:	BAL5788 (ceftobiprole medocaril sodium) lot I030603; purity 102.4%/ vehicle 5% dextrose
Species/strain:	Rats/Sprague Dawley
GLP compliance	Yes
Number/sex/group:	42-50/sex/group (main and recovery); 18/sex/group (TK)
Study design:	F0 generation dams were at gestation days 13, 14 or 15 on arrival. At the start of treatment, pups (F1) were on Day 1 post-partum; weight: 4.9 to 9.6 g (Day 0 post-partum), and 28.3 to 61.6 g (Days 18 post-partum). Culling performed at Day 1 post-partum. Weaning on day 21 post-partum.
Deviation from study protocol affecting interpretation of results:	None that affected the study results interpretation

Source: Reviewer generated table
Abbreviations: GLP, good laboratory practice; TK, toxicokinetic

Reference ID: 5357793

Table 179. Observations and Results, TOX8611. Ceftobiprole Medocaril Sodium (BAL5788)

Parameters	Major Findings
Mortality	A total of 15 pups were found dead or euthanized during the pre-weaning dosing period. One control group female was found dead on day 3 post-partum. At 50 mg/kg/day, 3 female pups were found dead (days 3, 13 and 2 post-partum). Another female in the 50 mg/kg/day group was subject to unscheduled euthanasia due to severe decreased health (abnormal gait, dehydration, decreased activity, lack of coordination, tremors, limited use of hindlegs). At 250 mg/kg/day 6 male pups and 2 female pups were found dead between days 2 and 15 post-partum. Clinical signs included thinness, skin pallor and empty stomach. One moribund male showed skin pallor, increased activity, decreased respiratory rate, increased vocalization and convulsions on day post-partum 3. There were no significant necropsy findings.
Clinical signs	At 250 mg/kg/day, post dosing (days 14-17) increased (5/50 males, 4/50 females) or decreased activity (5/50 males, 4/60 females), biting (3/50 males, 3/50 females), hypersensitivity, muscle tone increased (5/50 males, 3/50 females), post-dosing lack of coordination (6/50 males and females) and increased vocalization (8/50 males, 5/50 females). Findings were no longer observed 18 days post-partum. Red skin around the injection site observed mostly in the 250 mg/kg/day male and female pups at 30 minutes, 1 hour, 2 hours and 4 hours post dosing for the first 3 days of dosing.
Body weights	Measured on all animals daily from Days 1 to 7 post-partum and on Days 10, 14, 18 and 21 post-partum. At 250 mg/kg/day, decreased weight gains compared to controls were observed in males (up to -12% by day 10 post-partum, slightly recovered at -8% by day 21 post-partum) and females (up to -13% by day 14 post-partum, slightly recovered at -8% by day 21 post-partum). At recovery, female weights were similar to controls, male weights remained slightly lower than controls (-3%).
Physical development	Crown to rump measurements: Measured post-cull day 1 and days post-partum 3, 7, 14 and 21. During pre-weaning crown-to-rump length was lower than controls (-3 to -5%) between days 21-24 post-partum at 250 mg/kg/day, consistent with lower body weights. Physical development: Preputial separation days for group litters were slightly delayed at 100 and 250 mg/kg/day compared to concurrent controls (42.2 days for control and 44.2 and 44.4 days for treated males). However, group litter mean development values for treated males were comparable to the historical control range (41.5 to 44.7 days). There were no differences in mean day development of vaginal opening in treated females compared to controls. Bone measurements: BAL5788-related consisted of a statistically significant decreased length of the tibia and femur in males at 250 mg/kg/day and decreased femur length of males at 100 mg/kg/day that were not observed at recovery.
Feed consumption	Feed consumption was decreased in 250 mg/kg/day males (-3%) and females (-8%) between post-partum days 21-24.
Ophthalmoscopy	No test article related findings
Hematology	No test article related findings

Reference ID: 5357793

Parameters	Major Findings
Clinical chemistry	No test article related findings
Gross pathology	Injection site dark areas and foci observed in all groups with higher incidence at the high dose (near complete resolution at the end of recovery).
Organ weights	No test article related findings
Histopathology	Injection site: minimal to slight inflammation and hemorrhage (primarily at the high dose) in all groups, at higher incidence in treated animals (3-4/15 in controls, 5-14/15 in treated animals) Kidney: minimal to slight cytoplasmic globules in the pelvis collecting ducts at the high dose in nearly all males and females. In the absence of additional kidney findings, this was not considered adverse.

Source: Reviewer generated table

Table 180. Toxicokinetics of BAL5788 (Ceftobiprole Medocaril Sodium)

DOSING PERIOD								
Daily Dose (mg/kg)[a]	0 (0) (Control)		50 (37.5) (Group 2)		100 (75.0) (Group 3)		250 (187.5) (Group 4)	
No. of Animals	M: 18	F: 18	M: 18	F: 18	M: 18	F: 18	M: 18	F: 18
Toxicokinetics: BAL5788								
$AUC_{0-\infty}$ (µg·h/mL), Day 1	-	-	90.0	80.3	103	103	147	153
$AUC_{0-\infty}$ (µg·h/mL), Day 18	-	-	13.3	10.9	25.9	25.0	64.2	50.8
$AUC_{0-\infty}$ (µg·h/mL), Day 49	-	-	NR	NCR	NR	4.05	26.3	10.9
$AUC_{0-tlast}$ (µg·h/mL), Day 1	-	-	89.8	79.4	101	102	145	152
$AUC_{0-tlast}$ (µg·h/mL), Day 18	-	-	11.6	9.69	25.4	22.6	63.8	50.5
$AUC_{0-tlast}$ (µg·h/mL), Day 49	-	-	13.4	NCR	4.97	3.84	26.2	10.8
C_{max} (µg/mL), Day 1	-	-	50.2	42.1	63.3	68.7	114	107
C_{max} (µg/mL), Day 18	-	-	27.8	22.3	33.5	29.2	71.9	61.5
C_{max} (µg/mL), Day 49	-	-	5.06	3.48	9.82	9.24	26.8	12.0

[a] Doses expressed in terms of BAL5788, a prodrug of BAL9141 (Number in parenthesis is the BAL9141 equivalent)
NRValues not reported as the $AUC_{(0-\infty)}$ was extrapolated by more than 20% or coefficient of determination for the terminal elimination phase regression model was < 0.8
NCR Value not considered reportable, when the number of quantifiable plasma concentration time-points less than 3

Source: Reviewer generated table
Abbreviations: AUC0-∞, area under the concentration-time curve from time zero to infinity; AUClast, area under the concentration-time curve from the time of dosing to the time of the last measurable (positive) concentration; C_{max}, maximum plasma concentration

Table 181. Toxicokinetics of BAL9141 (Ceftobiprole)

DOSING PERIOD								
Daily Dose (mg/kg)[a]	0 (0) (Control)		50 (37.5) (Group 2)		100 (75.0) (Group 3)		250 (187.5) (Group 4)	
No. of Animals	M: 18	F: 18	M: 18	F: 18	M: 18	F: 18	M: 18	F: 18
Toxicokinetics: BAL9141								
$AUC_{0-\infty}$ (µg·h/mL), Day 1	-	-	138	152	281	292	839	772
$AUC_{0-\infty}$ (µg·h/mL), Day 18	-	-	81.6	73.6	148	133	469	400
$AUC_{0-\infty}$ (µg·h/mL), Day 49	-	-	71.6	60.8	139	119	295	258
$AUC_{0-tlast}$ (µg·h/mL), Day 1	-	-	123	138	265	261	751	722
$AUC_{0-tlast}$ (µg·h/mL), Day 18	-	-	80.9	72.8	148	132	465	396
$AUC_{0-tlast}$ (µg·h/mL), Day 49	-	-	70.0	60.2	138	118	290	256
C_{max} (µg/mL), Day 1	-	-	28.0	37.9	55.7	65.6	176	159
C_{max} (µg/mL), Day 18	-	-	62.2	56.0	92.6	101	302	252
C_{max} (µg/mL), Day 49	-	-	43.9	47.4	76.1	84.0	168	152

[a] Doses expressed in terms of BAL5788, a prodrug of BAL9141 (Number in parenthesis is the BAL9141 equivalent)

Source: Reviewer generated table
Abbreviations: AUC0-∞, area under the concentration-time curve from time zero to infinity; AUClast, area under the concentration-time curve from the time of dosing to the time of the last measurable (positive) concentration; C_{max}, maximum plasma concentration

Reference ID: 5357793

13.1.2.5. Other Toxicology

13.1.2.5.1. Other Studies

TOX 7589. An Antigenicity Study of BAL5788 in Guinea Pigs

Methods

For passive sensitization, male Hartley guinea pigs were injected subcutaneously (6 sites on the dorsal skin of 2 animals) with serum from the actively sensitized animals, then 4 hours later challenged with 25, 50 or 100 mg/kg of intravenously administered BAL5788 and Evan's blue dye. The dorsal skin was then examined for dye leakage. Actively sensitized animals were challenged with 100 mg/kg BAL5788 (pro-drug) and the reactions observed. Intravenous sensitization was evaluated at 1) 10 mg/kg/ BAL5788 (5 times week for 3 weeks, 2) 50 mg/kg/ BAL 5788 (5 times a week for 1 week) and 20 mg/kg (5 times week for 2 weeks, 3) 10 or 50 mg/kg, emulsified with Freund's complete adjuvant (FCA) or Freund's incomplete adjuvant (FIA) once weekly for 3 weeks. Positive control was 1 mg/kg subcutaneous ovalbumin emulsified with FCA once weekly for 3 weeks. The negative control was 5% dextrose IV or subcutaneous with FCA or FIA once weekly for 3 weeks. A 100 mg/kg challenge dose of BAL5788 (batch 30-4EXP, 93.8% purity) was used.

Results

One animal in the 50 mg/kg intravenous sensitization group died at day 4. No significant changes were noted in body weight. No abnormalities were seen in the sensitization with 5% dextrose or 10 mg/kg BAL with or without FCA/FIA. In the 50/20 mg/kg BAL alone groups, scratching and piloerection were observed in 1/5 guinea pigs (ASA grade 1). In the 50 mg/kg group with FCA/FIA, anxiety, tremor, piloerection, dyskinesia, dyspnea were seen in all animals within 60 minutes of challenge and 1/5 animals died (ASA reaction scores were 1/5 at 1, 2/5 at 2, 1/5 at 3 and 4). In the positive control group, one animal died within 6 minutes of challenge (ASA 4) while the remaining 4 animals had an ASA reaction grade of 2. No reactions were noted in the BAL5788 passively challenged animals. The positive control had 5/5 animals positive. BAL5788 was shown to have moderate antigenic potential.

Report 10016. Ro 63-9141/001: Phototoxicity Study (In Vitro)

Methods

The potential phototoxic potential of Ro 63-9141/001 (ceftobiprole, batch # 18116B2, 370-4500 mcg/mL) was evaluated an in vitro assay with Balb/c 3T3 mouse fibroblasts by incubating the test article in the cell culture system with or without exposure to a non-cytotoxic dose of ultraviolet light (ultraviolet A [UVA] wavelength of 240-4500 nanometers) or kept in the dark. Cytotoxicity was expressed as a dose dependent reduction of the growth rate of cells as determined by uptake of the vital dye Neutral Red one day after treatment. Negative control was the vehicle, PBS/ 3% dimethyl sulfoxide [DMSO]) and chlorpromazine was used as positive control.

Reference ID: 5357793

Results

There were no changes in cell viability at any concentration of drug tested or changes after exposure to UVA radiation as compared to cultures kept in the dark. Chlorpromazine, the positive control for UVA, behaved as expected (with a Dark/UVA discrimination factor for cytotoxicity of 66-fold). The study was valid and the test article was considered negative for phototoxicity.

Report 1004008. Ro 65-5788/001: In Vitro Assessment of Hemolysis, Plasma Turbidity and Plasma Precipitation in Dog Blood

Methods

The potential of ceftobiprole medocaril sodium (13.3% or 133.3 mg/mL pro-drug, batch# 90402B2171202) to induce hemolysis and plasma turbidity was evaluated in vitro using venous dog blood. Vehicles used were saline and 5% glucose. Hemolysis was measured by spectrophotometer (hemoglobin %) and turbidity was evaluated visually.

Results

No significant hemolysis or plasma turbidity or precipitation were seen in dog blood under in vitro conditions in a 13.33% test solution of ceftobiprole medocaril sodium pro-drug (corresponding to 10% or 100 mg/ml of the active drug Ro 63-9141/000) at concentrations corresponding to 1.25% (12.5 mg/ml pro-drug). At higher concentrations, hemolysis of up to 7.3% and moderate to marked plasma turbidity and precipitation were observed.

Tox7587. Haemocompatibility Test with Human, Rat, and Marmoset Blood

Methods

Ceftobiprole medocaril sodium was evaluated at 5 concentration levels (1, 5, 12.5, 25 and 50 mg/mL) for hemocompatibility with rat, marmoset, and human blood at a volume ratio of 0.2, 0.4 and 0.8 (1:5, 2:5 and 4:5) test material:blood. Reportedly, in the human, this ratio corresponds to administration of 1.6, 3.2 and 6.4 mL/min intravenous infusion rates. Hemoglobin release was determined following a 3-minute incubation at 37°C. For the plasma compatibility evaluation rat, marmoset, and human plasma were mixed with ceftobiprole medocaril sodium solutions at a ratio of 0.8 (4:5) test material:plasma. Samples were observed for flocculation, precipitation, and coagulation after 0.16, 0.5, 1, 2, 3, 5, 10, 30 and 60 minutes at room temperature.

Results

No test article related hemolysis was observed at any dose tested in rat, marmoset. or human blood. When ceftobiprole medocaril sodium was mixed with human, rat, or marmoset plasma at a ratio of 0.8 (equivalent to an infusion rate of 6.4 mL/minute), dose dependent adverse reactions were observed (flocculation, precipitation, and coagulation) with increasing ceftobiprole medocaril sodium concentrations and increasing time. In all three species the adverse reactions (primarily precipitation) were observed ≥2.5 mg/mL concentration level. At ≥25 and with increasing time periods, flocculation and coagulation were also observed.

Reference ID: 5357793

13.1.2.5.2. Safety of Extractables and Leachables

The container closure system includes a [(b) (4)] glass vial with a [(b) (4)] rubber stopper, sealed with an aluminum crimp seal with a plastic flip-off cap (see details in Table 182 below).

Table 182.183 Primary Packaging Container for Ceftobiprole Medocaril Sodium for Injection

Glass vial:	
Description	Vial 33 × 55 mm EP/USP, clear vial
Material	[(b) (4)] glass, [(b) (4)]
Butyl stopper:	
Description	Rubber stopper [(b) (4)]
Material	Main ingredient [(b) (4)] [(b) (4)]
Color	[(b) (4)]
Aluminum cap	
Description	Aluminum cap
Material	Aluminum / [(b) (4)] flip off
Color	[(b) (4)] aluminum with [(b) (4)] flip off

Source: Applicant Table 1 in section 3.2.P.7.
Abbreviations: EP, evaluation period; USP, United States Pharmacopeia

The analytical evaluation threshold for leachables (non-elemental impurities) detected in the drug product using the maximum recommended human dose (MRHD) of 2.67 g (4 vials of 10 mL with a total of 40 mL for the MRHD) and using a threshold of [(b) (4)]/day for sensitization and general toxicity was calculated at [(b) (4)] mcg level of detection per vial. Elemental leachables were evaluated according to ICH Q3D Guideline and because these leachables do not exceed the 5-mcg safety threshold, they are considered qualified for safety.

In a leachables assessment from samples stored both upright and in inverted position under both long-term (5 ± 3 °C, for 0, 6, 12, 24 and 48 months) and accelerated storage (25 ± 2 °C, 60% RH ± 5%, for 0, 3 and 6 months), three leachables ([(b) (4)] were identified > 5 mcg/day. A comprehensive toxicological assessment was not provided by the Applicant (only an ECHA dossier was cited), however, reviewer assessments and derived PDEs are included below for [(b) (4)]. The unknown leachable was reportedly measured below the 5 mcg/day threshold level (considered for both general toxicity and sensitization) under normal conditions for real time storage.

[(b) (4)] **risk assessment**

Published literature including comprehensive review of the toxicity of [(b) (4)] and genotoxicity evaluation ([(b) (4)]) were considered for this assessment.

Genotoxicity

- Negative for mutagenicity (Ames, L5178Y) and chromosomal aberration (Chinese hamster ovary cells)
- Negative for chromosomal aberration in vivo (rat) following whole-body inhalation to [(b) (4)] ppm (6 hr/day for 5 days)

Repeated-dose toxicity

- 24-month inhalation study (Fischer rat) NOAEC for general toxicity of [(b) (4)] ppm [(b) (4)] mg/m³), based on chronic nephropathy
- 3-week dermal study (New Zealand White rabbit) NOAEL was ≥ [(b) (4)] mL/kg/day (equivalent to ≥ [(b) (4)] mg/kg/day (protocol conducted similar to Organization for Economic Co-operation and Development410 and good laboratory practice (GLP))

Reproductive and Developmental Toxicity

- NOAECs of [(b) (4)] ppm (F) and [(b) (4)] ppm (M) for reproductive toxicity were determined in a 2-generation inhalation study (rat); decrease in mean live litter size, implantation sites, and number of corpora lutea were observed following [(b) (4)] and [(b) (4)] ppm
- Study examining critical windows of exposure in rat found single 6 hr exposure on day prior to mating resulted in a significant reduction in fertility (decreased ovulation).

Other

Non-sensitizing to skin of guinea pig (Organization for Economic Co-operation and Development Test Guideline 406)

Permitted Daily Exposure (PDE): The [(b) (4)] ppm NOAEC, corresponding to [(b) (4)] mg/m³, from the 24-month inhalation study in rat was used to derive a PDE:

$$NOAEL = NOAEC(mg/m^3) \times \frac{6hr}{24hr} \times \frac{5\ days}{7\ days} \times \frac{\text{Respiratory volume of rat } (L/day)}{Rat\ body\ weight\ (kg)} \times \frac{1m^3}{1000L}$$

$$NOAEL = [(b)\ (4)]\ \frac{mg}{m^3} \times \frac{6hr}{24hr} \times \frac{5\ days}{7\ days} \times [(b)\ (4)] \times \frac{1m^3}{1000L} = [(b)\ (4)]\ \frac{mg}{kg.day}$$

Applying modifying factors of 5 for the extrapolation of rat data to human, 10 for variability between individuals, 1 for study duration, 1 for severity of toxicity studies, 1 for availability of a NOAEL and 10 for bioavailability. (The reported mean inhalation absorption of [(b) (4)] in rat is [(b) (4)]%).

This results in a PDE of [(b) (4)] mg/day of [(b) (4)] in parenteral route:

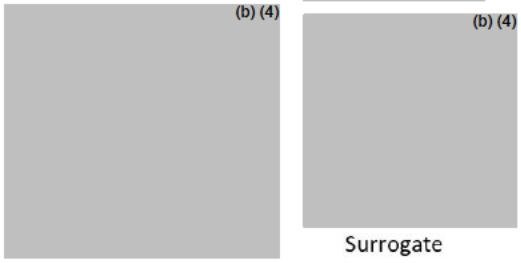
$$\text{PDE} = \frac{[(b)\ (4)]\ \frac{\text{mg}}{\text{kg}} * 50\ \text{kg}}{5 \text{ x } 10 \text{ x } 1 \text{ x } 1 \text{ x } 1 \text{ x } 10} * [(b)\ (4)] = [(b)\ (4)]\ mg/day$$

Maximum daily exposure of the [(b) (4)] in ceftobiprole medocaril sodium product would be [(b) (4)] mcg/day, which is ~30 times lower that the reviewer calculated PDE ([(b) (4)] mg/day). [(b) (4)] is considered qualified for safety.

[(b) (4)] risk assessment

Due to the lack of published toxicological information for [(b) (4)] from primary sources, a surrogate [(b) (4)] was considered as a reasonable selection based on prior safety assessments of [(b) (4)] in other parenteral drug products [(b) (4)]

Figure 22. Structure of [(b) (4)]



Source: Reviewer generated figure

Genotoxicity

[(b) (4)] was negative for mutagenicity in the Ames test and negative for clastogenicity (sister chromatid exchanges or chromosomal aberrations) in Chinese hamster ovary (CHO) cells in the presence or absence of S9.

Repeated-dose toxicity

Oral NOAEL of [(b) (4)] mg/kg/day from a 103-week rat study conducted by the National Toxicology Program (NTP)

Reproductive and Developmental Toxicity

NOAEL of [(b) (4)] mg/kg (rat) maternal and developmental effects.

Other

- Low (rabbit) to moderate (guinea pig) skin irritant; dermal irritant to rat at high concentrations
- Eye irritant (rabbit)
- There is evidence that [(b) (4)] can be oxidized by air into sensitizing compounds; unoxidized [(b) (4)] does not appear to be a sensitizer.

A NOAEL of [(b) (4)] mg/kg from a 103-week rat study conducted by the NTP was used to calculate a PDE. Applying modifying factors of 5 for interspecies extrapolation, 10 for intraspecies variation, 1 for study duration, 1 for toxicity severity, 1 for availability of NOAEL, 10 for use of a surrogate, and 10 for bioavailability correction (oral bioavailability < [(b) (4)]%):

$$\text{PDE} = \frac{[(b)(4)]\ \frac{\text{mg}}{\text{kg}} * 50\ \text{kg}}{5 \times 10 \times 1 \times 1 \times 1 \times 10 \times 10} = [(b)(4)]\ \text{mg/day}$$

Maximum daily exposure of the (b) (4) in ceftobiprole medocaril sodium drug product would be (b) (4) mcg/day, ~150-fold lower than the reviewer calculated PDE. The (b) (4) compound is qualified for safety.

13.1.2.5.3. Safety of Impurities

Ceftobiprole medocaril sodium for injection (pro-drug (BAL5788) for ceftobiprole, BAL9141) will be given as an intravenous infusion and will be marketed as a sterile lyophilized powder for reconstitution (inactive ingredients are citric acid monohydrate in sodium hydroxide). There are no pharmacology/toxicology concerns for the excipients. The unit dose is 667 mg of ceftobiprole medocaril sodium per vial (equivalent to 500 mg of ceftobiprole). The MRHD is 2.67 g/day (equivalent to 2.0 g ceftobiprole). The animal data supports safety of ceftobiprole medocaril sodium for up to 1 month duration, however, based on clinical data treatments for up to six weeks were permitted. We deferred to the clinical review team on the safety of ceftobiprole medocaril sodium administered for this extended duration.

The genotoxicity profile of ceftobiprole medocaril sodium was mixed including a negative Ames assay, a positive mouse lymphoma assay, a negative forward mutation assay, and positive chromosomal assays for both the pro-drug and active metabolite suggesting clastogenic potential. However, in vivo ceftobiprole medocaril sodium was negative in both the micronucleus assay and rat liver unscheduled DNA synthesis reducing concern for potential clastogenic activity.

In considering potential and actual impurities in the drug substance (DS) and DP, the Applicant assessed genotoxic potential of several impurities using Derek quantitative structure-activity relationship (QSAR) analysis (a second tool was not expected since initial phase 3 clinical trials were conducted prior to the publication of the ICH M7 Guidance). Expert analysis based on available scientific literature or data from studies conducted by the Applicant and purging assessments were also considered. In general, the Applicant followed ICH M7, particularly in assigning a classification of mutagenic potential to the impurities. The Applicant considered 155 compounds, classified 94 of them as class 4 or 5 (can be treated as nonmutagenic), and used purging calculations or direct analytical methods to demonstrate absence of 57 compounds. There were 5 impurities classified in classes 1, 2 or 3 and these were amongst the compounds demonstrated to be absent in the drug substance. The Applicant also provided a rationale for levels of (b) (4) guided by ICH Q3C Guidance, with special consideration of the short-term use of ceftobiprole medocaril sodium for injection. For limit setting of impurities based on manufacturing experience and commercial process capabilities, the Applicant proposed the use of alternative thresholds higher than ICH Q3A and Q3B Guidance, including a reporting threshold of (b) (4), and qualification thresholds of (b) (4) for the drug substance (DS) and (b) (4) for the DP. These higher thresholds were jointly considered acceptable by CMC and pharm/tox teams (see CMC's separate reviews of DS and DP in Panorama). The impurities identification threshold for DS and DP was considered at (b) (4), as per ICH Guidelines Q3A/B. Data was also used from toxicology studies to set impurity thresholds for the drug product over the control of its shelf life.

A review of select impurities including impurities evaluated for their genotoxic potential in in vitro and/or in vivo or for potential qualification based on nonclinical toxicology studies (primarily for those that exceeded the accepted DS and DP impurities thresholds) follows.

Reference ID: 5357793

Review of the Qualification of Impurities Based on Toxicological Studies

The Applicant evaluated the potential qualification of impurities detected in the DP based on toxicological studies conducted with several batches of formulations used for nonclinical studies for a duration of up to 4-weeks in rats, marmosets, and dogs. Calculations of qualification limits were based on the study NOAELs from the respective nonclinical studies (selecting those with higher levels of individual impurities) and comparison to the levels in the clinical formulations at the MRHD. A total daily dose of 2.67 grams of ceftobiprole medocaril sodium, equivalent to 2 grams of the active metabolite (ceftobiprole) was considered. Toxicological qualification levels considered in the calculations were (b) (4) in the DS and (b) (4) in the DP. The Applicant's calculations and assumptions were revisited and re-calculated by the reviewer using a similar approach to that used by the Applicant but including the application of a scaling allometric factor to determine a Human Equivalent Dose (HED) in the extrapolation of the individual impurities exposures to animals compared to humans. Tables 182 and 183 below, for the DS and DP (those not identified in the DP), show the list of impurities of concern (those found not to be fully qualified in toxicological studies), margins of exposure to the maximum recommended human dose and the individual impurities qualification status. In addition of impurity specifications for the DP, In Use specifications were considered for calculations when available.

Table 184. Drug Substance Impurities Not Fully Qualified in Toxicology Studies

Impurity (Code#)	Animal Dose (mg/kg/day)[a] Study: Species Duration ID# Batch	HED[b] (mg/kg/day)	Nonclinical Study Impurity Specification (%)[c]	Clinical Impurity Specification DS (%)	Impurity Level at Patient MDD (b) (4) mg/kg/day)[d]	Margin HED/impurity at human MMD (Fold)[e]	Qualificat Status
(b) (4)							No
							No
							No
							No
							No
							No

Source: Reviewer generated table

(b) (4)

Table 185. Drug product Impurities Not Fully Qualified in Toxicology Studies

Impurity Identifier	Animal Dose (mg/kg/day)[a] Study: Species Duration ID# Batch	HED[b] (mg/kg/day)	Nonclinical Study Impurity Specification (%)	Clinical Impurity Specification DP/ In-use Spec limits (%)[c]	Impurity Level MRHD (b) (4) mg/kg/day)[d]	Margin HED/impurity at MRHD[e]	Q
(b) (4)							No
							No
							No
							No
							No
							No
							No
							No
							No
							No
							No
							No

Source: Reviewer generated table

(b) (4)

Conclusion of the Review of Impurities not Fully Qualified in Toxicology Studies

The impurity qualification review indicates that the select individual impurities in the DS and DP are not adequately qualified based on the toxicology studies considered. However, the levels of these impurities in ceftobiprole medocaril sodium for the intended clinical treatment durations and indications are considered acceptable based on the following considerations: 1) The impurities specified below share significant structural similarities with ceftobiprole medocaril sodium and represent a small fraction of the DP, therefore, these individual impurities are not likely to cause greater toxicities than those observed with exposure to the DP. 2) The overall analysis of the mutagenic potential of ceftobiprole medocaril sodium (prodrug), which shares similar structural alerts with the individual impurities evaluated, indicates that ceftobiprole medocaril sodium and associated impurities are not likely to have mutagenic potential. 3) Although mixed results have been observed with ceftobiprole medocaril sodium and ceftobiprole in in vitro mutagenicity tests (negative in a limited Ames test, positive in the mouse lymphoma assay, but negative in a more recent HPRT forward mutation assay), primarily associated with the presence of (b) (4) further in silico QSAR analysis based on application of expert knowledge and comparison to the most structurally similar analogs indicate that both compounds are predicted to be negative for bacterial mutagenicity. The analysis performed by FDA's Computational Toxicology Consultation Service experts included three QSAR state of the art models: Derek Nexus six 6.3.0 (DX), Leadscope Model Applier 2022.0.2.3 Bacterial Mut V2 model (LMA) model and CASE Ultra 1.9.0.8 GT1_BMUT model 1.9.0.2 (CU) and was consistent with ICH M2(R7) Guideline (i.e., prediction of bacterial mutagenicity using multiple complementary methodologies).

Although there are limitations in the qualification of impurities based on toxicological studies, the levels of impurities in ceftobiprole medocaril sodium are considered acceptable and no further evaluations of impurities for safety is warranted.

Review of Select Impurities ((b) (4) Evaluated for Genotoxic Potential In Vitro and/or In Vivo

The following impurities were associated with the drug substance, including those from starting materials ((b) (4)) or intermediates (b) (4)) and were further evaluated by the Applicant for their genotoxic potential. Some of these impurities include (b) (4) which in older QSAR analysis may have shown a mutagenic alert. Genotoxicity assays reviewed under this NDA as well as a summary table with the assay results are provided below.

Table 186: [redacted]: Bacterial Reverse Mutation Assay

Study Features and Methods	Details
Study No	[redacted]
Study Title	[redacted]: Bacterial Reverse Mutation Assay
Conducting laboratory	[redacted]
GLP Compliance	Yes
Drug, lot #, % purity	[redacted], batch 013, 96.2%
Strains:	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, *E. coli* WP2 uvrA
Concentrations in the definitive study/method	0, 15.81, 158.1, 500, 1581, 5000 mcg/plate (with or without S9 from phenobarbital and beta-naphthoflavone induced rats)
Basis of concentration selection	Based on preliminary solubility test and range finding test
Negative control	DMSO
Positive control	[redacted]
Formulation/vehicle	DMSO
Results	Negative. [redacted] did not induce gene mutations under the conditions tested
Validity	Valid. Positive and negative controls produced appropriate responses. High dose was appropriately selected. Precipitation observed at or above 1581 mcg/plate, however it did not affect colony counting at up to 5000 mcg/plate

Source: Reviewer generated table
Abbreviations: GLP, good laboratory practice

Table 187. [redacted]: Bacterial Reverse Mutation Assay

Study Features and Methods	Details
Study No	17/220-007M
Study Title	[redacted]: Bacterial Reverse Mutation Assay
Conducting laboratory	[redacted]
GLP Compliance	Yes
Drug, lot #, % purity	[redacted], 98.4%
Strains:	Salmonella typhimurium TA98, TA100, TA1535, TA1537, E. coli WP2 uvrA
Concentrations in the definitive study/method	0, 15.81, 158.1, 500, 1581, 5000 mcg/plate (with or without S9 from phenobarbital and beta-naphthoflavone induced rats)
Basis of concentration selection	Based on preliminary solubility test and range finding test
Negative control	DMSO
Positive control	[redacted]
Formulation/vehicle	DMSO
Results	Negative. [redacted] did not induce gene mutations under the conditions tested.
Validity	Valid. Positive and negative controls produced appropriate responses. High dose was appropriately selected.

Source: Reviewer generated table
Abbreviations: GLP, good laboratory practice

Table 188. [redacted] Bacterial Reverse Mutation Assay

Study Features and Methods	**Details**
Study No	17/221-007M
Study Title	[redacted]: Bacterial Reverse Mutation Assay
Conducting laboratory	[redacted]
GLP Compliance	Yes
Drug, lot #, % purity	[redacted] 98.2%
Strains:	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, *E. coli* WP2 uvrA
Concentrations in the definitive study/method	0, 15.81, 158.1, 500, 1581, 5000 mcg/plate (with or without S9 from phenobarbital and beta-naphthoflavone induced rats)
Basis of concentration selection	Based on preliminary solubility test and range finding test
Negative control	DMSO
Positive control	[redacted]
Formulation/vehicle	DMSO
Results	Negative. [redacted] did not induce gene mutations under the conditions tested.
Validity	Valid. Positive and negative controls produced appropriate responses. High dose was appropriately selected.

Source: Reviewer generated table
Abbreviations: GLP, good laboratory practice

Table 189. TOX8697: Bacterial Reverse Mutation Assay of (b) (4)

Study Features and Methods	Details
Study No	TOX8697
Study Title	Bacterial Reverse Mutation Assay of (b) (4)
Conducting laboratory	(b) (4)
GLP Compliance	Yes
Drug, lot #, % purity	(b) (4) lot# 961/38, 94.4%
Strains:	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, *E. coli* WP2 uvrA
Concentrations in the definitive study/method	0, 0.33, 1, 3.33, 10, 33, 100, 333, 1000, 3330, 5000 mcg/plate (with or without S9)
Basis of concentration selection	Based on preliminary solubility test and range finding test
Negative control	DMSO
Positive control	(b) (4)
Formulation/vehicle	DMSO
Results	Negative. (b) (4) did not induce gene mutations under the conditions tested.
Validity	Valid. Positive and negative controls produced appropriate responses. High dose was appropriately selected.

Source: Reviewer generated table
Abbreviations: GLP, good laboratory practice

Table 190. *Salmonella typhimurium* and *Escherichia coli* Reverse Mutation Assay with (b) (4)

Study Features and Methods	Details
Study No	RMD853
Study Title	*Salmonella typhimurium* and *Escherichia coli* reverse mutation assay with (b) (4)
Conducting laboratory	(b) (4)
GLP Compliance	Yes
Drug, lot #, % purity	(b) (4) 98.4%
Strains:	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, *E. coli* WP2 uvrA
Concentrations in the definitive study/method	0, 10, 100, 333, 1000, 2500, 5000 mcg/plate (with or without S9 from phenobarbital and beta-naphthoflavone induced rats)
Basis of concentration selection	Based on preliminary solubility test and toxicity range finding test
Negative control	DMSO
Positive control	(b) (4)
Formulation/vehicle	DMSO
Results	Negative. (b) (4) did not induce increases in revertant colony numbers under the conditions tested.
Validity	Valid. Positive and negative controls produced appropriate responses. High dose was appropriately selected.

Source: Reviewer generated table
Abbreviations: GLP, good laboratory practice

Table 191. In Vitro Chromosome Aberration Test in Chinese Hamster V79 Cells With [redacted] (RMD854)

Study Features and Methods	Details
Study title	In vitro chromosome aberration test in Chinese hamster V79 cells with [redacted] (RMD854)
Study No	RMD854
Basis of dose selection	Range finder pre-test, toxicity (according to recommendations in OECD Guidelines)
Cell line	V79 (cells from lung of Chinese hamster)
Conducting laboratory	[redacted]
Doses	56.3, 112.5, 225 mcg/Ml [redacted]; 225, 450, 900 mcg/Ml [redacted] (18-hour preparation interval, 4-hour exposure period, recovery 14 hours)
Drug, lot #, % purity	[redacted] batch 6R0C012 99.9%
Formulation/vehicle	DMSO
GLP Compliance	Yes
Incubation time	4 hours (100 metaphase plates, per culture, were scored for structural chromosome aberration)
Positive control	[redacted]
Results	[redacted] induced chromosome aberrations under the conditions of the test.
Study Validity	Valid

Source: Reviewer generated table
Abbreviations: GLP, good laboratory practice; OECD, Organization for Economic Cooperation and Development

Table 192. Micronucleus Assay in Bone Marrow Cells of the Mouse With [redacted]

Study Features and Methods	Details
Study title	Micronucleus assay in bone marrow cells of the mouse with [redacted]
Study No	RMD963
Basis of dose selection	Preliminary study, MTD
Species/strain	Mouse/ NMRI
Conducting laboratory	[redacted]
Doses	0, 500 and 2000 mg/kg (6 animals/sex/group)
Drug, lot #, % purity	[redacted] batch 6R0C012 99.9%
Formulation/vehicle	30% DMSO/ 70% PRG 400
GLP Compliance	Yes. OECD
Incubation time	Marrows obtained at 24, 48 hours post-dose
Positive control	[redacted]
Results	No cytotoxicity observed. [redacted] did not induce micronucleated cells.
Study Validity	Study considered valid [redacted] increased the number of micronucleated PCEs approximately 2-fold. At least 2000 PCEs per animal scored for micronuclei

Source: Reviewer generated table
Abbreviations: MTD, maximum tolerated dose; OECD, Organization for Economic Cooperation and Development; PCE, polychromatic erythrocytes

Table 193. Bone Marrow Micronucleus Assay in Mice Dosed by Intravenous Administration With [redacted] (Study TOX8696)

Study Features and Methods	Details
Study title	Bone marrow micronucleus assay in mice dosed by intravenous administration with [redacted]
Study No	TOX8696
Basis of dose selection	Preliminary study, MTD (30 mg/kg)
Species/strain	Mouse/ Crl:CD-1
Conducting laboratory	[redacted]
Doses	0, 10, 25 and 30 mg/kg (3/sex/group), once daily for 2 days
Drug, lot #, % purity	[redacted], batch 02903AH 98%
Formulation/vehicle	10% [redacted] in purified sterile water
GLP Compliance	Yes. OECD
Incubation time	Marrows obtained at 24, 48 hours post-dose
Positive control	[redacted]
Methods	Only cage side observations conducted (1, 4 and 24 hours post dose)
Results	Mortality in 1/12 male and 2/12 females, days 0 and 1, respectively; clinical observations at 25 mg/kg included bruising and discoloration of the site of injection (tail) in males and females (and some control animals); Erythema and wet and or stained urogenital region ≥ 25 mg/kg in males and females. No findings observed with positive control article. Negative. [redacted] was not cytotoxic to the bone marrow and did not induce increases in frequency of micronucleated PCEs. Study considered negative under the conditions tested.
Study Validity	Study considered valid ([redacted] increased the number of micronucleated PCEs approximately 2-fold. At least 2000 PCEs per animal scored for micronuclei

Source: Reviewer generated table
Abbreviations: MTD, maximum tolerated dose; OECD, Organization for Economic Cooperation and Development; PCE, polychromatic erythrocytes

Table 194. CHO/HPRT Forward Mutation Assay of [redacted] in Duplicate Cultures With Confirmatory Assay

Study Features and Methods	Details
Study No	TOX8698
Study Title	CHO/HPRT Forward Mutation Assay of [redacted] in Duplicate Cultures with Confirmatory Assay
Conducting laboratory	[redacted]
GLP Compliance	Yes
Drug, lot #, % purity	[redacted] lot# 961/38, 94.4%
Cell line	Chinese hamster ovary (CHO) cells
Concentrations in the definitive study/method	125, 250, 750, 1000 and 1500 mcg/mL
Basis of concentration selection	Based on cytotoxicity in range finding preliminary assay
Negative control	Vehicle (DMSO)
Positive control	[redacted]
Formulation/vehicle	DMSO
Results	Negative. The 2 lowest concentrations were discarded (125 and 250 mcg/mL. Average relative cell population growth was [redacted]% [redacted] and [redacted]% [redacted] at 1500 mcg/mL. The criteria for a positive assay consisted of a significantly elevated mutant frequency of at least [redacted] with activation. Although there were some statistically significant increases above concurrent controls at some test article concentrations, mutant frequencies were within the range of values in historical controls ([redacted] mutants in [redacted] cells).
Validity	Considered valid.

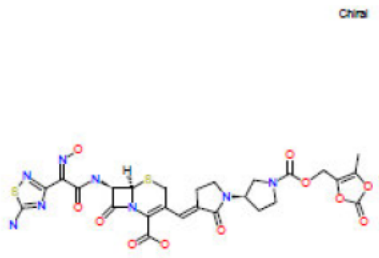
Source: Reviewer generated table
Abbreviations: CHO, Chinese hamster ovary; GLP, good laboratory practice; HPRT

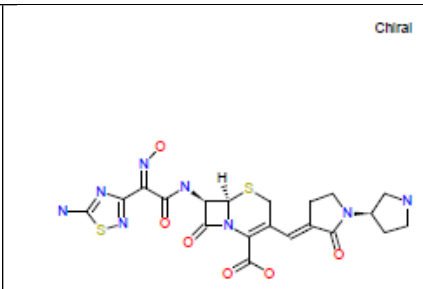
Table 195. TOX8809: Bacterial Reverse Mutation Assay of (b) (4)

Study Features and Methods	Details
Study No	TOX8697
Study Title	Bacterial Reverse Mutation Assay of (b) (4)
Conducting laboratory	(b) (4)
GLP Compliance	Yes
Drug, lot #, % purity	(b) (4), lot# 961/38, 94.4%
Strains:	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537, *E. coli* WP2 uvrA
Concentrations in the definitive study/method	Confirmatory assay -TA98 and TA100: 0.333, 1.0, 3.33, 10, 33.3, 100, 333 mcg/plate -TA1535 and TA1537: 0, 0.001, 0.00367, 0.01, 0.0367, 0.1, 0.333, 1.0, 3.33, 10, 33.3 mcg/plate -WP2uvrA: 0, 0.001, 0.00367, 0.01, 0.0367, 0.1, 0.333, 1.0, 3.33, 10 mcg/plate
Basis of concentration selection	Based on cytotoxicity in preliminary tests
Negative control	DMSO
Positive control	(b) (4)
Formulation/vehicle	DMSO
Results	Although revertant frequencies at all doses tested were similar or less than controls, however, only results with TA98 and TA100 strains may be interpretable, due to the high cytotoxicity with other bacterial strains and low doses tested in the assay. However, because only 2 bacterial strains may be interpreted, the assay is not considered valid.
Validity	

Source: Reviewer generated table
Abbreviations: GLP, good laboratory practice

Table 196. Summary of Genotoxicity Assay Results for (b) (4), (b) (4) (Ceftobiprole Medocaril Sodium and Ceftobiprole Are Included for Reference)

Identifier	Structure	Test Result	Reviewer Comments on Potential Structural Alerts
Ceftobiprole medocaril Sodium (pro-drug) BAL5788		Ames (-) Mouse Lymphoma (+) CHO/HPRT (-) Chromosomal aberration (+) QSAR (-)	(b) (4)

Ceftobiprole BAL9141		Mouse Lymphoma (+) QSAR (-)	(b) (4)
(b) (4)		Ames (-)	Purged
		Ames (-)	
		Ames (-)	
		Ames (-) In vivo micronucleus (-) Chromosomal aberration (+)	
		Ames (-) CHO/HPRT (-)	(b) (4)

(b) (4)	Ames assay uninterpretable due to significant bacterial toxicity.	(b) (4)
	In vivo micronucleus (-)	

Source: Reviewer generated table
Abbreviations: CHO, Chinese hamster ovary; HPRT, hypoxantine phosphoribosyl transferase; QSAR, quantitative structure-activity relationship

13.1.2.5.4. (b) (4) Assessment

The Applicant conducted a risk assessment and determined the risk is extremely low. In consult with the CMC review team, no (b) (4) were identified in the quality data provided

13.2. Individual Reviews of Studies Submitted With the New Drug Application

N/A

14. Clinical Pharmacology

14.1. In Vitro Studies

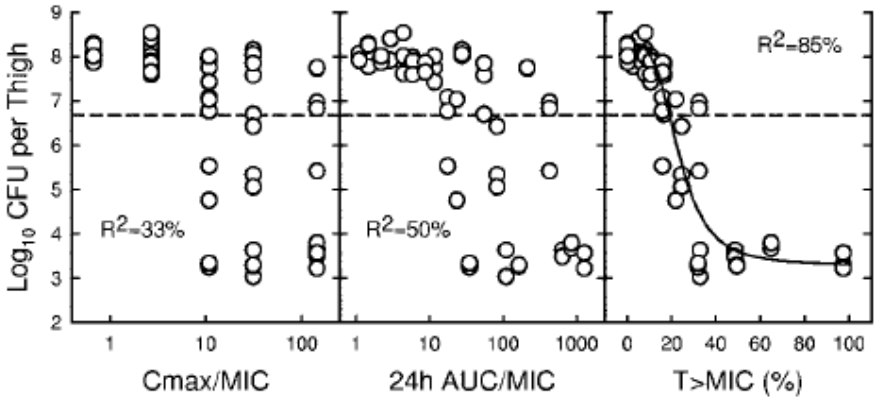
14.1.1. Preclinical Studies to Determine the PK/PD Target of Ceftobiprole

Identification of PK/PD Index

The percentage of time during a dosing interval when the unbound drug concentration exceeds the minimum inhibitory concentration (%*f*T>MIC) has been identified as the PK/PD index that best correlates with the bactericidal activity of most β-lactam drugs.

Dose fractionation studies conducted with *S. aureus* American type culture collection (ATCC) 33591 confirmed the PK/PD index best correlated with in vivo efficacy was %*f*T > MIC (Figure 23).

Figure 23. Correlation of Ceftobiprole PK-PD Indices With Efficacy Against *Staphylococcus aureus* ATCC 33591.



Source: Craig WA, Andes DR. In vivo pharmacodynamics of ceftobiprole against multiple bacterial pathogens in murine thigh and lung infection models. Antimicrob Agents Chemother. 2008 Oct;52(10):3492-6.
Each Circle Represents the Mean Data Per Mouse From Two Thighs.
Abbreviations: AUC, area under the concentration-time curve; ATCC, American type culture collection; CFU, colony forming unit; C_{max}, maximum plasma concentration; MIC, minimum inhibitory concentration; PD, pharmacodynamic; PK, pharmacokinetic; T, time

Identification of PK/PD Target

The activity of ceftobiprole was evaluated in a mouse neutropenic thigh-infection model. Mice were given single subcutaneous doses (0.2 mL/ dose) of ceftobiprole medocaril sodium (10, 40, and 160 mg/kg). A sigmoid dose-response model derived from the four-parameter Hill equation was used to calculate the dose of ceftobiprole producing a net bacteriostatic effect and 1-log10 kill over 24 hours. The %*f*T > MIC values for each static and 1-log kill dose were estimated from PK and MICs. Ceftobiprole was tested against a total of 14 gram-positive strains (n = 8 *S. aureus* and n = 6 *S. pneumoniae*) and five strains of gram-negative bacteria, including *E. coli*, *K. pneumoniae*, *P. aeruginosa*, and *E. cloacae*. The results of %*f*T > MIC to achieve net bacterial stasis, 1-log10 kill and 2-log kill are presented in Table 197.

Since free-drug plasma %*f*T>MIC targets from this study were only reported for net bacterial stasis and a 2-log10 colony forming unit (CFU) reduction from baseline, free-drug plasma %*f*T>MIC targets associated with a 1-log10 CFU reduction from baseline were linearly interpolated by averaging the targets for net bacterial stasis and a 2-log10 CFU reduction from Baseline.

Overall, these pharmacodynamics studies suggested that bactericidal (1-log kill) %*f*T>MIC values of approximately 30% and 50% would provide efficacious dosing for ceftobiprole for treatment of infections caused by gram-positive and gram-negative pathogens, respectively.

Table 197. Summary Statistics for Ceftobiprole Free-Drug Plasma %T>MIC Targets Associated With Net Bacterial Stasis and 1- and 2-log10 CFU Reductions From Baseline in a Neutropenic Murine-Thigh Infection Model

Pathogen	Measure	Free-drug plasma %T>MIC by bacterial reduction endpoint[a]		
		Net bacterial stasis	1-log_{10} CFU reduction from baseline[b]	2-log_{10} CFU reduction from baseline
S. aureus (n = 8)	Minimum	14.1	20.3	24.4
	Median	21.1	24.7	28.5
	Maximum	25.4	32.1	39.1
S. pneumoniae (n = 6)	Minimum	15.2	17.4	18.4
	Median	19.0	23.1	25.9
	Maximum	22.2	26.6	31.8
Enterobacterales (n = 4)	Minimum	35.6	38.3	40.9
	Median	41.6	50.0	58.5
	Maximum	44.6	72.3	100

Note: Abbreviations are provided in the Abbreviation Listing.
a. Free-drug plasma %T>MIC targets associated with net bacterial stasis and a 2-log_{10} CFU reduction from baseline were based on Hill-type models for individual isolates, as described in reference 20.
b. Free-drug plasma %T>MIC targets associated with a 1-log_{10} CFU reduction from baseline were interpolated.

Source: (Craig and Andes 2008)
Abbreviations: CFU, colony forming unit; MIC, minimum inhibitory concentration; T, time

PK/PD Target in Acute Pneumonia Model

Additional PK/PD studies in the neutropenic mouse lung infection model demonstrated that antibacterial effects were induced with %*f*T>MIC values at 15 – 25% of the dosing interval for S. *pneumoniae* and *S. aureus*, including MRSA.

In the first study, neutropenic mice were infected with four strains of *S. pneumoniae* (including one penicillin-sensitive strain, one penicillin-resistant strain and two highly penicillin-, ceftriaxone- and cefotaxime-resistant strains) and administered either ceftobiprole or ceftriaxone. For the four tested strains of *S. pneumoniae*, the %*f*T>MIC as a percent of the dosing interval ranged from 9 to 18% for ceftobiprole. This study evaluated total-drug, rather than free-drug, time over MIC.

Table 198. Activity of Ceftobiprole (Dosed as Ceftobiprole Medocaril Sodium) and Ceftriaxone in a Mouse Model of Acute Pneumococcal Pneumonia

Strain	Phenotype	Ceftobiprole				Ceftriaxone			
		MIC (µg/mL)	Active Dose [b] (mg/kg)	% Survival	T>MIC [a]	MIC (µg/mL)	Active dose [b] (mg/kg)	% Survival	T>MIC [a]
P-52181	Pen-S, Cro-S, Ctx-S	0.008	1.05 q12h	91	18	0.03	10 3 × q12h	100	>50
P-15986	Pen-R, Cro-S, Ctx-S	0.25	4.2 q12h	93	9	0.5	50 3 × q12h	75	50
P-40422	Pen-R, Cro-R, Ctx-R	1	17 q8h	80	13	4	100 3 × q12h	85	38
P-40984	Pen-R, Cro-R, Ctx-R	1	25 q8hh	80	15	8	200 3 × q12h	83	30

Source: (Azoulay-Dupuis 2004)
Cro-R = cefotaxime-resistant; Cro-S = cefotaxime- susceptible; Ctx-R = ceftriaxone-resistant; Ctx-S = ceftriaxone-susceptible; Pen-S = penicillin-susceptible; Cipro-R = ciprofloxacin-resistant; Pen-R = penicillin-resistant; MIC = minimal inhibitory concentration; T>MIC = Time (hours) above the minimal inhibitory concentration.
[a] Percentage of dosing interval.
[b] Dose and dosing interval achieving highest observed survival for that strain. Animals were dosed for a total of three days.

Source: (Azoulay-Dupuis et al. 2004)
Abbreviations: MIC, minimum inhibitory concentration; q8h, every 8 hours; q12h, every 12 hours; T, time

In the second study, neutropenic female mice were administered an oral inoculum of ceftobiprole with the animals' nostrils blocked until the fluid was aspirated. Eight *S. aureus* isolates (two MSSA, three community-acquired- MRSA, and three hospital-acquired- MRSA isolates) with ceftobiprole MIC values of 0.25 to 2 µg/mL were used for the PD evaluation of ceftobiprole. The PK of ceftobiprole in serum, lung tissue and epithelial lining fluid (ELF) were determined after a single subcutaneous dose in neutropenic, infected animals. PD parameters were calculated based on the unbound or free fraction of the drug with the assumption of a mouse plasma protein-binding level of 19% (free fraction, 81%).

Table 199. %*f*T>MICs for Corresponding Effective Doses of Ceftobiprole Against *Staphylococcus aureus* Isolates in an Immunocompromised Murine Pneumonia Model

Staphylococcus aureus strain	%*f*T>MIC			Maximum log_{10} CFU reduction[d]
	ED_{80}[a]	ED_{50}[b]	Stasis[c]	
MSSA 25923	10.2	8.1	7.6	4.2
MSSA 29213	19.5	14.8	13.3	3.9
HA-MRSA 56	15.5	13.7	13.1	3.9
HA-MRSA 149	13.8	8.6	6.6	4.1
HA-MRSA 152	15.9	14	13.4	3.8
CA-MRSA 144	14.3	13.8	13.6	2.9
CA-MRSA 146	6	5.5	5.6	3.6
CA-MRSA 147	21.6	17.1	14.9	3.2
Mean (SD)	14.6 (4.9)	11.9 (4)	11 (3.7)	3.7 (0.5)

Source: (Laohavaleeson 2008)
CFU = colony forming unit; ED = effective dose; CA-MRSA = community-acquired methicillin-resistant *Staphylococcus aureus*; HA-MRSA = hospital-acquired methicillin-resistant *Staphylococcus aureus*; MIC = minimal inhibitory concentration; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *Staphylococcus aureus*; SD = standard deviation; T>MIC = Time (hours) above the minimal inhibitory concentration.
[a] 80% effective dose
[b] 50% effective dose
[c] bacterial stasis exposure value
[d] log_{10} change in the numbers of CFU at 24 h versus control
Source: (Laohavaleeson et al. 2008)

A third study conducted by the same group employed the same model and eight strains as in Laohavaleeson et al (Laohavaleeson et al. 2008). but with a more detailed analysis of the PK/PD relationship correlating both plasma and ELF concentrations of ceftobiprole with the PD antibacterial effect against the eight *S. aureus* isolates in the lung.

The time kill data correlated well with %*f*T>MIC in murine plasma (coefficient of determination or $R^2 = 0.817$) and total-drug time>MIC in ELF ($R^2 = 0.801$). The ceftobiprole %*f*T>MIC and total-drug %T>MIC in ELF, required to produce a static, 1-log10, and 2-log10 kill were then calculated (Table 200). The %*f*T>MIC in plasma calculated to achieve a static dose is 8.8%, which is lower than the 11.7% calculated from their previous study.

Table 200. Relationship Between Ceftobiprole Exposure, Expressed as %fT>MIC in Murine Plasma or %T>MIC in Murine ELF and Cell Kill for Eight Strains of *Staphylococcus aureus*

	Fraction of dosing interval time>MIC	
	Plasma[a]	ELF[b]
Stasis	8.8%	7.7%
1 log_{10} kill	13.5%	12.9%
2 log_{10} kill	23%	24%

Source: (Rodvold 2009)
MIC = minimal inhibitory concentration; ELF = epithelial lining fluid; %T > MIC = percent time above MIC.
[a] %*f*T>MIC in murine plasma
[b] %T>MIC in murine ELF
Source: (Rodvold et al. 2009)

14.1.2. Protein Binding

Initial studies investigated the plasma protein binding of ceftobiprole by ultrafiltration in mouse, rat, rabbit, dog, marmoset, Cynomolgus monkey, and human (BAP00112, BAP00566). Results from both studies indicated that plasma protein binding was low, ranging from approximately 10% to 45% across species, and independent of drug concentrations (10 or 100 µg/mL). In humans, plasma protein binding ranged from 22.1% to 40.8%. These initial studies used a small sample size and showed a high intra- and inter-experimental variability for human plasma protein binding.

Table 201. Plasma Protein Binding of Ceftobiprole in Animal Species and Human

Species[Ref]	Plasma (%) Bound Ceftobiprole Conc. (µg/mL)			
	10	25	50	100
Mouse[a]	16.5	-	-	36.7
Mouse[a]	20.8	10.3	18.5	13.5
Human[a]	22.1	-	-	33.4
Rat[b]	25.0	-	-	17.1
Rabbit[b]	23.3	-	-	17.6
Dog[b]	26.9	-	-	10.8
Cyno. Monkey[b]	44.4	-	-	45.3
Marmoset[b]	25.0	-	-	35.3
Human[b]	35.2	-	-	40.8

[a] Results from two separate experiments were reported in report BAP00566; in the first experiment, plasma from mice and humans was spiked with concentrations of 10 and 100 µg/mL; in the second study, plasma from mice only were spiked with concentrations of 10, 25, 50 and 100 µg/mL. Plasma protein binding was determined by ultrafiltration. Samples (N = 2) were analyzed via LC-MS/MS.

[b] Samples (N = 2) from report BAP00112 were analyzed via a reversed-phase HPLC-UV, with a LOQ of 80 ng/mL in plasma.

Conc. = concentration; Cyno. = *Cynomolgus*; HPLC-UV = high-performance liquid chromatography; LC-MS/MS = liquid chromatographic-triple quadrupole mass spectrometry; LOQ = limit of quantification; - = not applicable; concentration not tested

Source: Study BAP00556; Study BAP00112

Due to the variability noted in studies BAP00112 and BAP00566, two additional studies were conducted to investigate human plasma protein binding. The first study utilized ultrafiltration to investigate ceftobiprole binding to human plasma protein (FK5789). Protein binding was measured at concentrations ranging from 0.5 to 100 µg/mL in pooled plasma samples from male and female healthy normal volunteers. Results indicated that plasma protein binding was low and concentration independent, with the mean percent binding equaling 17.3%.

A second study (FK6157) was conducted to confirm the extent of plasma protein binding observed, due to differences noted in the later study versus the preliminary studies. The study used freshly obtained (i.e., within 72 hours), non-pooled human plasma samples, which were incubated with ceftobiprole at concentrations of 3.5 and 35 µg/mL. Results again indicated that plasma protein binding was low and concentration independent, with a mean percent binding of 15.4%.

Reference ID: 5357793

Table 202. Plasma Protein Binding of Ceftobiprole in Humans

	Plasma (%) bound Ceftobiprole Conc. (µg/mL)					
	0.5	3.5	5	25	35	100
Human[a,c]	17.8	-	19.2	19.0	-	13.2
Human[b,c]	-	16.7	-	-	14.1	-

[a] Samples (N = 5) were obtained from healthy male and female donors (pooled). (FK5789)

[b] Samples (N = 5) were obtained from healthy male donors (6 donors, non-pooled). (FK6157)

[c] Plasma protein binding was determined by ultrafiltration. Samples were analyzed by LC-MS/MS.

Conc. = concentration; LC-MS/MS = liquid chromatographic-triple quadrupole mass spectrometry; - = not applicable; concentration not tested

Source: Study FK5789; Study FK6157

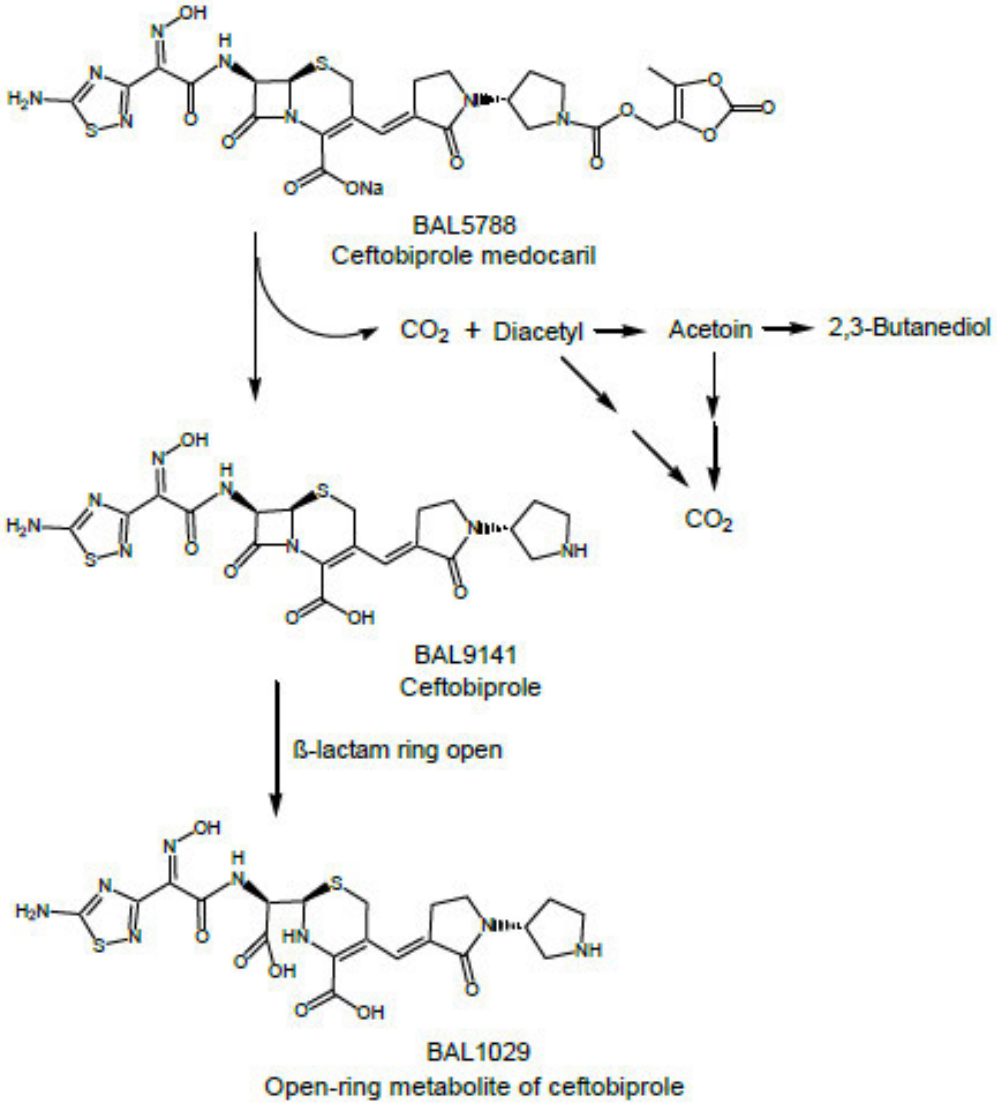
Taken together, the average protein binding of ceftobiprole is noted to be 16% and independent of ceftobiprole concentration across the range of 0.5 to 100 µg/mL.

14.1.3. Metabolism

Conversion of ceftobiprole medocaril sodium to ceftobiprole is very rapid in human plasma (38 seconds; study BAP00072). Inhibition studies with ethylenediaminetetraacetic acid suggested that type A plasma esterases are involved in the cleavage of ceftobiprole medocaril sodium to ceftobiprole (study BAP00207). A mechanistic study investigating the enzymes involved in the hydrolysis of ceftobiprole medocaril sodium demonstrated a lack of specificity of this conversion which occurred both enzymatically (by paraoxonases and other hydrolytic enzymes) and non-enzymatically (Study FK6700).

In vitro hepatocyte studies indicated the primary metabolite is the open-ring hydrolysis product (study BAP00070). The prodrug ceftobiprole medocaril sodium is rapidly hydrolyzed, in contrast to the active moiety ceftobiprole, which is slowly metabolized. At least three additional, unidentified metabolites were present in trace amounts. Thus, ceftobiprole does not appear to be a substrate of CYP enzymes. The proposed metabolism of ceftobiprole medocaril sodium is presented in Figure 24.

Figure 24. In Vitro and In Vivo Metabolism of Ceftobiprole Medocaril Sodium



Source: Study BAP00072; Study BAP00207; Study FK6700; Study BAP00070

14.1.4. Potential for CYP Enzyme-Mediated Drug-Drug Interactions

No clinical drug-drug interaction studies of ceftobiprole have been performed.

In vitro CYP inhibition data (ceftobiprole concentration up to 200 µM; 107 µg/mL) are summarized in Table 203. Only a slight (6% to 28%) inhibitory potential was apparent in the highest concentration range tested (50 to 200 µM; 26.7 to 107 µg/mL; 1009572, FK6366, and FK6604). Ceftobiprole was not a time-dependent inhibitor of prototypical CYP substrates at the highest concentrations tested (200 µM; 107 µg/mL; studies FK6366 and FK6604). Due to solubility constraints, subsequent attempts to evaluate the direct and metabolism-dependent in vitro inhibition of human CYP enzymes at higher concentrations of ceftobiprole were unsuccessful (Study FK5807).

Reference ID: 5357793

Table 203. In Vitro Cytochrome P450 Inhibition Assessment

Enzyme	Study	Highest concentration (μM)	% Inhibition
CYP1A2	1009572	100	22
	FK6604	200	NA
CYP2B6	FK6604	200	7.4
CYP2C8	FK6366	200	< 6%
CYP2C9	1009572	100	8
	FK6604	200	NA
CYP2D6	1009572	100	28
	FK6604	200	NA
CYP2C19	1009572	100	0
	FK6604	200	NA
CYP3A4/5	1009572	50	13
	FK6604	200	NA

CYP = cytochrome P450
NA = Not applicable, no value was obtained as the rates at the highest concentration evaluated were higher than the solvent control rates.

Source: Study FK6366; Study FK6604; Study FK5807

In cultured human hepatocytes treated with vehicle, ceftobiprole (up to 200 μM; 107 μg/mL) or human cytochrome P450 enzyme inducers (i.e., omeprazole, phenobarbital, and rifampin), ceftobiprole did not induce CYP1A2, CYP2B6, CYP2C9, CYP2C19, or CYP3A4/5 (Studies FK5831/XT053012, FK6603/XT083004, and XT223040).

14.1.5. Potential for Transporter-Mediated Drug-Drug Interactions

Ceftobiprole as a Substrate Of P-Glycoprotein and Breast Cancer Resistance Protein

In vitro experiments were conducted to determine whether ceftobiprole is a substrate of drug (efflux) transporters P-gp and breast cancer resistance protein in a bidirectional permeability assay across MDCKII cells (studies FK5942, XT138008, and XT228043). The bi-directional permeability of ceftobiprole (1, 10, and 100 μM; 0.535, 7.14, and 53.5 μg/mL) across MDCKII-MDR1, MDCKII-BCRP and control cells was low at all conditions (less than 3×10^{-6} cm/sec, similar to the control). The net efflux ratio of ceftobiprole was ≤2 at all concentrations and on all cell lines suggesting that ceftobiprole is not a substrate of either P-gp or BCRP.

Ceftobiprole as a Substrate of the Hepatic Transporters Organic Anion Transporter P1B1, Organic Anion Transporter P1B3, and Organic Cation Transporter 1

In vitro studies in transporter-expressing and control HEK293 cells were conducted to determine whether ceftobiprole is a substrate of the hepatic uptake transporters OATP1B1, OATP1B3, and OCT1 (Studies XT138008 and XT228043).

In Study XT138008, ceftobiprole (1, 5, and 10 μM; 0.535, 2.68, and 7.14 μg/mL) was incubated with transporter (OATP1B1, OATP1B3, or OCT1) expressing cells and control cells.

Ceftobiprole did not accumulate in transporter-expressing cells or control cells to a great extent and did not appear to be a substrate for OATP1B1, OATP1B3, or OCT1.

In Study XT228043, ceftobiprole (0.084, 0.24, 0.84, 2.4, 8.4, 28 and 84 μM) was incubated with OATP1B1 and OATP1B3 transporter expressing cells and control cells. Ceftobiprole did not show accumulation of probe substrate in transporter-expressing cells or control cells to a great extent with half-maximal inhibitory concentration (IC50) above 84 μM. The uptake ratio of 84 μM (44.5 μg/mL) ceftobiprole was less than two in the absence of OATP1B1 or OATP1B3 inhibitors. These results indicated that ceftobiprole is not a substrate of OATP1B1 or OATP1B3 at 84 μM but results at lower concentrations were inconclusive.

Ceftobiprole as a Substrate Of The Renal Transporters Organic Cation Transporter 1, Organic Cation Transporter 3, and Organic Cation Transporter 2

In vitro studies in transporter-expressing and control HEK293 cells were conducted to determine whether ceftobiprole is a substrate of the renal transporters OAT1, OAT3, and OCT2 (Study XT138008). The highest concentration feasible to be tested in these assays was 10 μM (7.14 μg/mL). Ceftobiprole accumulated in OAT1 and OCT2 expressing cells at higher levels than control cells, suggesting it may be a possible substrate of those two transporters. However, the results should be interpreted with caution, as the amount of compound that accumulated in the cells was very low, which can have a large impact on the results.

Ceftobiprole as a Substrate of the Transporters *BSEP, and MRP2*

In vitro studies in transporter-expressing and control vesicles in the presence and the absence of ATP were conducted to determine whether ceftobiprole is a substrate of the efflux transporters BSEP and MRP2. Ceftobiprole (1, 5, and 10 μM; 0.535, 2.68, and 7.14 μg/mL) did not accumulate in MRP2 or BSEP expressing vesicles in the presence of ATP at levels greater than in the absence of ATP suggesting it is not a substrate of either MRP2 or BSEP (Study XT138008).

Ceftobiprole as an Inhibitor of Transporters

In vitro experiments were conducted to determine whether ceftobiprole is an inhibitor of drug efflux transporters P-gp and BCRP in a bidirectional permeability assay across Caco-2 cells and/or MDCKII cells (Studies FK5942, XT138008, and XT228043). The potential for ceftobiprole to inhibit P-gp was evaluated in a MDR-MDCK cell assay using digoxin as the probe substrate. The permeability of digoxin in the presence and absence of ceftobiprole did not show any increase in the presence of 40 μM (21.4 μg/mL) ceftobiprole. The efflux ratios did not change significantly. As such, the results indicated that ceftobiprole is not a P-gp inhibitor. Similarly, ceftobiprole did not reduce the net efflux ratio of prazosin across MDCKII-BCRP and control cells, suggesting it is not an inhibitor of BCRP in vitro.

In vitro experiments (Studies XT138008, XT228043) were also conducted to determine whether ceftobiprole is an inhibitor of uptake transporters OATP1B1, OATP1B3, OCT1, OCT2, OAT1, and OAT3 and of efflux transporters MATE1 and MATE2-K by measuring the accumulation of a probe substrate in a transporter-expressing and control HEK293 cells.

At the concentrations tested (0.3 to 200 μM; 0.16 to 107 μg/mL) (XT138008), ceftobiprole inhibited the accumulation of estradiol glucuronide in the OATP1B1 and OATP1B3 expressing

cells with IC_{50} values of 67.6 and 44.1 μM (36.14 μg/mL and 23.57 μg/mL), respectively. In a second study (study XT228043), ceftobiprole IC50 for OATP1B1 and OATP1B3 inhibition were determined to be above 84 μM (44.5 μg/mL, maximum achievable concentration). An investigational drug has the potential to inhibit OATP1B1/3 in vivo if the R value is >1.1. The R values for OATP1B1 and OATP1B3 were 1.50 and 1.76, respectively. Thus, ceftobiprole may increase concentrations of drugs eliminated by OATP1B1 and OATP1B3. Since the in vitro studies indicate that a drug is an OATP1B1 or OATP1B3 inhibitor, we recommend the Applicant conduct an in vivo drug interaction study evaluating ceftobiprole as an inhibitor of OATP1B1 and OATB1B3 transporters as a post-marketing requirement (see Section 8.2.1).

Ceftobiprole was not an inhibitor of MATE1, OAT1, OAT3, OCT1, or OCT2 as it did not show accumulation of probe substrate in transporter-expressing cells or control cells to a great extent with IC_{50} were above 84 μM (44.5 μg/mL) (Studies XT138008 and XT228043).

It was not possible to determine the inhibition potential of ceftobiprole on MATE2-K due to possible solvent-related issues with the in vitro assay (Study XT228043).

In vitro experiments were conducted to determine whether ceftobiprole is an inhibitor of efflux transporters BSEP and MRP2 by measuring the accumulation of a probe substrate (taurocholic acid or estradiol glucuronide) in vesicles in the presence of ceftobiprole (Study XT138008). The transport of taurocholic acid was reduced to less than 25% of the control in the presence of all concentrations of ceftobiprole (0.3 to 200 μM; 0.16 to 107 μg/mL) indicating that the IC_{50} could be lower than 0.3 μM. The Applicant attributes this inhibition to the acetic acid in the incubation that could have had an effect on the activity. Ceftobiprole did not inhibit the MRP2 mediated transport of estradiol 17-β-D-glucuronide.

14.2. In Vivo Studies

14.2.1. Single Ascending Dose

Study NP16104

NP16104 was a phase 1 single-center, single-dose, open-label, intra-subject, dose-escalation study in three healthy male volunteers aged 18 to 30 years. Each subject received single 30-min infusions of 250 mg, 500 mg, and 750 mg of ceftobiprole medocaril sodium with a washout period of 72 hours between treatments.

Blood samples were collected prior to each drug administration and up to 24 hours after start of infusion. Urine was collected pre-dose and up to 24 hours post-dose. Ceftobiprole and ceftobiprole medocaril sodium were quantified using a validated high-performance liquid chromatography method and PK parameters were derived by non-compartmental and 2-compartmental methods. Plasma and urine PK parameters of ceftobiprole are summarized in Table 204 and Table 205, respectively.

Plasma concentrations of ceftobiprole medocaril sodium at the end of the infusion amounted to only 2% to 4% of those of the active principle, ceftobiprole. Thus, the PK of ceftobiprole medocaril sodium could not be determined.

Reference ID: 5357793

Table 204. Pharmacokinetic Parameters of Ceftobiprole After Single Ascending Intravenous Infusions (n=3)

Variable	BAL5788 250 mg/30 min	BAL5788 500 mg/30 min	BAL5788 750 mg/30 min
$AUC_{0-\infty}$ ($\mu g \cdot h/mL$)	48.7 (6.24)	103 (10.4)	135 (6.50)
C_{max} ($\mu g/mL$)	23.9 (14.0)	41.5 (30.5)	62.1 (6.83)
$^*t_{1/2\alpha}$ (h)	0.45 (± 0.13)	1.07 (± 0.68)	0.43 (± 0.20)
$t_{1/2\beta}$ (h)	2.90 (± 0.24)	3.16 (± 0.17)	3.37 (± 0.35)
V_{ss} (L)	14.9 (± 2.00)	15.4 (± 2.39)	17.6 (± 1.27)
CL_S (L/h)	5.14 (6.27)	4.87 (10.6)	5.56 (6.46)
CL_R (L/h)	2.86 (43.9)	2.54 (20.4)	2.90 (12.4)

*obtained by 2-compartmental analysis
Geometric means (geometric CV%) are reported for AUC, C_{max}, CL_S, and CL_R.
Arithmetic means (± SD) are presented for $t_{1/2\alpha}$, $t_{1/2\beta}$, and V_{ss}.
Source: Study NP16104
Abbreviations: AUC0-∞, area under the concentration-time curve from time zero to infinity; CL, clearance; C_{max}, maximum plasma concentration; t1/2, half-life; Vs, steady state rate achieved by the system;

Table 205. Urinary Excretion of Ceftobiprole and the β-Lactam Ring-Open metabolite (BAL2070) after Single Ascending Intravenous Infusions (N=3)

Urinary Excretion 0-24h (% of dose)	BAL5788 250 mg/30 min	BAL5788 500 mg/30 min	BAL5788 750 mg/30 min
BAL9141	59.6% (± 24.1)	53.6% (± 14.5)	52.8% (± 10.0)
BAL2070	3.2%*	2.9% (± 1.63)	2.7% (± 1.69)

Data are mean (± SD).
*only one value
Source: Study NP16104

Study BAP00006

BAP00006 was a phase 1, single-center, double-blind, randomized, placebo-controlled single, ascending dose study involving five sequential dose levels of ceftobiprole medocaril sodium. In total, 40 healthy, male subjects between the ages of 20 and 40 years old were randomly assigned to one of the following five dose groups: 125, 250, 500, 750, or 1000 mg ceftobiprole medocaril sodium. Each dose group included 8 subjects (ceftobiprole medocaril sodium, n = 6; placebo, n = 2).

Blood samples were collected immediately before infusion start and at up to 24 hours after the start of infusion. Subjects were asked to void urine immediately before starting the first urine collection interval, 2 hours before dosing. Subsequently, urine was collected at –2 to 0 h (control) and up to 24 hours after the start of infusion. Ceftobiprole medocaril sodium and ceftobiprole were quantitated by use of a validated LC/LC-MS/MS method and PK parameters were derived by non-compartmental and two-compartmental methods. A one-way analysis of variance was used to assess dose-proportionality. The mean (standard deviation [SD]) %fT >

Reference ID: 5357793

MIC accounting for 16% protein binding in the 125-mg dosage group was 12.3 (2.4) and 8.2 (1.6) for q8h and q12h, respectively. In the 250-mg dosage group, the mean (SD) %fT>MIC was 35.5 (5.9) and 23.7 (3.9) for q8h and q12h, respectively.

Pharmacokinetic parameters for ceftobiprole and cumulative urinary recovery following single intravenous administration of 125, 250, 500, 750 and 1000 mg of ceftobiprole medocaril sodium are summarized in Table 206. No significant dose effect was found for AUC ($p = 0.187$) or C_{max} ($p = 0.599$), thus AUC and C_{max} were presumed to be dose proportional over the tested dose range.

Table 206. Summary of Ceftobiprole Pharmacokinetic Parameters Following Single Intravenous Administration of 125, 250, 500, 750 and 1000 mg of Ceftobiprole Medocaril Sodium in Healthy, Male Subjects

	Treatment A 125 mg/30 min	Treatment B 250 mg/30 min	Treatment C* 500 mg/30 min	Treatment D 750 mg/30 min	Treatment E 1000 mg/30 min
$AUC_{0-\infty}$ (µg·h/mL)	20.3 (± 2.82)	43.7 (± 5.99)	76.6 (± 3.88)	135 (± 27.6)	151 (± 9.04)
C_{max} (µg/mL)	9.87 (± 0.78)	19.5 (± 2.75)	35.5 (± 6.79)	59.6 (± 10.7)	72.2 (± 8.78)
$t_{1/2}$ (α)** (h)	0.37 (± 0.14)	0.47 (± 0.15)	0.57 (± 0.22)	0.48 (± 0.27)	0.56 (± 0.36)
$t_{1/2}$ (β) (h)	2.84 (± 0.21)	3.42 (± 0.29)	3.44 (± 0.30)	3.47 (± 0.37)	3.25 (± 0.20)
V_{SS} (L)	17.9 (± 2.00)	17.8 (± 3.11)	19.8 (± 1.95)	18.4 (± 2.63)	18.9 (± 2.31)
CL_S (L/h)	6.27 (± 0.97)	5.81 (± 0.84)	6.54 (± 0.34)	5.74 (± 1.13)	6.64 (± 0.41)
CL_R (L/h)	4.60 (± 0.38)	4.35 (± 0.57)	5.07 (± 0.22)	4.08 (± 0.75)	4.16 (± 0.57)
Urinary Recovery (% of dose)	74.2 (± 8.14)	76.1 (± 14.4)	77.5 (± 3.27)	71.3 (± 1.48)	62.5 (± 6.33)

Values are presented as arithmetic means (±SD) and were obtained by noncompartmental analysis with N = 6 unless indicated
*n=5. One subject (No. (b) (6)) received an incomplete dose and was excluded from analysis
**obtained by 2-compartmental analysis
Source: BAP00006
Abbreviations: AUC0-∞, area under the concentration-time curve from time zero to infinity; CL, clearance; C_{max}, maximum plasma concentration; t1/2, half-life; Vs, steady state rate achieved by the system

Because of low plasma concentrations, no PK evaluation was performed for ceftobiprole medocaril sodium. No measurable concentrations of the β-lactam ring-open metabolite BAL2070 were detected in plasma.

Reviewer Comments

Pharmacokinetic analyses were conducted after the clinical study report was issued to either further characterize the PK of ceftobiprole (accumulation index), correct a data discrepancy (urine volume), or incorporate new information (protein binding). The overall mean predicted accumulation index for the 8-hour and 12-hour dosing intervals was 1.23 and 1.09, respectively. Individual and mean ceftobiprole urine PK parameters are outlined in Table 207.

Table 207. Individual And Mean Ceftobiprole Urine Pharmacokinetic Parameters Following Intravenous Infusion of Ceftobiprole 125 mg to Healthy Male Volunteers

Subject ID	CL_R (L/h)	Ae,% of dose
(b) (6)	4.51	80.8
	4.81	71.9
	4.87	91.7
	6.02	75.2
	4.25	70.0
	4.33	72.6
N	6	6
Mean	4.80	77.0
SD	0.65	8.11
Min	4.25	70.0
Max	6.02	91.7
Median	4.66	73.9

Source: Study BAP00006
Abbreviations: Ae, amount of drug excreted in urine or feces; CL, clearance

Study *BAP00036*

BAP00036 was a single dose, single center, open-label, comparative study with 24 healthy subjects, 12 females and 12 males. Ceftobiprole medocaril sodium at a dose of 750 mg (ceftobiprole equivalents) was administered as a single 30-minute intravenous infusion on Study Day 1. Blood samples were collected 15 to 30 minutes before infusion start and up to 24 hours after the start of infusion. Urine was collected at –2 to 0 hour (control and last portion of the 24-hour urine collection on Study Day –1) and up to 24 hours after the start of infusion. Ceftobiprole medocaril sodium and ceftobiprole were quantitated by a validated LC-MS/MS method and PK parameters were derived by non-compartmental methods.

Pharmacokinetic parameters and cumulative urinary recovery for ceftobiprole following single intravenous administration of 750 mg of ceftobiprole medocaril sodium in healthy male and female subjects are summarized in Table 208. The mean (SD) %fT>MIC was 81.6 (6.83) and 55.6 (7.85) for subjects receiving q8h and q12h dosing, respectively.

Because ceftobiprole medocaril sodium was not measurable in most plasma samples obtained after infusion, no PK evaluation was possible. Assessment of lactam ring open metabolite BAL2070 was not performed.

Table 208. Summary of Ceftobiprole Pharmacokinetic Parameters Following Single Intravenous Administration of 750 mg of Ceftobiprole Medocaril Sodium in Healthy Male and Female Subjects

Parameter	Males N=12	Females N=12	Estimated Geometric Mean Ratios	p-Value
$AUC_{0-\infty}$ (μg·h/mL)	137 (± 14.5)	157 (± 21.5)	(nd)	(nd)
AUC_{last} (μg·h/mL)	136 (± 14.4)	156 (± 21.4)	1.14	0.020
AUC_{0-12h} (μg·h/mL)	131 (± 13.6)	153 (± 21.2)	(nd)	(nd)
C_{max} (μg/mL)	65.6 (± 8.44)	79.3 (± 13.3)	1.20	0.008
$t_{1/2}$ (β) (h)	3.42 (± 0.28)	2.78 (± 0.45)	0.80	0.002
V_{SS} (L)	17.0 (± 1.83)	12.1 (± 2.55)	0.70	< 0.0001
CL_S (L/h)	5.54 (± 0.58)	4.87 (± 0.73)	0.88	0.022
CL_R (L/h)	5.11 (± 0.91)	4.67 (± 0.75)	0.92	0.209
Urinary Recovery* (% of dose)	92.3 (± 12.7)	96.1 (± 9.92)	(nd)	(nd)

Values are presented as arithmetic means (±SD); (nd): analysis not done; * 0-24 hour cumulative recovery

Source: BAP00036
Abbreviations: AUC0-12, area under the concentration-time curve from time 0 to 12 hours; AUC0-∞, area under the concentration-time curve from time zero to infinity; AUClast, area under the concentration-time curve from the time of dosing to the time of the last measurable (positive) concentration; CL, clearance; C_{max}, maximum plasma concentration; T½, half-life; Vss, steady state rate achieved by the system

Study BAP00210

BAP00210 was a single-center, open-label, randomized, parallel group, single-dose phase 1 study. A total of 36 subjects (18 male, 18 female) were randomly allocated in a 1:1 ratio to one of two dosing regimens: ceftobiprole medocaril sodium (as ceftobiprole equivalents) 750 mg infused over 30 minutes or 500 mg infused over 60 minutes. Each dosing regimen included 18 (9 male, 9 female) subjects. Blood samples were collected on Study Day 1 immediately before start of infusion and up to 24 hours after start of infusion. Ceftobiprole medocaril sodium and ceftobiprole were quantitated using a validated LC/LC-MS/MS method and PK parameters were derived by non-compartmental methods. Time above the minimum inhibitory concentration (T > MIC) was determined using 4 μg/mL as an MIC value and 12 hours as the dosing interval.

Pharmacokinetic parameters for ceftobiprole following single intravenous administration of 500 mg and 750 mg infusions of ceftobiprole medocaril sodium in healthy subjects are summarized Table 209.

Because ceftobiprole medocaril sodium was not measurable in plasma samples obtained after infusion, no PK evaluation was possible.

Table 209. Summary of Ceftobiprole Pharmacokinetic Parameters Following Single Intravenous Administration of 500 and 750 mg Infusions of Ceftobiprole Medocaril Sodium in Healthy Subjects

Parameter	BAL5788	
	750 mg in 30 min N = 18	500 mg in 60 min N = 18
$AUC_{0-\infty}$ (μg·h/mL)	154 (± 19.2)	116 (± 20.2)
AUC_{last} (μg·h/mL)	152 (± 20.3)	113 (± 21.3)
C_{max} (μg/mL)	57.9 (± 11.5)	34.2 (± 6.05)
$t_{1/2}$ (h)	2.89 (± 0.47)	2.85 (± 0.55)
Vss (L)	13.7 (± 2.98)	11.0 (± 2.93)
CL_S (L/h)	4.94 (± 0.62)	4.46 (± 0.84)

Values are presented as arithmetic means (±SD)

Source: BAP00210
Abbreviations: AUC0-∞, area under the concentration-time curve from time zero to infinity; AUClast, area under the concentration-time curve from the time of dosing to the time of the last measurable (positive) concentration; CL, clearance; C_{max}, maximum plasma concentration; T½, half-life; Vss, steady state rate achieved by the system

Mean plasma concentrations of total ceftobiprole and free (unbound) ceftobiprole determined at various times after start of infusion with the dosing regimens studies are presented in Table 210. The mean (SD) %fT>MIC for subjects receiving 500 mg was 65.3 (9.12) and 43.6 (6.1) for q8h and q12h, respectively. The mean (SD) %fT>MIC for subjects receiving 750-mg was 80.2 (7.8) and 53.4 (5.2) for q8h and q12h, respectively.

Table 210. Mean Plasma Concentrations of ceftobiprole at Various Times After the Start of Infusion Following Single Intravenous Administration of 500 mg and 750 mg Infusions of Ceftobiprole Medocaril Sodium in Healthy Subjects

Time after Start of Infusion	Plasma Concentration of BAL9141 (μg/mL)	
	Total BAL9141	Free (Unbound) BAL9141*
750 mg/ 30 min (N=18)		
4 hours	10.0	6.20
5 hours	6.92	4.29
6 hours	5.34	3.31
500 mg/ 60 min (N=18)		
4 hours	7.69	4.77
5 hours	5.21	3.23
6 hours	4.01	2.49

* Corrected for 38% protein binding in human plasma.

Source: BAP00210

Study CSI-1004

CSU-1004 was a single center, open-label study in a total of 28 healthy men and nonpregnant women between the ages of 18 and 55 years, inclusive. Subjects received a total of 8 intravenous doses (1 single dose and 7 multiple doses) at approximately the same time(s) each day during the study. Each dose of 500 mg ceftobiprole was infused over a 2-hour period. On Day 1, a single dose was administered; 3 doses were each administered on Days 3 and Day 4, and 1 dose was infused on Day 5.

Blood for PK analysis was collected for 24 hours following the infusions on Days 1 and 5, before each infusion on Days 3 and 4, and at the end of each infusion on Day 4. Urine was collected for 48 hours after dosing on Day 1 and up to 24 hours after dosing on Day 5.

Ceftobiprole medocaril sodium and ceftobiprole plasma and urine concentrations were assayed using validated LC-MS/MS method. Pharmacokinetic parameters of ceftobiprole and/or the open-ring metabolite were estimated on Days 1 and 5. Accumulation ratio was calculated by AUCτ on Day 5/ AUCτ on Day 1. In addition, the percentage of time at which ceftobiprole was above the MIC for the duration of the dosing interval (%T>MIC) was calculated for each individual and summarized descriptively.

Reviewer Comments:

The methods by which PK parameters were derived were not specified (i.e., non-compartmental, compartmental).

Pharmacokinetic parameters for ceftobiprole following single and multiple intravenous administration of ceftobiprole medocaril sodium are summarized in Table 211. Weight-normalized PK parameters are summarized in Table 211.

Reference ID: 5357793

Table 211. Summary of Ceftobiprole Pharmacokinetic Parameters Following Single (Day 1) and Multiple (Day 5) Intravenous Administration of Ceftobiprole Medocaril Sodium in Healthy Adults

	Day 1			Day 5		
Pharmacokinetic Parameters	All Subjects N=28	Male N=14	Female N=14	All Subjects N = 27	Male N=14	Female N=13
t_{max} (h)[a]	1.97	1.97	1.97	1.97	1.91	1.97
C_{max} (µg/mL)	29.2 (5.52)	25.2 (2.92)	33.3 (4.36)	33.0 (4.83)	30.6 (4.59)	35.5 (3.71)
$AUC_{0\text{-}8h}$ (µg•h/mL)	90.0 (12.4)	81.5 (7.59)	98.6 (10.2)	102 (11.9)[b]	96.2 (9.66)[b]	107 (11.7)[b]
AUC_{last} (µg•h/mL)	104 (13.9)	95.3 (10.5)	112 (11.9)	117 (14.5)	113 (13.2)	122 (14.9)
AUC_{∞} (µg•h/mL)	104 (13.9)	95.8 (10.5)	112 (12.0)	NC	NC	NC
$t_{1/2}$ (h)	3.1 (0.3)	3.2 (0.3)	3.0 (0.1)	3.3 (0.3)	3.5 (0.3)	3.2 (0.3)
CL_S (L/h)	4.89 (0.687)	5.28 (0.616)	4.50 (0.522)			
CL_{SS} (L/h)				4.98 (0.582)	5.25 (0.547)	4.70 (0.491)
Vd_z (L)	21.7 (3.37)	24.0 (2.76)	19.4 (2.14)			
Vd_{SS} (L)				15.5 (2.33)	17.2 (1.75)	13.7 (1.19)
accRatio	NA	NA	NA	1.14 (0.101)	1.18 (0.105)	1.10 (0.0769)
accIndex				1.20 (0.0358)	1.21 (0.044)	1.19 (0.0188)
CL_R (L/h)	4.08 (0.718)	4.40 (0.798)	3.76 (0.458)	4.28 (0.572)[c]	4.45 (0.520)	4.09 (0.587)[d]
A_e%	83.1 (9.06)	82.8(10.33)	83.4 (7.98)	98.8 (5.76)[c]	99.3 (5.27)	98.2 (6.5)[d]

[a] Median
[b] AUC_τ
[c] n=26
[d] n=12
NC = Not calculated
NA = Not applicable

Source: CSI-1004Study Report, Section 4.3
Abbreviations: Ae, amount of drug excreted in urine or feces; AUC0-8h, area under the concentration-time curve from time 0 to 8 hours; AUC∞, area under the concentration-time curve from time zero to infinity; AUClast, area under the concentration-time curve from the time of dosing to the time of the last measurable (positive) concentration; CL, clearance; C_{max}, maximum plasma concentration; T½, half-life; Vss, steady state rate achieved by the system

Ceftobiprole medocaril sodium plasma concentrations were not detectable at 10 minutes or later after the end of the infusion. No PK analysis was performed for ceftobiprole medocaril sodium.

Pharmacokinetic parameters for the ring-opened metabolite following single and multiple intravenous administration of ceftobiprole medocaril sodium are summarized in Table 212.

Table 212. Summary of Open-Ring Metabolite Pharmacokinetic Parameters Following Single (Day 1) and Multiple (Day 5) Intravenous Administration of Ceftobiprole Medocaril Sodium in Healthy Adults

	Day 1			Day 5		
Pharmacokinetic Parameters	All Subjects N=28	Male N=14	Female N=14	All Subjects N = 27	Male N=14	Female N=13
t_{max} (h)[a]	1.97	1.97	1.90	1.97	1.97	1.97
C_{max} (µg/mL)	0.804 (0.214)	0.681 (0.106)	0.927 (0.226)	1.07 (0.254)	0.963 (0.184)	1.19 (0.270)
$AUC_{0\text{-}8h}$ (µg•h/mL)	3.68 (0.882)	3.16 (0.507)	4.20 (0.884)	5.45 (1.35)[b]	5.03 (1.20)[b]	5.91 (1.40)[b]
AUC_{last} (µg•h/mL)	5.01 (1.35)	4.35 (0.853)	5.68 (1.46)	8.13 (2.40)	7.67 (2.29)	8.63 (2.51)
AUC_{∞} (µg•h/mL)	5.61 (1.39)	4.97 (0.998)	6.24 (1.47)	NC	NC	NC
$t_{1/2}$ (h)	4.7 (0.8)	4.8 (0.9)	4.5 (0.7)	5.8 (0.9)	6.0 (0.8)	5.6 (1.1)
accRatio	NA	NA	NA	1.48 (0.195)	1.58 (0.192)	1.37 (0.134)
accIndex	NA	NA	NA	1.44 (0.129)	1.47 (0.138)	1.41 (0.118)
A_e%[c]	4.71 (0.845)	4.61 (0.766)	4.81 (0.935)	6.66 (0.719)	6.99 (0.666)	6.27 (0.594)[d]

[a] Median
[b] AUC_{τ}
[c] A_e normalized by the ratio of molecular weights of ceftobiprole to the open-ring metabolite
[d] n=12
NC = Not calculated
NA = Not applicable

Source: CSI-1004
Abbreviations: Ae, amount of drug excreted in urine or feces; AUC0-8h, area under the concentration-time curve from time 0 to 8 hours; AUC∞, area under the concentration-time curve from time zero to infinity; AUClast, area under the concentration-time curve from the time of dosing to the time of the last measurable (positive) concentration; CL, clearance; C_{max}, maximum plasma concentration; T½, half-life; Vss, steady state rate achieved by the system

The total amount of each analyte excreted in the urine, expressed in terms of ceftobiprole equivalents based on molecular weight, and the percent of dose excreted, are presented in Table 213. The mean (SD) %fT>MIC for all subjects enrolled was 78.2 (6.54).

Table 213. Mean Urinary Recovery (Expressed as a Percentage of Dose) of Ceftobiprole Prodrug, Active Moiety, and Open Ring Metabolite Following Single (Day 1) and Multiple (Day 5) Intravenous Administration of Ceftobiprole Medocaril Sodium in Healthy Adults

	Day 1		Day 5	
Analyte	A_e (mg)	A_e (% of 500 mg dose)	A_e (mg)	A_e (% of 500 mg dose)
Ceftobiprole (BAL9141)	416 (45.3)	83.1 (9.06)	494 (28.8)	98.8 (5.76)
Ceftobiprole Medocaril (BAL5788)	3.38 (1.68)	0.68 (0.34)	3.92 (1.66)	0.78 (0.33)
Open-Ring Metabolite (BAL1029)	23.5 (4.22)	4.71 (0.84)	33.3 (3.60)	6.66 (0.72)
Total Urinary Recovery	442 (48.1)	88.5 (9.63)	531 (30.0)	106 (6.01)

Source: CSI-1004 Study Report
Abbreviations: Ae, amount of drug excreted in urine or feces

CSI-1006

CSI-1006 was 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 antibacterial drugs.

Approximately 60 male and female pediatric subjects (≥3 months to <18 years of age) were divided into four groups of 15 subjects. Ceftobiprole was sequentially dosed in subjects ≥12 to <18 years of age to subjects ≥3 months to <2 years only after evaluation of the safety and PK in each age group.

Each subject received a 2-hour IV infusion of ceftobiprole administered alone at any time after the first dose of systemic antibacterial therapy. The following doses were administered to each age group:

- ≥12 and <18 years: 7 mg/kg
- ≥6 and <12 years: 10 mg/kg
- ≥2 and <6 years of age and ≥3 months and <2 years of age: 15 mg/kg

Ceftobiprole medocaril sodium, ceftobiprole, and the open-ring metabolite open-ring metabolite was quantified in plasma and urine samples using a validated LCMS-MS/MS method.

The plasma and urine PK parameters for ceftobiprole across all age groups studied following administration of ceftobiprole are presented in Table 214 .

Table 214. Mean (SD) Pharmacokinetic Parameters of Ceftobiprole per Age Group

PK Parameter		3months to <2years 15 mg/kg	2years to <6years 15 mg/kg	6years to <12years 10 mg/kg	12years to <18years 7 mg/kg[b]
n		13	13	15	14
C_{max}	(µg/mL)	24.4 (9.13)	28.7 (7.04)	25.2 (4.91)	17.4 (3.21)
t_{max}	(h)[a]	1.98 (1.97-3.10)	1.98 (1.93-2.00)	1.98 (1.92-2.25)	1.98 (1.95-2.10)
t_{last}	(h)[a]	12.00 (8.00-24.00)	12.00 (10.73-24.00)	12.00 (11.87-24.07)	12.17 (11.25-24.08)
AUC_{last}	(µg•h/mL)	79.2 (29.4)	85.7 (27.0)	78.3 (16.2)	62.3 (14.2)
AUC_{∞}	(µg•h/mL)	80.7 (30.0)	87.7 (28.2)	79.5 (16.2)	63.5 (14.3)
$t_{½}$	(h)	2.10 (0.784)	2.08 (0.437)	2.22 (0.509)	2.41 (0.471)
λ_z	(h^{-1})	0.361 (0.0927)	0.346 (0.0645)	0.327 (0.0720)	0.297 (0.0527)
Vd_{ss}	(L)	6.65 (3.62)	9.99 (3.83)	13.8 (5.16)	23.0 (3.66)
Vd_{ss}/BW	(L/kg)	0.631 (0.294)	0.558 (0.209)	0.414 (0.1140)	0.392 (0.0735)
CL	(L/h)	2.25 (1.16)	3.40 (1.27)	4.35 (1.29)	6.73 (1.14)
CL/BW	(mL/min/kg)	3.57 (1.56)	3.19 (1.20)	2.19 (0.494)	1.93 (0.507)
CL_{CR}	(mL/min)	120 (36.4)	164 (35.3)	173 (62.4)	137 (38.4)
CL_R	(L/h)	1.47 (0.998)[c]	2.38 (1.74)[e]	4.55 (3.46)	5.58 (1.77)
CL_R/BW	(mL/min/kg)	2.29 (1.47)[c]	2.10 (1.43)[e]	2.23 (1.26)	1.60 (0.651)
Ae	(%dose)	62.6 (41.3)[d]	63.3 (40.7)[f]	102 (51.8)	86.4 (27.9)[d]

BW - Body Weight

[a] Median (range)

[b] 2 subjects in the PK Analysis Set received the protocol-defined maximum ceftobiprole dose of 500 mg.

[c] n=12

[d] n=15

[e] n=13

[f] n=14

Source: Study CSI-1006

Abbreviations: Ae, amount of drug excreted in urine or feces; AUC∞, area under the concentration-time curve from time zero to infinity; AUClast, area under the concentration-time curve from the time of dosing to the time of the last measurable (positive) concentration; BW, body weight; CL, clearance; CLcr, creatine clearance; C_{max}, maximum plasma concentration; n, number of subjects meeting criteria; T_{last}, time to maximum concentration from last dosing; T_{max}, time to maximum concentration; T½, half-life; Vdss, steady state volume of distribution; λz, terminal phase elimination rate constant

Reference ID: 5357793

14.2.2. Multiple Ascending Dose

Study BAP00010

BAP00006 was a phase 1, single-center, double-blind, randomized, placebo-controlled multiple ascending dose study involving two dose levels of ceftobiprole medocaril sodium (500 mg and 750 mg of ceftobiprole equivalents).

Sixteen subjects were randomly assigned to one of the two dose groups. Each dose group included 8 subjects (ceftobiprole medocaril sodium, n = 6; placebo, n = 2). A third dose group (1000 mg) was planned but no subjects received this dose, due to the occurrence of elevated liver transaminase levels in approximately 50% of subjects dosed with placebo or ceftobiprole medocaril sodium. Adverse changes were noted in 2 of 4 subjects receiving placebo and in 7 of 12 subjects receiving BAL5788 at 500 mg (3 of 6 subjects) or 750 mg (4 of 6 subjects).

On Study Days 1 and 8, blood samples were collected immediately before infusion start and up to 24 hours after the start of infusion. To determine the trough levels of ceftobiprole, blood samples were collected before the morning infusion on Study Days 3, 5, and 7. Urine was collected at –2 to 0 hours (control) and up to 24 hours after the start of infusion on Study Days 1 and 8.

Ceftobiprole medocaril sodium and ceftobiprole were quantitated by a validated LC/LC-MS/MS method and PK parameters were derived by non-compartmental and two-compartmental methods. Drug accumulation, R_{ACC}, was estimated by $AUC_{0\text{-}12h}$ on Day 8 divided by $AUC_{0\text{-}12h}$ on Day 1. Time above the minimum inhibitory concentration (T > MIC) was determined (MIC_{90} for MRSA = 2 μg/mL). A one-way analysis of variance was used to assess dose-proportionality.

Pharmacokinetic parameters and cumulative urinary recovery for ceftobiprole following multiple intravenous administration of 500 and 750 mg of ceftobiprole medocaril sodium in healthy, male subjects are summarized in

Table 215. The mean (SD) %fT>MIC for subjects receiving 500 mg was 47.9 (4.2) on Day 1 and 49.9 (5.3) on Day 8. The mean (SD) %fT>MIC for subjects receiving 750 mg was 61.2 (5.4) on Day 1 and 62.5 (4.4) on Day 8.

Reference ID: 5357793

Table 215. Summary of Ceftobiprole Pharmacokinetic Parameters Following Multiple Intravenous Administration of 500 and 750 mg of Ceftobiprole Medocaril Sodium in Healthy, Male Subjects

Dose (infused over 30 min)	500 mg Day 1	500 mg Day 8	750 mg Day 1	750 mg Day 8
$AUC_{0-\infty}$ (µg·h/mL)	101 (± 9.04)	108 (± 22.2)	156 (± 19.3)	165 (± 12.8)
AUC_{0-12h} (µg·h/mL)	95.9 (± 7.59)	102 (± 20.0)	148 (± 17.6)	156 (± 11.1)
C_{max} (µg/mL)	40.6 (± 7.38)	44.2 (± 10.8)	60.7 (± 4.55)	60.6 (± 9.99)
$t_{1/2\alpha}$ * (h)	1.06 (± 0.46)	1.03 (± 0.42)	0.96 (± 0.59)	0.99 (± 0.50)
$t_{1/2\beta}$ (h)	3.63 (± 0.48)	4.04 (± 0.31)	3.64 (± 0.32)	4.11 (± 0.41)
V_{SS} (L)	16.4 (± 2.11)	16.7 (± 3.58)	16.3 (± 1.82)	16.1 (± 2.20)
CL_S (L/h)	4.99 (± 0.46)	5.06 (± 0.95)	4.85 (± 0.57)	4.83 (± 0.34)
CL_R (L/h)	4.12 (± 0.75)	4.47 (±1.07)	4.05 (± 0.47)	4.08 (± 0.59)
Urinary recovery ** (% of dose)	82.2 (± 9.11)	87.8 (± 9.30)	83.7 (± 3.91)	84.4 (± 9.23)

Values are arithmetic means (± SD).
* Value obtained by 2-compartmental analysis.
** 0-24 h recovery on Day 1 and 0-12 h recovery on Day 8.

Source: Study BAP00010
N = 6 per group
Abbreviations: AUC0-∞, area under the concentration-time curve from time zero to infinity; AUC0-12, area under the concentration-time curve from time 0 to 12 hours; CL, clearance; C_{max}, maximum plasma concentration; T½, half-life; Vss, steady state rate achieved by the system

Reviewer Comments

In the original study report, urinary excretion was not calculated during the 16-24 h time interval due to missing urine volumes. Review of the raw data, however, revealed that the values were not missing, and the amount excreted was provided in errata report. Total urinary recovery ranged from 73 to 100% in individual subjects when updated with these values.

Study BAP00058

BAP00058 was a double-blind, randomized, placebo-controlled, multiple dose study, conducted at a single center. Twelve male subjects were randomly assigned to receive ceftobiprole medocaril sodium (750 mg of ceftobiprole equivalents; 6 subjects) or placebo (6 subjects) as intravenous (i.v.) infusions for 12 days. Administration was once daily on Days 1 and 12 in order to allow 24-hour sampling for PK, and was twice daily, every 12 hours, on Days 2 to 11.

On Days 1 and 12, blood samples were collected immediately before start of infusion and up to 24 hours after infusion start. Subjects were encouraged to void urine at the end of each collection interval, i.e., at 0, 2, 4, 8, and 24 hours.

Reference ID: 5357793

Ceftobiprole medocaril sodium and ceftobiprole were quantitated with a validated LC/LC-MS/MS method and PK parameters were derived by non-compartmental and two-compartmental methods. Drug accumulation, R_{ACC}, was estimated by $AUC_{0\text{-}12h}$ on Day 12 divided by $AUC_{0\text{-}12h}$ on Day 1. Time above the minimum inhibitory concentration (T > MIC) was determined using 4 µg/mL as an MIC value and 12 hours as the dosing interval.

Pharmacokinetic parameters and cumulative urinary recovery for ceftobiprole following multiple intravenous administration of 750 mg of ceftobiprole medocaril sodium in healthy, male subjects are summarized in Table 216. The mean (SD) %fT>MIC for all subjects enrolled was 69.2 (8.42).

Table 216. Summary of Ceftobiprole Pharmacokinetic Parameters Following Multiple Intravenous Administration of 750 mg of Ceftobiprole Medocaril Sodium for 12 Days in Healthy, Male Subjects

	Study Day and Dose			
Parameter	Day 1 750 mg		Day 12 750 mg	
$AUC_{0\text{-}\infty}$ (µg·h/mL)	N=6	180 (± 10.4)	N=6	184 (± 22.4)
$AUC_{0\text{-}12h}$ (µg·h/mL)	N=6	171 (± 8.85)	N=6	174 (± 19.7)
C_{max} (µg/mL)	N=6	76.6 (± 16.2)	N=6	75.2 (± 16.0)
$t_{1/2}$ (α)* (h)	N=6	0.89 (± 0.27)	N=6	0.55 (± 0.14)
$t_{1/2}$ (β) (h)	N=6	3.51 (± 0.20)	N=6	3.41 (± 0.31)
Vss (L)	N=6	13.0 (± 1.75)	N=6	13.4 (± 2.31)
CL_S (L/h)	N=6	4.18 (± 0.24)	N=6	4.35 (± 0.55)
CL_{R1}§ (L/h)	N=6	3.35 (± 0.21)	N=6	3.61 (± 0.53)
CL_{R2}§ (L/h)	N=6	3.53 (± 0.21)	N=6	3.60 (± 0.54)
Urinary Recovery** (% of dose)	N=6	80.5 (± 7.06)	N=6	82.8 (± 6.29)

Values are presented as arithmetic means (±SD)
* Obtained by 2-compartmental analysis
** 0-24 hours on Day 1 and 0-12 hours on Day 12
§ CL_{R1} calculated as $CL_S \times f_u$ (unbound fraction); CL_{R2} calculated as $Ae_{0\text{-}12} / AUC_{0\text{-}12}$.

Source: Study BAP00058Study Report
Abbreviations: AUC0-∞, area under the concentration-time curve from time zero to infinity; AUC0-12, area under the concentration-time curve from time 0 to 12 hours; CL, clearance; C_{max}, maximum plasma concentration; T½, half-life; Vss, steady state rate achieved by the system

Because ceftobiprole medocaril sodium was not measurable in plasma samples obtained after infusion, no PK evaluation was possible. Urine concentrations of ceftobiprole medocaril sodium were low and were below the level of quantification in most samples. Plasma and urine concentrations of the ring-opened metabolite, BAL2070, were below the limit of quantification in all samples.

14.2.3. Renal Impairment

BAP00018 was a phase 1, single-center, open-label, non-randomized parallel group study. Twenty male subjects (5 per group) were enrolled into the following groups according to their creatinine clearance (CL_{CR}) determined at screening:

- Group A (normal renal function: CL_{CR} >80 mL/min),
- Group B (mild renal impairment: CL_{CR} = 51-80 mL/min),
- Group C (moderate renal impairment: CL_{CR} = 30-50 mL/min), and
- Group D (severe renal impairment: CL_{CR} <30 mL/min)

On study Day 1, each subject received a single dose ceftobiprole medocaril sodium 30 minutes. Blood samples were collected immediately before infusion start and up to 24 hours after the start of infusion. Urine was collected at –2 to 0 hours (control and last portion of the 24-hour urine collection on Study Day –1) and up to 24 hours after the start of infusion.

Ceftobiprole medocaril sodium and ceftobiprole were quantitated by a validated LC/LC-MS/MS method. Pharmacokinetic parameters were derived by non-compartmental and two-compartmental methods. Time above the minimum inhibitory concentration (T > MIC) was determined; in these calculations, the dosing interval was defined as 12 hours (corresponding to twice daily administration), and the MIC value defined as 4 μg/mL, since this is the highest MIC for ceftobiprole in the case of MRSA.

Pharmacokinetic parameters and cumulative urinary recovery for ceftobiprole following single intravenous administration of 250 mg of ceftobiprole medocaril sodium in healthy and renally impaired male subjects are summarized in Table 217.

Table 217. Summary of Ceftobiprole Pharmacokinetic Parameters Following Single Intravenous Administration of 250 mg of Ceftobiprole Medocaril Sodium in Healthy and Renally Impaired Male Subjects

	Renal Function			
	Normal	Mild	Moderate	Severe
Parameter	CL_{CR}: >80 mL/min N=5	CL_{CR}: 50-80 mL/min N=5	CL_{CR}: 30-<50 mL/min N=5	CL_{CR}: <30 mL/min N=5
C_{max} (μg/ml)	20.6 (2.06)	20.1 (1.45)	24.4 (1.65)	22.8 (3.48)
AUC_{last} (μg•h/ml)	52.4 (6.95)	72.7 (13.9)	139 (15.7)	174 (44.50)
$AUC_{0-\infty}$ (μg•h/ml)	52.8 (6.91)	74.8 (15.6)	151 (21.6)	222 (71.00)
$t_{1/2\alpha}$* (h)	0.82 (0.45)	0.57 (0.20)	0.41 (0.24)	0.55 (0.26)
$t_{1/2\beta}$ (h)	3.45 (0.37)	4.75 (0.81)	6.87 (1.12)	11.1 (1.96)
V_{SS} (L)	15.8 (1.81)	18.0 (0.76)	14.2 (0.80)	16.9 (2.39)
CL_S (L/h)	4.80 (0.61)	3.46 (0.71)	1.68 (0.25)	1.21 (0.36)
CL_R (L/h)	4.38 (0.51)	2.48 (0.63)	0.88 (0.25)	0.407 (0.24)
A_e, %	91.6 (6.55)	71.1 (7.32)	51.9 (9.93)	31.5 (9.65)

Values are presented as arithmetic means (SD);
* obtained by 2-compartmental analysis

Source: BAP00018Study Report
Abbreviations: Ae, amount of drug excreted in urine or feces; AUC0-∞, area under the concentration-time curve from time zero to infinity; AUClast, area under the concentration-time curve from the time of dosing to the time of the last measurable (positive) concentration; CL, clearance; C_{max}, maximum plasma concentration; T½, half-life; Vss, steady state rate achieved by the system

A PK evaluation of the pro-drug ceftobiprole in plasma was not possible given low or undetectable concentrations in most subjects. Urinary concentrations of the pro-drug ceftobiprole medocaril sodium were very low, and only detectable in the 2-hour collection intervals in 14 out of 20 subjects. The mean (SD) %fT>MIC values in normal, mild, moderate and severe renal impairment were 15.6 (2.14), 21.0 (4.74), 45.3 (9.92) and 60.7 (21.3), respectively.

Reviewer Comments

Of note, mean age differed between the groups (specifically, the renally impaired groups versus normal subjects), as follows: normal subjects, 23.8 ± 3.9 years; subjects with mild impairment, 44.6 ± 9.2 years; subjects with moderate impairment, 47.2 ± 15.3 years; and subjects with severe impairment, 55.8 ± 5.36 years. The Applicant did not study the effect of age in a Phase 1 healthy volunteer study. Age was not identified as a significant covariate affecting ceftobiprole PK in adults (see Section 14.5).

Study CSI-1007 was a single-dose PK study in subjects with end-stage renal disease (ESRD). Twelve subjects were enrolled in this study: six healthy male subjects with normal renal function and six male subjects with ESRD (CL_{CR} of 0 to 15 mL/min) on hemodialysis. Healthy subjects were enrolled after all ESRD subjects had completed the study and were matched on a 1:1 basis by age and weight.

Healthy subjects were given a single 2-hour infusion of 250 mg ceftobiprole; subjects with ESRD on hemodialysis were given a 2-hour infusion of 250 mg ceftobiprole 3 hours before dialysis in Period 1 and immediately after dialysis in Period 2, with a washout period of at least 14 days between periods.

Blood and urine samples were collected for up to 48 hours post-dose administration. Venous blood samples were collected immediately before the infusion, during the infusion, and up to 48 hours after the start of infusion in all subjects and all periods. Venous blood samples were also collected before and at the end (4 hours) of the hemodialysis on Day 3 and Day 5 in ESRD subjects in Period 1 and Period 2. Arterial blood samples were taken at 4, 5, 6, and 7 hours during the 4-hour hemodialysis in ESRD subjects in Period 1. During this time frame, dialysate samples were also collected every 30 minutes. Additional pre-dose, 2-hour blood, and 24 hours post-start of the infusion blood samples were taken on Day 1 for the determination of plasma protein binding by ultra-filtration.

Urine was collected before the infusion and over the intervals of 0 to 2, 2 to 4, 4 to 8, 8 to 12, 12 to 24, and 24 to 48 hours after the infusion in healthy subjects only.

Ceftobiprole medocaril sodium and ceftobiprole were quantitated by a validated LC/LC-MS/MS method.

Pharmacokinetic parameters and cumulative urinary recovery for ceftobiprole following single intravenous administration of 250 mg of ceftobiprole medocaril sodium in healthy and ESRD subjects is summarized in Table 218.

Table 218. Mean (SD) Ceftobiprole PK Parameters in Healthy Subjects and End-Stage Renal Disease Subjects Following a Single Intravenous Infusion of 250 mg Ceftobiprole Administered Over 2 Hours

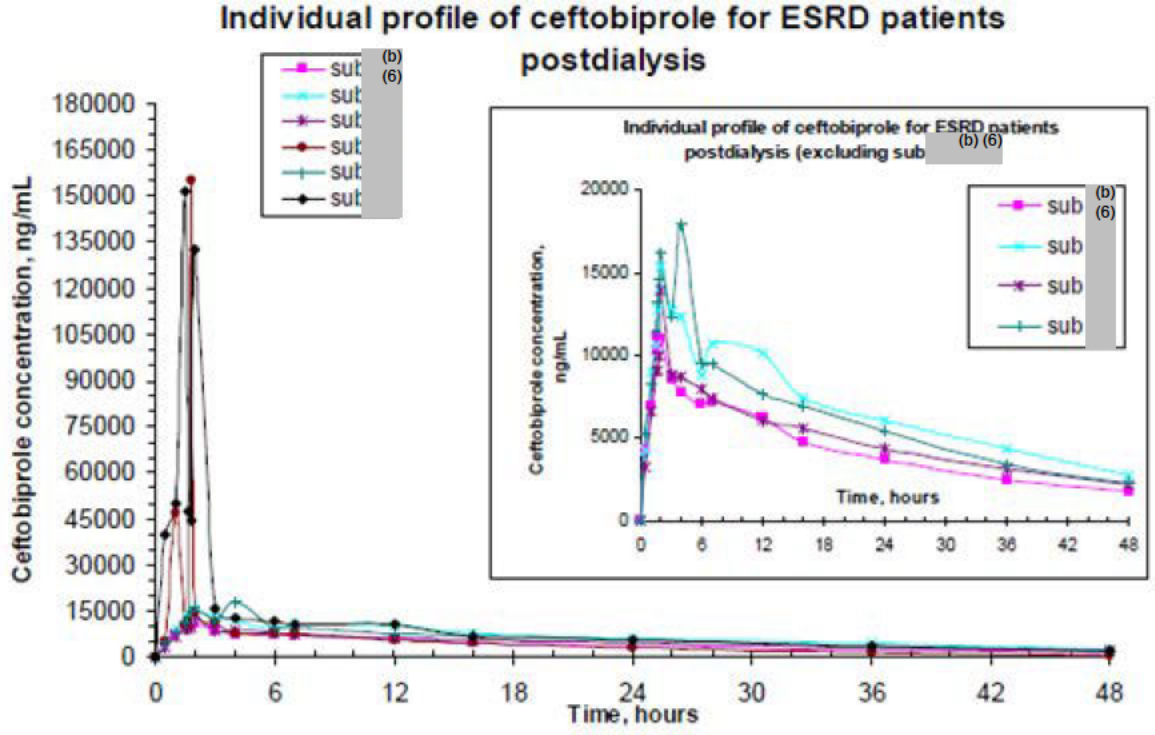
Parameter	Healthy N=6	Pre-dialysis N=5[a]	Post-dialysis N=5[b]
C_{max} (µg/mL)	11.1 (1.77)	13.3 (2.33)	21.1 (14.7)
T_{max} (h)[c]	2.00 (2.00, 2.00)	2.00 (2.00, 2.00)	2.13 (1.00, 4.00)
AUC_{last} (h•µg/mL)	44.3 (7.12)	118 (8.73)	249 (49.0)
AUC_{0-inf} (h•µg/mL)	45.2 (6.84)	143 (8.53)	311 (75.1)
$t_{½}$ (h)	3.0 (0.4)	20.7 (1.83)	20.5 (5.33)
Vd_z (L)	24.4 (3.68)	52.5 (5.23)	23.9 (5.14)
CL (L/h)	5.62 (0.731)	1.76 (0.102)	0.845 (0.212)
CL_R (L/h)	5.11 (0.814)	NC	NC
CL_{HD} (L/h)	NC	7.91 (1.21)	NC

Source: CSI-1007 CSR Table 5
AUC_{0-inf} = area under the plasma concentration-time curve from time 0 extrapolated to infinity; AUC_{last} = area under the plasma concentration-time curve from time 0 to last measurable concentration; CL = clearance; CL_{HD} = hemodialysis clearance; CL_R = renal clearance of ceftobiprole; C_{max} = maximum plasma concentration; NC = not calculated; $t_{1/2}$ = elimination half-life; T_{max} = time to maximum plasma concentration; Vd_z = apparent volume of distribution.
[a] without Subject (b) (6)
[b] without Subject
[c] Values presented were median and the minimum/maximum

Reviewer Comments

The reviewer identified that the plasma concentration data for ceftobiprole dosed after hemodialysis was switched between 30 min and 90 min in the Applicant's report. Upon further analysis, the reviewer concluded that the concentration-time profiles for ceftobiprole are questionable for four out of six ESRD subjects when dosed after hemodialysis. As illustrated in Figure 25, ceftobiprole concentrations approximately ten-fold higher than expected were observed in Subjects (b) (6) during the infusion phase. Furthermore, the plasma concentration time profiles were considered abnormal for Subjects (b) (6) as well due to unexpected additional peaks after the infusion was over. Taken together, the questionable data in 4 out of the 6 ESRD subjects studied precluded reliable estimation on ceftobiprole PK characteristics using data from this study.

Figure 25. Individual Ceftobiprole Concentration-Time Profiles in the Plasma Following a 2-Hour Intravenous Infusion of Ceftobiprole 250 mg to Subjects With ESRD Dosed After Hemodialysis.



Source: Study CSI-1007, reviewer analysis
Subject (b) (6) Were Excluded in the Insert
Abbreviations: ESRD, end-stage renal disease

14.2.4. Obesity

CSI-1008 was an open-label, single-dose, parallel-group PK study of ceftobiprole in morbidly obese and non-obese subjects. Twenty-five (12 morbidly obese, defined as a BMI of ≥40 kg/m^2, and 13 demographically-matched non-obese, defined as a BMI between 18 and 30 kg/m^2) subjects were enrolled in the study and received a single 2-hour infusion of 500 mg ceftobiprole. The mean weight and BMI were 130.9 kg and 45.5 kg/m^2 for morbidly obese subjects and 73.5 kg and 24 kg/m^2 for non-obese subjects, respectively.

Blood and urine were collected pre-dose and up to 24 hours following the end of infusion. An additional 2-hour blood sample was taken for the determination of plasma protein binding by ultra-filtration. Plasma, ultra-filtrate, and urine samples were analyzed for ceftobiprole medocaril sodium, ceftobiprole and the open-ring metabolite using a validated LC-MS/MS method.

Ceftobiprole AUC was approximately 17% lower among morbidly obese compared to non-obese subjects (Table 219).

Table 219. Mean (SD) Plasma Ceftobiprole Pharmacokinetic Parameters Following a Single 2-Hour Infusion of Ceftobiprole 500 mg in Morbidly Obese and Non-Obese Subjects

Pharmacokinetic Parameters	Morbidly Obese 500 mg 2-h infusion. (N=11)[c]	Non-Obese 500 mg 2-h infusion. (N=13)
AUC_{last} (µg•hr/mL)	90.5 (11.6)	109 (20.0)[a]
AUC_{∞} (µg•hr/mL)	91.0 (11.7)	110 (20.1)[a]
C_{max} (µg/mL)	21.4 (2.99)	30.2 (4.32)
t_{max} (hr)[b]	1.90 (1.67-2.17)	1.98 (1.67-2.02)
$t_{1/2}$ (hr)	3.38 (0.258)	3.21 (0.472)[a]
CL (L/hr)	5.58 (0.745)	4.65 (0.652)[a]
λ_z (1/hr)	0.206 (0.0155)	0.221 (0.0385)[a]
Vd_z (L)	27.2 (3.91)	21.6 (5.09)[a]
f_u (%)	86.0 (4.29)[d]	84.4 (3.96)
Ceftobiprole Bound (%)[e]	14.0 (4.29)[d]	15.6 (3.96)

[a] N= 12
[b] Median (Min-Max)
[c] Subject (b) (6) displayed plasma ceftobiprole concentration profile over the 2-hour infusion period inconsistent with dosing information. Since no protocol deviation was recorded for this subject, the source of the unexpected plasma concentration profile during the infusion period remains unknown. Subject (b) (6) was excluded from descriptive statistics of pharmacokinetic parameters for morbidly obese subjects.
[d] N=9
[e] Calculated as (100-f_u)
Source: Study CSI-1008
Ceftobiprole medocaril sodium was only measurable during infusion in both morbidly obese and non-obese subjects. There were no major differences in plasma and urine exposure to the open-ring metabolite in morbidly obese and non-obese subjects.
Abbreviations: AUC∞, area under the concentration-time curve from time zero to infinity; AUClast, area under the concentration-time curve from the time of dosing to the time of the last measurable (positive) concentration; CL, clearance; C_{max}, maximum plasma concentration; fu, fraction unbound; T½, half-life; Tmax, time to maximum concentration; Vd, volume of distribution; λz, terminal phase elimination rate constant

The %*f*T>MIC in morbidly obese and non-obese subjects using a targeted ceftobiprole MIC of 4 µg/mL and protein binding of 16% is shown in Table 220.

Table 220. Mean (SD) Time Above MIC and Percent Time Above MIC for Ceftobiprole Following a 2-Hour Intravenous Infusion of Ceftobiprole 500 mg in Morbidly Obese and Non-Obese Subjects

Parameter	Morbidly Obese	Non-Obese
8 hr dosing interval	N = 11	N = 13
Ceftobiprole		
T>MIC (hr)	6.77 (0.674)	6.94 (0.621)
%T>MIC (%)	84.0 (8.80)	86.8 (7.79)
Free Ceftobiprole		
T>MIC (hr)	6.14 (0.735)[b]	6.37 (0.581)
%T>MIC (%)	76.6 (9.17)[b]	79.7 (7.28)
12 hr dosing interval	N = 11	N = 12[a]
Ceftobiprole		
T>MIC (hr)	6.77 (0.674)	7.17 (0.919)
%T>MIC (%)	56.4 (5.60)	59.8 (7.66)
Free Ceftobiprole		
T>MIC (hr)	6.14 (0.735)[b]	6.51 (0.839)
%T>MIC (%)	51.2 (6.13)[b]	54.3 (7.00)

[a] Subject (b) (6) not included in calculation
[b] N = 9. Protein binding data for Subjects (b) (6) are missing
Source: Study CSI-1008
Abbreviations: MIC, minimum inhibitory concentration; T, time

14.2.5. Drug Penetration

Soft Tissue Penetration

CSI-1002 was an exploratory study to evaluate the penetration of ceftobiprole into soft tissue determined by in vivo microdialysis in healthy subjects.

This Study was conducted in two sequential parts: a pilot study and a main study. The pilot study was conducted in 3 control subjects. Ceftobiprole was locally administered via microdialysis followed by a washout period of 3 hours during which dialysate samples were taken every 30 minutes for 4 hours.

The main study was conducted in 12 healthy subjects. Ceftobiprole was administered locally via microdialysis followed by a washout period of 3 hours. After the washout period, each subject received a single 2-hour IV infusion of 500 mg ceftobiprole medocaril sodium. Dialysate samples were collected pre-dose and every 20 min from start of infusion through 12 hours post-start of dosing. Blood samples were collected at time 0 (pre-dose) up to 24 hours after the start of the infusion.

Ceftobiprole medocaril sodium concentrations were only assessed in plasma. Protein binding in plasma was determined by ultra-filtration at pre-dose, 2, and 12 hours after the start of the infusion. Concentrations of ceftobiprole in dialysate were quantified using a validated high-performance liquid chromatography/ultraviolet method.

Individual PK parameters for ceftobiprole in plasma, skeletal muscle, and adipose tissue are summarized in Table 221. Penetration of ceftobiprole into soft tissues was demonstrated and was 69% of the unbound plasma exposure for skeletal muscle and 49% of the unbound plasma exposure for adipose tissue.

Reference ID: 5357793

Table 221. Mean (SD) Ceftobiprole Pharmacokinetic Parameters in Plasma, Skeletal Muscle, and Adipose Tissue Following a Single 2-Hour Intravenous Infusion of Ceftobiprole 500 mg to Healthy Subjects

Parameter	Plasma	Skeletal Muscle	Adipose Tissue
C_{max} (µg/mL)	25.8 (2.96)	14.0 (3.22)	9.61 (4.74)
t_{max} (h)	1.92 (0.15)	2.25 (0.14)	2.25 (0.21)
AUC_{last} (h.µg/mL)	97.1 (10.3)	50.6 (10.9)	34.3 (19.0)
$AUC_{last\ unbound}$ (h.µg/mL)	76.0 (8.81)	NA	NA
AUC_{∞} (h.µg/mL)	98.0 (10.5)	53.2 (11.5)	36.5 (19.4)
$AUC_{\infty\ unbound}$ (h.µg/mL)	76.9 (8.94)	NA	NA
$t_{1/2}$ (h)	2.61 (0.33)	2.61 (0.52)	2.56 (0.39)
Vd_z (L)	19.4 (3.61)	NA	NA
CL (L/h)	5.15 (0.53)	NA	NA
%T>MIC*	71.6 (5.63)	53.6 (9.62)	35.1 (22.2)

NA = Not Assessed
* unbound ceftobiprole concentrations, corrected for individual protein binding
Cross Reference: Attachments 1.2.1, 1.2.2, and 1.2.3

Source: CSI-1002study report
Abbreviations: AUC∞, area under the concentration-time curve from time zero to infinity; AUClast, area under the concentration-time curve from the time of dosing to the time of the last measurable (positive) concentration; AUClast unbound, area under the concentration-time curve from the time of dosing to the time of the last unbound measurable (positive) concentration; CL, clearance; C_{max}, maximum plasma concentration; T½, half-life; Tmax, time to maximum concentration; Vd, volume of distribution

Mean ceftobiprole medocaril sodium concentrations in plasma were below the limit of quantification and no subject had measurable levels after the end of the infusion. PK parameters were not calculated for ceftobiprole medocaril sodium.

Lung Penetration

CSI-1005 was an exploratory, open-label study to assess the bronchoalveolar distribution and PK of ceftobiprole administered as 500 mg every 8 hours to healthy adult subjects.

Twenty-eight healthy subjects were enrolled to receive ceftobiprole and undergo bronchoalveolar lavage (BAL) sampling. Of these, 25 were evaluable for PK and 24 subjects underwent the BAL procedure. Two control subjects were enrolled to undergo the BAL procedure only to validate the bioanalytical assay and did not receive ceftobiprole. All subjects, except for the control subjects, received four 2-hour infusions of ceftobiprole (500 mg) 8 hours apart. Following the fourth infusion, a single BAL sample was collected in each subject at either 2.5, 4, 6, or 8 hours after the start of the infusion.

Blood samples were also collected in all pre-dose and up to 8 hours after the start of the infusion. Ceftobiprole concentrations in plasma and BAL fluid was quantified using a validated LC-MS/MS method.

Overall penetration in ELF and alveolar macrophages (as measured by the AUC ratio of the tissue concentration to the unbound plasma concentration) was 16% and 2%, respectively. Plasma and BAL ceftobiprole concentrations are outlined in Table 222 and Table 223, respectively.

Table 222. Mean Ceftobiprole Plasma PK Parameters on Day 2

PK Parameters	N = 25
t_{max} (h)[a]	2.00
C_{max} (µg/mL)	28.6 (6.94)
AUC_{0-8h} (µg.h/mL)	100 (14.4)
$t_{1/2}$ (h)	2.4 (0.4)
CL_s (L/h)	5.08 (0.657)
V_{ss} (L)	14.9 (2.16)
% T>MIC (Total)	92.4 (7.08)
% T>MIC (Unbound)	85.7 (6.78)

[a] Median

Source: Study CSI-1005
Abbreviations: AUC0-8, area under the concentration-time curve from time 0 to 8 hours; CL, clearance; C_{max}, maximum plasma concentration; PK, pharmacokinetic; T, time; T½, half-life; Tmax, time to maximum concentration; Vss, steady state volume

Table 223. Mean (SD) Ceftobiprole Concentrations at BAL Sampling Time Points in the ELF and AM and the Ratios of the ELF and AM Concentrations on Day 2 Compared to Unbound Plasma Concentrations

	N	2H 30 min	4H	6H	8H
ELF[a]	6	2.55 (0.988)	1.67 (1.26)	2.29 (4.46)	0.503 (0.798)
AM[a]	6	0.278 (0.102)	0.286 (0.144)	0.138 (0.0642)	0.0859 (0.0432)
ELF/Unbound Plasma	6	0.189(0.110)	0.159 (0.118)	0.431 (0.887)	0.147 (0.230)
AM/Unbound Plasma	6	0.0202 (0.0112)	0.0285 (0.0153)	0.00920 (0.0145)	0 (NA)

[a]: Concentrations in µg/mL

Source: Study CSI-1005
Abbreviations: AM, alveolar macrophage; BAL, bronchoalveolar lavage; ELF, epithelial lining fluid; NA not applicable

Unbound ceftobiprole plasma concentrations (based on 16% protein binding) were above the MIC of 4 µg/mL for a mean time of at least 6 hours following administration of ceftobiprole 500 mg over 2 hours on Day 2, corresponding to %*f*T>MIC of 85.7% over an 8-hour dosing interval.

The mean ceftobiprole concentrations in the ELF across all time points were below an MIC of 4 µg/mL. Ratios of the ELF to unbound plasma concentrations ranged from 15% to 43%. Mean alveolar macrophages to unbound plasma concentration ratios were all less than 3%.

Reference ID: 5357793

14.3. Bioanalytical Method Validation and Performance

Bioanalytical methods used to measure ceftobiprole medocaril sodium and ceftobiprole concentrations in human plasma, urine, BAL fluid, bone, ultrafiltrate and dialysate were fully validated and met precision and accuracy acceptance criteria (±15%, ±20% at the lower limit of quantification, see Table 224).

Reference ID: 5357793

Table 224. Bioanalytical Methods Used to Quantify Ceftobiprole Plasma, Urine, Ultrafiltrate, Dialysate, Bone and BAL Samples

Method Number	Analytical Technique	Analyte Measured	Calibration Range (ng/mL)	Matrix/Anticoagulant	Long-Term Stability	Supported Clinical Studies
B-169505	HPLC-UV	ceftobiprole medocaril sodium ceftobiprole	For human plasma: ceftobiprole medocaril sodium: 500 ng/mL to 100000 ng/mL ceftobiprole: 100 ng/mL to 100000 ng/mL For human urine: ceftobiprole: 2000 ng/mL to 2500000 ng/mL	Human Plasma Human Urine	4 months at –80°C	NP16104
(b) (4)-01-027	LC-MS/MS	ceftobiprole medocaril sodium ceftobiprole	20.0 to 6400 ng/ml	Human Plasma	393 days at –80°C	BAP00006 BAP00010 BAP00036 BAP00058 BAP00018
(b) (4)-01-029	LC-MS/MS	ceftobiprole medocaril sodium ceftobiprole	20.00 to 1600 ng/ml	Human Urine	649 days at –80°C	BAP00006 BAP00010 BAP00036 BAP00058 BAP00018
(b) (4)-04-002	LC-MS/MS	ceftobiprole medocaril sodium ceftobiprole	50.00 to 6400 ng/ml	Human Plasma	393 days at –80°C	BAP0210
(b) (4)-04-043	LC-MS/MS	ceftobiprole medocaril sodium ceftobiprole	50.00 to 6400 ng/ml	Human Plasma	393 days at -80±10°C	BAP0393 CSI-1001 CSI-1003
(b) (4)-04-044	HPLC-MS/MS	ceftobiprole medocaril sodium ceftobiprole	50 ng/mL to 6400 ng/mL	Human Urine	649 days at -80±10°C	BAP0393
(b) (4)-16040	HPLC-MS/MS	ceftobiprole medocaril sodium ceftobiprole open-ring metabolite	10 ng/mL to 10000 ng/mL	Human Plasma	282 to 283 days at -85±10°C	BPR-CS-008 BPR-PIP-001 BPR-PIP-002

Reference ID: 5357793

Method Number	Analytical Technique	Analyte Measured	Calibration Range (ng/mL)	Matrix/Anticoagulant	Long-Term Stability	Supported Clinical Studies
(b) (4)-16163	HPLC-MS/MS	ceftobiprole medocaril sodium ceftobiprole open-ring metabolite	50 ng/mL to 10000 ng/mL	Human Urine	27 days at 85±10°C	BPR-PIP-001
(b) (4)-18237	HPLC-MS/MS	ceftobiprole medocaril sodium ceftobiprole open-ring metabolite	ceftobiprole medocaril sodium: 10 ng/mL to 10000 ng/mL ceftobiprole: 50 ng/mL to 50000 ng/mL open-ring metabolite: 10 ng/mL to 10000 ng/mL	Human Plasma	366 days at -85±10°C	BPR-CS-009
V060403	HPLC-MS/MS	ceftobiprole medocaril sodium ceftobiprole	ceftobiprole medocaril sodium: 50 ng/mL to 1000 ng/mL ceftobiprole: 50 ng/mL to 25000 ng/mL	Human Plasma	150 days at -70°C	BAP248_307 CAP3001 CSI-1002 CSI-1005 CSI-1006 CSI-1007 CSI-1008
V060606	HPLC-MS/MS	ceftobiprole medocaril sodium ceftobiprole	ceftobiprole medocaril sodium: 50 ng/mL to 5000 ng/mL ceftobiprole: 400 ng/mL to 200000 ng/mL	Human Urine	201 days at -70°C	BAP248_307 CAP3001 CSI-1006 CSI-1007 CSI-1008
V060302	HPLC-MS/MS	Open ring metabolite of	50 ng/mL to 25000 ng/mL	Human Plasma with citric acid	159 days at -70°C	CSI-1004
V060503	HPLC-MS/MS	open ring metabolite of	50 ng/mL to 25000 ng/mL	Human Urine with citric acid	296 days at -70°C	CSI-1004
V060505	HPLC-MS/MS	open ring metabolite of	50 ng/mL to 25000 ng/mL	Human Plasma	296 days at -70°C	CSI-1004 CSI-1007 CSI-1008
V060607	HPLC-MS/MS	Open ring metabolite of	200 ng/mL to 100000 ng/mL	Human Urine	191 days at -70°C	CSI-1004 CSI-1006 CSI-1007 CSI-1008
V060812	HPLC-MS/MS	ceftobiprole	20 ng/mL to 10000 ng/mL	BAL	68 days at -70°C	CSI-1005

Reference ID: 5357793

Method Number	Analytical Technique	Analyte Measured	Calibration Range (ng/mL)	Matrix/Anticoagulant	Long-Term Stability	Supported Clinical Studies
BTM-1219-R0	HPLC-MS/MS	ceftobiprole	50 ng/g to 5000 ng/g	Cancellous bone	357 days at -70°C	Cefto-PED-1001
BTM-1233-R0	HPLC-MS/MS	ceftobiprole	50 ng/g to 5000 ng/g	Cortical bone	362 days at -70°C	Cefto-PED-1001
BTM-1171-R0	HPLC-MS/MS	ceftobiprole medocaril sodium ceftobiprole	ceftobiprole medocaril sodium: 50 ng/mL to 1000 ng/mL ceftobiprole: 50 ng/mL to 25000 ng/mL	Human Plasma	150 days at -70°C	Cefto-PED-1001
FK5789	HPLC-MS/MS	ceftobiprole	ceftobiprole: 20 ng/mL to 10000 ng/mL	Human Ultrafiltrate	Not reported (partial validation)	CSI-1002 CSI-1008
CSI-1002	HPLC-UV	ceftobiprole	ceftobiprole: 0.1 µg/mL to 50 µg/mL	Human Dialysate	32 days in lactated Ringer's solution	CSI-1002
BTM-1171-R0	HPLC-MS/MS	ceftobiprole medocaril sodium ceftobiprole	ceftobiprole medocaril sodium: 50 ng/mL to 1000 ng/mL ceftobiprole: 50 ng/mL to 25000 ng/mL	Human Plasma	150 days at -70°C	CSI-1006 (Frontage)

Source: Studies listed in "Supported Clinical Studies" column.
Abbreviations: BAL, bronchoalveolar lavage

APPEARS THIS WAY ON ORIGINAL

14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety

N/A

14.5. Pharmacometrics Assessment

14.5.1. Population PK Analysis

14.5.1.1. Review Summary

In this submission, the Applicant performed population PK (PopPK analyses including phase 3 studies in adult subjects with SAB, ABSSSIs, and CABP). PopPK analyses were also performed for pediatric subjects.

In general, the Applicant's PopPK analyses (for SAB, ABSSSI, and CABP in adult subjects and for CABP in pediatric subjects) are considered acceptable for the characterization of ceftobiprole disposition and evaluation of covariate impacts. The PopPK models were also acceptable for the generation of exposure metrics for exposure-efficacy analyses, clinical scenario simulations, and PTA analyses. Overall, the PopPK, PK/PD, and PTA analysis results support dosage selections for the indicated general and special populations requiring dosage adjustments. The Applicant's analyses were verified by the reviewer, with no significant discordance identified. Specifically, the developed models corresponding to the indications were used to support the current submission as outlined in Table 225. Of note, the labeling language reflects review team conclusions at the time of writing this review but may not reflect the finalized labeling language.

Reference ID: 5357793

Table 225. Specific Comments on Applicant's Final Population PK model

Utility of the Final Model			Reviewer's Comments
Support Applicant's proposed labeling statements about intrinsic and extrinsic factors	Intrinsic factor	Section 8.5 Geriatric Use No dosage adjustment is required for elderly patients. Dosage adjustment for elderly patients should be based on renal function. Section 8.6 Renal Impairment <u>Adult Patients</u> The ZEVTERA dosage is reduced in adult patients with CL_{CR} < 50 mL/min, including patients with a CL_{CR} < 15 mL/min either receiving or not receiving hemodialysis. Renal impairment (CL_{CR} < 50 mL/min) increases ceftobiprole AUC in adult patients, which may increase the risk of ZEVTERA adverse reactions. <u>Pediatric Patients</u> The ZEVTERA dosage is reduced in pediatric patients 2 years of age and older with renal impairment (eGFR 15 to < 50 mL/min/1.73 m^2). Use in pediatric patients 2 years of age and older with renal impairment (eGFR 15 to < 50 mL/min/1.73 m^2) is predicted to increase ceftobiprole AUC, which may increase the risk of ZEVTERA adverse reactions. The effect of any degree of renal impairment in pediatric patients younger than 2 years of age or in pediatric patients 2 years of age and older with an eGFR < 15 mL/min/1.73 m^2 either receiving or not receiving hemodialysis on ceftobiprole PK is unknown. <u>8.7 Augmented Renal Clearance</u> Increase the ZEVTERA dosing frequency in adult patients with augmented renal clearance (CL_{CR} > 150 mL/min). Use in adult patients with augmented renal clearance (CL_{CR} > 150 mL/min) is predicted to decrease ceftobiprole exposure, which may reduce ZEVTERA efficacy. The effect of augmented renal clearance function (CL_{CR} > 150 mL/min) on ceftobiprole PK in pediatric patients is unknown. Section 12.3 Pharmacokinetics <u>Specific Populations</u> No clinically significant differences in the PK of ceftobiprole were observed in adults based on age (18 to 91 years), gender (36% female), or race/ethnicity (88% White, 3% Black, 5% Asian). The effect of hepatic impairment on ceftobiprole PK is unknown.	Based on population PK modeling, exposure-efficacy analyses, Monte Carlo simulations, and probability of target attainment analyses, these statements are acceptable to support dosing recommendations. The population PK models demonstrate that no clinically significant impacts are observed on the PK of ceftobiprole based on age, gender, or race/ethnicity. No patients with hepatic impairment were evaluated in the population PK modeling.

Reference ID: 5357793

		Patients with Renal Impairment No clinically significant differences in the PK of ceftobiprole were observed in adult subjects and subjects with mild renal impairment (CL_{CR} 50 to 80 mL/min). Ceftobiprole AUC increased 2.5-fold in adult subjects with moderate renal impairment (CL_{CR} 30 to < 50 mL/min) and 3.3-fold in severe renal impairment (CL_{CR} < 30 mL/min). *End-stage Renal Disease Requiring Dialysis* No clinically significant difference in the PK of ceftobiprole were observed in adult patients with ESRD (CL_{CR} < 15 mL/min) compared to healthy adult subjects based on limited PK data and PK modeling and simulation. *Patients with Augmented Renal Clearance* A clinically significant reduction in ceftobiprole exposure is predicted in adult patients with augmented renal clearance (CL_{CR} > 150 mL/min) based upon a mechanistic understanding of this drug. The effect of augmented renal clearance (CL_{CR} > 150 mL/min) on ceftobiprole PK in pediatric patients is unknown. *Pediatric Use* No clinically significant differences in the PK of ceftobiprole were observed between pediatric patients from (b) (4) to < 18 years with normal renal function following administration of an intravenous dose of ZEVTERA.	
	Extrinsic factor	N/A	N/A
Derive exposure metrics for Exposure-response analyses	Free-drug AUC (for exposure-efficacy analysis), free-drug %T>MIC		The Applicant's final population PK models for ABSSSI, CABP and SAB are generally acceptable for generating exposure metrics for exposure-efficacy analyses, for simulations to support dosing recommendations across renal subgroups, and for supporting breakpoints. The Applicant's final population PK model for pediatric patients is acceptable for generating exposure metrics for summary and for

Reference ID: 5357793

		simulations to support dosing recommendations across renal subgroups.
Predict exposures at alternative dosing regimen	The Applicant performed simulations to predict exposures for alternative regimens in ESRD patients not on intermittent hemodialysis to support ESRD dosing recommendations.	Based on population PK modeling and simulations, 250 mg q12h dosing may result in higher ceftobiprole accumulation beyond Day 1 dosing compared to q24h dosing, resulting in exposure levels not observed in available nonclinical and clinical data. Additionally, the exposures from 250 mg q24h regimen in ESRD achieves PTA >90% across target pathogens based on surveillance MIC data. The final recommendation of 250 mg q24h dosing is reasonable from an efficacy and safety perspective.

Source: reviewer's comments based on finalized labeling language
Note: 667 mg of ceftobiprole medocaril sodium is equivalent to 500 mg of ceftobiprole. For pediatric patients: 13.3 mg/kg is equivalent to 10 mg/kg of ceftobiprole. 26.7 mg/kg of ceftobiprole medocaril sodium is equivalent to 20 mg/kg of ceftobiprole. Dosing adjustments for each indication are based on renal function
Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; AUC, area under the concentration-time curve; CABP, community-acquired bacterial pneumonia; CLcr, creatinine clearance; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; MIC, minimum inhibitory concentration; PK, pharmacokinetic; PTA, probability of target attainment; q12h, every 12 hours; q24h, every 24 hours; SAB, *Staphylococcus aureus* Bacteremia; T, time

Reference ID: 5357793

14.5.1.2. Introduction of Analysis Reports

Multiple pharmacometric analysis reports stratified by indication (i.e., infection) and population types were submitted under this NDA. The submitted reports are summarized in Table 226. Non-compartmental analysis reports were not reviewed but included in this table for completeness.

Table 226. Summary of Submitted PK and PK/PD Reports

Report ID Number	Report Type	Population Type	EDR Link
ABSSSI and CABP in Adults			
00594-1	NCA	ABSSSI[a]	…\nda218275\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\00594-1\00594-1-nca-bpr-cs-008-pk-report-fepdf.pdf
00594-2	PopPK	ABSSSI, CABP, and NP/VAP in patients and healthy subjects	…\nda218275\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\00594-2\00594-2-poppk-ceftobiprole-absssi-cap-fepdf.pdf
00594-3	PK/PD	ABSSSI and CABP[a]	…\nda218275\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\00594-3\00594-3-pkpd-ta-ceftobiprole-absssi-cabp-fe.pdf
SAB in Adults			
00594-4	NCA	SAB, including IE[a]	…\nda218275\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\00594-4\00594-4-nca-bpr-cs-009-pk-report-fepdf.pdf
00594-5	PopPK	SAB, including IE[b]	…\nda218275\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\00594-5\00594-5-poppk-bpr-cs-009-ceftobiprole-sab-fepdf.pdf
00594-6	PK/PD	SAB, including IE[a]	…\nda218275\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\00594-5\00594-5-poppk-bpr-cs-009-ceftobiprole-sab-fepdf.pdf
CABP in Pediatric Patients (3 month to <18 years)[c]			
00616-2	NCA	HAP/CABP requiring hospitalization	…\nda218275\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\00616-2\00616-2-nca-pk-pediatrics-pip-002.pdf
00616-3A	PopPK, PK/PD	HAP/CABP requiring hospitalization[d]	…\nda218275\0001\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\00616-3\00616-3a-addendum.pdf

Source: reviewer's summary table based on submitted data

[a] Phase 3 patients only; [b] pooled with PK subjects from Report 00594-2; [c] an NCA report was submitted for pediatric patients under 3 months old but is considered irrelevant in this review; [d] pooled with Phase 1 adult PK data; the original PopPK model for pediatric patients was only fitted to the pediatric data and is not discussed in this review.

Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; CABP, community-acquired bacterial pneumonia; HAP, hospital acquired pneumonia; IE, infective endocarditis; NCA, non-compartmental analysis; NP, nosocomial pneumonia; PD, pharmacodynamic; PK, pharmacokinetic; PopPK, population pharmacokinetic; SAB, *Staphylococcus aureus* Bacteremia; VAP, ventilator acquired pneumonia

The overall objectives of the Applicant's PopPK analyses were to: 1) develop a PopPK model for ceftobiprole in varying infection types and 2) describe ceftobiprole disposition and quantify covariate impacts. Objectives of the pediatric PopPK analyses are described in respective sections in this appendix.

14.5.1.3. ABSSSI and CABP

14.5.1.3.1. Model Development

Data

A total of 12 studies were included for PopPK model development, including nine phase 1 and three phase 3 studies. Study design, PK sampling, and dosages are summarized in Table 227. The final NONMEM dataset included 773 subjects (healthy subjects and patients) who contributed 4,890 evaluable plasma concentrations. Nine observations were considered outliers and excluded based on high conditional weighted residuals values. Summaries of baseline characteristics for phase 1 and phase 3 are provided in Table 228 and Table 229, respectively. Summary statistics for the pooled PK population can be referenced in the Applicant's PopPK report (not shown).

Reference ID: 5357793

Table 227. Summary of Studies Included in the PopPK Analysis

Study (Phase)	Title	Ceftobiprole dose	PK sampling strategy
BAP00006 (Phase 1) [2]	Assessment of pharmacokinetics and safety after single ascending dose infusion of BAL5788 in healthy male volunteers	Single dose of 125, 250, 500, 750, or 1000 mg IV over 30 min	Plasma: pre-dose and 5, 15, 30, and 45 minutes, and 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 16, and 24 h after start of infusion. Urine: pre-dose and 0-2, 2-4, 4-6, 6-8, 8-12, 12-16, and 16-24 h after start of infusion.
BAP00010 (Phase 1) [3]	Assessment of pharmacokinetics and safety after multiple ascending dose infusions of BAL5788 in healthy male volunteers	500 or 750 mg IV over 30 min, QD on Days 1 and 8 and q12h on Days 2-7	Plasma: Days 1 and 8 pre-dose, 5, 15, 30, and 45 minutes, and 1, 1.25, 1.5, 2, 3, 4, 6, 8, 10, 12, 14, 16, and 24 h after start of infusion. Additional samples drawn pre-dose on Days 2-7. Urine: Days 1 and 8 pre-dose and 0-2, 2-4, 4-6, 6-8, 8-12, 12-16, and 16-24 h after start of infusion.
BAP00058 (Phase 1) [4]	Assessment of safety and pharmacokinetics after multiple infusions of BAL5788 in healthy male volunteers	750 mg IV over 30 min, QD on Days 1 and 12 and q12h on Days 2-11	Plasma: Days 1 and 12 pre-dose, at 15, 30, and 45 minutes, and 1, 2, 4, 8, 12, 16, and 24 h after start of infusion. Additional samples collected pre-dose on Days 3, 5, 7, 9, and 11. Urine: Days 1 and 12 pre-dose and 0-2, 2-4, 4-8, and 8-24 h after start of infusion.

Study (Phase)	Title	Ceftobiprole dose	PK sampling strategy
BAP00018 (Phase 1) [5]	Assessment of pharmacokinetics and safety of BAL9141 in subjects with varying degrees of renal impairment after IV infusion of its prodrug BAL5788	Single dose of 250 mg IV over 30 min	Plasma: pre-dose, at 5, 15, 30 and 45 minutes, and 1, 1.5, 2, 4, 6, 8, 12, 14, 16, and 24 h after start of infusion. Urine: pre-dose and 0-2, 2-4, 4-6, 6-12, and 12-24 h after start of infusion.
BAP00036 (Phase 1) [6]	Assessment of the pharmacokinetics and safety of BAL9141 after single intravenous infusion of BAL5788 in healthy female and male subjects	Single dose of 750 mg IV over 30 min	Plasma: pre-dose, at 5, 15, 30 and 45 minutes, and 1, 1.5, 2, 4, 6, 8, 12, 14, 16, and 24 h after start of infusion. Urine: pre-dose and 0-2, 2-4, 4-6, 6-12, and 12-24 h after start of infusion.
BAP00210 (Phase 1) [7]	Assessment of tolerability and pharmacokinetics of two different dosing regimens of BAL5788 in healthy subjects	Single dose of 750 mg IV over 30 min or 500 mg IV over 1 h	Plasma: Pre-dose and at 0.25, 0.5, 1, 4, 5, 6, 7, 8, and 24 h after start of infusion.
BAP00393 (Phase 1) [8]	Safety and pharmacokinetics of multiple infusions with 1g-equivalent ceftobiprole (BAL9141), administered as ceftobiprole medocaril (BAL5788) in healthy male volunteers	1 g IV over 1.5 h QD on Days 1 and 8, q8h Days 2-7	Plasma: Days 1 and 8 pre-dose and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 h after start of infusion. Additional samples collected prior to the morning infusion on Days 3, 5, and 7. Urine: Days 1 and 8 pre-dose, 0-2, 2-4, 4-8, 8-16, and 16-24 h after start of infusion.

Study (Phase)	Title	Ceftobiprole dose	PK sampling strategy
CSI-1004 (Phase 1) [9]	An open-label, pharmacokinetic study of single and multiple intravenous infusions of ceftobiprole 500 mg administered to healthy, adult subjects	500 mg IV q8h over 2 h for 5 days	Plasma: Days 1 and 5 pre-dose and 0.5, 1, 1.5, 1.67, 1.83, 2, 2.17, 2.33, 3, 4, 6, 8, 12, 16, and 24 h after start of infusion. Additional samples collected on Day 3 pre-dose and 8 and 16 h after start of infusion, and on Day 4 pre-dose and at 2, 8, 10, 16, and 18 h after start of infusion. Urine: pre-dose, 0-2, 2-4, 4-8, 8-12, 12-24 hours after start of infusion on Days 1 and 5. Samples also collected 24-48 h after start of infusion on Day 1.
CSI-1005 (Phase 1) [10]	An exploratory, open-label study to assess the bronchoalveolar distribution and pharmacokinetics of ceftobiprole administered as 500 mg every 8 hours to healthy, adult subjects	500 mg IV q8h over 2 h for 4 doses	Plasma: pre-dose each infusion and 0.5, 1.25, 2, 2.5, 3, 4, 6, and 8 h after the 4th infusion BAL: 2.5, 4, 6, or 8 h after 4th infusion
BPR-CS-008 (Phase 3) [11]	A randomized, double-blind, multicenter study to establish the safety and efficacy of ceftobiprole medocaril compared with vancomycin plus aztreonam in the treatment of acute bacterial skin and skin structure infections	500 mg IV q8h over 2 h for 5-10 days with adjustment for renal impairment	Sparse: Day 4 pre-dose and 2 and 4-6 h after the start of infusion Rich: Day 4 pre-dose and 2, 3, 4, 6, and 8 h after the start of infusion

Study (Phase)	Title	Ceftobiprole dose	PK sampling strategy
BAP248/307 (Phase 3) [12]	Randomized, double-blind, multicenter study of ceftobiprole versus linezolid plus ceftazidime in the treatment of HAP, including patients with VAP	500 mg IV q8h over 2 h for 4-5 days with adjustment for renal impairment	Sparse: 2 and 6 h after first dose, and on Day 4 at any time during dosing interval at least 30 minutes after start of morning infusion Rich: Day 4 pre-dose and at 0.25, 1, 2, 4, 6, and 8 h after the start of the morning infusion.
CAP-3001 (Phase 3) [13]	Randomized, double-blind, multicenter study of ceftobiprole medocaril versus ceftriaxone with/without linezolid in treatment of subjects hospitalized with community-acquired pneumonia	500 mg IV q8h over 2 h for 5-10 days (could be extended to 14 days) with adjustment for renal impairment	Sparse: Day 1 at 2 (immediately prior to end of infusion) and 6 h after morning infusion and one sample on Day 4 at any time starting at least 0.5 h after start of morning infusion Rich: Day 4 pre-dose and 0.25, 1, 2, (immediately prior to end of infusion), 4, 6, and 8 h after start of morning infusion

Source: Applicant's PopPK report for ABSSSI and CAP, Table 1, pages 21-24. CAP refers to CABP in the table.
Note: 667 mg of ceftobiprole medocaril sodium is equivalent to 500 mg of ceftobiprole. Dosing adjustments for each indication are based on renal function
Abbreviations: HAP, hospital acquired pneumonia; IV, intravenous; PK, pharmacokinetic; PopPK, population pharmacokinetic; QD, once a day (daily); q8h, every 8 hours; VAP, ventilator acquired pneumonia

Table 228. Summary of Baseline Characteristics in Phase 1 Subjects

Variable	Phase 1								
	BAP00006	BAP00010	BAP00018	BAP00036	BAP000058	BAP00210	BAP00393	CSI-1004	CSI-1005
Age (yr)	28.4 (5.22) 28 (22-40)	25.3 (5.42) 25.5 (19-38)	42.8 (14.9) 49.5 (19-60)	23.7 (5.12) 21.5 (18-36)	34.5 (9.65) 35.5 (20-44)	37.5 (10.2) 38 (20-54)	37.7 (6.89) 40 (24-42)	40.2 (11.1) 44.5 (19-54)	30.1 (6.28) 30 (21-42)
Height (cm)	179 (7.84) 178 (165-194)	183 (5.8) 182 (173-193)	183 (6.71) 184 (170-192)	171 (9.41) 170 (154-189)	182 (6.75) 184 (170-189)	171 (7.47) 170 (157-184)	172 (5.88) 172 (161-178)	172 (8.57) 172 (159-185)	175 (10.3) 174 (152-190)
Weight (kg)	80.6 (7.76) 79.5 (62-94)	78.5 (8.78) 78.7 (66.7-92.1)	83.1 (9.17) 81.6 (65.2-99)	67.7 (11.3) 67.4 (49-87.8)	71 (6.06) 72.7 (62.9-78.2)	73.4 (10) 72.8 (55-92.5)	69.8 (7.17) 70 (60.5-80.9)	70.9 (10.5) 72.2 (53-91.5)	78.1 (13.3) 76.3 (54-103)
BSA (m^2)	1.99 (0.133) 2.01 (1.68-2.22)	2 (0.125) 2 (1.8-2.23)	2.05 (0.127) 2.06 (1.77-2.26)	1.79 (0.183) 1.77 (1.47-2.12)	1.92 (0.114) 1.96 (1.73-2.02)	1.85 (0.152) 1.86 (1.56-2.15)	1.82 (0.105) 1.81 (1.72-1.99)	1.83 (0.173) 1.86 (1.57-2.12)	1.93 (0.208) 1.88 (1.59-2.31)
BMI (kg/m^2)	25.2 (1.82) 25.1 (21.4-29.4)	23.4 (2.16) 23.5 (18.6-26.4)	24.8 (2.7) 24.9 (20.1-29.4)	23.1 (2.99) 24 (18-29.3)	21.3 (1.11) 21.4 (19.6-22.8)	25.1 (2.73) 24.8 (19.8-30)	23.7 (2.42) 23.8 (20.4-26.7)	23.8 (2.25) 23.9 (19.7-27.9)	25.5 (2.97) 26 (18.7-29.3)
CLcr (mL/min/1.73 m^2)	109 (10.1) 109 (91.4-130)	97 (10.6) 96.7 (84.8-118)	50.1 (29.4) 42.7 (8.48-110)	107 (16.6) 104 (82.6-145)	94.3 (11.4) 91.8 (81.2-112)	104 (15.3) 104 (76.9-128)	103 (22.9) 97.8 (78.7-145)	97.7 (16.8) 91 (78-148)	90.5 (14.2) 89.7 (53.8-116)
Sex									
Male	30/30 (100%)	12/12 (100%)	20/20 (100%)	12/24 (50%)	6/6 (100%)	18/36 (50%)	6/6 (100%)	14/28 (50%)	15/26 (57.7%)
Female	—	—	—	12/24 (50%)	—	18/36 (50%)	—	14/28 (50%)	11/26 (42.3%)
Race									
White	30/30 (100%)	12/12 (100%)	20/20 (100%)	17/24 (70.8%)	6/6 (100%)	36/36 (100%)	5/6 (83.3%)	28/28 (100%)	16/26 (61.5%)
Black	—	—	—	4/24 (16.7%)	—	—	—	—	1/26 (3.85%)
Asian	—	—	—	—	—	—	—	—	—
American Indian/ Alaska Native	—	—	—	—	—	—	—	—	—
Native Hawaiian or other Pacific islander	—	—	—	—	—	—	—	—	—
Other	—	—	—	3/24 (12.5%)	—	—	1/6 (16.7%)	—	9/26 (34.6%)

Source: Applicant's PopPK report for ABSSSI and CAP, Table 4, pages 41-42
Summary statistics presented as mean (%CV) and median (Min. – Max.) or n/N (%)
Abbreviations: BMI, body mass index; BSA, body surface area; CLcr, creatinine clearance

Table 229. Summary of Baseline Characteristics in Phase 3 Subjects

Variable	Phase 3		
	BPR-CS-008	CAP-3001	BAP248/307
Age (yr)	49.5 (13.6) 51 (18-85)	54.1 (20.1) 56 (18-90)	60.4 (20.9) 66 (18-91)
Height (cm)	172 (10.4) 172 (145-200)	168 (10.3) 168 (144-195)	168 (11.1) 170 (127-188)
Weight (kg)	82.2 (18.7) 79.3 (41.3-165)	71.7 (17.4) 70 (29.5-123)	73 (15.6) 72.7 (40-115)
BSA (m^2)	1.94 (0.233) 1.93 (1.29-2.78)	1.8 (0.241) 1.8 (1.2-2.4)	1.82 (0.22) 1.83 (1.36-2.38)
BMI (kg/m^2)	27.9 (5.81) 26.6 (16.5-50.9)	25.3 (5.04) 24.6 (11.5-44.9)	25.8 (5.27) 25.1 (15.6-41.4)
CLcr (mL/min/1.73 m^2)	106 (35.5) 104 (20.2-239)	78.2 (29.3) 78.5 (18.8-176)	89.7 (48.3) 74.3 (19.9-196)
Sex			
Male	184/309 (59.5%)	122/209 (58.4%)	51/67 (76.1%)
Female	125/309 (40.5%)	87/209 (41.6%)	16/67 (23.9%)
Race			
White	294/309 (95.1%)	146/209 (69.9%)	53/67 (79.1%)
Black	6/309 (1.94%)	8/209 (3.83%)	6/67 (8.96%)
Asian		39/209 (18.7%)	4/67 (5.97%)
American Indian/ Alaska Native	3/309 (0.971%)		
Native Hawaiian or other Pacific islander	1/309 (0.324%)		
Other	5/309 (1.62%)	16/209 (7.66%)	4/67 (5.97%)
Infection Type			
ABSSSI	309/309 (100%)		
CABP		209/209 (100%)	
NP			44/67 (65.7%)
VAP			23/67 (34.3%)

Source: Applicant's PopPK report for ABSSSI and CAP, Table 5, page 43
Summary statistics presented as mean (%CV) and median (Min. – Max.) or n/N (%)
Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; BMI, body mass index; BSA, body surface area; CABP, community-acquired bacterial pneumonia; CLcr, creatinine clearance; NP, nosocomial pneumonia; VAP, ventilator acquired pneumonia

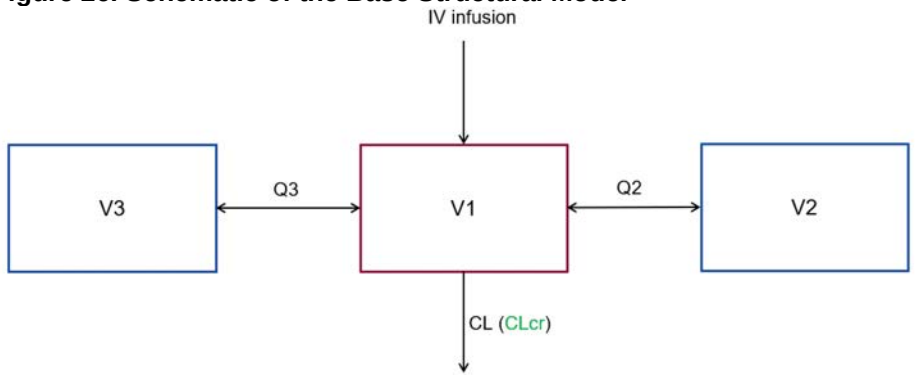
Base Model

The final base model was a 3-compartment PK model with linear elimination from the central compartment, and baseline creatinine clearance (CLcr) was included on CL *a priori*. Additive error models (in the log domain) were separate for phase 1 and phase 3 studies. The model structure is shown in Figure 26.

Interindividual variability (IIV) was modelled assuming a log-normal distribution for patient level random effects. Residual variability was tested as additive, proportional, or combined. Model evaluation and selection of the base model were based on standard statistical criteria of goodness-of-fit (GoF) such as a decrease in the minimum objective function value (OFV), accuracy of parameter estimation (i.e., 95% confidence interval excluding 0), successful model convergence, and diagnostic plots.

Reference ID: 5357793

Figure 26. Schematic of the Base Structural Model



Source: Applicant's PopPK report for ABSSSI and CAP, Figure 8, page 53
Abbreviations: CL, clearance; CLcr, creatinine clearance at baseline; Q2 and Q3, inter-compartmental flows; V1, central compartment; V2 and V3, peripheral compartments

Covariate Analysis

The base model was used for covariate analysis. A list of covariates evaluated is provided in Table 230.

Table 230. Covariates Evaluated During Model Development

Covariate	Continuous/ Categorical	Rationale
Age (yr)	Continuous	Evaluate potential for age-related changes in PK not accounted for by renal function
Weight (kg)	Continuous	Evaluate impact of body size
Height (cm)	Continuous	Alternative body size descriptor
BSA (m^2)	Continuous	Alternative body size descriptor
BMI (kg/m^2)	Continuous	Evaluate potential impact of obesity
CLcr ($mL/min/1.73\ m^2$)[a]	Continuous	Evaluate potential impact of renal function
Sex	Categorical	Evaluate potential sex-related differences in PK
Race	Categorical	Evaluate potential for race-based differences in PK
Infection type (INFTYPN)	Categorical	Evaluate potential differences between healthy volunteers and infected patients

Source: Applicant's PopPK report for ABSSSI and CAP, Table 2, page 33
CLcr was calculated using Cockcroft-Gault equation and normalized to body surface area (BSA)
Abbreviations: BMI, body mass index; BSA, body surface area; CLcr, creatinine clearance; PK, pharmacokinetic

Forward selection and backwards elimination steps were undertaken during Applicant's model development. Clinical judgment, physiologic relevance, and mechanistic plausibility were applied. Additionally, collinearity of covariates was assessed to ensure that no collinear covariates were added to the model. Continuous covariates were evaluated using a power function and categorical covariates were parameterized as a fractional change.

14.5.1.3.2. Final Model

The parameter estimates for the final covariate model for ABSSSI and CABP subjects are listed in Table 231. The GoF and normalized prediction distribution errors (NPDE) plots for the final covariate model Figure 27 and Figure 28. The prediction-corrected visual predictive check (VPC) plot for the final covariate model is shown in Figure 29. Forest plot of the statistically

Reference ID: 5357793

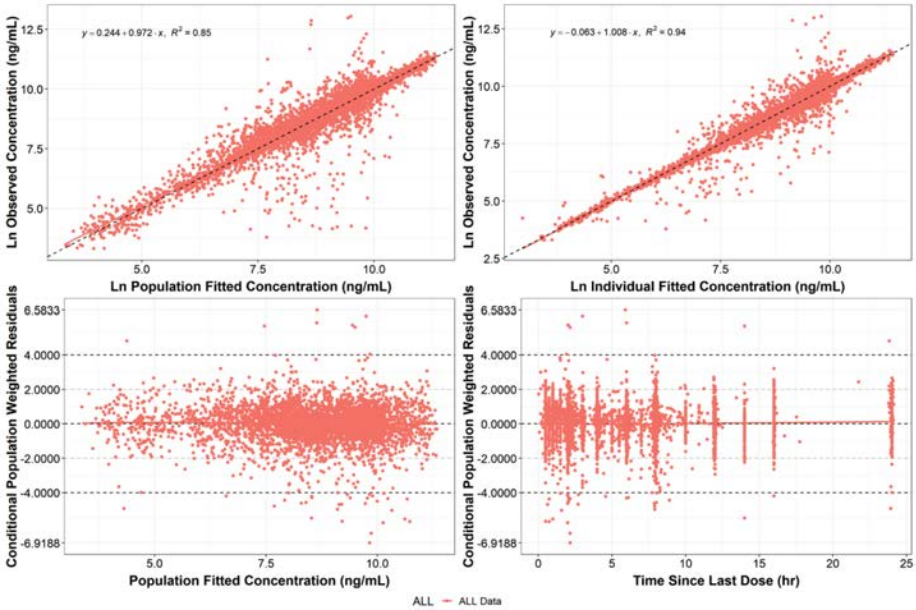
significant covariates on Day 1 area under the concentration-time curve (AUC) is shown in Figure 31.

Table 231. Parameter Estimates for the Final PopPK Model for ABSSSI and CABP

Parameter	Final Model			Resample statistics (N = 1000)			
	Estimate	%SEM	Shrinkage	Mean	Median	%CV	90% CI
CL (L/hr)	5.02	1.49		5.02	5.02	1.08	[4.93, 5.11]
V1 (L)	8.65	2.84		8.65	8.65	2.38	[8.31, 8.98]
Q2 (L/hr)	0.616	4.92		0.615	0.614	5.35	[0.564, 0.672]
V2 (L)	2.88	3.04		2.88	2.87	3.19	[2.73, 3.03]
Q3 (L/hr)	8.15	5.48		8.16	8.13	5.33	[7.45, 8.91]
V3 (L)	5.69	3.03		5.7	5.7	2.55	[5.48, 5.93]
CL:CLcr power coefficient	0.705	3.12		0.704	0.705	3.03	[0.667, 0.739]
CL:WTKG power coefficient	0.563	10.4		0.563	0.56	10.1	[0.476, 0.656]
CL shift for ABSSSI, CABP, VAP	0.334	11.3		0.334	0.333	9.77	[0.282, 0.390]
V1:WTKG power coefficient	0.876	11.1		0.872	0.873	10.9	[0.718, 1.03]
V1 shift for ABSSSI, CABP	0.988	8.97		0.991	0.991	9.8	[0.826, 1.15]
V1 shift for NP, VAP	1.42	21.9		1.44	1.42	20.6	[0.976, 1.92]
V2 shift for females	-0.216	12.1		-0.217	-0.216	9.22	[-0.250, -0.185]
V3:WTKG power coefficient	1.02	8.5		1.02	1.01	9.15	[0.874, 1.17]
ω^2_{V1}	0.0332 (18.2%)	15.6	54.2	0.0335	0.0333	13.8	[0.0264, 0.0414]
ω^2_{V2}	0.0119 (10.9%)	22.7	66.3	0.0123	0.0121	19.3	[0.00892, 0.0164]
ω^2_{V3}[c]	0.0241 (15.5%)	16.6	16.9	0.0247	0.0244	19.4	[0.0174, 0.0327]
CL ω^2_{V3} scaling factor	2.46	9.4		2.47	2.45	10.3	[2.08, 2.90]
Healthy ω^2_{CL} scaling factor	-0.598	4.48		-0.596	-0.598	4.48	[-0.638, -0.550]
$\sigma^2_{plasma\ Phase\ 1,\ Additive\ in\ log\ domain}$	0.0124 (0.111)	1.34	7.59	0.0124	0.0124	2.22	[0.0120, 0.0129]
$\sigma^2_{plasma\ Phase\ 3,\ Additive\ in\ log\ domain}$	0.354 (0.595)	1.7	9.35	0.355	0.355	2.58	[0.339, 0.369]

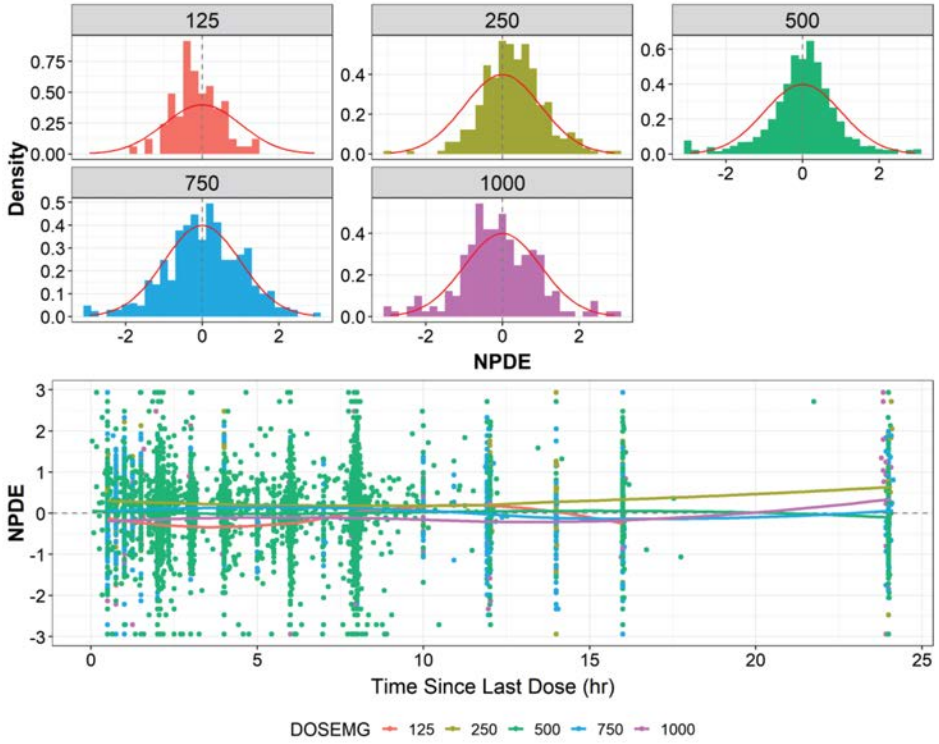
Source: Applicant's PopPK report for ABSSSI and CAP, Table 10, page 61
Values in parenthesis, CV%; additive error in log domain is reported as standard deviation; shared ETA between CL and V3; code implements scaling when estimating the IIV in CL; CLcr, BSA-normalized creatinine clearance in the final model
Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; CABP, community-acquired bacterial pneumonia; CI, confidence interval; CL, clearance; CLcr, creatinine clearance; CV, coefficient of variation; PopPK, population pharmacokinetic; Q, flow rate; V, volume

Figure 27. Goodness-of-Fit Plots for the Final PopPK Model for ABSSSI and CABP



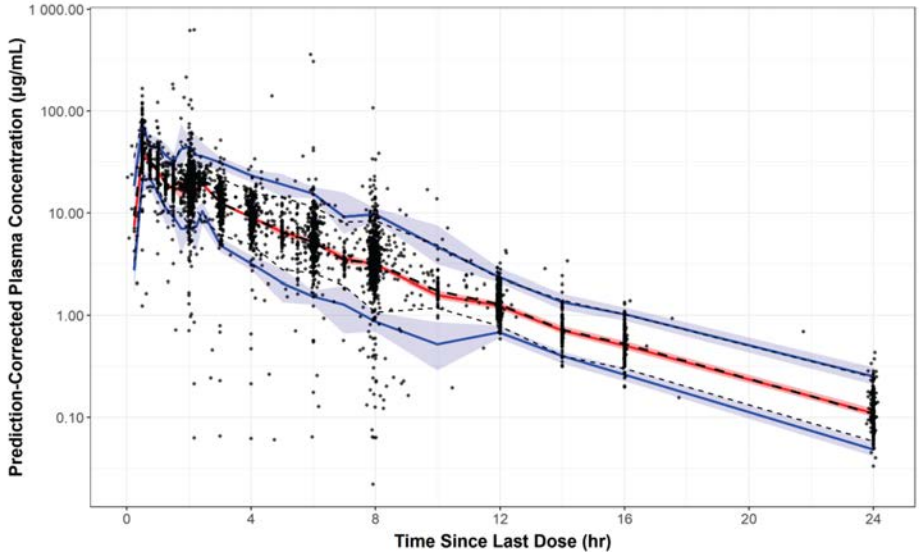
Source: Applicant's PopPK report for ABSSSI and CAP, Figure 11, page 62
Plots are presented in the natural log scale
Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; CABP, community-acquired bacterial pneumonia; PopPK, population pharmacokinetic

Figure 28. Histograms of NPDE by Dose Levels and Scatterplot of NPDE by Time for the Final PopPK Model for ABSSSI and CABP



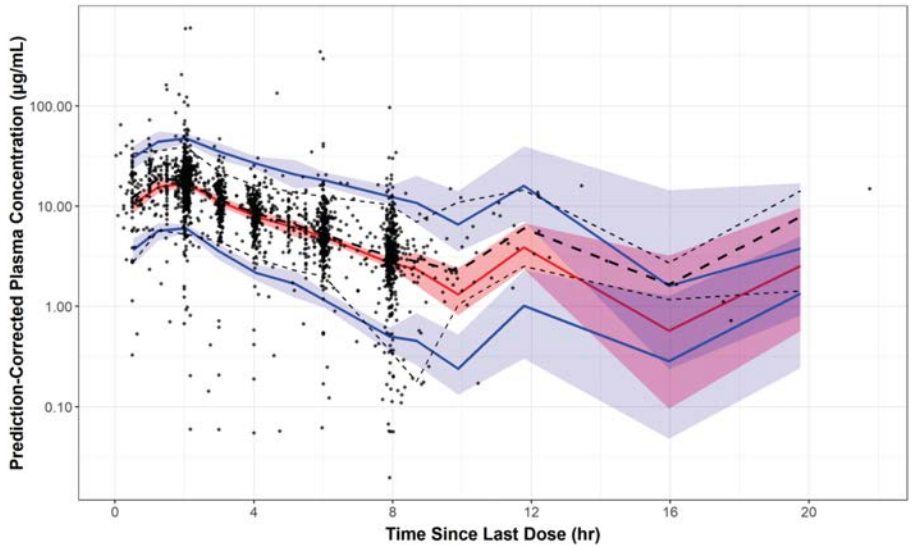
Source: Applicant's PopPK report for ABSSSI and CAP, Figure 12, page 63
Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; CABP, community-acquired bacterial pneumonia; NPDE, normalized prediction distribution errors; PopPK, population pharmacokinetic

Figure 29. Prediction-corrected VPC Plot for the Final PopPK Model for ABSSSI and CABP



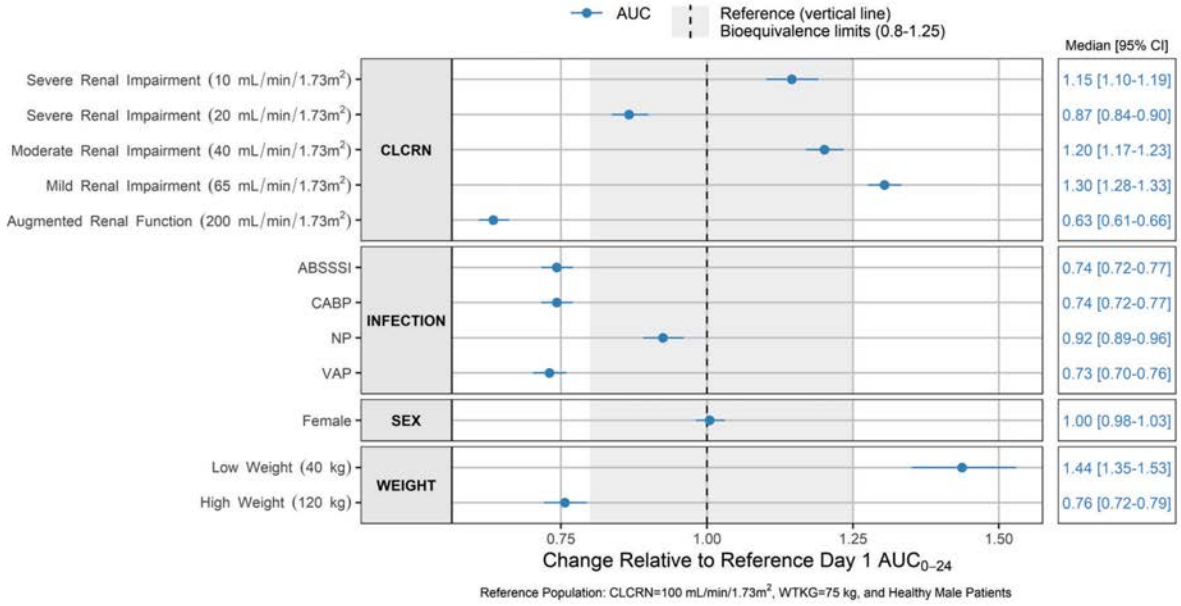
Source: Applicant's PopPK report for ABSSSI and CAP, Figure 13, page 64
Circles are observed concentrations, black solid lines are the median observed concentrations, black dashed lines are the 5th and 95th percentiles of the observed concentrations. Red and blue shaded regions are the 90% confidence intervals for the median, 5th, and 95th percentiles from the simulations
Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; CABP, community-acquired bacterial pneumonia; VPC, visual predictive check

Figure 30. Prediction-Corrected VPC Plot for the Final PopPK Model for ABSSSI and CABP Using Phase 3 PK Data



Source: Applicant's PopPK report for ABSSSI and CAP, Figure 15, page 66
Circles are observed concentrations, black solid lines are the median observed concentrations, black dashed lines are the 5th and 95th percentiles of the observed concentrations. Red and blue shaded regions are the 90% confidence intervals for the median, 5th, and 95th percentiles from the simulations
Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; CABP, community-acquired bacterial pneumonia; PK, pharmacokinetic; PopPK, population pharmacokinetic; VPC, visual predictive check

Figure 31. Forest Plot Showing Impact of Statistically Significant Covariate-Parameter Relationships on Day 1 AUC



Source: Applicant's PopPK report for ABSSSI and CAP, Figure 25, page 90
Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; AUC, area under the concentration-time curve; AUC0-24, area under the concentration-time curve from time 0 to 24 hours; CABP, community-acquired bacterial pneumonia; CI, confidence interval; NP, nosocomial pneumonia; VAP, ventilator acquired pneumonia

Reviewer Comments

The reviewer was able to reproduce the Applicant's final PopPK model for ABSSSI and CABP subjects. The Applicant's final model is acceptable in describing the ceftobiprole PK characteristics pooling phase 1 and phase 3 subjects. The model qualification is demonstrated

through precision of parameter estimates (all %SEM under 12.1% except one parameter at 21.9%) and alignment of resampled parameter estimates (90% CI contains model parameter estimates). Additionally, there is no obvious bias or misspecification in the GoF plots for the final model (observed vs. predicted concentrations show good agreements and mostly align with the line of unity; the CWRES scatter around y = 0 without obvious trends). The NPDE and prediction-corrected VPC plots show that the final model is able to capture the observed data; however, when the prediction-corrected VPC plot is further stratified by phase 1 vs. phase 3 subjects, the phase 3 prediction-corrected VPC plot demonstrates bias beyond 8 hours (Figure 30), and this is likely due to the relatively sparse PK available in that time frame in phase 3 studies.

Of note, the Applicant fixed the nosocomial pneumonia effect (NP) on CL to zero in the final model. As such, the reviewer performed a sensitivity analysis by re-estimating this parameter to assess the impact of NP on CL. The resulting model did not provide statistically meaningful improvement over the Applicant's final model (minimal change in OFV). This is likely due to the relatively low percent of NP subjects (5.69%) in the pooled dataset. Overall, the Applicant's final covariate model is acceptable in describing ceftobiprole disposition, in deriving exposure metrics for exposure-response *analysis, and in simulating for target attainment analysis in adult subjects with ABSSSI or CABP.*

14.5.1.4. *Staphylococcus aureus* Bacteremia

14.5.1.4.1. Model Development

Data

Trial BPR-CS-009 enrolled adult subjects with SAB, and the ceftobiprole group was pooled with the ABSSSI and CABP PopPK model dataset for SAB model development and refinement. A summary of study design, PK sampling, and dosages are summarized in Table 232. Overall, a total of 180 SAB subjects (including n = 20 who were randomized to ceftobiprole and continued to receive intermittent hemodialysis or iHD) were included in the final NONMEM dataset, contributing 1,134 plasma concentrations.

After pooling with the phase 1 and phase 3 ABSSSI and CABP PK data, a total of 953 subjects who contributed 6024 evaluable plasma concentrations were available for analysis (i.e., a total of 13 studies). Summaries of baseline characteristics for SAB subjects are provided in Table 233. For baseline characteristics of the 12 studies included in the ABSSSI and CABP PopPK model, refer to Table 228. No notable difference was observed with baseline characteristics between the SAB and ABSSSI/CABP phase 3 subjects.

Reference ID: 5357793

Table 232. Summary of *Staphylococcus aureus* Bacteremia Clinical Trial

Study (Phase)	Title	Ceftobiprole dose	PK sampling strategy
BPR-CS-009 (Phase 3) [2]	A randomized, double-blind, multi-center study to establish the efficacy and safety of ceftobiprole medocaril compared to daptomycin in the treatment of *Staphylococcus aureus* bacteremia, including infective endocarditis	500 mg IV q6h over 2 h for 8 days and q8h for Day 9 onwards with adjustment for renal impairment	Sparse: Days 3 and 12 pre-dose, 2 h (end of infusion), and 4-6 h after the start of infusion Rich: Day 3 pre-dose, 2 h (end of infusion), 3, 4, and 6 h after the start of infusion. Day 12 pre-dose, 2 h (end of infusion), 4, and 6 h after the start of infusion.

Source: Applicant's PopPK report for SAB, Table 1, page 19
Note: 667 mg of ceftobiprole medocaril sodium is equivalent to 500 mg of ceftobiprole. Dosing adjustments for each indication are based on renal function
Abbreviations: IV, intravenous; PK, pharmacokinetic; q6h, every 6 hours; q8h, every 8 hours; SAB, *Staphylococcus aureus* Bacteremia

Table 233. Summary of Baseline Characteristics of Phase 3 *Staphylococcus aureus* Bacteremia Subjects and Phase 3 ABSSSI and CABP Subjects

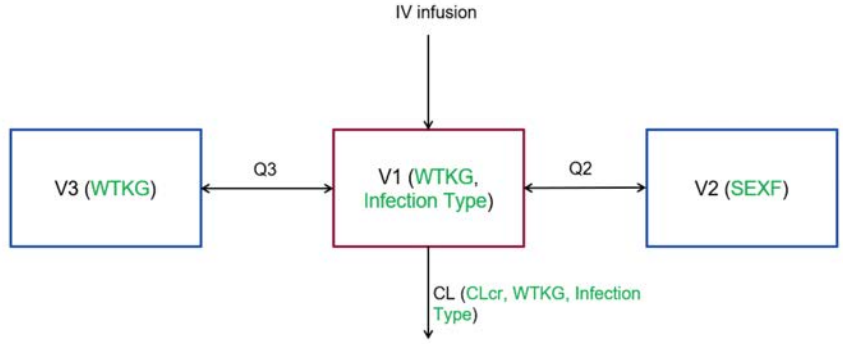
Variable	Previous Phase 3 Studies			Current Phase 3 Study
	BPR-CS-008	CAP-3001	BAP248/307	BPR-CS-009
Age (yr)	49.5 (13.6) 51 (18-85)	54.1 (20.1) 56 (18-90)	60.4 (20.9) 66 (18-91)	54.5 (14.7) 57 (20-89)
Height (cm)	172 (10.4) 172 (145-200)	168 (10.3) 168 (144-195)	168 (11.1) 170 (127-188)	172 (7.58) 172 (154-190)
Weight (kg)	82.2 (18.7) 79.3 (41.3-165)	71.7 (17.4) 70 (29.5-123)	73 (15.6) 72.7 (40-115)	80.7 (17.1) 80 (40-130)
BSA (m^2)	1.94 (0.233) 1.93 (1.29-2.78)	1.8 (0.241) 1.8 (1.2-2.4)	1.82 (0.22) 1.83 (1.36-2.38)	1.93 (0.206) 1.94 (1.33-2.55)
BMI (kg/m^2)	27.9 (5.81) 26.6 (16.5-50.9)	25.3 (5.04) 24.6 (11.5-44.9)	25.8 (5.27) 25.1 (15.6-41.4)	27.3 (5.47) 26.7 (15.9-53.4)
CLcr ($mL/min/1.73\ m^2$)	106 (35.5) 104 (20.2-239)	78.2 (29.3) 78.5 (18.8-176)	89.7 (48.3) 74.3 (19.9-196)	81.7 (48.7) 76.9 (6.11-291)
Sex				
Male	184/309 (59.5%)	122/209 (58.4%)	51/67 (76.1%)	119/180 (66.1%)
Female	125/309 (40.5%)	87/209 (41.6%)	16/67 (23.9%)	61/180 (33.9%)
Race				
White	294/309 (95.1%)	146/209 (69.9%)	53/67 (79.1%)	171/180 (95%)
Black	6/309 (1.94%)	8/209 (3.83%)	6/67 (8.96%)	4/180 (2.22%)
Asian		39/209 (18.7%)	4/67 (5.97%)	1/180 (0.556%)
American Indian/ Alaska Native	3/309 (0.971%)			
Native Hawaiian or other Pacific islander	1/309 (0.324%)			
Other	5/309 (1.62%)	16/209 (7.66%)	4/67 (5.97%)	4/180 (2.22%)
Infection Type				
ABSSSI	309/309 (100%)			
CABP		209/209 (100%)		
NP			44/67 (65.67%)	
SAB				180/180 (100%)
VAP			23/67 (34.33%)	

Note: Summary statistics presented as mean (%CV) and median (Min. – Max.) or n/N (%).
Source: Applicant's PopPK report for SAB, Table 3, page 29
Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; BMI, body mass index; BSA, body surface area; CABP, community-acquired bacterial pneumonia; CLcr, creatinine clearance; NP, nosocomial pneumonia; SAB, *Staphylococcus aureus* Bacteremia; VAP, ventilator acquired pneumonia

Base Model

The model structure of the ABSSSI and CABP PopPK model was used for PK parameter re-estimation as the external evaluation demonstrated model prediction bias (not shown). A schematic of the structural model applied to the pooled PK data is shown in Figure 32.

Figure 32. Schematic of the Initial PopPK Model



Source: Applicant's PopPK report for SAB, Figure 5, page 34
Abbreviations: CL, clearance; CLcr, creatine clearance; IV, intravenous; V, volume

Model Refinement

No formal stepwise covariate selection was performed with the assumption that SAB subjects have PK similarity compared to the ABSSSI or CABP populations for the infection type covariate effects. To improve model fit, a separate covariate effect on CL for SAB infection type and SAB, NP and VABP infection types on V1 were modelled and selected.

14.5.1.4.2. Final Model

The parameter estimates for the final covariate model for ABSSSI and CABP subjects are listed in Table 234. The GoF and NPDE plots for the final covariate model Figure 33 and Figure 34. The prediction-corrected VPC plot for the final covariate model is shown in Figure 35 and Figure 36. A forest plot is shown in Figure 37. Key ceftobiprole exposures and relevant PK parameters across phase 3 studies for ABSSSI, CABP, and SAB are summarized in Table 235.

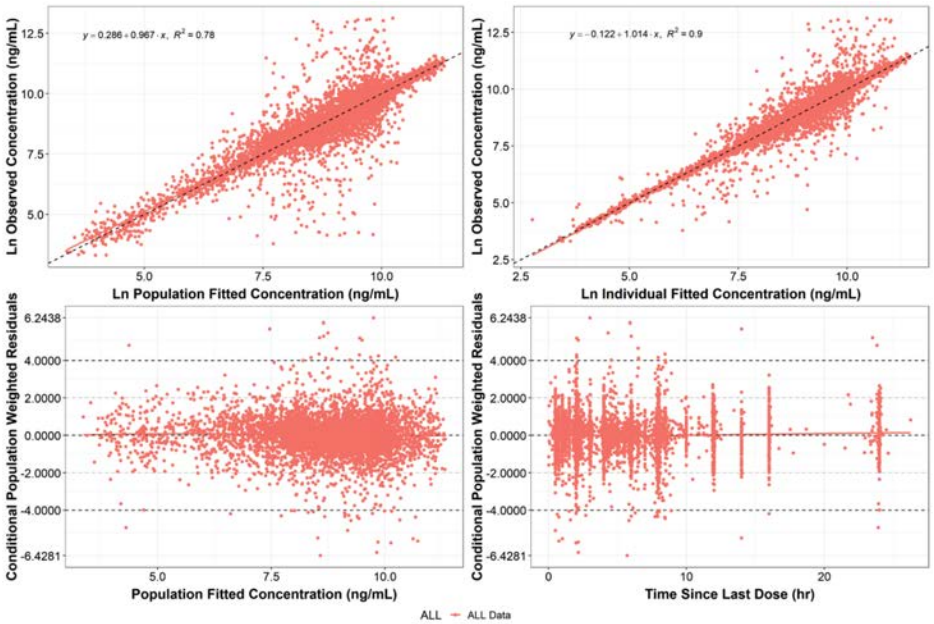
Table 234. Parameter Estimates for the Final PopPK Model for *Staphylococcus aureus* Bacteremia

Parameter	Refined Model Fit			Resample statistics (N = 1000)			
	Estimate	%SEM	Shrinkage	Mean	Median	%CV	90% CI
CL (L/hr)	5.02	1.47		5.01	5.01	1.11	[4.92, 5.11]
V1 (L)	8.65	2.85		8.65	8.65	2.52	[8.28, 9.00]
Q2 (L/hr)	0.616	4.93		0.617	0.617	4.63	[0.570, 0.666]
V2 (L)	2.88	3.04		2.88	2.88	2.85	[2.75, 3.02]
Q3 (L/hr)	8.13	5.51		8.16	8.14	5.45	[7.41, 8.90]
V3 (L)	5.69	2.98		5.68	5.68	2.75	[5.42, 5.93]
CL:CLcr power coefficient	0.704	2.9		0.704	0.704	2.92	[0.669, 0.737]
CL:WTKG power coefficient	0.545	10.8		0.542	0.542	10.3	[0.446, 0.637]
CL shift for ABSSSI, CABP, VAP	0.333	13.3		0.335	0.335	10.7	[0.276, 0.393]
CL shift for SAB	0.104	36.7		0.105	0.103	38.5	[0.0406, 0.170]
V1:WTKG power coefficient	0.813	11.9		0.815	0.814	12	[0.651, 0.976]
V1 shift for ABSSSI, CABP	1.04	10		1.04	1.04	9.56	[0.887, 1.21]
V1 shift for NP, VAP, SAB	1.65	9.04		1.65	1.64	10.2	[1.38, 1.92]
V2 shift for females	-0.216	12.1		-0.216	-0.216	9.29	[-0.249, -0.183]
V3:WTKG power coefficient	1.01	8.71		1.01	1.01	9.73	[0.850, 1.17]

Parameter	Refined Model Fit			Resample statistics (N = 1000)			
	Estimate	%SEM	Shrinkage	Mean	Median	%CV	90% CI
ω^2_{V1}	0.0336 (18.3%)	15.3	58.4	0.0339	0.0338	13.7	[0.0264, 0.0416]
ω^2_{V2}	0.0119 (10.9%)	22.7	69.7	0.0122	0.0121	19.3	[0.00880, 0.0164]
ω^2_{V3}[c]	0.0221 (14.9%)	17.3	15.6	0.0228	0.0226	18.9	[0.0163, 0.0300]
CL ω^2_{V3} scaling factor	2.92	9.41		2.92	2.89	10.3	[2.48, 3.47]
Healthy ω^2_{CL} scaling factor	-0.651	3.4		-0.649	-0.649	3.4	[-0.684, -0.611]
$\sigma^2_{\text{plasma Phase 1, Additive in log domain}}$	0.0124	1.34	7.59	0.0124	0.0124	2.3	[0.0119, 0.0128]
$\sigma^2_{\text{plasma Phase 3, Additive in log domain}}$	0.434	1.14	8.44	0.434	0.434	1.89	[0.421, 0.448]

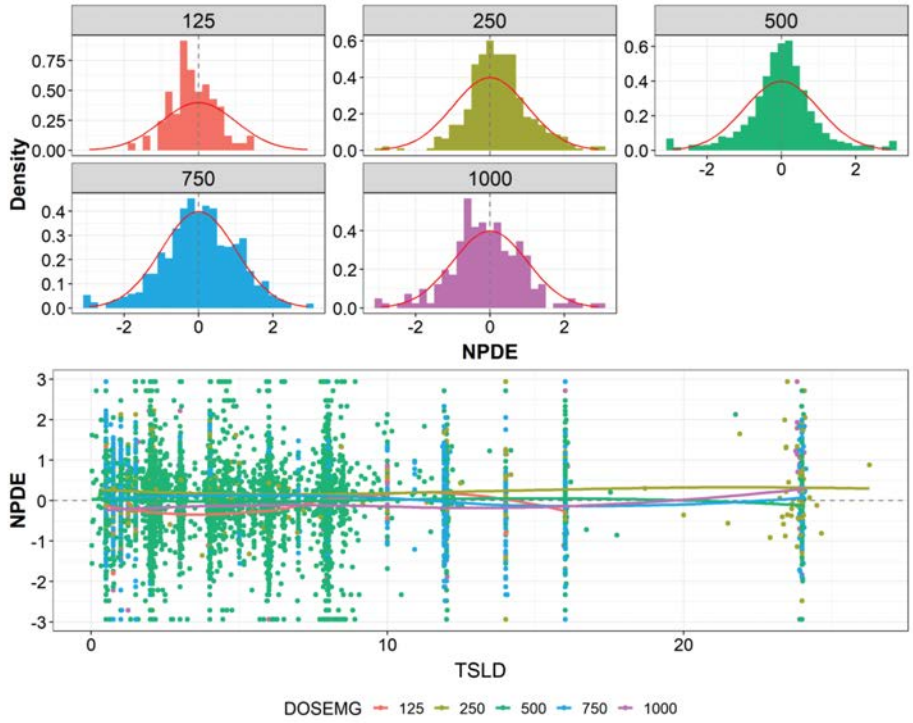
Source: Applicant's PopPK report for SAB, Table 4, pages 39-40
Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; CABP, community-acquired bacterial pneumonia; CI, confidence interval; CL, clearance; CV, coefficient of variation; NP, nosocomial pneumonia; PopPK, population pharmacokinetic; Q, flow rate; SAB, *Staphylococcus aureus* Bacteremia; SEM, standard error of the mean; V, volume; VAP, ventilator acquired pneumonia

Figure 33. Goodness-of-Fit Plots for the Final PopPK Model for *Staphylococcus aureus* Bacteremia



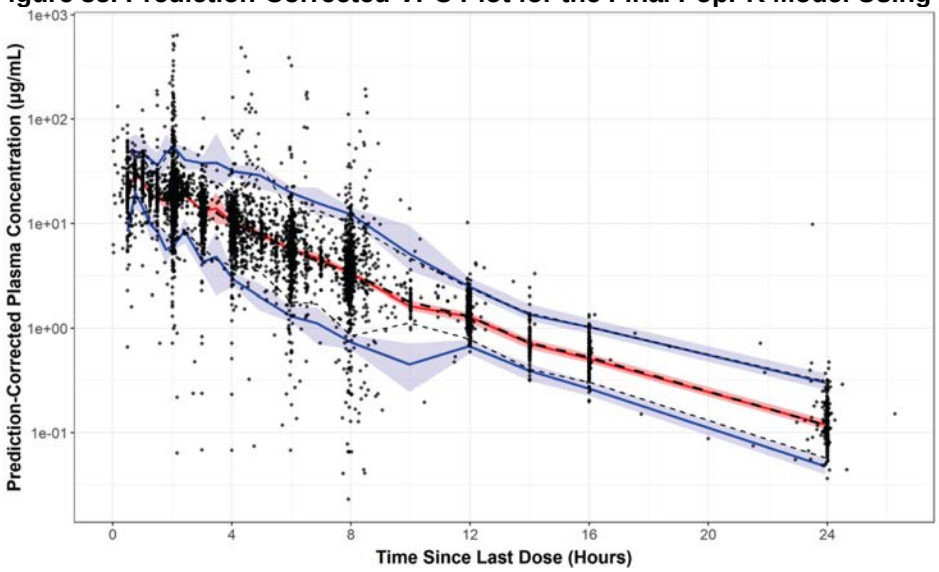
Source: Applicant's PopPK report for SAB, Figure 7, page 41
Abbreviations: PopPK, population pharmacokinetic; SAB, *Staphylococcus aureus* Bacteremia

Figure 34. Histograms of NPDE by Dose Levels and Scatterplot of NPDE by Time for the Final PopPK Model for *Staphylococcus aureus* Bacteremia



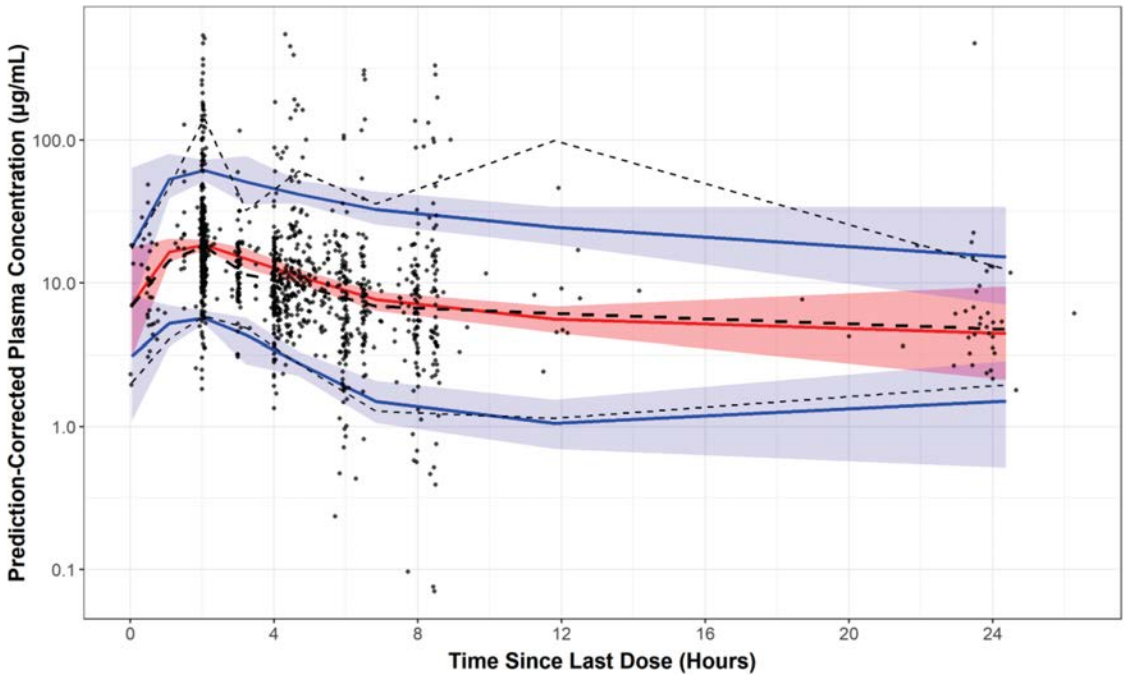
Source: Applicant's PopPK report for SAB, Figure 8, page 42
Abbreviations: NPDE, normalized prediction distribution errors; PopPK, population pharmacokinetic; SAB, *Staphylococcus aureus* Bacteremia; TSLD, time scaled logic diagram

Figure 35. Prediction-Corrected VPC Plot for the Final PopPK Model Using the Pooled Dataset



Source: Applicant's PopPK report for SAB, Figure 9, page 43
Circles are observed concentrations, black solid lines are the median observed concentrations, black dashed lines are the 5th and 95th percentiles of the observed concentrations. Red and blue shaded regions are the 90% confidence intervals for the median, 5th, and 95th percentiles from the simulations
Abbreviations: PopPK, population pharmacokinetic; VPC, visual predictive check

Figure 36. Prediction-Corrected VPC Plot for the Final PopPK Model for *Staphylococcus aureus* Bacteremia Subjects Only



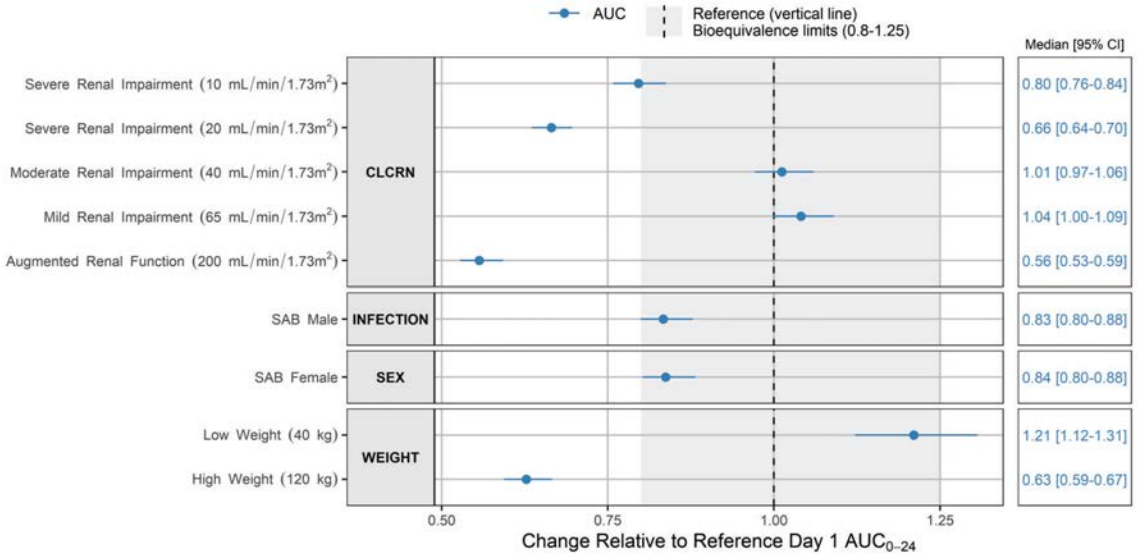
Source: Applicant's PopPK report for SAB, Figure 10, page 44
Circles are observed concentrations, black solid lines are the median observed concentrations, black dashed lines are the 5th and 95th percentiles of the observed concentrations. Red and blue shaded regions are the 90% confidence intervals for the median, 5th, and 95th percentiles from the simulations
Abbreviations: PopPK, population pharmacokinetic; SAB, *Staphylococcus aureus* Bacteremia; VPC, visual predictive check

Table 235. Summary of Ceftobiprole Exposures and PK Parameters for Phase 3 Subjects by Trial Including ABSSSI and CABP Studies

Parameter	BPR-CS-009 (n = 180)	BPR-CS-008 (n = 309)	CAP-3001 (n = 209)[a]	BAP248/307 (n = 67)[b]
AUC_{0-24}, Day 1 (mg•h/L)	262 (43.1%)	182 (34.4%)	230 (35.0%)	228 (40.1%)
AUC_{0-24}, Day 2 (mg•h/L)	323 (50.5%)	193 (38.8%)	255 (38.5%)	277 (45.4%)
AUC_{0-24}, Day 3 (mg•h/L)	335 (50.7%)	195 (38.1%)	259 (37.8%)	291 (47.4%)
C_{max}, Day 1 (µg/mL)	18.6 (39.5%)	16.9 (25.8%)	20.7 (25.3%)	19.1 (26.8%)
C_{max}, Day 2 (µg/mL)	20.3 (39.4%)	17.1 (26.4%)	21.2 (26.2%)	20.8 (31.9%)
C_{max}, Day 3 (µg/mL)	20.8 (39.5%)	17.2 (26.8%)	21.3 (26.4%)	21.2 (32.2%)
CL (L/h)	4.49 (73.3%)	7.58 (40.0%)	5.61 (41.1%)	4.87 (56.0%)
V1 (L)	23.8 (17.3%)	18.6 (17.8%)	16.5 (20.2%)	21.9 (17.3%)
Vss (L)	32.6 (17.0%)	27.4 (17.5%)	24.5 (19.5%)	30.1 (17.0%)
$t_{1/2,\alpha}$ (h)	0.391 (22.4%)	0.357 (21.3%)	0.322 (23.3%)	0.357 (20.4%)
$t_{1/2,\beta}$ (h)	2.36 (15.5%)	1.92 (17.4%)	2.01 (18.3%)	2.31 (15.7%)
$t_{1/2,\gamma}$ (h)	6.08 (58.6%)	3.79 (17.7%)	4.19 (22.1%)	5.34 (36.1%)
AUC accumulation ratio	1.18 (0.712 - 4.91)	1.06 (0.690 - 1.79)	1.07 (0.000119 - 1.94)	1.15 (0.0000224 - 2.42)
C_{max} accumulation ratio	1.04 (0.662 - 3.59)	1.01 (0.636 - 1.70)	1.01 (0.000225 - 1.33)	1.03 (0.000464 - 1.93)
CLcr (mL/min/1.73 m^2)[c]	76.9 (6.11 - 291)	104 (20.2 - 239)	78.5 (18.8 - 176)	74.3 (19.9 - 196)
Weight (kg)[c]	80.0 (40.0 - 130)	79.3 (41.3 - 165)	70.0 (29.5 - 123)	72.7 (40.0 - 115)

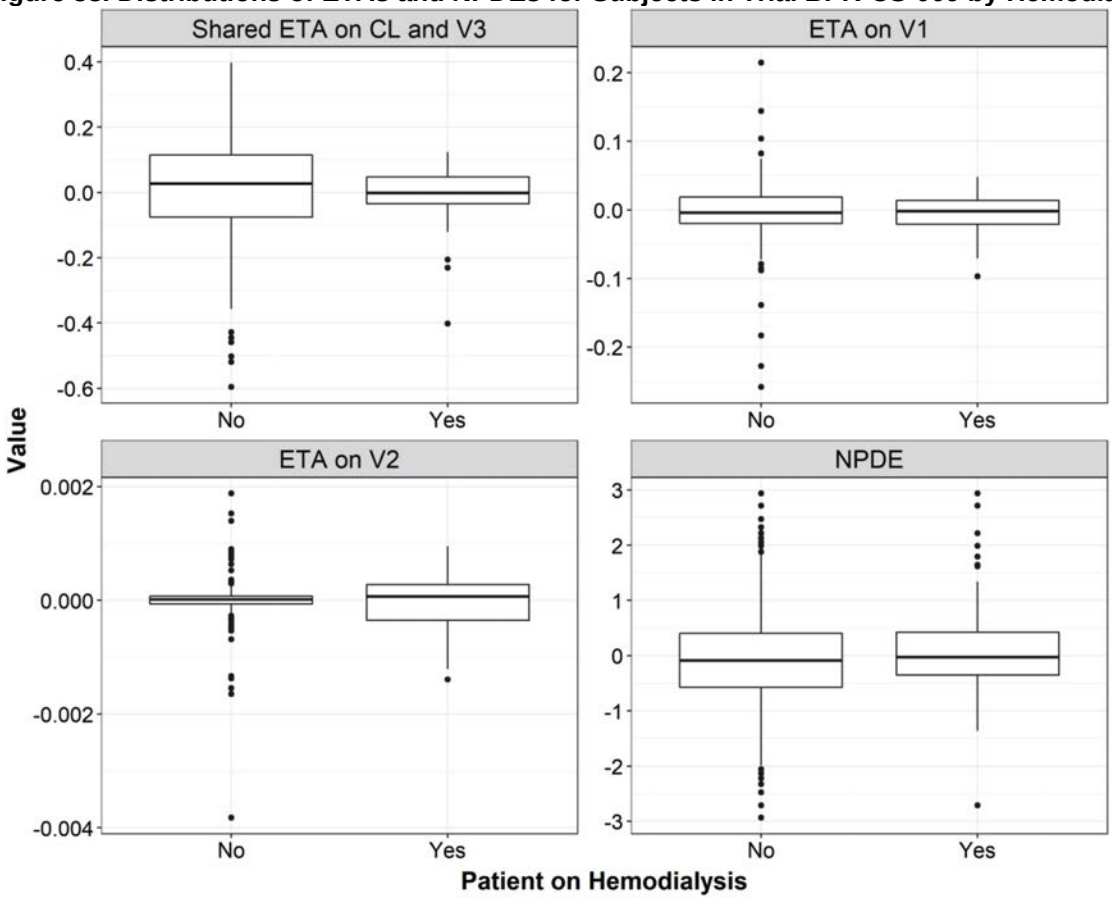
Source: Applicant's PopPK report for SAB, Table 5, page 48
Statistics are shown as geometric mean and coefficient of variation as a percentage
[a]Due to shortened treatment durations (b) (6) subjects from Study CAP-3001 are excluded from the summary statistics for Days 2 and 3, respectively; [b]Due to shortened treatment durations, (b) (6) subjects from Study BAP248/307 are excluded from the summary statistics for Days 2 and 3, respectively; [c]Summary statistics for CLcr and weight are shown as median (Min. – Max.)
Abbreviations: ABSSSI, acute bacterial skin and skin structure infections; AUC, area under the concentration-time curve; AUC0-24, area under the concentration-time curve from time 0 to 24 hours; CABP, community-acquired bacterial pneumonia; CLcr, creatinine clearance; C_{max}, maximum plasma concentration; n, number of subjects in treatment arm; PK, pharmacokinetic; T½, half-life; V, volume; Vss, steady state volume

Figure 37. Forest Plot Showing Impact of Statistically Significant Covariate-parameter Relationships on Day 1 AUC



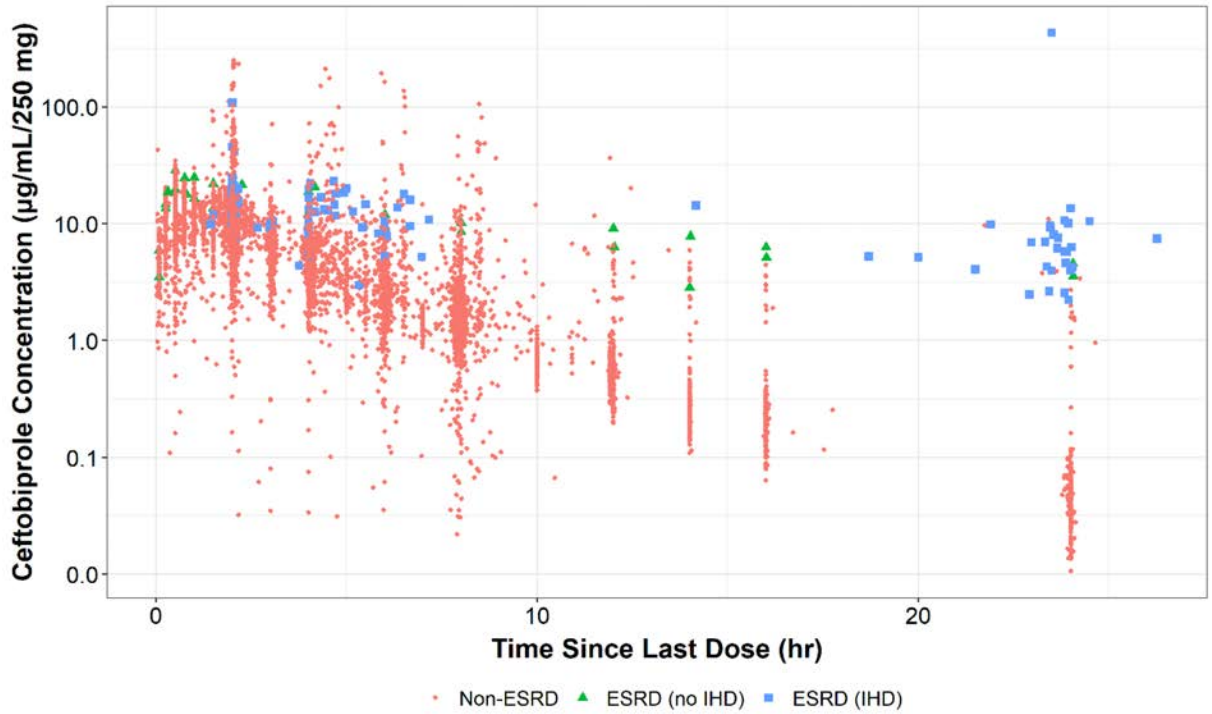
Source: Applicant's PopPK report for SAB, Figure 15, page 53
Abbreviations: AUC, area under the concentration-time curve; AUC0-24, area under the concentration-time curve from time 0 to 24 hours; CI, confidence interval; SAB, *Staphylococcus aureus* Bacteremia

Figure 38. Distributions of ETAs and NPDEs for Subjects in Trial BPR-CS-009 by Hemodialysis



Source: Applicant's PopPK report for SAB, Figure 12, page 46
ETA, a term denoting individual random effects in the PopPK model structure
Abbreviations: CL, clearance; ETA, individual random effects; NPDE, normalized prediction distribution errors; V, volume

Figure 39. Dose-normalized Ceftobiprole Plasma Concentrations Versus. Time Since Last Dose Stratified by ESRD and Hemodialysis Status



Source: Applicant's response to Information Request [request dated 2NOVEMBER2023; EDR link: IR_SEQ026]
Abbreviations: ESRD, end-stage renal disease; IHD, intermittent hemodialysis

Reviewer Comments

The reviewer was able to reproduce the Applicant's refined PopPK model for SAB (i.e., final model). The final parameter estimates were precise (all %SEM under 13.3% except CL shift for SAB was moderate at 36.7%) and aligned with the resampled parameter estimates (90% confidence interval *[CI] contains model parameter estimates). Similar to the final PopPK model for ABSSSI and CABP, there is no obvious bias or misspecification observed in the GoF plots (observed vs. predicted concentrations show good agreements and mostly align with the line of unity; the CWRES scatter around y = 0 without obvious trends). The NPDE and prediction-corrected VPC plots show that the refined SAB PopPK model can capture the observed data; however, when the prediction-corrected VPC plot is limited to SAB subjects, some under-predictions are shown and are more prominent beyond 8 hours. This is likely due to the relatively sparse PK available in the 8-to-24-hour timeframe (based on time from last dose). Overall, the model reasonably captures central tendency of the SAB PK data. The Applicant's final SAB model is acceptable in describing ceftobiprole disposition, in deriving exposure metrics for* exposure-response *analysis for the SAB population, and in simulating for target attainment analysis (i.e., PTA) in adult subjects with SAB.*

In the phase 3 trial in SAB subjects, a total of 21 subjects with ESRD were randomized to continue iHD renal replacement modality while receiving ceftobiprole (n=20 in the final NONMEM dataset); however, the reviewer noted in the Applicant's report that, "the exact times at which hemodialysis was started and stopped was not recorded, the trial protocol stipulated that drug dosing and PK sampling on the hemodialysis day was to occur after the completion of the hemodialysis session." The uncertainty regarding iHD effect in ESRD subjects is further complicated by the unreliable results of the dedicated phase 1 study in ESRD subjects (see discussion in Section 8. The Applicant suggested that the study protocol was likely followed

based on: 1) PopPK model performance in this subgroup, 2) no obvious bias observed based on diagnostic plots of the PopPK model by ESRD status (Figure 38 and Figure 39); refer to Applicant's PopPK report and Information Request responses for additional plots), and 3) visual comparisons of concentration-time profiles of non-ESRD subjects vs. ESRD subjects not on iHD vs. ESRD subjects on iHD. Additionally, the Applicant's response to a follow-up Information Request indicated that 8 of the 20 subjects had confirmed administration and PK sampling times post iHD sessions. The reviewer agrees that these aspects overall may increase the confidence of the data to be used for comparison, model-based simulation, and dose selection in the setting of ESRD regardless of iHD because the doses are administered post dialysis sessions. One limitation to acknowledge is that model-based simulations cannot be conducted in the setting of iHD due to a lack of information for extraction ratio (i.e., unreliable phase 1 data). Despite this limitation, the SAB PTA results provide further support of the dosing selection in the ESRD population regardless of extraction ratio. Refer to Section 14.5.2.3 for further discussion of dosing recommendation. The Information Requests and responses related to ESRD can be found at these EDR links: IR_SEQ026, IR_SEQ036, and IR_SEQ041.

14.5.1.5. Pediatrics CABP

14.5.1.5.1. Model Development

The Applicant submitted 2 technical reports for the indicated pediatric age group for CABP (Report 00616-3 and Report 00616-3A). The first report utilized pediatric data only for PopPK model development (referred to as the original pediatric only PopPK model), and the latter report is an addendum to Report 00616-3 with pooled pediatric and adult data, including adult subjects with renal impairment. Per Applicant, this addendum was requested by the Swedish Medical Products Agency. While both reports were submitted under this NDA, emphasis is placed on the addendum report (i.e., 00616-3A) as the final model is used for exposure derivation, simulations, and PTA analysis to support dosing recommendation in pediatric subjects down to 3 months of age for CABP. The overall objectives of the analyses in pediatric subjects were to:

- Identity the renal function estimate equation that provides the best model fit to the observed PK data
- Develop a pediatric PopPK model using a pooled dataset of pediatric and adult subjects (including adults with renal impairment [RI])
- Provide dosing recommendations in pediatric subjects with renal impairment

Data

A total of 3 pediatric studies were included for pediatric PopPK model development. Study design and dosages are summarized in Table 236. For pediatric subjects, the final NONMEM dataset included 112 subjects who contributed 606 evaluable plasma concentrations. The pooled phase 1 adult PK data included an additional 187 subjects with 2,761 evaluable plasma concentrations in addition to the pediatric PK data. A summary of baseline characteristics for pediatric subjects included in the model development are provided in Table 237. Of note, the proposed indication in this NDA is down to 3 months of age.

In regard to estimation of glomerular filtration rate (GFR) in pediatric subjects, including those undergoing renal function maturation, the Applicant utilized 4 approaches for model fitting: 1) bedside Schwartz (mL/min/1.73 m^2) (Schwartz et al. 2009), 2) Rhodin formula using normalized

Reference ID: 5357793

fat mass (mL/min), 3) Rhodin formula using fat-free mass (mL/min) (Rhodin et al. 2009) and 4) renal maturation function using DeCock et al (De Cock et al. 2014).

Table 236. Summary of Pediatric Studies

Study	Design	Dosage
BPR-CSI-1006[a]	Phase 1, multicenter, open-label, single-dose study conducted to evaluate the PK and safety of ceftobiprole in hospitalized and ambulatory pediatric subjects (≥3 month to <2 years) who had documented or presumed, or were at risk for, bacterial infections and were undergoing treatment with systemic antibiotics	≥3 month to <2 years: 15 mg/kg ≥2 years to <6 years: 15 mg/kg ≥6 to <12 years: 10 mg/kg ≥12 to <18 years: 7 mg/kg
BPR-PIP-001	Phase 1, multicenter, open-label, single-dose study conducted to evaluate the single-dose PK and safety of ceftobiprole in neonate and infant subjects aged up to 3 months undergoing treatment with systemic antibiotics	7.5 mg/kg single dose infused over 4 hours
BPR-PIP-002[b]	Phase 3, multicenter, randomized, investigator-blind, active-controlled study to evaluate the safety, tolerability, PK, and efficacy of ceftobiprole versus IV standard-of-care cephalosporin treatment with or without vancomycin in pediatric subjects aged 3 months to <18 years of age with HAP or CAP requiring hospitalization	≥3 month to <2 years[c]: 20 mg/kg ≥2 years to <6 years: 20 mg/kg ≥6 to <12 years: 15 mg/kg ≥12 to <18 years: 10 mg/kg

[a,b]Doses were capped at 500 mg; [c]infused over 4 hours
Note: 667 mg of ceftobiprole medocaril sodium is equivalent to 500 mg of ceftobiprole. For pediatric patients: 13.3 mg/kg is equivalent to 10 mg/kg of ceftobiprole. 26.7 mg/kg of ceftobiprole medocaril sodium is equivalent to 20 mg/kg of ceftobiprole. Dosing adjustments for each indication are based on renal function.
Source: reviewer's table adapted from Applicant's original PopPK Report 00616-3
Abbreviations: CAP, community acquired pneumonia; HAP, hospital acquired pneumonia; IV, intravenous; PK, pharmacokinetic

Table 237. Summary of Baseline Characteristics for All Pediatric Subjects

Variable	BPR-CSI-1006 N = 63 Median (Min – Max)	BPR-PIP-001 N = 15 Median (Min – Max)	BPR-PIP-002 N = 29 Median (Min – Max)	Total N = 107 Median (Min – Max)
Age (years)	5.00 (0 - 17.0)	0.0220 (0.00500 - 0.178)	5.00 (1.00 - 17.0)	4.00 (0 - 17.0)
Age (months)	70.3 (3.25 - 215)	0.263 (0.0660 - 2.14)	60.0 (12.0 - 204)	58.0 (0.0660 - 215)
Postnatal Age (weeks)	306 (14.1 - 935)	1.14 (0.285 - 9.26)	260 (52.0 - 884)	252 (0.285 - 935)
Gestational Age (weeks)	—[a]	39.4 (37.6 - 41.4)	40.0 (40.0 - 40.0)	40.0 (37.6 - 41.4)
Postconceptional Age (weeks)	—[a]	42.0 (38.4 - 48.5)	300 (92.0 - 924)	248 (38.4 - 924)
Height (cm)	118 (55.9 - 189)	54.0 (49.0 - 61.0)	116 (83.0 - 180)	109 (49.0 - 189)
Weight (kg)	21.4 (5.60 - 75.3)	3.98 (2.50 - 5.27)	23.0 (11.0 - 67.0)	18.5 (2.50 - 75.3)
BMI (kg/m^2)	18.1 (11.0 - 38.8)	13.8 (10.0 - 15.6)	16.2 (13.6 - 23.3)	17.2 (10.0 - 38.8)
BSA (m^2)	0.850 (0.280 - 1.95)	0.230 (0.180 - 0.290)	0.850 (0.510 - 1.81)	0.740 (0.180 - 1.95)
GFR – $Rhodin_{FFM}$ (mL/min)	64.3 (11.5 - 144)	5.90 (3.83 - 10.4)	58.9 (38.2 - 134)	52.3 (3.83 - 144)
	n (%)	**n (%)**	**n (%)**	**n (%)**
Gender				
Male	35 (55.6%)	10 (66.7%)	16 (55.2%)	61 (57.0%)
Female	28 (44.4%)	5 (33.3%)	13 (44.8%)	46 (43.0%)
Race				
White	34 (54.0%)	13 (86.7%)	29 (100%)	76 (71.0%)
Black	23 (36.5%)	1 (6.67%)	0 (0%)	24 (22.4%)
Other/Unspecified	6 (9.52%)	1 (6.67%)	0 (0%)	7 (6.54%)

Note: Abbreviations are provided in the Abbreviation Listing.
a. Gestational age not reported in data for Study BPR-CSI-1006
Source: Applicant's original PopPK report 00616-3, Table 5, page 32
Abbreviations: BMI, body mass index; BSA, body surface area; FFM, fat-free mass; GFR, glomerular filtration rate; n, number of subjects in treatment arm;

Base Model

The original PopPK model structure was fitted to the pooled pediatric and adult dataset. The final base model (from pediatric data alone) was a linear 3-compartment with a direct relationship between renal clearance (CL) and GFR based on Rhodin and fat-free mass ($GFR_{Rhodin, FFM}$). Body weight was included on volume (estimated exponent) and clearance related terms (fixed exponent of 0.75). IIV was included on central volume of distribution (Vc) only.

For the final base model, IIV was modelled assuming a log-normal distribution for subject level random effects. Residual variability was tested as additive, proportional, or combined. Model evaluation and selection of the base model were based on standard statistical criteria of GoF such as a decrease in the OFV, accuracy of parameter estimation (i.e., 95% confidence interval excluding 0), successful model convergence, and diagnostic plots.

Covariate Model

Covariate screening was undertaken via plots in the original pediatric only PopPK model, but no obvious relationships were observed. As such, no formal stepwise covariate modeling was

Reference ID: 5357793

conducted (i.e., forward selection and backwards elimination) when the model was fitted to the pooled dataset.

14.5.1.5.2. Final Model

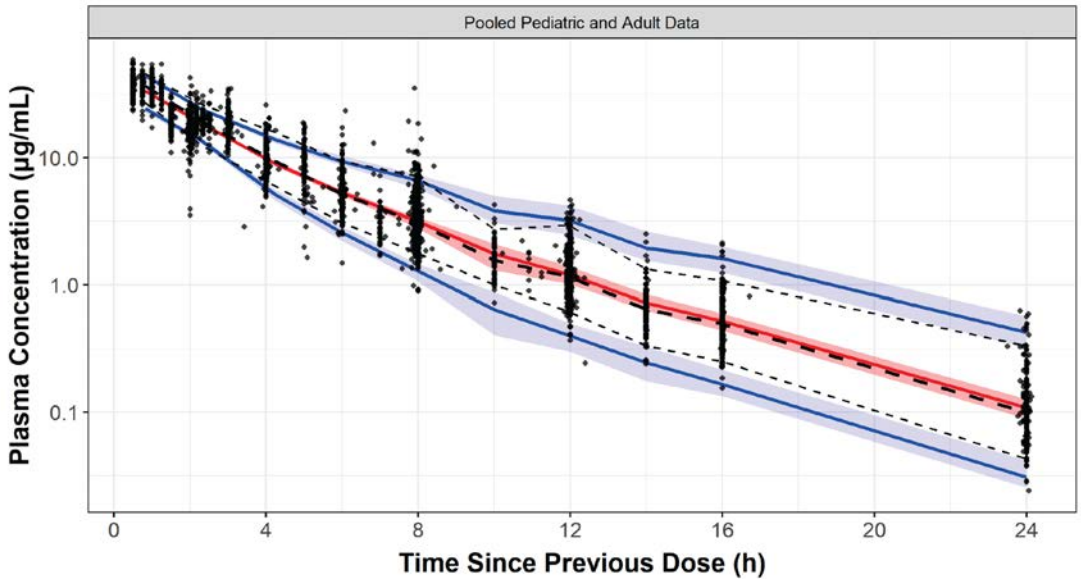
The final PopPK model (revised with pooled data) has the same model structure as the final base model. The parameter estimates of the original and revised pediatric PopPK model are summarized in Table 238. The relationship between CL and GFR was estimated to be quite similar when fit to the pooled dataset (slope of 0.0555 vs. slope of 0.0548 from the pediatric model), and the population mean estimates for Q1 (intercompartmental flow from Vc to Vp1, volume of distribution for peripheral compartment 1) and Q2 (intercompartmental flow from Vc to Vp2, volume of distribution for peripheral compartment 2) were similar as well. The Applicant acknowledged that the addition of adult phase 1 data resulted in marked decreases in the population mean Vc and V1 estimates such that the population mean volume of distribution at steady-state (Vss) (i.e., sum of all volume of distribution terms) is calculated to be 17.3 L versus 71.7 L when the model was fit to the pediatric data alone. Prediction-correct VPC plots are shown in Figure 40, Figure 41, and Figure 42. A comparison of the two models is illustrated in Figure 43.

Table 238. Parameter Estimates for the Final PopPK Model for Pediatric and Adult Subjects

	Fit to Pediatric Data Only		Fit to Pooled Pediatric/Adult Data	
Parameter	**Final Estimate**	**%SEM**	**Final Estimate**	**%SEM**
$CL\text{-}GFR_{slope}$ (L/h per mL/min)[a]	0.0548	4.93	0.0555	24.2
Vc intercept (L)	16.1	6.14	9.58	76.0
Q1 (L/h)[c]	0.545	45.8	0.548	1970
Vp1 (L)	49.5	104	2.52	1100
Q2 (L/h)[c]	3.46	13.4	6.71	757
Vp2 (L)	6.13	7.76	5.21	370
Volume scaling factor[b]	0.911	3.88	0.782	40.2
ω^2_{CL}	0.0547 (23.4 %CV)	19.4	0.0415 (20.4% CV)	77.6
ω^2_{Vc}	0.0711 (26.7 %CV)	58.4	0.115 (33.9% CV)	299
$\sigma^2_{Proportional}$	0.0701 (26.5 %CV)	15.9	0.021 (14.5 %CV)	10.1
$\sigma^2_{Additive}$	0.000156 (0.0125 SD)	–	0.000156 (0.0125 SD)	–

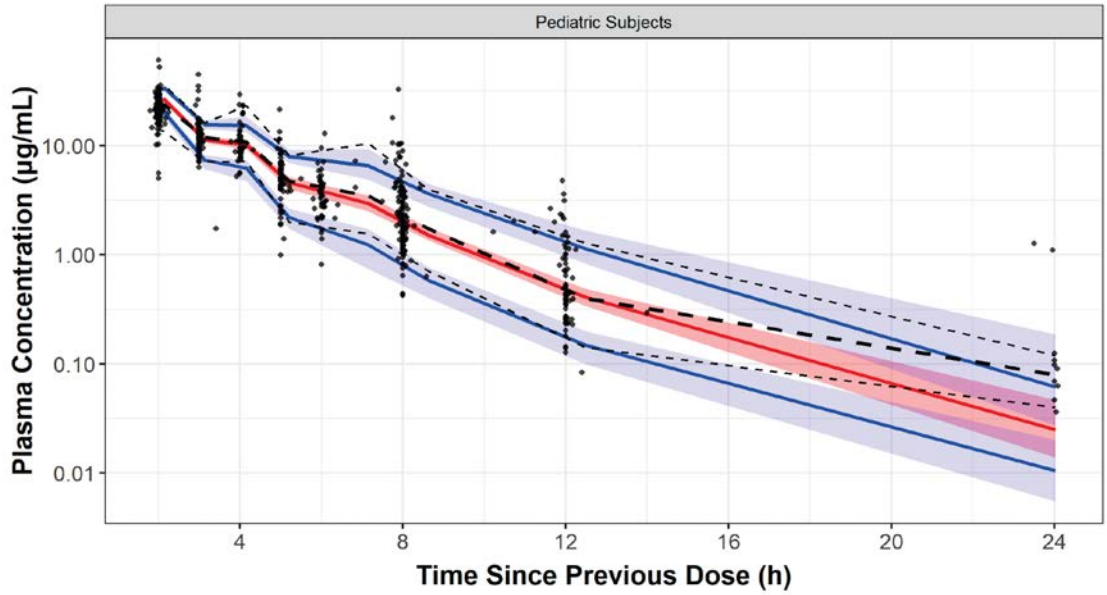
Source: Applicant's revised PopPK report 00616-3A, Table 2, page 17
Eta shrinkage estimates were 9.56 and 38.4% for the IIV terms from the pediatric fit (CL and Vc, respectively) and 3.75 and 13.4% for the pooled fit. Epsilon shrinkage was 11.4% for the pediatric fit and 7.43% for the pooled fit.
[a]Population mean CL = CL-GFRslope * GFR; [b]Scaling factor (power coefficient) for Vc, Vp1, and Vp2;
[c]Intercompartmental clearances scaled using factor (power coefficient) of 0.75
Abbreviations: CL, clearance; CV, coefficient of variation; GFR, glomerular filtration rate; Q, flow rate; SEM, standard error of the mean; V, volume

Figure 40. Prediction-Corrected VPC Plot for the Final PopPK Model Using the Pooled Dataset



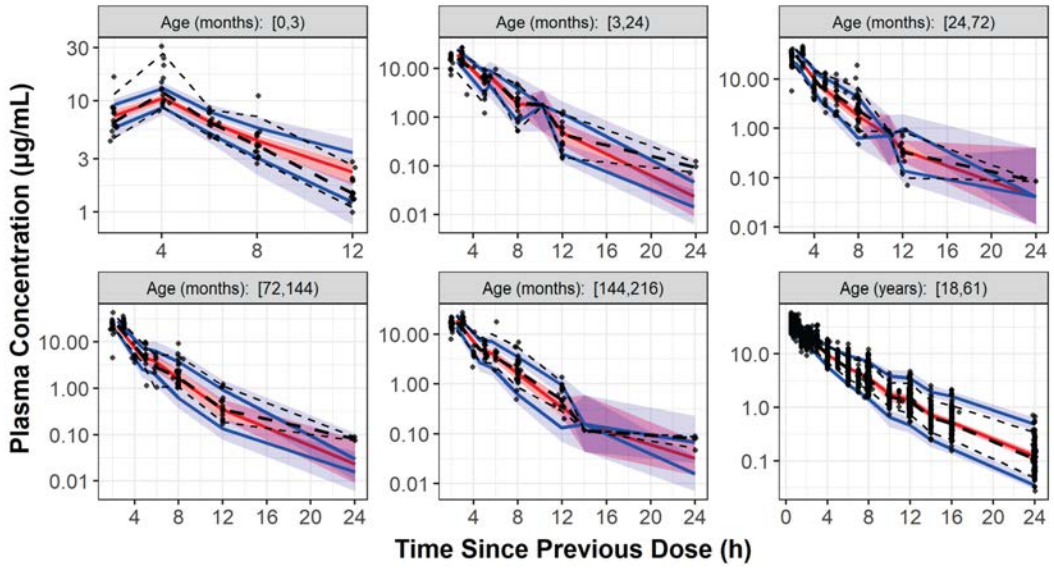
Source: Applicant's revised PopPK report 00616-3A, Figure 1, page 18
Circles are observed concentrations, black solid lines are the median observed concentrations, black dashed lines are the 5th and 95th percentiles of the observed concentrations. Red and blue shaded regions are the 90% confidence intervals for the median, 5th, and 95th percentiles from the simulations
Abbreviations: PopPK, population pharmacokinetic; VPC, visual predictive check

Figure 41. Prediction-Corrected VPC Plot for the Final PopPK Model for Pediatric Subjects Only



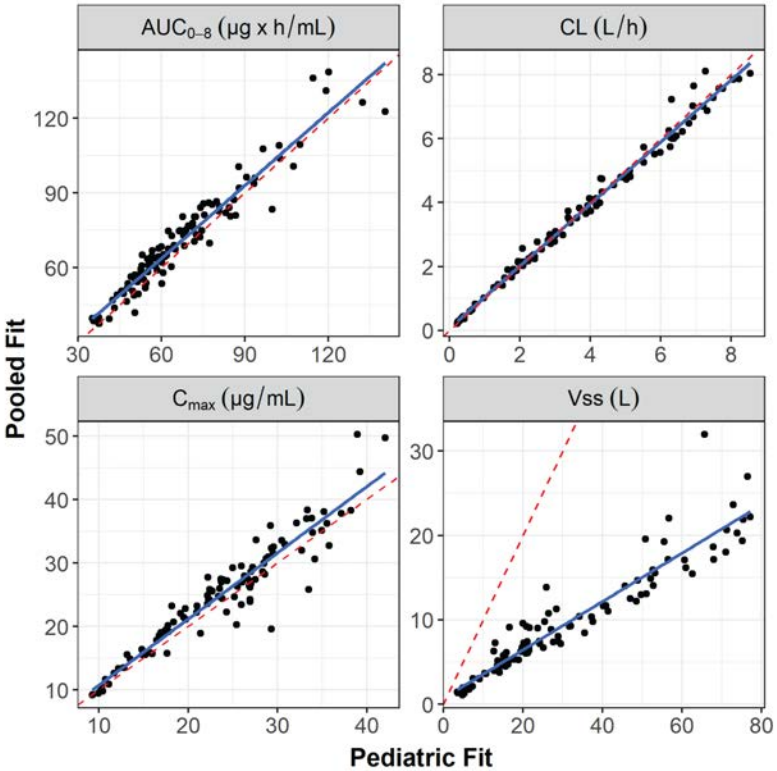
Source: Applicant's revised PopPK report 00616-3A, Figure 2, page 19
Circles are observed concentrations, black solid lines are the median observed concentrations, black dashed lines are the 5th and 95th percentiles of the observed concentrations. Red and blue shaded regions are the 90% confidence intervals for the median, 5th, and 95th percentiles from the simulations
Abbreviations: PopPK, population pharmacokinetic; VPC, visual predictive check

Figure 42. Prediction-Corrected VPC Plot for the Final PopPK Model by Age Group for the Pooled Dataset



Source: Applicant's revised PopPK report 00616-3A, Figure 4, page 21
Circles are observed concentrations, black solid lines are the median observed concentrations, black dashed lines are the 5th and 95th percentiles of the observed concentrations. Red and blue shaded regions are the 90% confidence intervals for the median, 5th, and 95th percentiles from the simulations
Abbreviations: PopPK, population pharmacokinetic; VPC, visual predictive check

Figure 43. Comparison of PK Individual PK Parameters and Exposure Between the Pediatric PopPK Models



Source: Applicant's revised PopPK report 00616-3A, Figure 7, page 26
Solid circles, individual estimates; blue lines, lines of best fit through the data; red, dashed lines, lines of unity; pediatric fit, pediatric only PopPK model; pooled fit, revised final PopPK model
Abbreviations: AUC0-8, area under the concentration-time curve from time 0 to 8 hours; CL, clearance; C_{max}, maximum plasma concentration; PK, pharmacokinetic; PopPK, population pharmacokinetic; Vss, steady state volume

Reviewer Comments

The original pediatric only PopPK model had reasonable model estimates (parameter precision of low to high standard error of the mean (%SEM) and low to moderate shrinkage for relevant parameters). When fitted to the pooled dataset of pediatric and phase 1 adult PK data, the renal elimination parameter was numerically similar and the ETA shrinkages were reduced; however, the volume of distribution terms had large numeric changes and large increase in %SEM. Overall, the prediction-corrected VPC plots demonstrate that the revised PopPK model is able to capture the central tendency of ceftobiprole PK in the target pediatric subject population of 3 month to <18 years).

The reviewer performed a sensitivity analysis (not shown) with additional parameters to model the proportional shifts (from typical values) of clearance and volume of distribution related terms for pediatric vs. adult subjects. The final model parameter estimates are similar to those reported by the Applicant for the revised PopPK model with reduced %SEM values. Notably, the OFV values remain unchanged. In general, the Applicant's final PopPK model is acceptable for derivation of individual exposure metrics and used for Monte Carlo simulation to support dosing recommendation in subjects with normal renal function and those with renal impairment (for pediatric subjects aged 2 years and older).

14.5.2. Exposure-Response Analysis and PTA

14.5.2.1. ABSSSI and CABP PK/PD Analysis

14.5.2.1.1. Introduction

The Applicant performed PK/PD analyses for ABSSSI and CABP populations with the following objects:

- To evaluate exposure-efficacy relationships in phase 3 subjects
- To assess nonclinical PK/PD target attainment in phase 3 subjects
- To conduct PTA to support ceftobiprole dosing regimens and support susceptibility testing interpretive criteria against *S. aureus*, *Streptococcus* species, and *Enterobacterales*

14.5.2.1.2. Exposure-Efficacy Analysis

14.5.2.1.2.1. ABSSSI

Exposure-efficacy relationship was evaluated for ABSSSI using PK and clinical data from microbiological evaluable (ME) subjects in Trial BPR-CS-008. A total of 174 and 150 subjects were included in the ABSSSI ME (defined as subjects in the ME Population who had an analysis pathogen selected with an MIC value, PK data, and were evaluable for at least one efficacy endpoint) and ME *S. aureus* (defined as subjects in the ME Population who had *S. aureus* pathogen selected with an MIC value, PK data, and were evaluable for at least one efficacy endpoint) analysis populations, respectively. Refer to the Applicant's PK/PD report (Tables 16 and 17 in the submitted report) for a summary of baseline characteristics of the analysis populations. Ceftobiprole MIC, free-drug AUC, and Day 1 free-drug plasma %T>MIC for both analysis populations are summarized in Table 239. Given that individual %T>MIC aggregate at

Reference ID: 5357793

the high end of 0% to 99.6%, the exposure-efficacy analyses (univariable or multivariable) were not performed by the Applicant.

Table 239. Summary Statistics for Baseline MIC, Day 1 Free-Drug AUC, and %T>MIC in Analysis Populations

Analysis population	Median or MIC_{50}, MIC_{90}(Min, Max)		
	Ceftobiprole baseline MIC (µg/mL)	Day 1 free-drug plasma AUC (µg•h/mL)	Day 1 free-drug plasma %T>MIC
ME[a] (n = 174)	0.5, 1 (0.015, >64)	161.0 (60.8, 321.4)	99.6 (0, 99.6)
ME *S. aureus* (n = 150)	0.5, 1 (0.12, 1)	160.0 (60.8, 321.4)	99.6 (52.7, 99.6)

Source: Applicant's PK/PD report for ABSSSI and CAP, Table 21, page 84
[a]In the ME Analysis Population, three subjects (BPR-CS-008-(b) (6) BPR-CS-008-(b) (6) and BPR-CS-008(b) (6) (b) (6) had an MIC value of > 64 µg/ml and a ceftobiprole free-drug plasma % T>MIC = 0%
Abbreviations: AUC, area under the concentration-time curve; ME, microbiological evaluable; MIC, minimum inhibitory concentration; T, time

14.5.2.1.2.2. CABP

Exposure-efficacy relationship was evaluated for CABP using PK and clinical data from (ME and microbiological intent-to-treat (mITT) subjects in Trial CAP-3001. The Applicant assessed mortality (30-day all-cause and 30-day pneumonia-specific). The ME analysis population was used to evaluate clinical response on Day 3 and at test-of-cure (TOC) and late follow-up and microbiological response at TOC and late follow-up. A total of 57 and 43 subjects were included in the mITT and ME analysis populations, respectively. Refer to the Applicant's PK/PD report (Tables 25 and 26) for a summary of baseline characteristics of the analysis populations. Efficacy endpoints evaluated and percent of responses are shown in Table 240. Ceftobiprole MIC, free-drug AUC, and Day 1 free-drug plasma %T>MIC for both analysis populations are summarized in Table 241.

Of note, the CABP mITT analysis population included 2 subjects with *Pseudomonas aeruginosa* at baseline and with respective MIC values of >16 and 4 µg/mL (free-drug %T>MIC of 0% and 80.5%) and 1 subject with *Acinetobacter baumannii* at baseline and an MIC value of 8 µg/mL (free-drug %T>MIC of 69.5%). The subject with *Acinetobacter baumannii* was the only subject with all-cause mortality within 30 days. For the ME Analysis Population, the subject with *P. aeruginosa* at baseline and an MIC value of 4 µg/mL was the only one with free-drug plasma %T>MIC <99.2%. Given that the majority of subjects had %T>MIC at the high end of the range, the exposure-efficacy analyses (univariable or multivariable) were not performed by the Applicant.

Table 240. Summary of Successful Response for Efficacy Endpoints by Analysis Populations and Subpopulations

Population	Efficacy Endpoint	Visit	Percentage of responses by efficacy endpoint and visit (n/N)				
			All patients	Patients with the following pathogen at baseline			
				S. pneumoniae	*S. aureus*	*H. influenzae*/ *H. parainfluenzae*	Enterobacterales
mITT	30-day all-cause mortality	Day 30	1.8 (1/57)	0 (0/20)	0 (0/9)	0 (0/10)	0 (0/11)
	30-day pneumonia-specific mortality	Day 30	0 (0/57)	0 (0/20)	0 (0/9)	0 (0/10)	0 (0/11)
ME	Clinical response	Day 3	83.7 (36/43)	86.7 (13/15)	100 (4/4)	66.7 (6/9)	90.0 (9/10)
		TOC	86.0 (37/43)	93.3 (14/15)	100 (4/4)	77.8 (7/9)	80.0 (8/10)
		LFU	86.0 (37/43)	93.3 (14/15)	100 (4/4)	77.8 (7/9)	80.0 (8/10)
	Microbiological response	TOC	88.4 (38/43)	93.3 (14/15)	100 (4/4)	88.9 (8/9)	80.0 (8/10)
		LFU	86.0 (37/43)	93.3 (14/15)	100 (4/4)	77.8 (7/9)	80.0 (8/10)
	30-day all-cause mortality	Day 30	0 (0/43)	0 (0/15)	0 (0/4)	0 (0/9)	0 (0/10)
	30-day pneumonia-specific mortality	Day 30	0 (0/43)	0 (0/15)	0 (0/4)	0 (0/9)	0 (0/10)

Source: Applicant's PK/PD report for ABSSSI and CAP, Table 27, page 95
Abbreviations: AUC, area under the concentration-time curve;

Table 241. Summary Statistics for Baseline MIC, Day 1 Free-Drug AUC, and %T>MIC in Analysis Populations

Analysis population		Patients grouped by selected pathogen at baseline for PK-PD analyses				Patients with a baseline pathogen, including pathogens not selected for PK-PD analyses[a]			
		N	Median or MIC_{50}, MIC_{90} (Min, Max)			N	Median or MIC_{50}, MIC_{90} (Min, Max)		
			Ceftobiprole baseline MIC (µg/mL)	Day 1 free-drug plasma AUC (µg•h/mL)	Day 1 free-drug plasma %T>MIC		Ceftobiprole baseline MIC (µg/mL)	Day 1 free-drug plasma AUC (µg•h/mL)	Day 1 free-drug plasma %T>MIC
mITT	All mITT	57	0.12, 1 (0.004, 32)	212.1 (74.0, 434.3)	99.6 (0, 99.6)				
	S. pneumoniae	20	0.015, 0.12 (0.008, 1)	211.3 (74.0, 434.3)	99.6 (99.6, 99.6)	20	0.015, 0.12 (0.008, 1)	211.3 (74.0, 434.3)	99.6 (99.6, 99.6)
	S. aureus	9	0.5, 2 (0.25, 2)	213.8 (137.2, 380.9)	99.6 (99.2, 99.6)	12	0.25, 0.5 (0.25, 2)	202.5 (120.0, 434.3)	99.6 (99.2, 99.6)
	H. influenzae or *H. parainfluenzae*	10	0.09[b], 0.12 (0.004, 0.25)	179.6 (115.2, 231.6)	99.6 (99.6, 99.6)				
	Enterobacterales	11	0.12, 0.12 (0.03, 1)	224.4 (155.8, 299.9)	99.6 (99.6, 99.6)	13	0.12, 0.12 (0.03, 1)	213.8 (155.8, 299.9)	99.6 (99.6, 99.6)
ME	All ME	43	0.06, 0.5 (0.004, 4)	215.7 (115.2, 434.3)	99.6 (80.5, 99.6)				
	S. pneumoniae	15	0.015, 0.25 (0.008, 1)	218.1 (120.0, 434.3)	99.6 (99.6, 99.6)	15	0.015, 0.25 (0.008, 1)	218.1 (120.0, 434.3)	99.6 (99.6, 99.6)
	S. aureus	4	0.5, 0.5 (0.25, 0.5)	178.3 (137.2, 253.3)	99.6 (99.6, 99.6)	7	0.25, 0.5 (0.25, 0.5)	191.2 (120.0, 434.3)	99.6 (99.6, 99.6)
	H. influenzae or *H. parainfluenzae*	9	0.06, 0.25 (0.004, 0.25)	179.9 (115.2, 231.6)	99.6 (99.6, 99.6)				
	Enterobacterales	10	0.09, 0.12 (0.03, 1)	230.4 (166.9, 299.9)	99.6 (99.6, 99.6)	10	0.09, 0.12 (0.03, 1)	230.4 (166.9, 299.9)	99.6 (99.6, 99.6)

Source: Applicant's PK/PD report for ABSSSI and CAP, Table 28, page 97

Table 242. Summary Statistics for Baseline MIC, Day 1 Free-Drug AUC, and %T>MIC in Pooled Analysis Populations

Analysis population			Median or MIC_{50}, MIC_{90}(Min, Max)		
			Ceftobiprole baseline MIC (µg/mL)	Day 1 free-drug plasma AUC (µg•h/mL)	Day 1 free-drug plasma %T>MIC
mITT	ABSSSI	*S. aureus* (n = 171)	0.5, 1 (0.015, 1)	157.8 (60.8, 321.4)	99.6 (52.7, 99.6)
		S. pneumoniae (n = 0)			
		Streptococcus species[a] (n = 20)	0.015, 0.03 (0.015, 0.03)	172.5 (106.4, 258.2)	99.6 (99.6, 99.6)
		Enterobacterales (n = 16)	0.015, >64 (0.015, >64)	161.9 (96.2, 229.4)	99.6 (0, 99.6)
	CABP	*S. aureus* (n = 12)	0.25, 0.5 (0.25, 2)	202.5 (120.0, 434.3)	99.6 (99.2, 99.6)
		S. pneumoniae (n = 20)	0.015, 0.12 (0.008, 1)	211.3 (74.0, 434.3)	99.6 (99.6, 99.6)
		Streptococcus species[a] (n = 0)			
		Enterobacterales (n = 13)	0.12, 0.12 (0.03, 1)	213.8 (155.8, 299.9)	99.6 (99.6, 99.6)
	HABP/VAP	*S. aureus* (n = 13)	0.5, 1 (0.25, 2)	148.4 (38.1, 301.0)	99.6 (43.0, 99.6)
		S. pneumoniae (n = 5)	0.015, 0.06 (0.008, 0.06)	147.8 (107.4, 354.5)	99.6 (99.6, 99.6)
		Streptococcus species[a] (n = 0)			
		Enterobacterales (n = 18)	0.09, >16 (0.03, >16)	188.8 (106.9, 381.5)	99.6 (0, 99.6)
	Pooled	*S. aureus* (n = 196)	0.5, 1 (0.015, 2)	158.2 (38.1, 434.3)	99.6 (43.0, 99.6)
		S. pneumoniae (n = 25)	0.015, 0.12 (0.008, 1)	210.6 (74.0, 434.3)	99.6 (99.6, 99.6)
		Streptococcus species[a] (n = 20)	0.015, 0.03 (0.015, 0.03)	172.5 (106.4, 258.2)	99.6 (99.6, 99.6)
		Enterobacterales (n = 47)	0.06, >16 (0.015, >64)	181.7 (96.2, 381.5)	99.6 (0, 99.6)

Analysis population			Median or MIC_{50}, MIC_{90}(Min, Max)		
			Ceftobiprole baseline MIC (µg/mL)	Day 1 free-drug plasma AUC (µg•h/mL)	Day 1 free-drug plasma %T>MIC
ME	ABSSSI	*S. aureus* (n = 150)	0.5, 1 (0.12, 1)	160.0 (60.8, 321.4)	99.6 (52.7, 99.6)
		S. pneumoniae (n = 0)			
		Streptococcus species[a] (n = 18)	0.015, 0.03 (0.015, 0.03)	172.5 (106.4, 258.2)	99.6 (99.6, 99.6)
		Enterobacterales (n = 15)	0.015, >64 (0.015, >64)	167.6 (96.2, 229.4)	99.6 (0, 99.6)
	CABP	*S. aureus* (n = 7)	0.25, 0.5 (0.25, 0.5)	191.2 (120.0, 434.3)	99.6 (99.6, 99.6)
		S. pneumoniae (n = 15)	0.015, 0.25 (0.008, 1)	218.1 (120.0, 434.3)	99.6 (99.6, 99.6)
		Streptococcus species[a] (n = 0)			
		Enterobacterales (n = 10)	0.09, 0.12 (0.03, 1)	230.4 (166.9, 299.9)	99.6 (99.6, 99.6)
	HABP/VAP	*S. aureus* (n = 7)	0.5, 2 (0.25, 2)	159.4 (107.4, 289.5)	99.6 (90.0, 99.6)
		S. pneumoniae (n = 4)	0.015, 0.06 (0.008, 0.06)	231.1 (107.4, 354.5)	99.6 (99.6, 99.6)
		Streptococcus species[a] (n = 0)			
		Enterobacterales (n = 9)	0.03, >16 (0.03, >16)	229.0 (148.4, 381.5)	99.6 (0, 99.6)
	Pooled	*S. aureus* (n = 164)	0.5, 1 (0.12, 2)	160.0 (60.8, 434.3)	99.6 (52.7, 99.6)
		S. pneumoniae (n = 19)	0.015, 0.25 (0.008, 1)	218.1 (107.4, 434.3)	99.6 (99.6, 99.6)
		Streptococcus species[a] (n = 19)	0.015, 0.03 (0.015, 0.03)	172.5 (106.4, 258.2)	99.6 (99.6, 99.6)
		Enterobacterales (n = 34)	0.045, >16 (0.015, >64)	182.8 (96.2, 381.5)	99.6 (0, 99.6)

Source: Applicant's PK/PD report for ABSSSI and CAP, Table 34, pages 106-107

Table 243. Summary of Percentage of Subjects in the Pooled ABSSSI, CABP, and HAP/VAP mITT and ME Analysis Populations Achieving Nonclinical Targets

Analysis Population	Endpoint for free-drug plasma %T>MIC targets[b]	% (n/N) of patients with baseline pathogen[a]							
		S. aureus		*S. pneumoniae*		*Streptococcus* species		Enterobacterales	
		mITT	ME	mITT	ME	mITT	ME	mITT	ME
ABSSSI	Net bacterial stasis	100 (171/171)	100 (150/150)			100 (20/20)	100 (18/18)	81.2 (13/16)	80.0 (12/15)
	1-log_{10} CFU reduction	100 (171/171)	100 (150/150)			100 (20/20)	100 (18/18)	81.2 (13/16)	80.0 (12/15)
	2-log_{10} CFU reduction	100 (171/171)	100 (150/150)			100 (20/20)	100 (18/18)	81.2 (13/16)	80.0 (12/15)
CABP	Net bacterial stasis	100 (12/12)	100 (7/7)	100 (20/20)	100 (15/15)			100 (13/13)	100 (10/10)
	1-log_{10} CFU reduction	100 (12/12)	100 (7/7)	100 (20/20)	100 (15/15)			100 (13/13)	100 (10/10)
	2-log_{10} CFU reduction	100 (12/12)	100 (7/7)	100 (20/20)	100 (15/15)			100 (13/13)	100 (10/10)
HABP/VAP	Net bacterial stasis	100 (13/13)	100 (7/7)	100 (5/5)	100 (4/4)			77.8 (14/18)	88.9 (8/9)
	1-log_{10} CFU reduction	100 (13/13)	100 (7/7)	100 (5/5)	100 (4/4)			77.8 (14/18)	88.9 (8/9)
	2-log_{10} CFU reduction	100 (13/13)	100 (7/7)	100 (5/5)	100 (4/4)			77.8 (14/18)	88.9 (8/9)
Pooled	Net bacterial stasis	100 (196/196)	100 (164/164)	100 (25/25)	100 (19/19)	100 (20/20)	100 (18/18)	85.1 (40/47)	88.2 (30/34)
	1-log_{10} CFU reduction	100 (196/196)	100 (164/164)	100 (25/25)	100 (19/19)	100 (20/20)	100 (18/18)	85.1 (40/47)	88.2 (30/34)
	2-log_{10} CFU reduction	100 (196/196)	100 (164/164)	100 (25/25)	100 (19/19)	100 (20/20)	100 (18/18)	85.1 (40/47)	88.2 (30/34)

Source: Applicant's PK/PD report for ABSSSI and CAP, Table 35, page 108
[a]All baseline cultures were considered; [b]Based on the assessment of median ceftobiprole free-drug plasma %T>MIC targets associated with net bacterial stasis and 1- and 2-10910 CFU reduction from baseline of 19.0, 23.1, and 25.9, respectively, for S. pneumoniae, 21, 1, 24.7, and 28.5, respectively, for *S. aureus*, and 41.6, 50.0, and 58.5, respectively for *Enterobacterales*

Reviewer Comments

The distributions of free-drug %T>MIC in the two analysis populations for ABSSSI and CABP being at or close to high end of the range likely indicate that the subjects were at the plateau of the exposure-efficacy relationships for ABSSSI and CABP infection types. When evaluated against nonclinical targets of %T>MIC (Table 243), fewer subjects with gram-negative pathogens achieved the stasis, 1-log kill, and 2-log kill targets (range, 77.8% to 100%) when compared to those with gram-positive pathogens (range, 100%-100%). This is further evaluated in PTA analysis section to support dosing selection.

14.5.2.1.3. PTA

Because the renal route is a major elimination pathway for ceftobiprole (and as described in the PopPK modeling section), the target attainment analysis utilized renal-based dosing groups to simulate ceftobiprole exposures to support dosing selection for ABSSSI and CABP. To simulate in a clinical scenario, virtual subjects resembling the respective subject populations (i.e., ABSSSI and CABP) were generated, and exposure metrics were derived from the virtual subjects. Note that given the lack of information on renal replacement modality impact on ceftobiprole PK (i.e., percent of drug being removed from iHD in the ceftobiprole development program), the Applicant's simulations were conducted without incorporating the extraction ratio (see Section 8 and Pharmacometric Assessment Appendix Section 14.5.1.4.2). Ceftobiprole dosing regimens for exposure derivation (via simulations) and PTA analyses are summarized in Table 244. For the PTA analysis, the nonclinical PK/PD targets are summarized in Section 5. The randomly assigned targets were derived based on an estimated log normal distribution of %T>MIC targets associated with a given endpoint (truncated within 2 standard deviations of the mean value).

Reference ID: 5357793

Reviewer Comments

For pathogens causing ABSSSI or CABP, the PTA analyses (based on median and random targets) demonstrate that the proposed dosing regimen (across renal function groups) provides sufficient coverage up to an MIC of 4 µg/mL for 1-log kill across MIC distributions for respective gram-positive pathogens; for gram-negative pathogens, the exposures cover up to an MIC of 2 µg/mL for 1-log kill.

Table 244. Ceftobiprole Regimens for Simulations

Renal function groups	CLcr group (mL/min)	Ceftobiprole dose	Dose interval
Supranormal	> 150 to ≤ 240	500 mg IV	q6h
Normal renal function	≥ 90 to ≤ 150	500 mg IV	q8h
Mild renal impairment	≥ 50 to < 90		
Moderate renal impairment	≥ 30 to < 50	500 mg IV	q12h
Severe renal impairment	≥ 15 to < 30	250 mg IV	q12h
ESRD	≥ 0 to < 15	250 mg IV	q24h

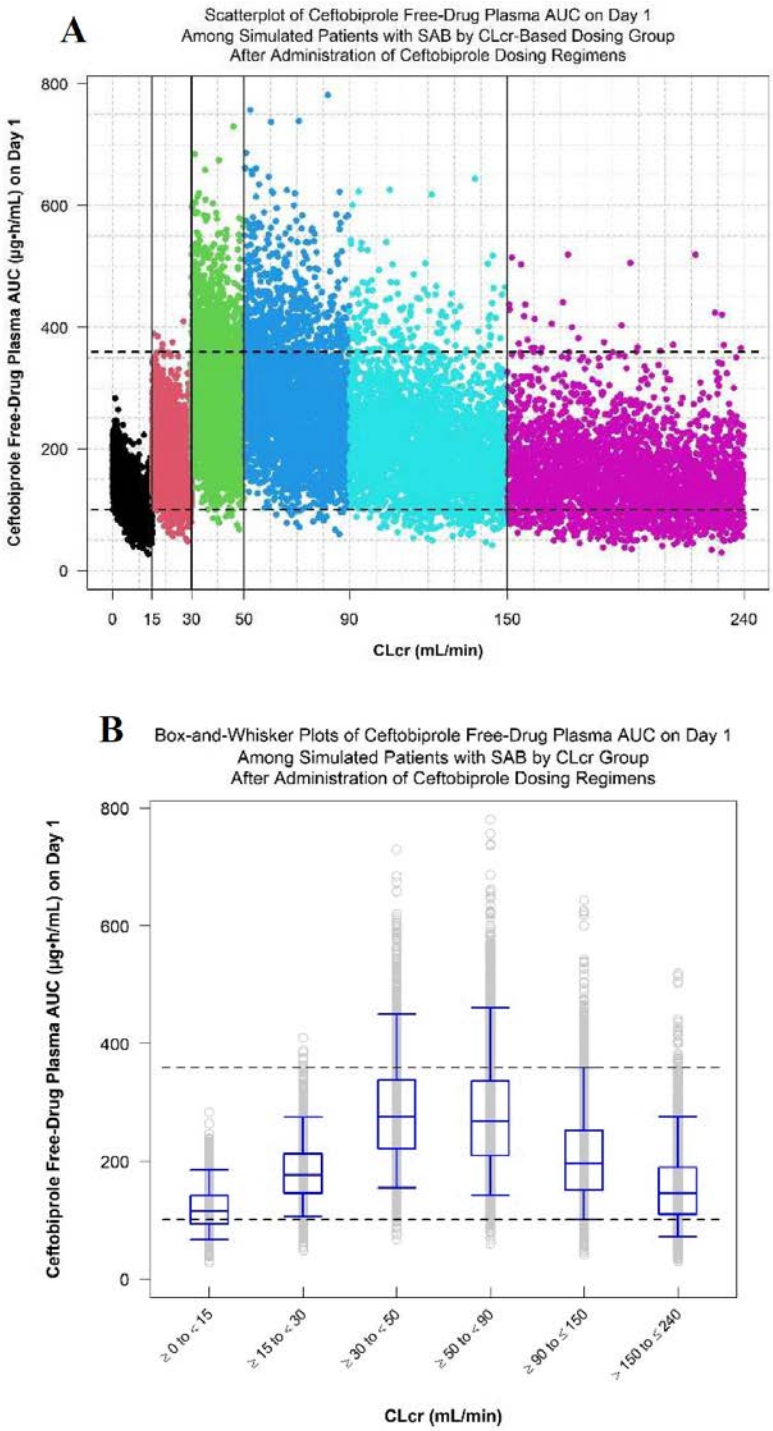
Source: Applicant's PK/PD report for ABSSSI and CAP, Table 36, page 109
Note: 667 mg of ceftobiprole medocaril sodium is equivalent to 500 mg of ceftobiprole. Dosing adjustments for each indication are based on renal function
All simulated dosing regimens were administered via a 2-hour infusion; no iHD

14.5.2.1.3.1.1. ABSSSI Exposures

For ABSSSI simulations, Day 1 exposures are illustrated in Figure 44 and Figure 45 and summarized in Table 245 and Table 246.

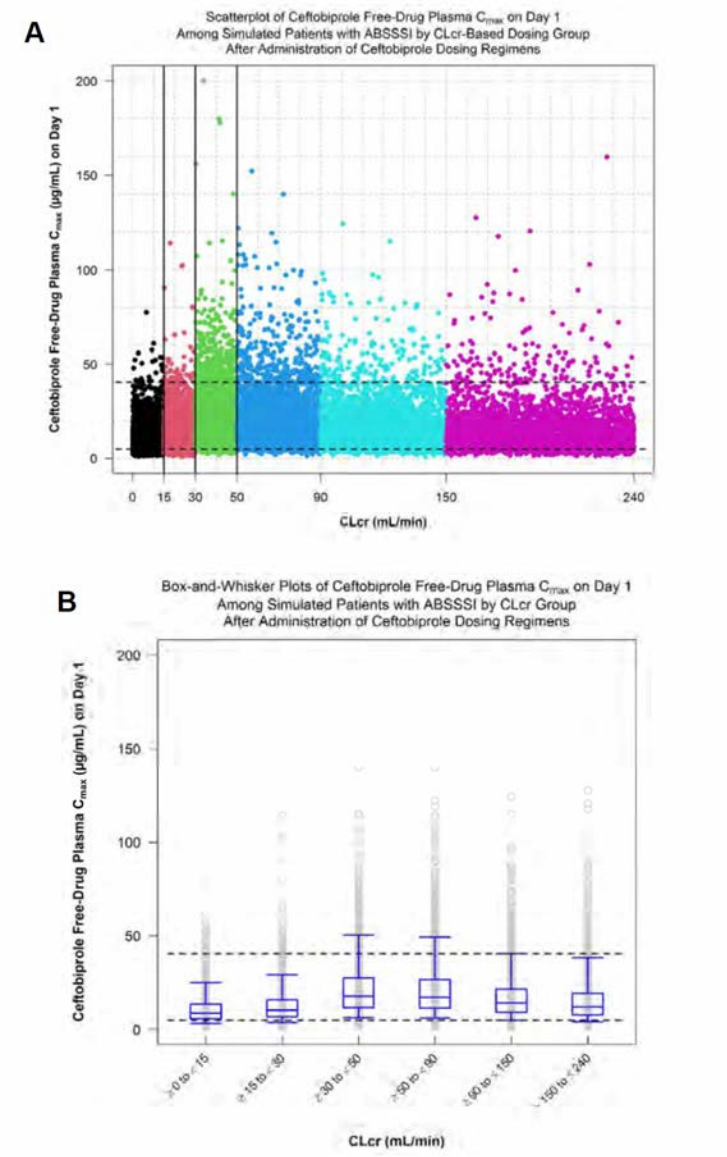
Reference ID: 5357793

Figure 44. Scatterplot and Boxplots for Simulated Ceftobiprole Day 1 AUC Across Renal Function Groups for ABSSSI



Source: Applicant's response to Information Request [dated 23JANUARY2024; *link*], Figure 2, page In panel A, the vertical black lines in the scatterplot represent the categorization of the CLcr groups for which different ceftobiprole dosing regimens were administered. The horizontal dashed lines represent 90 to 150 mL/min group, defined as the 5th and 95th percentiles for ceftobiprole exposure
Note: the original plot from the Applicant's PK/PD report for ABSSSI and CAP was based on q12h dosing frequency

Figure 45. Scatterplot and Boxplots for Simulated Ceftobiprole Day 1 C_{max} Across Renal Function Groups for ABSSSI



Source: Applicant's PK/PD report for ABSSSI and CAP, Figure 2, page 119
In panel A, the vertical black lines in the scatterplot represent the categorization of the CLcr groups for which different ceftobiprole dosing regimens were administered. The horizontal dashed lines represent 90 to 150 mL/min group, defined as the 5th and 95th percentiles for ceftobiprole exposure

Table 245. Summary Statistics for Simulated Ceftobiprole Day 1 AUC Across Renal Function Groups for ABSSSI

Variable	Summary statistics for ceftobiprole free-drug plasma AUC (µg•h/mL) on Day 1 by CLcr group (mL/min)					
	≥ 0 to < 15	≥ 15 to < 30	≥ 30 to < 50	≥ 50 to < 90	≥ 90 to ≤ 150	> 150 to ≤ 240
Count	3395	3395	3395	3395	3395	3395
Minimum	36.5	40.1	57.1	57.5	40.3	38.4
Maximum	317	311	501	582	487	509
Mean	121	132	204	217	159	154
%CV	30.9	28.5	31.5	33.9	36.6	37.9
Geometric mean	116	127	194	205	149	144
Geometric %CV	31.0	28.8	31.8	34.0	36.3	37.2

Source: Applicant's PK/PD report for ABSSSI and CAP, Table 37, page 116

Table 246. Summary Statistics for Simulated Ceftobiprole Day 1 C_{max} Across Renal Function Groups for ABSSSI

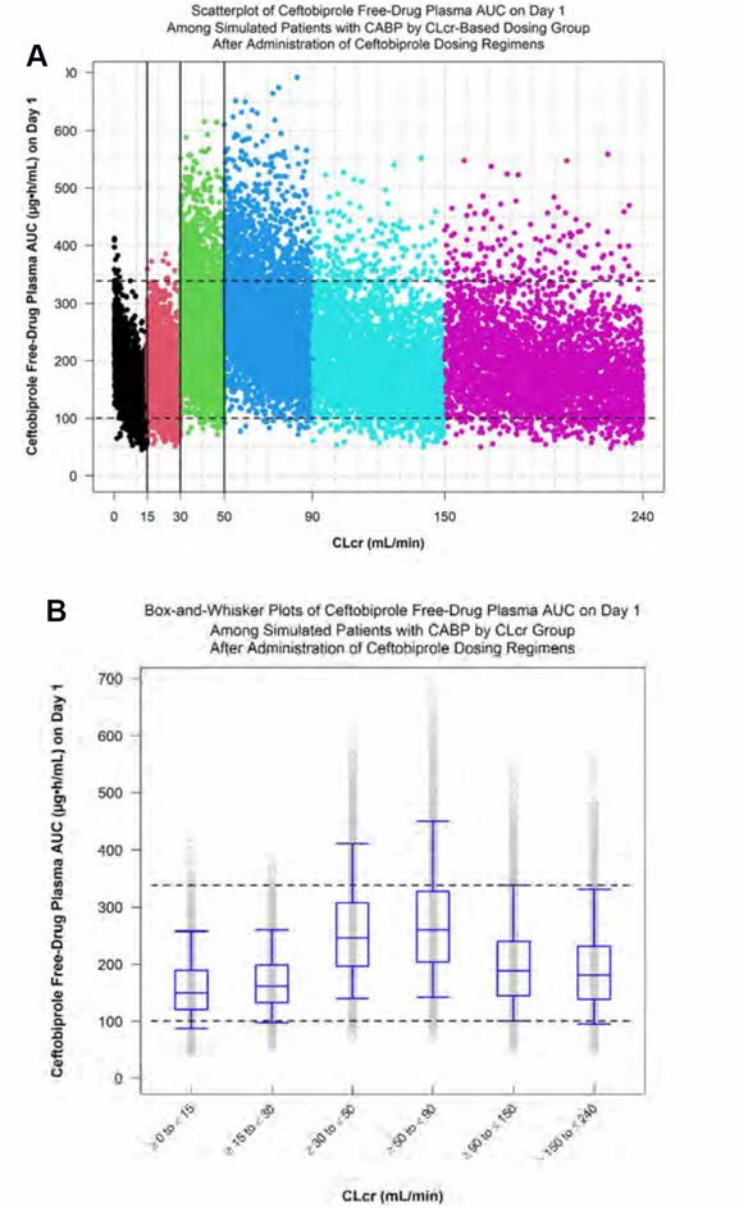
Variable	Summary statistics for ceftobiprole free-drug plasma C_{max} (µg/mL) on Day 1 by CLcr group (mL/min)					
	≥ 0 to < 15	≥ 15 to < 30	≥ 30 to < 50	≥ 50 to < 90	≥ 90 to ≤ 150	> 150 to ≤ 240
Count	3395	3395	3395	3395	3395	3395
Minimum	1.02	1.09	1.87	1.34	1.05	1.42
Maximum	77.4	114	200	152	124	160
Mean	10.7	12.5	21.7	21.3	17.4	15.5
%CV	68.7	70.4	70.5	71.9	72.0	79.4
Geometric mean	8.80	10.3	17.7	17.3	14.1	12.2
Geometric %CV	62.8	63.3	63.4	64.3	64.4	68.3

Source: Applicant's PK/PD report for ABSSSI and CAP, Table 38, page 118

14.5.2.1.3.1.2. CABP Exposures

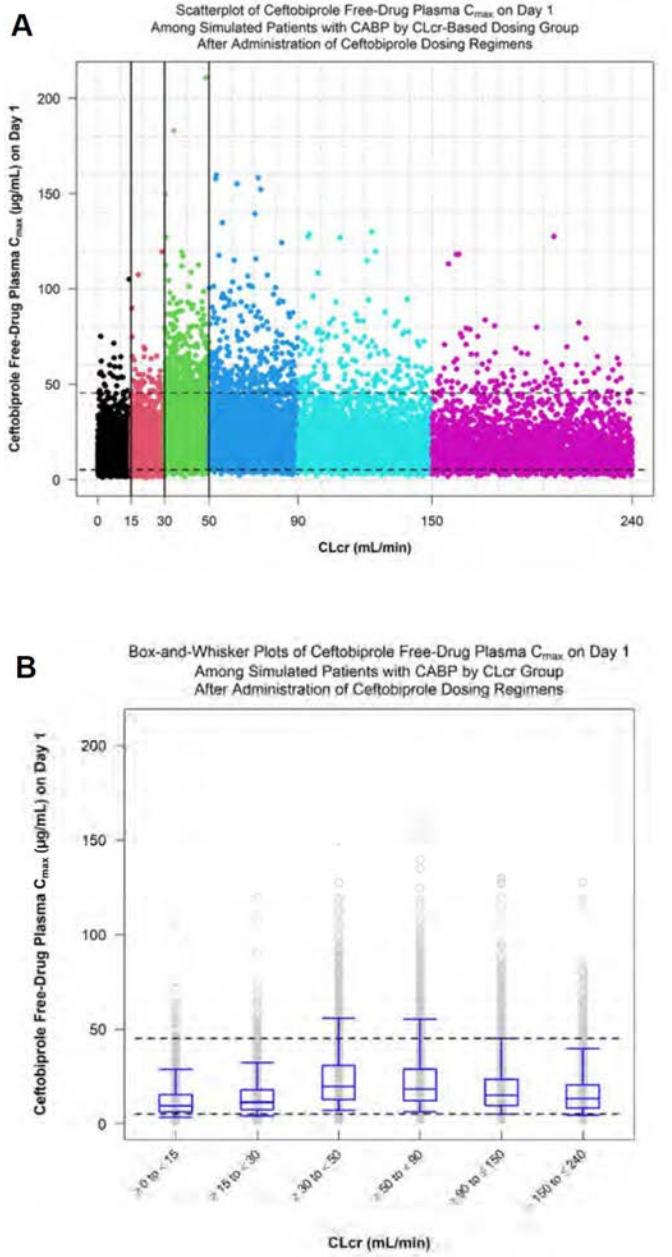
For CABP simulations, Day 1 exposures are illustrated in Figure 46 and Figure 47 and summarized in Table 247 and Table 248.

Figure 46. Scatterplot and Boxplots for Simulated Ceftobiprole Day 1 AUC Across Renal Function Groups for CABP



Source: Applicant's PK/PD report for ABSSSI and CAP, Figure 3, page 128
In panel A, the vertical black lines in the scatterplot represent the categorization of the CLcr groups for which different ceftobiprole dosing regimens were administered. The horizontal dashed lines represent 90 to 150 mL/min group, defined as the 5th and 95th percentiles for ceftobiprole exposure

Figure 47. Scatterplot and Boxplots for Simulated Ceftobiprole Day 1 C_{max} Across Renal Function Groups for CABP



Source: Applicant's PK/PD report for ABSSSI and CAP, Figure 4, page 130
In panel A, the vertical black lines in the scatterplot represent the categorization of the CLcr groups for which different ceftobiprole dosing regimens were administered. The horizontal dashed lines represent 90 to 150 mL/min group, defined as the 5th and 95th percentiles for ceftobiprole exposure

Table 247. Summary Statistics for Simulated Ceftobiprole Day 1 AUC Across Renal Function Groups for CABP

Variable	Summary statistics for ceftobiprole free-drug plasma AUC (µg•h/mL) on Day 1 by CLcr group (mL/min)					
	≥ 0 to < 15	≥ 15 to < 30	≥ 30 to < 50	≥ 50 to < 90	≥ 90 to ≤ 150	> 150 to ≤ 240
Count	3576	3576	3576	3576	3576	3576
Minimum	45.1	51.6	71.9	71.6	49.9	47.6
Maximum	412	385	616	692	552	559
Mean	158	168	257	272	199	191
%CV	33.4	29.7	32.6	35.0	37.4	38.6
Geometric mean	150	161	244	256	185	178
Geometric %CV	33.2	30.1	33.0	35.2	37.3	38.2

Source: Applicant's PK/PD report for ABSSSI and CAP, Table 39, page 127

Table 248. Summary Statistics for Simulated Ceftobiprole Day 1 C_{max} Across Renal Function Groups for CABP

Variable	Summary statistics for ceftobiprole free-drug plasma C_{max} (µg/mL) on Day 1 by CLcr group (mL/min)					
	≥ 0 to < 15	≥ 15 to < 30	≥ 30 to < 50	≥ 50 to < 90	≥ 90 to ≤ 150	> 150 to ≤ 240
Count	3576	3576	3576	3576	3576	3576
Minimum	1.17	0.826	1.37	2.19	1.78	1.71
Maximum	105	120	211	160	130	128
Mean	12.0	13.9	24.0	23.0	18.8	16.1
%CV	70.9	69.5	69.6	74.3	74.3	73.0
Geometric mean	9.76	11.4	19.6	18.5	15.1	13.0
Geometric %CV	64.3	63.8	63.8	65.6	65.7	65.9

Source: Applicant's PK/PD report for ABSSSI and CAP, Table 40, page 129

14.5.2.1.3.1.3. PTA for ABSSSI: *S. aureus*

The median ceftobiprole free-drug plasma %T>MIC targets associated with net bacterial stasis and a 1-log CFU reduction from baseline for *S. aureus* were 21.1 and 24.7, respectively. The demographic variables in simulated subjects with ABSSSI resembled the observed data from Trial BPR-CS-008. The ceftobiprole MIC distributions for 13,715 *S. aureus* isolates were collected from centers in the USA from 2016 to 2020.

Table 249. PTA Results by MIC on Day 1 Based on Median Nonclinical Ceftobiprole Free-Drug Plasma %T>MIC Targets Associated With *Staphylococcus aureus* Efficacy

Endpoints for PK-PD target	MIC (µg/mL)	Percent probabilities of PK-PD target attainment by ceftobiprole MIC and CLcr group (mL/min)						
		≥ 0 to < 15	≥ 15 to < 30	≥ 30 to < 50	≥ 50 to < 90	≥ 90 to ≤ 150	> 150 to ≤ 240	Clinical trial population[c]
Net bacterial stasis	0.03	100	100	100	100	100	100	100
	0.06	100	100	100	100	100	100	100
	0.12	100	100	100	100	100	100	100
	0.25	100	100	100	100	100	100	100
	0.5	100	100	100	100	100	100	100
	1	100	100	100	100	100	100	100
	2	100	100	100	100	100	100	100
	4	98.9	99.6	>99.9	100	99.7	99.7	99.8
	8	50.9	63.8	95.6	96.0	80.5	76.8	83.4
	16	0.88	1.50	30.8	38.4	12.2	10.4	17.6
	32	0	0	0.12	0.74	0.03	0.12	0.15
	Overall[d]							
	All isolates	>99.9	>99.9	>99.9	100	>99.9	>99.9	>99.9
	MRSA	>99.9	>99.9	>99.9	100	>99.9	>99.9	>99.9
	MSSA	100	100	100	100	100	100	100
1-log_{10} CFU reduction from baseline	0.03	100	100	100	100	100	100	100
	0.06	100	100	100	100	100	100	100
	0.12	100	100	100	100	100	100	100
	0.25	100	100	100	100	100	100	100
	0.5	100	100	100	100	100	100	100
	1	100	100	100	100	100	100	100
	2	100	100	100	100	100	100	100
	4	96.9	99.2	99.9	>99.9	99.4	99.3	99.3
	8	39.7	52.8	91.0	92.1	70.8	67.3	76.3
	16	0.38	0.71	20.9	28.4	7.69	6.63	12.0
	32	0	0	0.03	0.21	0	0	0.12
	Overall[d]							
	All isolates	>99.9	>99.9	>99.9	>99.9	>99.9	>99.9	>99.9
	MRSA	>99.9	>99.9	>99.9	>99.9	>99.9	>99.9	>99.9
	MSSA	100	100	100	100	100	100	100

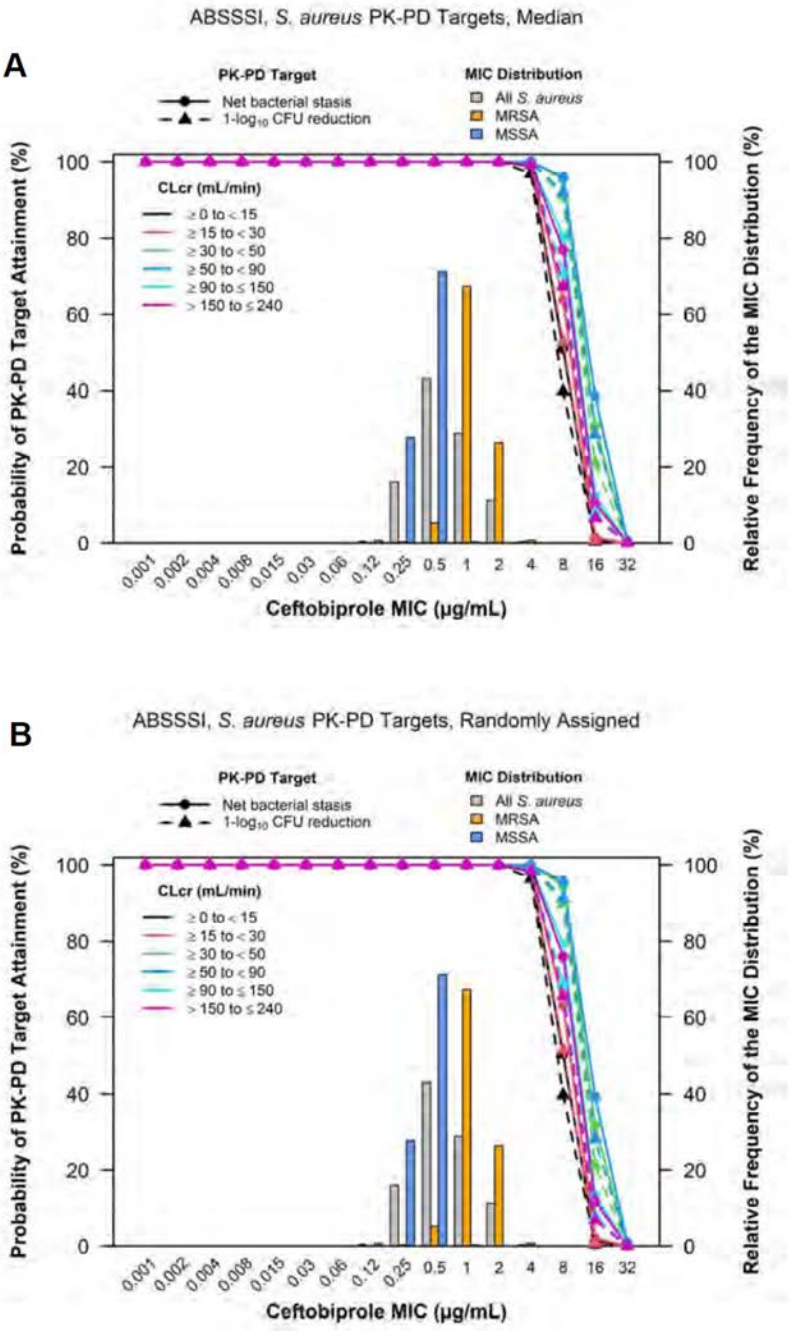
Source: Applicant's PK/PD report for ABSSSI and CAP, Table 41, page 134

Table 250. PTA Results by MIC on Day 1 Based on Randomly Assigned Nonclinical Ceftobiprole Free-Drug Plasma %T>MIC Targets Associated With *Staphylococcus aureus* Efficacy

Endpoints for PK-PD target	MIC (µg/mL)	Percent probabilities of PK-PD target attainment by ceftobiprole MIC and CLcr group (mL/min)						
		≥ 0 to < 15	≥ 15 to < 30	≥ 30 to < 50	≥ 50 to < 90	≥ 90 to ≤ 150	> 150 to ≤ 240	Clinical trial population[c]
Net bacterial stasis	0.03	100	100	100	100	100	100	100
	0.06	100	100	100	100	100	100	100
	0.12	100	100	100	100	100	100	100
	0.25	100	100	100	100	100	100	100
	0.5	100	100	100	100	100	100	100
	1	100	100	100	100	100	100	100
	2	>99.9	>99.9	100	100	>99.9	100	100
	4	98.3	99.3	>99.9	>99.9	99.5	99.5	99.6
	8	50.3	63.1	94.6	95.6	79.3	75.9	83.2
	16	1.27	2.09	31.7	39.2	13.3	11.7	18.4
	32	0	0	0.12	0.85	0	0.09	0.27
	Overall[d]							
	All isolates	>99.9	>99.9	>99.9	>99.9	>99.9	>99.9	>99.9
	MRSA	>99.9	>99.9	>99.9	>99.9	>99.9	>99.9	>99.9
	MSSA	100	100	100	100	100	100	100
1-$\log_{10}$ CFU reduction from baseline	0.03	100	100	100	100	100	100	100
	0.06	100	100	100	100	100	100	100
	0.12	100	100	100	100	100	100	100
	0.25	100	100	100	100	100	100	100
	0.5	100	100	100	100	100	100	100
	1	100	100	100	100	100	100	100
	2	>99.9	>99.9	100	100	>99.9	>99.9	>99.9
	4	96.5	98.5	99.8	>99.9	98.8	98.5	98.9
	8	39.6	51.4	89.9	91.3	68.7	65.6	74.7
	16	0.41	0.74	21.2	28.1	7.84	6.80	12.0
	32	0	0	0.03	0.21	0	0	0.12
	Overall[d]							
	All isolates	>99.9	>99.9	>99.9	>99.9	>99.9	>99.9	>99.9
	MRSA	>99.9	>99.9	>99.9	>99.9	>99.9	>99.9	>99.9
	MSSA	100	100	100	100	100	100	100

Source: Applicant's PK/PD report for ABSSSI and CAP, Table 42, page 135

Figure 48. PTA on Day 1 Based on Median and Randomly Assigned Nonclinical Targets of %T>MIC for *Staphylococcus aureus*



Source: Applicant's PK/PD report for ABSSSI and CAP, Figure 5, page 136
MIC distribution based on 13715 isolates in the USA

14.5.2.1.3.1.4. PTA for ABSSSI: *Streptococcus* spp.

The median ceftobiprole free-drug plasma %T>MIC targets associated with net bacterial stasis and a 1-log CFU reduction from baseline for *Streptococcus* species were 19.0 and 23.1, respectively. The demographic variables in simulated subjects with ABSSSI resembled the observed data from Trial BPR-CS-008. The ceftobiprole MIC distributions for 683 *S. agalactiae*, 219 *S. anginosus* group, and 797 *S. pyogenes* isolates were collected from centers in the USA from 2016 to 2020.

Table 251. PTA Results by MIC on Day 1 Based on Median Nonclinical Ceftobiprole Free-Drug Plasma %T>MIC Targets Associated With *Streptococcus* species Efficacy

Endpoints for PK-PD target	MIC (µg/mL)	Percent probabilities of PK-PD target attainment by ceftobiprole MIC and CLcr group (mL/min)						
		≥ 0 to < 15	≥ 15 to < 30	≥ 30 to < 50	≥ 50 to < 90	≥ 90 to ≤ 150	> 150 to ≤ 240	Clinical trial population[c]
Net bacterial stasis	0.03	100	100	100	100	100	100	100
	0.06	100	100	100	100	100	100	100
	0.12	100	100	100	100	100	100	100
	0.25	100	100	100	100	100	100	100
	0.5	100	100	100	100	100	100	100
	1	100	100	100	100	100	100	100
	2	100	100	100	100	100	100	100
	4	99.4	99.6	100	100	99.9	99.8	99.9
	8	57.3	70.2	97.2	97.5	85.3	81.8	88.1
	16	1.44	2.39	37.8	44.9	15.5	13.5	22.0
	32	0	0	0.27	1.09	0.06	0.12	0.33
	Overall[d]							
	S. agalactiae	100	100	100	100	100	100	100
	S. anginosus group	100	100	100	100	100	100	100
	S. pyogenes	100	100	100	100	100	100	100
1-log_{10} CFU reduction from baseline	0.03	100	100	100	100	100	100	100
	0.06	100	100	100	100	100	100	100
	0.12	100	100	100	100	100	100	100
	0.25	100	100	100	100	100	100	100
	0.5	100	100	100	100	100	100	100
	1	100	100	100	100	100	100	100
	2	100	100	100	100	100	100	100
	4	98.1	99.4	>99.9	>99.9	99.5	99.6	99.6
	8	44.3	57.6	93.1	94.1	74.3	71.5	79.2
	16	0.59	0.91	24.9	32.8	9.51	8.25	13.9
	32	0	0	0.12	0.29	0	0.06	0.15
	Overall[d]							
	S. agalactiae	100	100	100	100	100	100	100
	S. anginosus group	100	100	100	100	100	100	100
	S. pyogenes	100	100	100	100	100	100	100

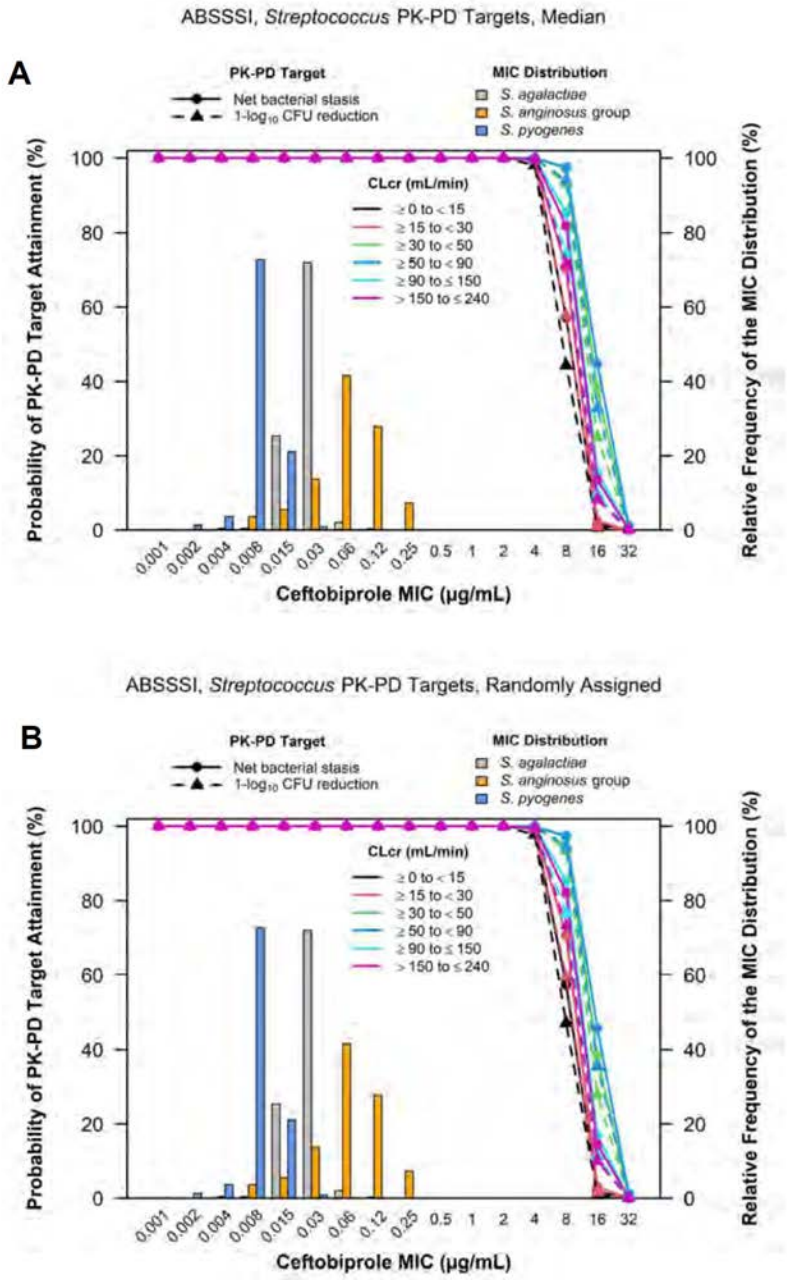
Source: Applicant's PK/PD report for ABSSSI and CAP, Table 43, page 140

Table 252. PTA Results by MIC on Day 1 Based on Randomly Assigned Non-Clinical Ceftobiprole Free-Drug Plasma %T>MIC Targets Associated With *Streptococcus* Species Efficacy

Endpoints for PK-PD target	MIC (µg/mL)	Percent probabilities of PK-PD target attainment by ceftobiprole MIC and CLcr group (mL/min)						
		≥ 0 to < 15	≥ 15 to < 30	≥ 30 to < 50	≥ 50 to < 90	≥ 90 to ≤ 150	> 150 to ≤ 240	Clinical trial population[c]
Net bacterial stasis	0.03	100	100	100	100	100	100	100
	0.06	100	100	100	100	100	100	100
	0.12	100	100	100	100	100	100	100
	0.25	100	100	100	100	100	100	100
	0.5	100	100	100	100	100	100	100
	1	100	100	100	100	100	100	100
	2	100	100	100	100	100	100	100
	4	99.2	99.7	>99.9	>99.9	99.9	99.8	>99.9
	8	57.4	70.5	97.1	97.4	85.2	82.2	88.0
	16	1.80	3.06	38.1	45.7	16.8	14.5	22.8
	32	0	0	0.32	1.27	0.09	0.12	0.42
	Overall[d]							
	S. agalactiae	100	100	100	100	100	100	100
	S. anginosus group	100	100	100	100	100	100	100
	S. pyogenes	100	100	100	100	100	100	100
1-log_{10} CFU reduction from baseline	0.03	100	100	100	100	100	100	100
	0.06	100	100	100	100	100	100	100
	0.12	100	100	100	100	100	100	100
	0.25	100	100	100	100	100	100	100
	0.5	100	100	100	100	100	100	100
	1	100	100	100	100	100	100	100
	2	>99.9	>99.9	100	100	>99.9	100	100
	4	97.8	99.2	>99.9	>99.9	99.5	99.5	99.5
	8	47.1	59.5	93.5	94.7	76.6	73.1	80.8
	16	0.82	1.56	27.8	35.4	11.3	9.99	16.2
	32	0	0	0.09	0.53	0	0.06	0.15
	Overall[d]							
	S. agalactiae	100	100	100	100	100	100	100
	S. anginosus group	100	100	100	100	100	100	100
	S. pyogenes	100	100	100	100	100	100	100

Source: Applicant's PK/PD report for ABSSSI and CAP, Table 44, page 141

Figure 49. PTA on Day 1 Based on Median and Randomly Assigned Nonclinical Targets of %T>MIC for *Streptococcus* Species



Source: Applicant's PK/PD report for ABSSSI and CAP, Figure 7, page 142

14.5.2.1.3.1.5. PTA for ABSSSI: *Enterobacterales*

The median ceftobiprole free-drug plasma %T>MIC targets associated with net bacterial stasis and a 1-log CFU reduction from baseline for *Enterobacterales* were 41.6 and 50.0, respectively. The demographic variables in simulated subjects with ABSSSI resembled the observed data from Trial BPR-CS-008. The ceftobiprole MIC distributions for 14,940 *Enterobacterales* isolates, including 5,398 *E coli*, 3,013 *K. pneumoniae*, 806 *K. oxytoca*, and 968 *P. mirabilis*, were collected from centers in the USA from 2016 to 2020. Subsets of extended spectrum β-lactamase (ESBL)-producing and non-ESBL-producing phenotypes are described in Table 253.

Table 253. Ceftobiprole MIC Distributions (*Enterobacterales* Isolates)

Isolate group (sample size)	Number of occurrences (cumulative %) by MIC (µg/mL)[b]														
	≤0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	>16	MIC_{50}	MIC_{90}
All *E. coli* (n = 5,398)	1 (0)	74 (1.4)	3236 (61.3)	874 (77.5)	127 (79.9)	68 (81.1)	38 (81.8)	18 (82.2)	7 (82.3)	9 (82.5)	7 (82.6)	10 (82.8)	929 (100)	0.03	>16
ESBL-producing phenotype (n = 1,120)			40 (3.6)	30 (6.2)	19 (7.9)	31 (10.7)	25 (12.9)	15 (14.3)	6 (14.8)	9 (15.6)	6 (16.2)	10 (17.1)	929 (100)	>16	>16
Non-ESBL-producing phenotype (n = 4,278)	1 (0)	74 (1.8)	3196 (76.5)	844 (96.2)	108 (98.7)	37 (99.6)	13 (99.9)	3 (100)	1 (100)	0 (100)	1 (100)	0 (100)	0 (100)	0.03	0.06
All *K. pneumoniae* (n = 3,013)	1 (0)	77 (2.6)	1835 (63.5)	448 (78.4)	80 (81.0)	26 (81.9)	15 (82.4)	21 (83.1)	26 (83.9)	9 (84.2)	8 (84.5)	9 (84.8)	458 (100)	0.03	>16
ESBL-producing phenotype (n = 578)			10 (1.7)	12 (3.8)	6 (4.8)	11 (6.7)	9 (8.3)	21 (11.9)	26 (16.4)	9 (18.0)	7 (19.2)	9 (20.8)	458 (100)	>16	>16
Non-ESBL-producing phenotype (n = 2,435)	1 (0)	77 (3.2)	1825 (78.2)	436 (96.1)	74 (99.1)	15 (99.7)	6 (100)	0 (100)	0 (100)	0 (100)	1 (100)	0 (100)	0 (100)	0.03	0.06
All *K. oxytoca* (n = 806)		1 (0.1)	48 (6.1)	125 (21.6)	177 (43.5)	173 (65.0)	115 (79.3)	33 (83.4)	16 (85.4)	4 (85.9)	2 (86.1)	2 (86.4)	110 (100)	0.25	>16
ESBL-producing phenotype (n = 124)						1 (0.8)	0 (0.8)	6 (5.6)	7 (11.3)	3 (13.7)	2 (15.3)	1 (16.1)	104 (100)	>16	>16
Non-ESBL-producing phenotype (n = 682)		1 (0.1)	48 (7.2)	125 (25.5)	177 (51.5)	172 (76.7)	115 (93.5)	27 (97.5)	9 (98.8)	1 (99.0)	0 (99.0)	1 (99.1)	6 (100)	0.12	0.5
All *P. mirabilis* (n = 968)	1 (0.1)	83 (8.7)	706 (81.6)	113 (93.3)	15 (94.8)	1 (94.9)	3 (95.2)	0 (95.2)	1 (95.4)	0 (95.4)	0 (95.4)	2 (95.6)	43 (100)	0.03	0.06
ESBL-producing phenotype (n = 69)			3 (4.3)	9 (17.4)	9 (30.4)	0 (30.4)	2 (33.3)	0 (33.3)	1 (34.8)	0 (34.8)	0 (34.8)	2 (37.7)	43 (100)	>16	>16
Non-ESBL-producing phenotype (n = 899)	1 (0.1)	83 (9.3)	703 (87.5)	104 (99.1)	6 (99.8)	1 (99.9)	1 (100)	0 (100)	0 (100)	0 (100)	0 (100)	0 (100)	0 (100)	0.03	0.06

a. Isolates, which originated from patients with bloodstream infections, community-acquired respiratory tract infections, pneumonia in hospitalized patients, skin/soft tissue infection, intra-abdominal infection, and other sites but which excluded those from urinary tract infections, were collected from medical in the US from 2016 to 2020. [23, 24, 25, 26, 27].
b. Shaded cells represent the MIC values up to and/or including the MIC_{90} value.

Source: Applicant's PK/PD report for ABSSSI and CAP, Table 13, page 69

Table 254. PTA Results by MIC on Day 1 Based on Median Nonclinical Ceftobiprole Free-Drug Plasma %T>MIC Targets Associated With *Enterobacterales* Efficacy

Endpoints for PK-PD target	MIC (µg/mL)	Percent probabilities of PK-PD target attainment by ceftobiprole MIC and CLcr group (mL/min)						
		≥ 0 to < 15	≥ 15 to < 30	≥ 30 to < 50	≥ 50 to < 90	≥ 90 to ≤ 150	> 150 to ≤ 240	Clinical trial population[c]
Net bacterial stasis	0.03	100	100	100	100	100	100	100
	0.06	100	100	100	100	100	100	100
	0.12	100	100	100	100	100	100	100
	0.25	100	100	100	100	100	100	100
	0.5	100	100	100	100	100	100	100
	1	100	100	100	100	>99.9	100	>99.9
	2	99.4	99.8	99.9	>99.9	99.2	99.4	99.4
	4	80.3	87.4	97.2	98.0	85.5	85.3	88.8
	8	10.7	14.0	59.5	66.3	30.7	28.1	37.7
	16	0	0	3.09	6.01	0.77	0.74	2.06
	32	0	0	0	0	0	0	0
	Overall[d]	87.2	87.3	87.6	87.6	87.3	87.3	87.4
1-$\log_{10}$ CFU reduction from baseline	0.03	100	100	100	100	100	100	100
	0.06	100	100	100	100	100	100	100
	0.12	100	100	100	100	100	100	100
	0.25	100	100	100	100	100	100	100
	0.5	100	100	100	100	>99.9	100	100
	1	>99.9	>99.9	>99.9	100	99.7	99.8	99.8
	2	97.8	99.3	99.6	99.6	96.9	97.1	97.6
	4	67.1	75.9	92.4	94.1	73.2	72.6	78.9
	8	4.89	5.68	41.8	50.0	17.2	16.1	24.7
	16	0	0	0.62	2.21	0.15	0.18	0.66
	32	0	0	0	0	0	0	0
	Overall[d]	87.1	87.2	87.4	87.5	87.1	87.1	87.2

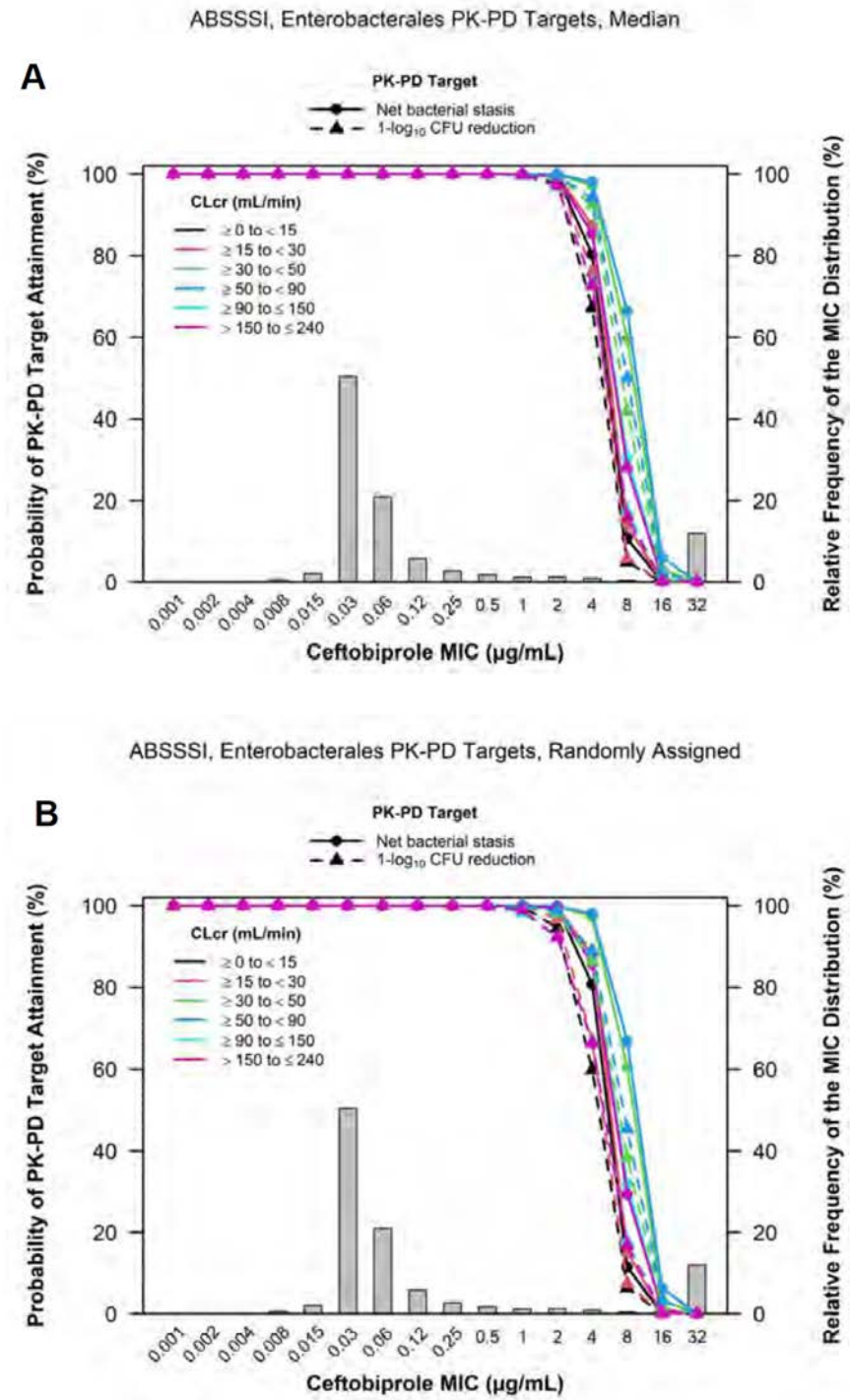
Source: Applicant's PK/PD report for ABSSSI and CAP, Table 45, page 147

Table 255. PTA Results by MIC on Day 1 Based on Randomly Assigned Nonclinical Ceftobiprole Free-Drug Plasma %T>MIC Targets Associated With *Enterobacterales* Efficacy

Endpoints for PK-PD target	MIC (µg/mL)	Percent probabilities of PK-PD target attainment by ceftobiprole MIC and CLcr group (mL/min)						
		≥ 0 to < 15	≥ 15 to < 30	≥ 30 to < 50	≥ 50 to < 90	≥ 90 to ≤ 150	> 150 to ≤ 240	Clinical trial population[c]
Net bacterial stasis	0.03	100	100	100	100	100	100	100
	0.06	100	100	100	100	100	100	100
	0.12	100	100	100	100	100	100	100
	0.25	100	100	100	100	100	100	100
	0.5	100	100	100	100	100	100	100
	1	100	100	100	100	>99.9	100	>99.9
	2	99.5	99.7	99.9	>99.9	99.1	99.4	99.3
	4	80.7	87.7	97.2	98.0	86.2	85.7	88.9
	8	11.5	15.3	60.5	66.8	31.9	29.4	39.9
	16	0	0	3.51	6.24	0.97	1.00	2.21
	32	0	0	0	0	0	0	0
	Overall[d]	87.2	87.3	87.6	87.6	87.3	87.3	87.4
1-$\log_{10}$ CFU reduction from baseline	0.03	100	100	100	100	100	100	100
	0.06	100	100	100	100	100	100	100
	0.12	100	100	100	100	100	100	100
	0.25	100	100	100	100	100	>99.9	>99.9
	0.5	>99.9	100	100	100	99.9	99.9	99.8
	1	99.6	>99.9	>99.9	>99.9	98.4	98.8	98.9
	2	94.6	96.8	98.1	98.7	92.3	92.4	93.8
	4	59.8	67.0	86.4	89.0	66.6	66.4	72.2
	8	6.33	7.39	38.4	45.4	17.7	16.8	23.6
	16	0	0	1.65	3.27	0.41	0.35	1.26
	32	0	0	0	0	0	0	0
	Overall[d]	87.0	87.0	87.4	87.4	87.0	87.0	87.1

Source: Applicant's PK/PD report for ABSSSI and CAP, Table 46, page 148

Figure 50. PTA on Day 1 Based on Median and Randomly Assigned Nonclinical Targets of %T>MIC for *Enterobacterales*



Source: Applicant's PK/PD report for ABSSSI and CAP, Figure 9, page 149

14.5.2.1.3.1.6. PTA for CABP: *S. pneumoniae*

The median ceftobiprole free-drug plasma %T>MIC targets associated with 1-log and 2-log CFU reductions from baseline for *S. pneumoniae* were 23.1 and 25.9, respectively. The demographic variables in simulated subjects with CABP resembled the observed data from Trial CAP-3001. The ceftobiprole MIC distributions for 3,247 *S. pneumoniae* isolates were collected from centers in the USA from 2016 to 2020.

Table 256. PTA Results by MIC on Day 1 Based on Median Nonclinical Ceftobiprole Free-Drug Plasma %T>MIC Targets Associated With *Streptococcus pneumoniae* Efficacy

Endpoints for PK-PD target	MIC (µg/mL)	Percent probabilities of PK-PD target attainment by ceftobiprole MIC and CLcr group (mL/min)						
		≥ 0 to < 15	≥ 15 to < 30	≥ 30 to < 50	≥ 50 to < 90	≥ 90 to ≤ 150	> 150 to ≤ 240	Clinical trial population[c]
1-log_{10} CFU reduction from baseline	0.03	100	100	100	100	100	100	100
	0.06	100	100	100	100	100	100	100
	0.12	100	100	100	100	100	100	100
	0.25	100	100	100	100	100	100	100
	0.5	100	100	100	100	100	100	100
	1	100	100	100	100	100	100	100
	2	100	100	100	100	100	100	100
	4	98.4	99.3	>99.9	100	99.6	99.4	99.8
	8	53.7	65.4	94.5	95.1	78.5	75.3	89.1
	16	1.87	2.27	32.2	38.8	12.6	11.1	27.8
	32	0	0	0.28	0.67	0.03	0	0.21
	Overall[d]	100	100	100	100	100	100	100
2-log_{10} CFU reduction from baseline	0.03	100	100	100	100	100	100	100
	0.06	100	100	100	100	100	100	100
	0.12	100	100	100	100	100	100	100
	0.25	100	100	100	100	100	100	100
	0.5	100	100	100	100	100	100	100
	1	100	100	100	100	100	100	100
	2	>99.9	100	100	100	100	100	100
	4	97.3	98.7	>99.9	>99.9	98.8	98.8	99.6
	8	46.4	56.9	91.5	92.4	71.2	68.4	85.0
	16	1.09	1.09	24.9	31.1	8.84	7.69	22.2
	32	0	0	0.08	0.31	0	0	0.06
	Overall[d]	>99.9	100	100	100	100	100	100

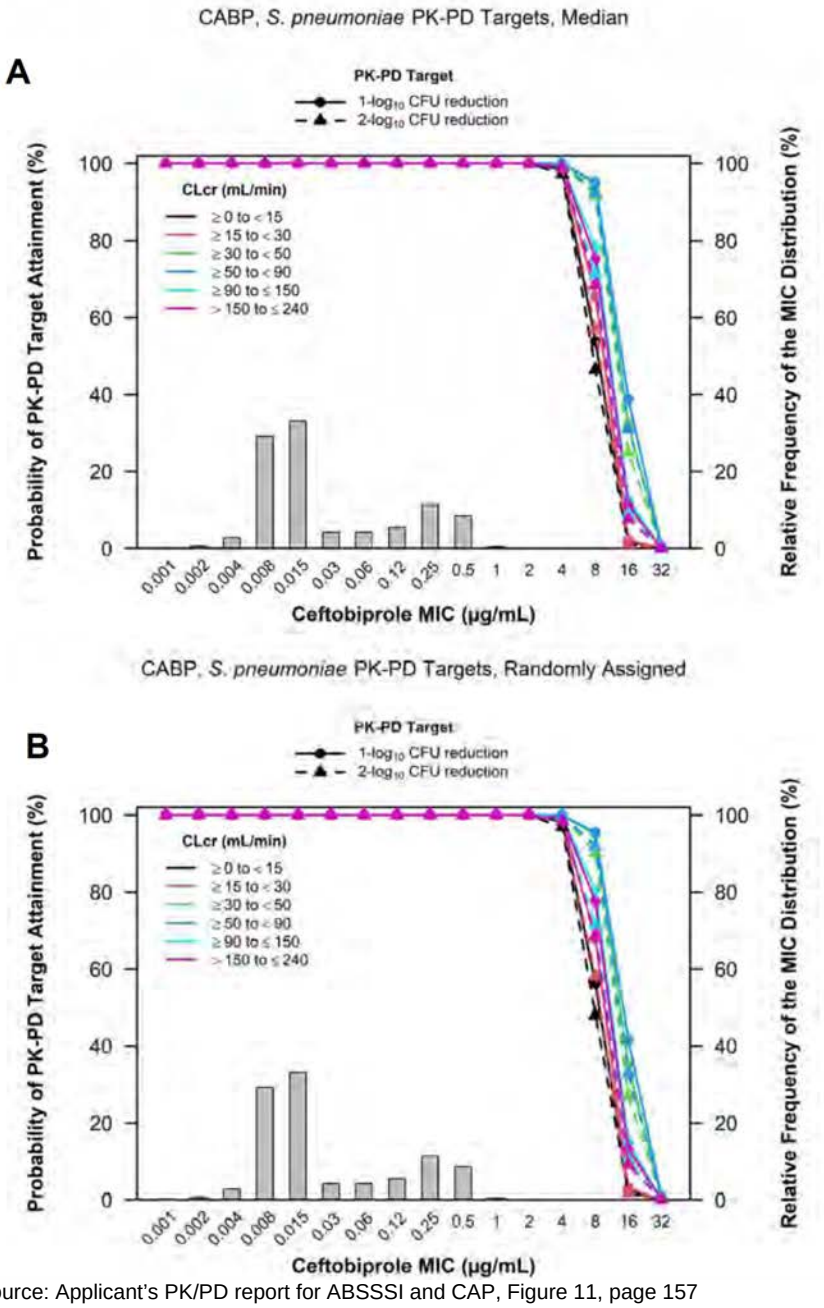
Source: Applicant's PK/PD report for ABSSSI and CAP, Table 47, page 155

Table 257. PTA Results by MIC on Day 1 Based on Randomly Assigned Nonclinical Ceftobiprole Free-Drug Plasma %T>MIC Targets Associated With *Streptococcus pneumoniae* Efficacy

Endpoints for PK-PD target	MIC (µg/mL)	Percent probabilities of PK-PD target attainment by ceftobiprole MIC and CLcr group (mL/min)						
		≥ 0 to < 15	≥ 15 to < 30	≥ 30 to < 50	≥ 50 to < 90	≥ 90 to ≤ 150	> 150 to ≤ 240	Clinical trial population[c]
1-log_{10} CFU reduction from baseline	0.03	100	100	100	100	100	100	100
	0.06	100	100	100	100	100	100	100
	0.12	100	100	100	100	100	100	100
	0.25	100	100	100	100	100	100	100
	0.5	100	100	100	100	100	100	100
	1	100	100	100	100	100	100	100
	2	100	100	100	100	100	100	100
	4	98.3	99.3	>99.9	>99.9	99.4	99.3	99.8
	8	56.1	67.8	94.9	95.4	80.5	77.5	89.6
	16	2.63	3.08	35.0	41.5	14.9	13.1	30.7
	32	0	0	0.34	0.98	0.03	0.03	0.41
	Overall[d]	100	100	100	100	100	100	100
2-log_{10} CFU reduction from baseline	0.03	100	100	100	100	100	100	100
	0.06	100	100	100	100	100	100	100
	0.12	100	100	100	100	100	100	100
	0.25	100	100	100	100	100	100	100
	0.5	100	100	100	100	100	100	100
	1	100	100	100	100	100	100	100
	2	>99.9	100	100	100	100	100	100
	4	96.9	98.4	99.7	99.9	98.4	98.4	99.1
	8	48.0	58.3	90.2	92.0	71.5	68.5	84.3
	16	1.71	1.79	27.2	32.7	10.4	9.14	23.6
	32	0	0	0.14	0.56	0	0	0.24
	Overall[d]	>99.9	100	100	100	100	100	100

Source: Applicant's PK/PD report for ABSSSI and CAP, Table 48, page 156

Figure 51. PTA on Day 1 Based on Median and Randomly Assigned Nonclinical Targets of %T>MIC for *Streptococcus pneumoniae*



Source: Applicant's PK/PD report for ABSSSI and CAP, Figure 11, page 157

14.5.2.1.3.1.7. PTA for CABP: *Staphylococcus aureus*

The median ceftobiprole free-drug plasma %T>MIC targets associated with 1-log and 2-log CFU reductions from baseline for *S. aureus* were 24.7 and 28.5, respectively. The demographic variables in simulated subjects with CABP resembled the observed data from Trial CAP-3001. The ceftobiprole MIC distributions for 13,715 *S. aureus* isolates were collected from centers in the USA from 2016 to 2020.

Table 258. PTA Results by MIC on Day 1 Based on Median Nonclinical Ceftobiprole Free-Drug Plasma %T>MIC Targets Associated With *Staphylococcus aureus* Efficacy

Endpoints for PK-PD target	MIC (µg/mL)	Percent probabilities of PK-PD target attainment by ceftobiprole MIC and CLcr group (mL/min)						
		≥ 0 to < 15	≥ 15 to < 30	≥ 30 to < 50	≥ 50 to < 90	≥ 90 to ≤ 150	> 150 to ≤ 240	Clinical trial population[c]
1-log_{10} CFU reduction from baseline	0.03	100	100	100	100	100	100	100
	0.06	100	100	100	100	100	100	100
	0.12	100	100	100	100	100	100	100
	0.25	100	100	100	100	100	100	100
	0.5	100	100	100	100	100	100	100
	1	100	100	100	100	100	100	100
	2	100	100	100	100	100	100	100
	4	97.8	98.9	>99.9	>99.9	99.1	99.3	99.6
	8	49.1	60.4	93.0	93.8	74.6	71.6	86.9
	16	1.43	1.68	28.2	34.6	10.5	8.89	24.4
	32	0	0	0.20	0.39	0	0	0.09
	Overall[d]							
	All isolates	>99.9	>99.9	>99.9	>99.9	>99.9	>99.9	>99.9
	MRSA	>99.9	>99.9	>99.9	>99.9	>99.9	>99.9	>99.9
	MSSA	100	100	100	100	100	100	100
2-log_{10} CFU reduction from baseline	0.03	100	100	100	100	100	100	100
	0.06	100	100	100	100	100	100	100
	0.12	100	100	100	100	100	100	100
	0.25	100	100	100	100	100	100	100
	0.5	100	100	100	100	100	100	100
	1	100	100	100	100	100	100	100
	2	>99.9	100	100	100	100	100	100
	4	95.8	98.1	99.8	99.8	98.1	98.2	99.2
	8	40.5	50.4	87.9	89.7	64.9	61.8	80.5
	16	0.67	0.67	19.4	25.5	6.40	5.87	18.1
	32	0	0	0	0.20	0	0	0.03
	Overall[d]							
	All isolates	>99.9	>99.9	>99.9	>99.9	>99.9	>99.9	>99.9
	MRSA	>99.9	>99.9	>99.9	>99.9	>99.9	>99.9	>99.9
	MSSA	100	100	100	100	100	100	100

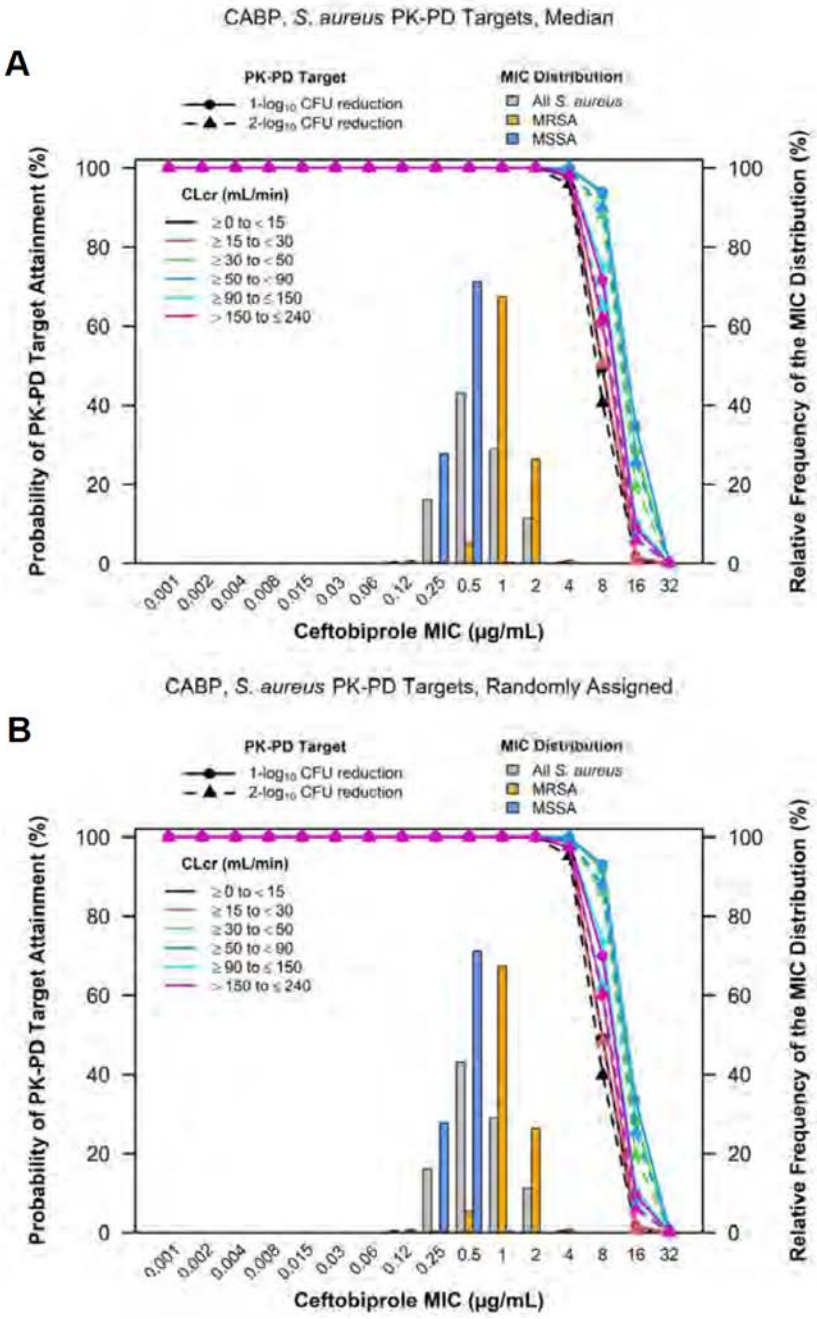
Source: Applicant's PK/PD report for ABSSSI and CAP, Table 49, page 162

Table 259. PTA Results by MIC on Day 1 Based on Randomly Assigned Nonclinical Ceftobiprole Free-Drug Plasma %T>MIC Targets Associated With *Staphylococcus aureus* Efficacy

Endpoints for PK-PD target	MIC (µg/mL)	Percent probabilities of PK-PD target attainment by ceftobiprole MIC and CLcr group (mL/min)						
		≥ 0 to < 15	≥ 15 to < 30	≥ 30 to < 50	≥ 50 to < 90	≥ 90 to ≤ 150	> 150 to ≤ 240	Clinical trial population[c]
1-log_{10} CFU reduction from baseline	0.03	100	100	100	100	100	100	100
	0.06	100	100	100	100	100	100	100
	0.12	100	100	100	100	100	100	100
	0.25	100	100	100	100	100	100	100
	0.5	100	100	100	100	100	100	100
	1	100	100	100	100	100	100	100
	2	>99.9	100	100	100	100	100	100
	4	97.3	98.7	>99.9	>99.9	98.8	99.0	99.4
	8	48.9	59.9	91.6	92.8	73.4	69.9	85.9
	16	1.71	1.73	28.0	33.2	10.7	9.26	24.4
	32	0	0	0.14	0.56	0	0	0.18
	Overall[d]							
	All isolates	>99.9	>99.9	>99.9	>99.9	>99.9	>99.9	>99.9
	MRSA	>99.9	>99.9	>99.9	>99.9	>99.9	>99.9	>99.9
	MSSA	100	100	100	100	100	100	100
2-log_{10} CFU reduction from baseline	0.03	100	100	100	100	100	100	100
	0.06	100	100	100	100	100	100	100
	0.12	100	100	100	100	100	100	100
	0.25	100	100	100	100	100	100	100
	0.5	100	100	100	100	100	100	100
	1	100	100	100	100	100	100	100
	2	>99.9	100	100	100	100	100	100
	4	95.1	97.5	99.6	99.7	97.3	97.4	98.5
	8	39.8	48.2	86.0	87.9	62.2	60.1	78.3
	16	0.78	0.67	19.4	25.3	6.68	5.76	17.6
	32	0	0	0.03	0.17	0	0	0.09
	Overall[d]							
	All isolates	>99.9	>99.9	>99.9	>99.9	>99.9	>99.9	>99.9
	MRSA	>99.9	>99.9	>99.9	>99.9	>99.9	>99.9	>99.9
	MSSA	100	100	100	100	100	100	100

Source: Applicant's PK/PD report for ABSSSI and CAP, Table 50, page 163

Figure 52. PTA Results by MIC on Day 1 Based on Median Nonclinical Ceftobiprole Free-Drug Plasma %T>MIC Targets Associated With *Staphylococcus aureus* Efficacy



Source: Applicant's PK/PD report for ABSSSI and CAP, Figure 13, page 164

14.5.2.1.3.1.8. PTA for CABP: *Enterobacterales*

The median ceftobiprole free-drug plasma %T>MIC targets associated with 1-log and 2-log CFU reductions from baseline for *Enterobacterales* were 50.0 and 58.5, respectively. The demographic variables in simulated subjects with CABP resembled the observed data from Trial CAP-3001. The ceftobiprole MIC distributions for 14,940 *Enterobacterales* isolates, including 5,398 *E coli*, 3,013 *K. pneumoniae*, 806 *K. oxytoca*, and 968 *P. mirabilis*, were collected from centers in the USA from 2016 to 2020. Subsets of ESBL-producing and non-ESBL-producing phenotypes are described in Table 253.

Table 260. PTA Results by MIC on Day 1 Based on Median Nonclinical Ceftobiprole Free-Drug Plasma %T>MIC Targets Associated With *Enterobacterales* Efficacy

Endpoints for PK-PD target	MIC (µg/mL)	Percent probabilities of PK-PD target attainment by ceftobiprole MIC and CLcr group (mL/min)						
		≥ 0 to < 15	≥ 15 to < 30	≥ 30 to < 50	≥ 50 to < 90	≥ 90 to ≤ 150	> 150 to ≤ 240	Clinical trial population[c]
1-log_{10} CFU reduction from baseline	0.03	100	100	100	100	100	100	100
	0.06	100	100	100	100	100	100	100
	0.12	100	100	100	100	100	100	100
	0.25	100	100	100	100	100	100	100
	0.5	100	100	100	100	100	100	100
	1	>99.9	100	>99.9	100	99.7	99.9	>99.9
	2	98.0	99.2	99.5	99.7	96.3	96.6	98.7
	4	72.2	79.8	92.4	94.3	73.5	73.3	87.7
	8	9.90	9.12	46.1	53.2	20.4	19.0	39.9
	16	0	0	1.54	3.47	0.36	0.31	1.42
	32	0	0	0	0	0	0	0
	Overall[d]	87.1	87.2	87.5	87.5	87.1	87.1	87.4
2-log_{10} CFU reduction from baseline	0.03	100	100	100	100	100	100	100
	0.06	100	100	100	100	100	100	100
	0.12	100	100	100	100	100	100	100
	0.25	100	100	100	100	100	100	100
	0.5	>99.9	100	100	100	99.9	>99.9	>99.9
	1	99.6	>99.9	99.9	>99.9	98.5	98.9	99.5
	2	95.0	97.5	98.1	98.9	90.4	91.2	96.4
	4	56.8	64.8	83.8	87.1	58.3	57.6	77.5
	8	4.17	3.33	28.7	36.9	10.5	10.2	25.3
	16	0	0	0.22	1.03	0.06	0.08	0.41
	32	0	0	0	0	0	0	0
	Overall[d]	86.9	87.0	87.3	87.4	86.9	86.9	87.2

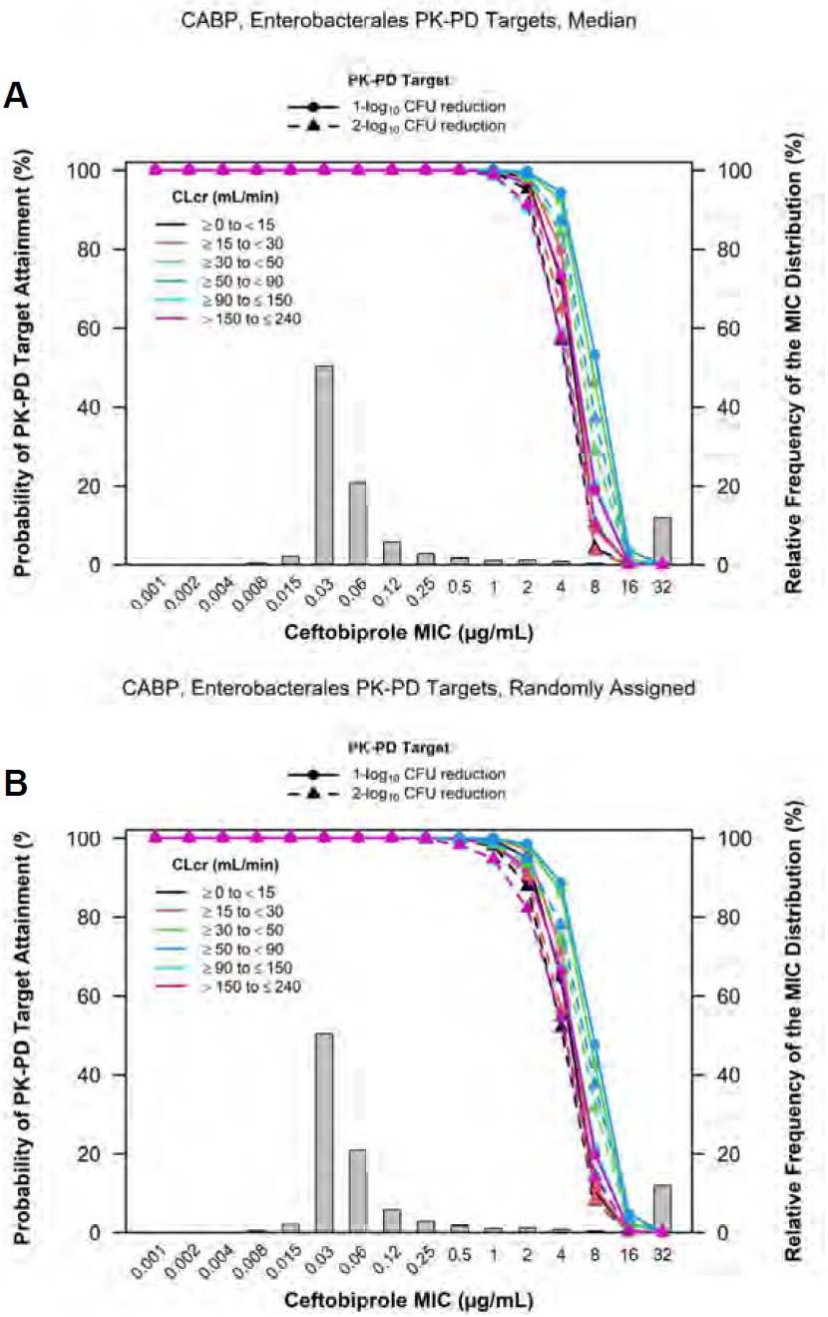
Source: Applicant's PK/PD report for ABSSSI and CAP, Table 51, page 169

Table 261. PTA Results by MIC on Day 1 Based on Randomly Assigned Nonclinical Ceftobiprole Free-Drug Plasma %T>MIC Targets Associated With *Enterobacterales* Efficacy

Endpoints for PK-PD target	MIC (µg/mL)	Percent probabilities of PK-PD target attainment by ceftobiprole MIC and CLcr group (mL/min)						
		≥ 0 to < 15	≥ 15 to < 30	≥ 30 to < 50	≥ 50 to < 90	≥ 90 to ≤ 150	> 150 to ≤ 240	Clinical trial population[c]
1-log_{10} CFU reduction from baseline	0.03	100	100	100	100	100	100	100
	0.06	100	100	100	100	100	100	100
	0.12	100	100	100	100	100	100	100
	0.25	100	100	100	100	100	100	100
	0.5	>99.9	100	100	100	99.8	99.8	>99.9
	1	99.6	99.8	99.7	99.9	98.2	98.5	99.0
	2	94.9	97.2	97.9	98.5	91.4	92.1	96.1
	4	64.5	71.2	86.2	88.5	66.7	66.1	81.7
	8	10.3	11.4	42.3	47.6	21.1	19.8	36.6
	16	0.03	0	2.24	4.64	0.64	0.64	2.65
	32	0	0	0	0	0	0	0
	Overall[d]	87.0	87.1	87.4	87.4	87.0	87.0	87.3
2-log_{10} CFU reduction from baseline	0.03	100	100	100	100	100	100	100
	0.06	100	100	100	100	100	100	100
	0.12	100	100	100	100	100	100	100
	0.25	>99.9	100	>99.9	100	99.6	99.7	100
	0.5	99.7	>99.9	99.8	99.9	98.4	98.3	99.6
	1	97.9	98.4	98.4	98.9	94.4	94.7	97.8
	2	87.7	90.3	93.5	94.7	82.2	82.0	89.3
	4	51.9	56.3	74.3	77.8	54.4	54.6	68.4
	8	7.86	8.11	31.8	37.3	14.7	13.9	28.5
	16	0	0.06	2.07	3.24	0.59	0.45	2.27
	32	0	0	0	0.03	0	0	0
	Overall[d]	86.8	86.9	87.1	87.2	86.7	86.7	87.0

Source: Applicant's PK/PD report for ABSSSI and CAP, Table 52, page 170

Figure 53. PTA on Day 1 Based on Median and Randomly Assigned Nonclinical Targets of %T>MIC for *Enterobacterales*



Source: Applicant's PK/PD report for ABSSSI and CAP, Figure 15, page 171
Reviewer comments: The Applicant also assessed impact of weight (≥80 kg) in the context of PTA based on forest plot in Figure 31. The PTA results using median and randomly assigned targets across studied pathogens did not demonstrate clinically significant differences of the subset of simulated subjects with body weight ≥80 kg from all simulated subjects across CLcr groups (analyses not shown; refer to Applicant's submitted PK/PD report for ABSSSI and CABP in Section 4.2.2.2.5 and Appendix 23).

14.5.2.2. *Staphylococcus aureus* Bacteremia PK/PD Analysis

14.5.2.2.1. Introduction

The Applicant performed PK/PD analyses for the SAB populations with the following objects:

- To evaluate exposure-efficacy relationships using the refined PopPK model for SAB
- To conduct PTA to support ceftobiprole dosing regimens and susceptibility testing interpretive criteria against *S. aureus*

14.5.2.2.2. Exposure-Efficacy Analysis

Exposure-efficacy relationship was evaluated for SAB using PK and clinical data from Trial BPR-CS-008. Dosing regimens administered in SAB subjects are summarized in Table 262. The primary endpoint was overall success in the treatment of SAB, including infective endocarditis, at the post-treatment evaluation (PTE) visit (Day 70 +/- 5 post-randomization) in the mITT population (defined as *the subset of subjects in the* intent-to-treat *(ITT) population who received any amount of study medication, and who had a blood culture positive for S. aureus at baseline based on a central microbiology laboratory assessment*). Overall success is defined if the following criteria were met:

- Subject was alive at PTE visit;
- No new metastatic foci or complications of the SAB infection;
- Resolution or improvement of SAB-related clinical signs and symptoms; and
- Two negative blood cultures for *S. aureus*
- At least one while subject was on active study treatment, and
- confirmed by at least one subsequent negative blood culture for *S. aureus* (either in the period between 7 days after the end-of-treatment (EOT) visit and PTE visit or at the PTE visit)

The Applicant employed two analysis populations for the exposure-efficacy analysis: 1) mITT population with baseline pathogen, microbiological data, and sufficient PK data and 2) a subpopulation of the first analysis population with *S. aureus* isolated at baseline. A total of 174 and 172 subjects were included in the mITT and mITT *S. aureus* analysis populations, respectively. Refer to the Applicant's PK/PD report (Tables 10 and 11 in the submitted report) for a summary of baseline characteristics of the analysis populations. The response for efficacy endpoints by visits in two analysis populations are summarized in Table 263. Ceftobiprole MIC, free-drug AUC, and Day 1 free-drug plasma %T>MIC for both analysis populations are summarized in Table 264. Percent of subjects in each analysis population achieving nonclinical targets is summarized in Table 265. Given that individual %T>MIC aggregate at the high end of respective ranges, the exposure-efficacy analyses (univariable or multivariable) were not performed by the Applicant.

Of note, two subjects had *A. baumannii* and *C. striatum* selected as baseline pathogens with MICs of >64 and >16 µg/mL, respectively. For these two subjects, the free-drug %T>MIC were of 0% on Days 1 and 10 and were categorized as failures regarding overall success endpoints at EOT and PTE. While the free-drug plasma %T>MIC with respect to the baseline *S. aureus*

Reference ID: 5357793

pathogens for these two subjects was 98.8%, the Applicant postulated that the clinical failure was potentially due to the other pathogens or other subject variables.

Table 262. Dosing Regimens Studied in BPR-CS-009

CLcr group (mL/min)	Ceftobiprole dosing regimens[a]
≥ 50	Days 1-8: 500 mg IV q6h
	Day 9 and onwards: 500 mg IV q8h
≥ 30 to < 50	Days 1-8: 500 mg IV q8h
	Day 9 and onwards: 500 mg IV q12h
< 30	Days 1-8: 250 mg IV q8h
	Day 9 and onwards: 250 mg IV q12h
Intermittent hemodialysis[b] or peritoneal dialysis	Days 1-8: 250 mg q24h
	Day 9 and onwards: 250 mg q24h

Source: Applicant's PKPD report for SAB, Table 3, page 34
Note: 667 mg of ceftobiprole medocaril sodium is equivalent to 500 mg of ceftobiprole. Dosing adjustments for each indication are based on renal function
All regimens employed 2-hour infusion (post iHD if applicable per study protocol)

Table 263. Summary of Response for Efficacy Endpoints by Visit

Efficacy endpoint	Visit	Percentage of responses by efficacy endpoint and visit (n/N)	
		mITT Analysis Population (n=174)	mITT *S. aureus* Analysis Population (n=172)
DRC-assessed overall success[a]	EOT	78.7 (137/174)	79.7 (137/172)
	PTE	73.6 (128/174)	74.4 (128/172)
Microbiological eradication	Day 4	53.4 (93/174)	52.9 (91/172)
	Day 8	87.9 (153/174)	87.8 (151/172)
	EOT	92.0 (160/174)	91.9 (158/172)
	PTE	86.2 (150/174)	86.6 (149/172)
Development of new metastatic foci after Day 7	Between Day 8 and PTE	6.3 (11/174)	6.4 (11/172)
All-cause mortality	Day 28	5.2 (9/174)	5.2 (9/172)
	PTE	8.0 (14/174)	7.6 (13/172)

Source: Applicant's PKPD report for SAB, Table 12, page 54

Table 264. Summary Statistics for Baseline MIC, Day 1 Free-Drug AUC, and %T>MIC in Analysis Populations

Analysis Population	Ceftobiprole baseline MIC_{50}, MIC_{90} (Min, Max) (µg/mL)	Day	Median (Min, Max)	
			Free-drug plasma AUC (µg•h/mL)	Free-drug plasma %T>MIC
mITT (n = 174)	0.5, 1 (0.12, > 64)	1	217.8 (76.3, 570.3)	99.6 (0, 99.6)
		10 (n = 163)[a]	201.8 (48.3, 1224.3)	100 (0, 100)
mITT *S. aureus* (n = 172)	0.5, 1 (0.12, 2)	1	214.6 (76.3, 570.3)	99.6 (97.9, 99.6)
		10 (n = 161)[a]	200.1 (48.3, 1224.3)	100 (59.8, 100)

Source: Applicant's PKPD report for SAB, Table 13, page 60

Table 265. Summary of Percentage of Subjects in the *Staphylococcus aureus* Bacteremia mITT and ME Analysis Populations Achieving Nonclinical Targets

Endpoint for free-drug plasma %T>MIC targets[b]	% (n/N) of patients achieving non-clinical the target[a]			
	mITT Analysis Population		mITT *S. aureus* Analysis Population	
	Day 1 (n = 174)	Day 10 (n = 163)	Day 1 (n = 172)	Day 10 (n = 161)
Net bacterial stasis	98.9[c] (172/174)	98.8[c] (161/163)	100 (172/172)	100 (161/161)
1-log_{10} CFU reduction from baseline	98.9[c] (172/174)	98.8[c] (161/163)	100 (172/172)	100 (161/161)

Source: Applicant's PKPD report for SAB, Table 14, page 61
[a]Based only on *S. aureus* pathogens at baseline; [b]Based on the assessment of median nonclinical ceftobiprole free-drug plasma %T>MIC targets associated with net bacterial stasis and a 1-log10 CFU reduction from baseline of 21.1 and 24.7, respectively, for *S. aureus*; [c]Two subjects, BPR-SC-009-(b) (6) and BPRS-CS-009(b) (6), in the mITT Analysis Population had free-drug plasma %T>MIC on Day 1 of 99.6 and 98.8%, respectively, and 100 and 100% on Day 10, for *S. aureus*. For their selected analysis pathogens, C. striatum and A. baumannii, free-drug plasma %T>MIC was 0% on both Days 1 and 10.

Reviewer Comments

The distributions of free-drug %T>MIC in the two analysis populations for SAB being at or close to the high end of the range likely indicate that the subjects were at the plateau of the exposure-efficacy relationships. This is further evaluated in PTA to support dosing selection for SAB.

The reviewer also examined the exposures (i.e., free-drug AUC) and free-drug %T>MIC on Days 1 and 10 for subjects with right-sided infective endocarditis (RIE) as assessed by investigators in the mITT population. A total of 13 subjects were flagged as having RIE, and the %T>MIC aggregate towards the higher end of the range on both Day 1 and Day 10 in this subgroup (median, 99.6% and 100% on Day 1 and Day 10, respectively). Overall, the target attainment did not differ between RIE vs. others in the mITT population.

14.5.2.2.3. PTA

The Applicant conducted simulations and PTA using the dosing regimens described in Table 266. The lack of data on extraction ratio is discussed in other sections (see Section 8). For the PTA analysis, the nonclinical PK/PD targets are summarized in Section 5. The randomly assigned targets were derived based on an estimated log normal distribution of %T>MIC targets associated with a given endpoint (truncated within 2 standard deviations of the mean value).

Reviewer Comments

The PTA analyses (based on median and random targets) demonstrate that the proposed dosing regimen (across renal function groups) provides sufficient coverage up to an MIC of 4 µg/mL for 1-log kill across MIC distributions of S. aureus on Day 1 and Day 10.

Table 266. Ceftobiprole Regimens for Simulations

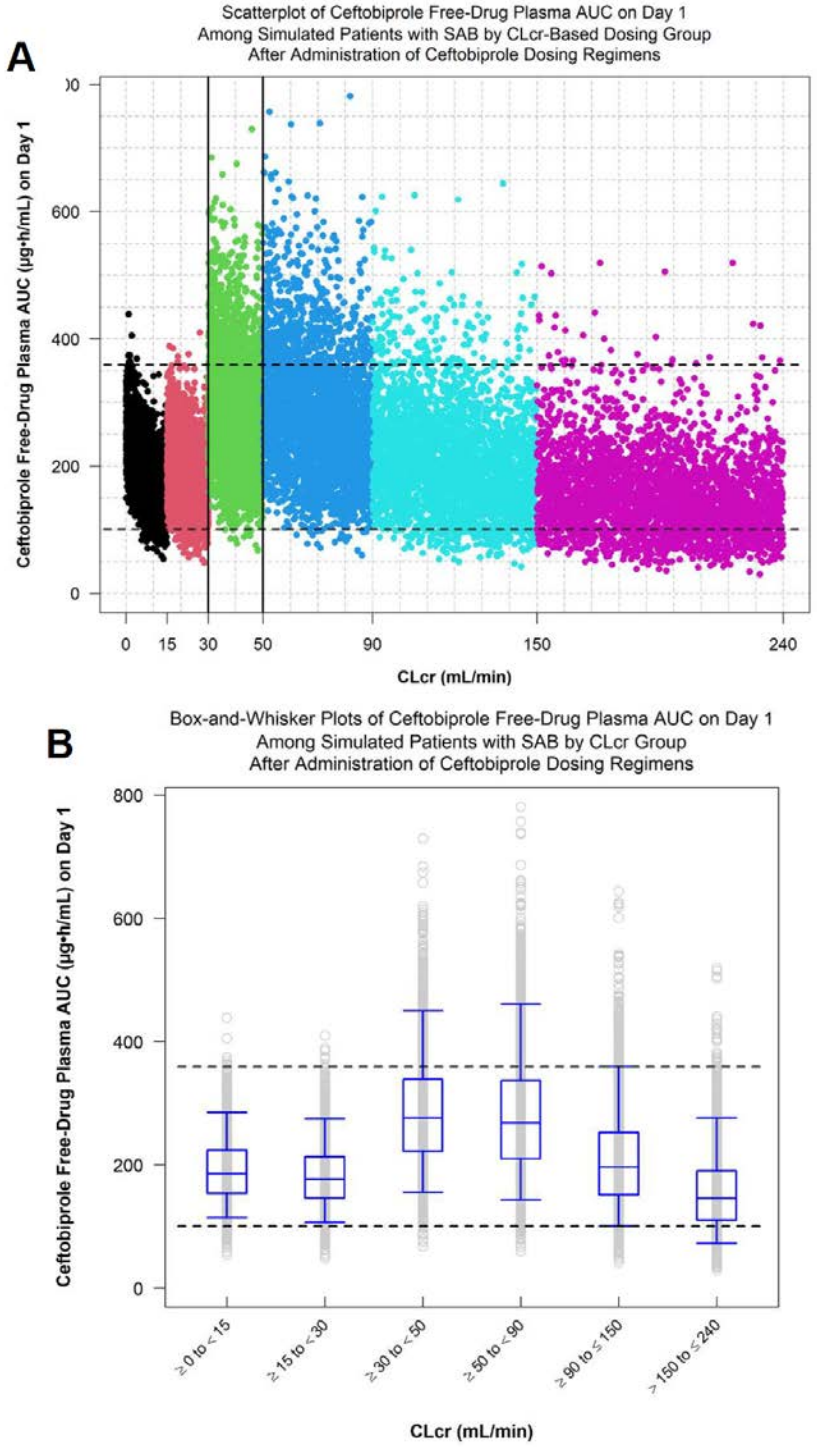
Renal function groups	CLcr group (mL/min)	Ceftobiprole dose on Days 1 to 8[a]	Ceftobiprole dose on Day 9 and onwards[a]
Supranormal	> 150 to ≤ 240	500 mg IV q6h	500 mg IV q6h
Normal renal function	≥ 90 to ≤ 150		500 mg IV q8h
Mild renal impairment	≥ 50 to < 90		
Moderate renal impairment	≥ 30 to < 50	500 mg IV q8h	500 mg IV q12h
Severe renal impairment	≥ 15 < 30	250 mg IV q8h	250 mg IV q12h
End stage renal disease[b]	≥ 0 < 15	250 mg IV q12h	250 mg IV q24h

Source: Applicant's PKPD report for SAB, Table 15, page 64
Note: 667 mg of ceftobiprole medocaril sodium is equivalent to 500 mg of ceftobiprole. Dosing adjustments for each indication are based on renal function
All simulated dosing regimens were administered via a 2-hour infusion; no iHD

14.5.2.2.3.1. Exposures

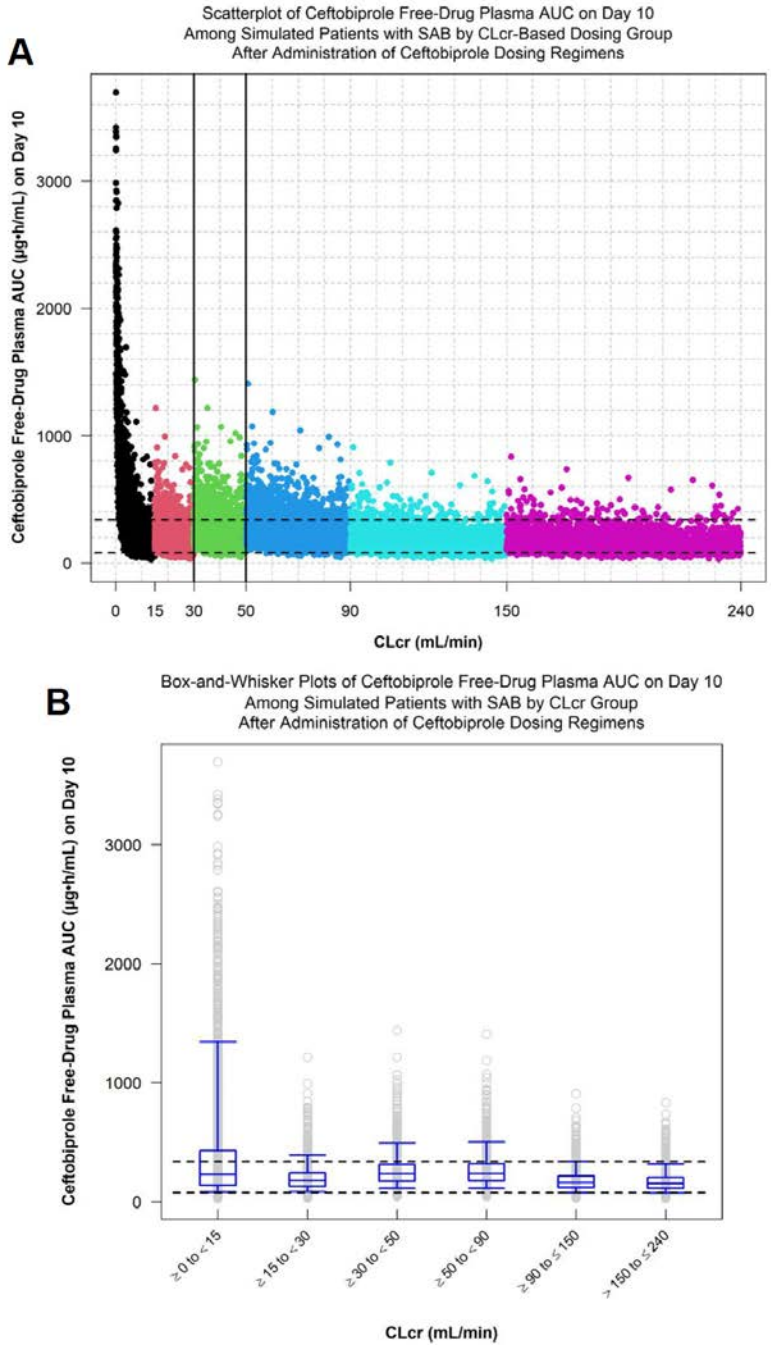
Exposures for SAB were simulated and summarized for Days 1 and 10 in the figures and tables below for AUC and C_{max}.

Figure 54. Scatterplot and Boxplots for Simulated Ceftobiprole Day 1 AUC Across Renal Function Groups for *Staphylococcus aureus* Bacteremia



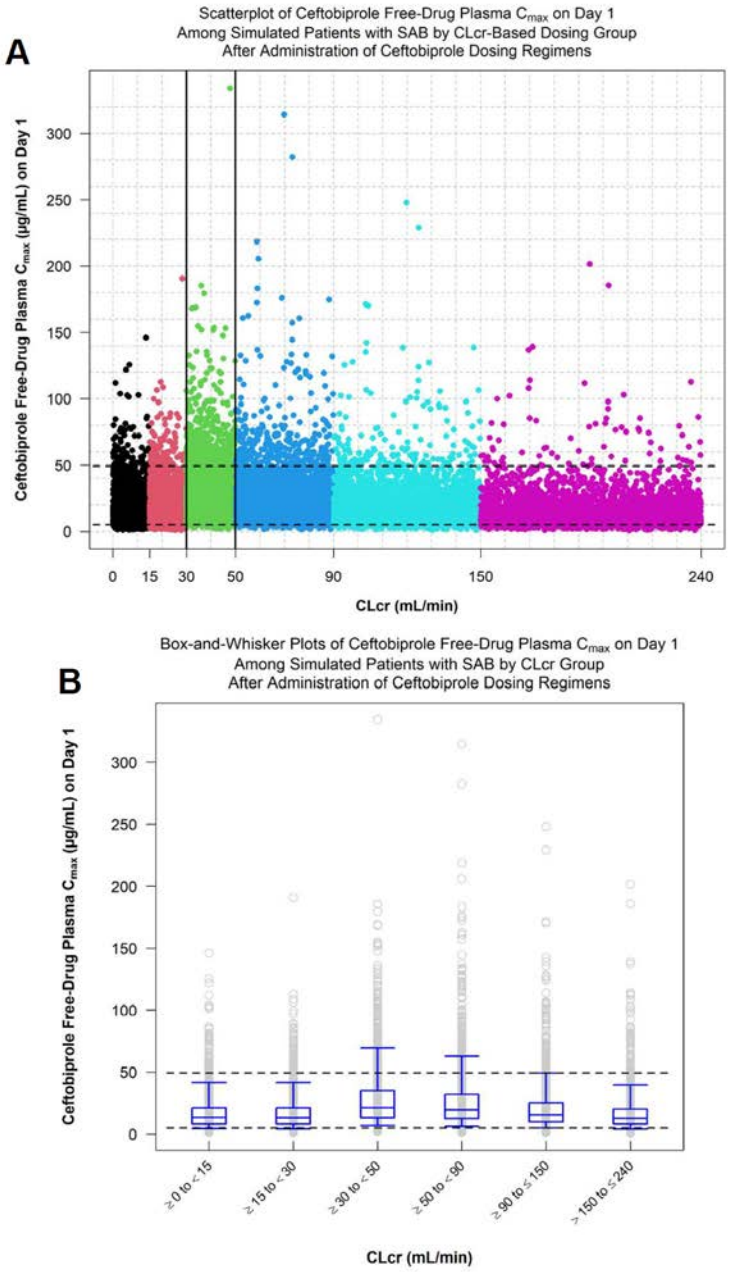
Source: Applicant's PKPD report for SAB, Figure 3, page 69
In panel A, the vertical black lines in the scatterplot represent the categorization of the CLcr groups for which different ceftobiprole dosing regimens were administered. The horizontal dashed lines represent 90 to 150 mL/min group, defined as the 5th and 95th percentiles for ceftobiprole exposure

Figure 55. Scatterplot and Boxplots for Simulated Ceftobiprole Day 10 AUC Across Renal Function Groups for *Staphylococcus aureus* Bacteremia



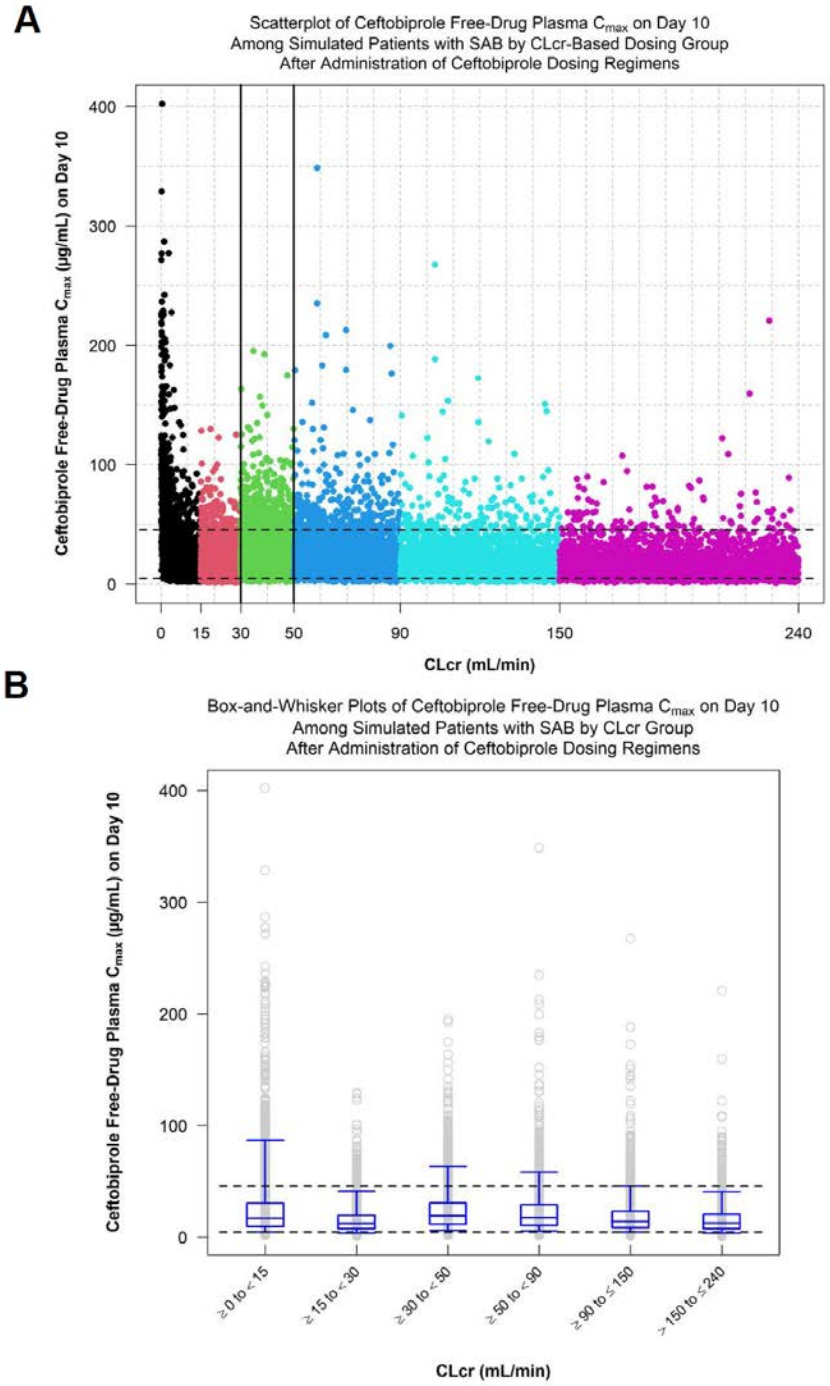
Source: Applicant's PKPD report for SAB, Figure 3, page 69
In panel A, the vertical black lines in the scatterplot represent the categorization of the CLcr groups for which different ceftobiprole dosing regimens were administered. The horizontal dashed lines represent 90 to 150 mL/min group, defined as the 5th and 95th percentiles for ceftobiprole exposure

Figure 56. Scatterplot and Boxplots for Simulated Ceftobiprole Day 1 C_{max} Across Renal Function Groups for *Staphylococcus aureus* Bacteremia



Source: Applicant's PKPD report for SAB, Figure 5, page 73
In panel A, the vertical black lines in the scatterplot represent the categorization of the CLcr groups for which different ceftobiprole dosing regimens were administered. The horizontal dashed lines represent 90 to 150 mL/min group, defined as the 5th and 95th percentiles for ceftobiprole exposure

Figure 57. Scatterplot and Boxplots for Simulated Ceftobiprole Day 10 C_{max} Across Renal Function Groups for *Staphylococcus aureus* Bacteremia



Source: Applicant's PKPD report for SAB, Figure 6, page 75
In panel A, the vertical black lines in the scatterplot represent the categorization of the CLcr groups for which different ceftobiprole dosing regimens were administered. The horizontal dashed lines represent 90 to 150 mL/min group, defined as the 5th and 95th percentiles for ceftobiprole exposure

Table 267. Summary Statistics for Simulated Ceftobiprole Day 1 AUC Across Renal Function Groups for *Staphylococcus aureus* Bacteremia

Variable	Summary statistics for ceftobiprole free-drug plasma AUC (µg•h/mL) on Day 1 by CLcr group (mL/min)					
	≥ 0 to < 15	≥ 15 to < 30	≥ 30 to < 50	≥ 50 to < 90	≥ 90 to ≤ 150	> 150 to ≤ 240
Count	3088	3088	3088	3088	3088	3088
Minimum	54.2	48.4	67.6	59.8	41.7	30.0
Maximum	439	410	730	781	644	519
Mean	191	182	286	281	209	156
%CV	27.4	28.2	31.8	35.3	38.7	41.3
Geometric mean	184	175	272	264	194	144
Geometric %CV	27.8	28.9	32.5	35.8	38.6	40.6

Source: Applicant's PKPD report for SAB, Table 16, page 68

Table 268. Summary Statistics for Simulated Ceftobiprole Day 10 AUC Across Renal Function Groups for *Staphylococcus aureus* Bacteremia

Variable	Summary statistics for ceftobiprole free-drug plasma AUC (µg•h/mL) on Day 10 by CLcr group (mL/min)					
	≥ 0 to < 15	≥ 15 to < 30	≥ 30 to < 50	≥ 50 to < 90	≥ 90 to ≤ 150	> 150 to ≤ 240
Count	3088	3088	3088	3088	3088	3088
Minimum	27.6	32.7	45.4	45.1	31.4	30.0
Maximum	3696	1215	1438	1408	909	834
Mean	391	198	258	261	178	168
%CV	117	51.8	49.0	48.6	47.9	47.6
Geometric mean	259	177	233	236	161	152
Geometric %CV	84.4	46.8	45.0	45.0	44.6	44.4

Source: Applicant's PKPD report for SAB, Table 17, page 70

Table 269. Summary Statistics for Simulated Ceftobiprole Day 1 C_{max} Across Renal Function Groups for *Staphylococcus aureus* Bacteremia

Variable	Summary statistics for ceftobiprole free-drug plasma C_{max} (µg/mL) on Day 1 by CLcr group (mL/min)					
	≥ 0 to < 15	≥ 15 to < 30	≥ 30 to < 50	≥ 50 to < 90	≥ 90 to ≤ 150	> 150 to ≤ 240
Count	3088	3088	3088	3088	3088	3088
Minimum	1.38	1.16	1.94	1.45	1.15	0.936
Maximum	146	191	334	314	248	202
Mean	16.7	16.7	27.6	25.6	20.2	16.3
%CV	78.6	79.9	80.6	84.9	85.2	85.3
Geometric mean	13.0	13.0	21.4	19.8	15.6	12.6
Geometric %CV	70.1	71.2	71.5	71.5	71.6	71.8

Source: Applicant's PKPD report for SAB, Table 18, page 72

Table 270. Summary Statistics for Simulated Ceftobiprole Day 10 C_{max} Across Renal Function Groups for *Staphylococcus aureus* Bacteremia

Variable	Summary statistics for ceftobiprole free-drug plasma C_{max} (µg/mL) on Day 10 by CLcr group (mL/min)					
	≥ 0 to < 15	≥ 15 to < 30	≥ 30 to < 50	≥ 50 to < 90	≥ 90 to ≤ 150	> 150 to ≤ 240
Count	3088	3088	3088	3088	3088	3088
Minimum	1.72	1.00	1.61	1.36	1.10	0.760
Maximum	402	130	195	349	268	221
Mean	27.0	15.8	24.5	23.2	18.5	16.1
%CV	121	83.2	80.0	88.7	87.7	83.3
Geometric mean	17.6	12.1	19.0	17.7	14.2	12.4
Geometric %CV	88.6	73.0	71.4	72.8	72.3	73.4

Source: Applicant's PKPD report for SAB, Table 19, page 74

14.5.2.2.3.2. PTA for SAB: Day 1

The median ceftobiprole free-drug plasma %T>MIC targets associated with net bacterial stasis and a 1-log CFU reduction from baseline for *S. aureus* were 21.1 and 24.7, respectively. The demographic variables in simulated subjects with SAB resembled the observed data from Trial BPR-CS-009. The ceftobiprole MIC distributions for 13,715 *S. aureus* isolates were collected from centers in the USA from 2016 to 2020.

Table 271. PTA Results by MIC on Day 1 Based on Median Nonclinical Ceftobiprole Free-Drug Plasma %T>MIC Targets Associated With *Staphylococcus aureus* Efficacy

Endpoints for PK-PD target	MIC (µg/mL)	Percent probabilities of PK-PD target attainment by ceftobiprole MIC and CLcr group (mL/min)						
		≥ 0 to < 15	≥ 15 to < 30	≥ 30 to < 50	≥ 50 to < 90	≥ 90 to ≤ 150	> 150 to ≤ 240	Clinical trial population[c]
Net bacterial stasis	0.03	100	100	100	100	100	100	100
	0.06	100	100	100	100	100	100	100
	0.12	100	100	100	100	100	100	100
	0.25	100	100	100	100	100	100	100
	0.5	100	100	100	100	100	100	100
	1	100	100	100	100	100	100	100
	2	100	100	100	100	100	100	100
	4	100	>99.9	100	100	>99.9	99.4	>99.9
	8	95.9	93.5	99.4	99.0	93.9	79.9	95.3
	16	26.3	21.2	75.7	72.2	40.3	15.8	46.3
	32	0	0	6.09	7.16	1.33	0.26	3.39
	Overall[d]							
	All isolates	100	>99.9	100	100	>99.9	>99.9	>99.9
	MRSA	100	>99.9	100	100	>99.9	>99.9	>99.9
	MSSA	100	100	100	100	100	100	100
1-$\log_{10}$ CFU reduction from baseline	0.03	100	100	100	100	100	100	100
	0.06	100	100	100	100	100	100	100
	0.12	100	100	100	100	100	100	100
	0.25	100	100	100	100	100	100	100
	0.5	100	100	100	100	100	100	100
	1	100	100	100	100	100	100	100
	2	100	100	100	100	100	100	100
	4	>99.9	99.8	100	100	99.8	98.6	>99.9
	8	92.4	89.3	99.0	98.1	89.5	70.2	91.7
	16	15.8	12.6	65.6	62.3	29.4	10.4	37.4
	32	0	0	3.14	3.89	0.58	0.16	1.55
	Overall[d]							
	All isolates	>99.9	>99.9	100	100	>99.9	>99.9	>99.9
	MRSA	>99.9	>99.9	100	100	>99.9	>99.9	>99.9
	MSSA	100	100	100	100	100	100	100

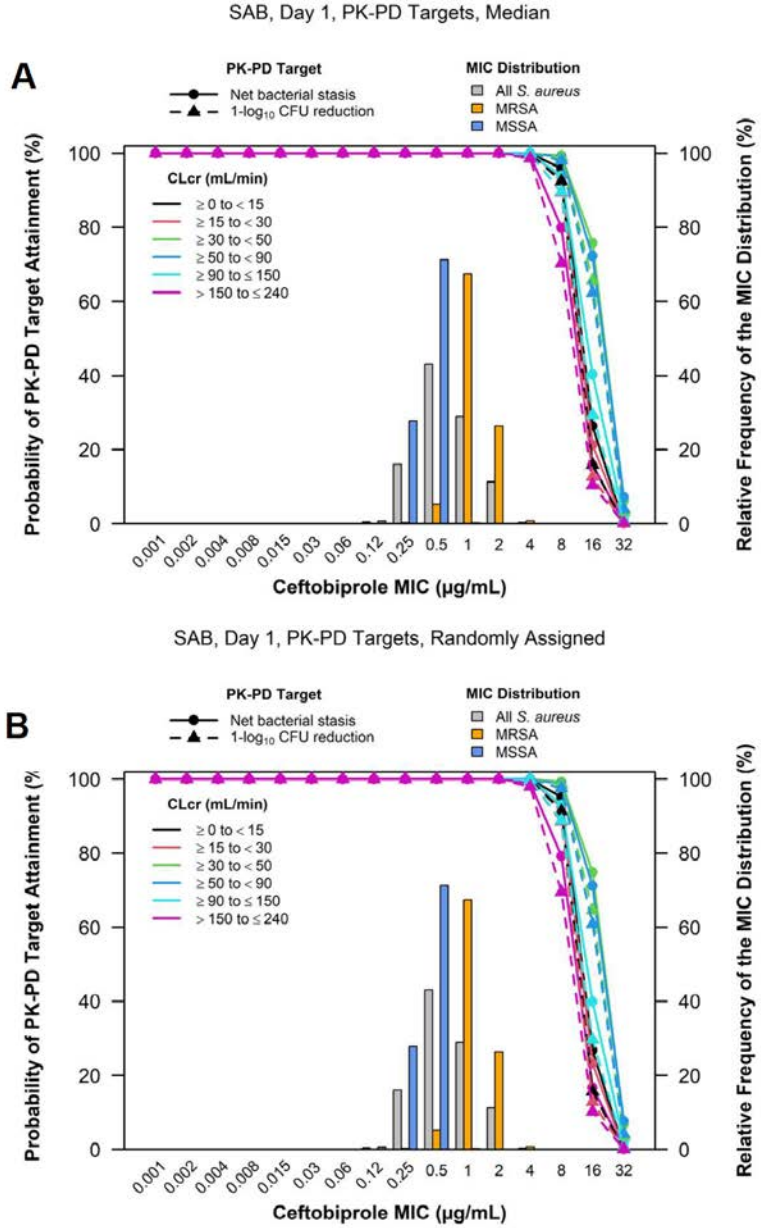
Source: Applicant's PKPD report for SAB, Table 22, page 90

Table 272. PTA Results by MIC on Day 1 Based on Randomly Assigned Nonclinical Ceftobiprole Free-Drug Plasma %T>MIC Targets Associated With *Staphylococcus aureus* Efficacy

Endpoints for PK-PD target	MIC (µg/mL)	Percent probabilities of PK-PD target attainment by ceftobiprole MIC and CLcr group (mL/min)						
		≥ 0 to < 15	≥ 15 to < 30	≥ 30 to < 50	≥ 50 to < 90	≥ 90 to ≤ 150	> 150 to ≤ 240	Clinical trial population[c]
Net bacterial stasis	0.03	100	100	100	100	100	100	100
	0.06	100	100	100	100	100	100	100
	0.12	100	100	100	100	100	100	100
	0.25	100	100	100	100	100	100	100
	0.5	100	100	100	100	100	100	100
	1	100	100	100	100	100	100	100
	2	100	100	100	100	100	100	100
	4	100	>99.9	100	100	>99.9	98.9	99.8
	8	95.1	92.4	99.3	98.7	93.1	79.1	94.6
	16	26.7	23.2	74.8	71.1	39.8	16.7	46.2
	32	0.06	0.03	6.70	7.67	1.85	0.26	3.68
	Overall[d]							
	All isolates	100	>99.9	100	100	>99.9	>99.9	>99.9
	MRSA	100	>99.9	100	100	>99.9	>99.9	>99.9
	MSSA	100	100	100	100	100	100	100
1-$\log_{10}$ CFU reduction from baseline	0.03	100	100	100	100	100	100	100
	0.06	100	100	100	100	100	100	100
	0.12	100	100	100	100	100	100	100
	0.25	100	100	100	100	100	100	100
	0.5	100	100	100	100	100	100	100
	1	100	100	100	100	100	100	100
	2	100	100	100	100	100	100	100
	4	>99.9	99.8	100	100	99.8	97.9	99.7
	8	91.3	88.4	98.5	97.5	88.7	69.5	91.0
	16	15.6	12.8	64.5	60.8	29.6	10.2	36.5
	32	0	0	3.40	4.15	0.49	0.13	1.81
	Overall[d]							
	All isolates	>99.9	>99.9	100	100	>99.9	>99.9	>99.9
	MRSA	>99.9	>99.9	100	100	>99.9	>99.9	>99.9
	MSSA	100	100	100	100	100	100	100

Source: Applicant's PKPD report for SAB, Table 23, page 91

Figure 58. PTA on Day 1 Based on Median and Randomly Assigned Nonclinical Targets of %T>MIC for *Staphylococcus aureus*



Source: Applicant's PKPD report for SAB, Figure 7, page 92

14.5.2.2.3.3. PTA for SAB: Day 10

Table 273. PTA Results by MIC on Day 10 Based on Median Nonclinical Ceftobiprole Free-Drug Plasma %T>MIC Targets Associated With *Staphylococcus aureus* Efficacy

Endpoints for PK-PD target	MIC (µg/mL)	Percent probabilities of PK-PD target attainment by ceftobiprole MIC and CLcr group (mL/min)						
		≥ 0 to < 15	≥ 15 to < 30	≥ 30 to < 50	≥ 50 to < 90	≥ 90 to ≤ 150	> 150 to ≤ 240	Clinical trial population[c]
Net bacterial stasis	0.03	100	100	100	100	100	100	100
	0.06	100	100	100	100	100	100	100
	0.12	100	100	100	100	100	100	100
	0.25	100	100	100	100	100	100	100
	0.5	100	100	100	100	100	100	100
	1	100	100	100	100	100	100	100
	2	100	100	100	100	100	100	100
	4	99.4	99.6	>99.9	>99.9	99.6	99.5	99.7
	8	86.0	85.3	96.2	96.7	84.0	81.2	89.1
	16	51.3	30.6	56.7	57.7	24.9	21.4	38.6
	32	23.6	2.59	8.00	8.03	1.36	0.94	4.61
	Overall[d]							
	All isolates	>99.9	>99.9	>99.9	>99.9	>99.9	>99.9	>99.9
	MRSA	>99.9	>99.9	>99.9	>99.9	>99.9	>99.9	>99.9
	MSSA	100	100	100	100	100	100	100
1-$\log_{10}$ CFU reduction from baseline	0.03	100	100	100	100	100	100	100
	0.06	100	100	100	100	100	100	100
	0.12	100	100	100	100	100	100	100
	0.25	100	100	100	100	100	100	100
	0.5	100	100	100	100	100	100	100
	1	100	100	100	100	100	100	100
	2	>99.9	>99.9	100	100	100	100	100
	4	98.8	99.0	99.8	>99.9	99.0	98.9	99.4
	8	81.7	80.0	93.3	93.8	76.0	72.8	83.3
	16	47.6	24.4	47.3	48.3	18.2	15.2	30.5
	32	21.0	1.91	5.60	5.67	0.87	0.71	3.12
	Overall[d]							
	All isolates	>99.9	>99.9	>99.9	>99.9	>99.9	>99.9	>99.9
	MRSA	>99.9	>99.9	>99.9	>99.9	>99.9	>99.9	>99.9
	MSSA	100	100	100	100	100	100	100

Source: Applicant's PKPD report for SAB, Table 24, page 97

Table 274. PTA Results by MIC on Day 10 Based on Randomly Assigned Nonclinical Ceftobiprole Free-Drug Plasma %T>MIC Targets Associated With *Staphylococcus aureus* Efficacy

Endpoints for PK-PD target	MIC (µg/mL)	Percent probabilities of PK-PD target attainment by ceftobiprole MIC and CLcr group (mL/min)						
		≥ 0 to < 15	≥ 15 to < 30	≥ 30 to < 50	≥ 50 to < 90	≥ 90 to ≤ 150	> 150 to ≤ 240	Clinical trial population[c]
Net bacterial stasis	0.03	100	100	100	100	100	100	100
	0.06	100	100	100	100	100	100	100
	0.12	100	100	100	100	100	100	100
	0.25	100	100	100	100	100	100	100
	0.5	100	100	100	100	100	100	100
	1	100	100	100	100	100	100	100
	2	>99.9	100	100	100	100	100	100
	4	99.3	99.3	>99.9	>99.9	99.3	99.3	99.6
	8	86.0	84.8	95.4	96.1	83.3	80.8	87.7
	16	52.0	31.3	56.7	57.5	25.6	21.9	38.9
	32	23.8	3.24	8.13	8.19	1.46	1.10	5.26
	Overall[d]							
	All isolates	>99.9	>99.9	>99.9	>99.9	>99.9	>99.9	>99.9
	MRSA	>99.9	>99.9	>99.9	>99.9	>99.9	>99.9	>99.9
	MSSA	100	100	100	100	100	100	100
1-$\log_{10}$ CFU reduction from baseline	0.03	100	100	100	100	100	100	100
	0.06	100	100	100	100	100	100	100
	0.12	100	100	100	100	100	100	100
	0.25	100	100	100	100	100	100	100
	0.5	100	100	100	100	100	100	100
	1	100	100	100	100	100	100	100
	2	>99.9	>99.9	100	100	100	100	100
	4	98.5	98.9	99.8	99.9	98.4	98.3	99.1
	8	81.1	79.3	92.4	92.8	74.9	72.3	82.8
	16	47.7	24.5	46.9	47.7	18.6	15.8	30.6
	32	20.8	2.20	5.41	5.51	0.91	0.65	3.26
	Overall[d]							
	All isolates	>99.9	>99.9	>99.9	>99.9	>99.9	>99.9	>99.9
	MRSA	>99.9	>99.9	>99.9	>99.9	>99.9	>99.9	>99.9
	MSSA	100	100	100	100	100	100	100

Source: Applicant's PKPD report for SAB, Table 25, page 98

14.5.2.3. Assessment of End-Stage Renal Disease Dosing Regimen for Adults

For adult subjects with ESRD (on or not on iHD), 250 mg IV q24h is the recommended dosing regimen (for all indications); however, model-based simulations show that the exposure (i.e., Day 1 AUC) may be suboptimal in ESRD subjects (not on iHD) with renal function of 0-15 mL/min when compared to those with normal renal function (defined as 90-150 mL/min) in ABSSSI (Figure 45). Numerically lower model-predicted exposures on Day 1 are also seen with CABP and SAB infection types. As such, an Information Request was communicated to the Applicant to compare ESRD dosing (not on iHD) at q12h vs. q24h dosing frequencies and provide safety assessment for the q12h dosing regimen.

While the q12h dosing may seem reasonable based on Day 1 exposure metrics, the exposures (after multiple-day administrations) on Day 5 for SAB and Day 7 for ABSSSI and CABP are higher than those observed to date in clinical and nonclinical studies (Table 275). Additionally, the Applicant stated that there has been no clinical safety experience at the predicted exposures that would be reached based on the q12h dosing regimen in ESRD subjects.

Despite lower exposures at the proposed dosing regimen at q24h on Day 1, the accumulation observed in simulated ESRD subjects after 5 days of ceftobiprole administrations for the proposed dosing regimen led to exposures in a similar range to that observed in simulated subjects with normal renal function. Furthermore, the PTA results (representative PTA results for SAB based on the median target for 1-log kill is provided in Table 276) demonstrate that the q24h still provide sufficient exposure (>90% probability of target attainment) across SAB, ABSSSI, and CABP infection types (refer to the Applicant's response to Information Request for additional PTA results).

Table 275. Summary of Ceftobiprole Exposures (Model-predicted)

Indication and variable	Day 1			Day 5 (SAB) or Day 7 (ABSSSI and CABP)		
	≥ 0 to < 15 mL/min		≥ 90 to ≤ 150 mL/min	≥ 0 to < 15 mL/min		≥ 90 to ≤ 150 mL/min
	250 mg q12h (ABSSSI or CABP) q12h/q24h (SAB)	250 mg q24h/q24h	500 mg q6h/q8h	250 mg q12h/q24h	250 mg q24h/q24h	500 mg q6h/q8h
SAB[a]						
Mean AUC	191	120	209	498	253	237
Mean C_{max}	16.7	10.9	20.2	32.2	19.1	20.2
ABSSSI						
Mean AUC	194	121	159	538	271	174
Mean C_{max}	15.9	10.7	17.4	31.7	19.7	17.7
CABP						
Mean AUC	253	158	199	680	343	215
Mean C_{max}	17.9	12.0	18.8	34.0	21.2	19.0

Note: All dosing regimens were administered using a 2-hour infusion.

[a] In this document, the ceftobiprole dosing regimen on Days 1–8 and Day 9 onwards that was administered to simulated patients with SAB was represented as '500 mg q6h/q8h' for the CLcr ≥ 90 to ≤ 150 mL/min group. For the CLcr ≥ 0 to < 15 mL/min group, ceftobiprole 250 mg IV q12h on Days 1–8 followed by 250 mg IV q24h on Day 9 onwards was represented as '250 mg q12h/q24h' while ceftobiprole 250 mg IV q24h on Days 1–8 followed by 250 mg IV q24h on Day 9 onwards was represented as '250 mg q24h/q24h'.

Source: Applicant's response to Information Request [dated 23JANUARY2024; *link*], Table 2, page 10
Note: 667 mg of ceftobiprole medocaril sodium is equivalent to 500 mg of ceftobiprole. Dosing adjustments for each indication are based on renal function

Table 276. PTA for *Staphylococcus aureus* Bacteremia in ESRD Adult Subjects

Method	Target	MIC µg/mL	Percentage probabilities of PK/PD target attainment by day											
			Day 1			Day 5			Day 10			Day 15		
			0 to < 15[a] q12h/q24h	0 to < 15[a] q24h/q24h	≥ 90 to ≤ 150[a] 500 mg q6h/q8h	0 to < 15[a] q12h/q24h	0 to < 15[a] q24h/q24h	≥ 90 to ≤ 150[a] 500 mg q6h/q8h	0 to < 15[a] q12h/q24h	0 to < 15[a] q24h/q24h	90 to 150[a] 500 mg q6h/q8h	0 to < 15[a] q12h/q24h	0 to < 15[a] q24h/q24h	90 to 150[a] 500 mg q6h/q8h
Median	1-$\log_{10}$	0.25	100	100	100	100	100	100	100	100	100	100	100	100
		0.5	100	100	100	100	100	100	100	100	100	100	100	100
		1	100	100	100	100	100	100	100	100	100	100	100	100
		2	100	> 99.9	100	100	> 99.9	100	> 99.9	> 99.9	100	> 99.9	> 99.9	> 99.9
		4	**> 99.9**	**97.2**	**99.8**	**> 99.9**	**98.7**	**99.8**	**98.8**	**98.7**	**99.0**	**98.8**	**98.8**	**99.0**
		8	92.4	45.1	89.5	98.7	80.3	91.3	81.7	80.1	76.0	80.5	80.5	76.0
		16	15.8	0.32	29.4	79.6	39.0	39.3	47.6	41.2	18.2	40.9	40.7	18.1
		32	0	0	0.58	38.5	9.65	3.72	21.0	14.2	0.87	15.8	14.8	0.91
		All SA	> 99.9	> 99.9	> 99.9	> 99.9	> 99.9	> 99.9	> 99.9	> 99.9	> 99.9	> 99.9	> 99.9	> 99.9
		MRSA	> 99.9	> 99.9	> 99.9	> 99.9	> 99.9	> 99.9	> 99.9	> 99.9	> 99.9	> 99.9	> 99.9	> 99.9
		MSSA	100	100	100	100	100	100	100	100	100	100	100	100

Source: Applicant's response to Information Request [dated 23JANUARY2024; *link*], adapted from Table 9, page 61
Note: 667 mg of ceftobiprole medocaril sodium is equivalent to 500 mg of ceftobiprole. Dosing adjustments for each indication are based on renal function

Reviewer Comments

In the setting of iHD, the exact exposures are difficult to predict due to a lack of dedicated phase 1 study data to confirm the extraction ratio. As such, no modeling and simulations can be conducted with the extraction ratio from iHD to predict the concentrations over time. If a conservative measure of assuming 100% of ceftobiprole is removed during iHD sessions, the ceftobiprole administered post-dialysis would have been similar to the exposures derived on Day 1 as shown in Table 275 . Moreover, these model-predicted exposures achieved similar probability target attainments values of >90%. In general, the ESRD dosing of 250 mg IV q24h in the setting of iHD (administered post-dialysis) is acceptable. Refer to Section II.8.1.2 for discussions.

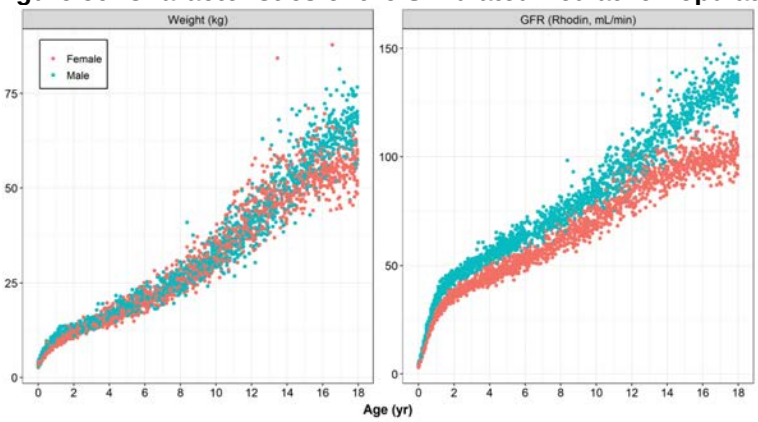
14.5.2.4. Pediatrics CABP PK/PD Analysis

The Applicant performed Monte Carlo simulations and dose optimization with the original pediatric only PopPK model (Report 00616-3). In this review, the emphasis is placed upon the optimized dosing regimen for pediatric subjects of 3 months to <18 years using the revised pediatric PopPK model. To perform Monte Carlo simulation in pediatric subjects, a dataset of 5,000 virtual subjects aged <18 years with appropriate body size and renal function was created. The characteristics of the virtual subjects are illustrated in Figure 59.

To evaluate ceftobiprole dosing regimens in pediatric age groups, including those of 2 year of age or older with renal impairment, the 24-hour AUC and C_{max} from the healthy adults serve as the reference exposure (receiving 500 mg q8h for 5 days; Study CSI-1004). For detailed methodology and results of the initial dose selection and optimization (i.e., exposure matching), refer to the Applicant's PopPK Report 00616-3.

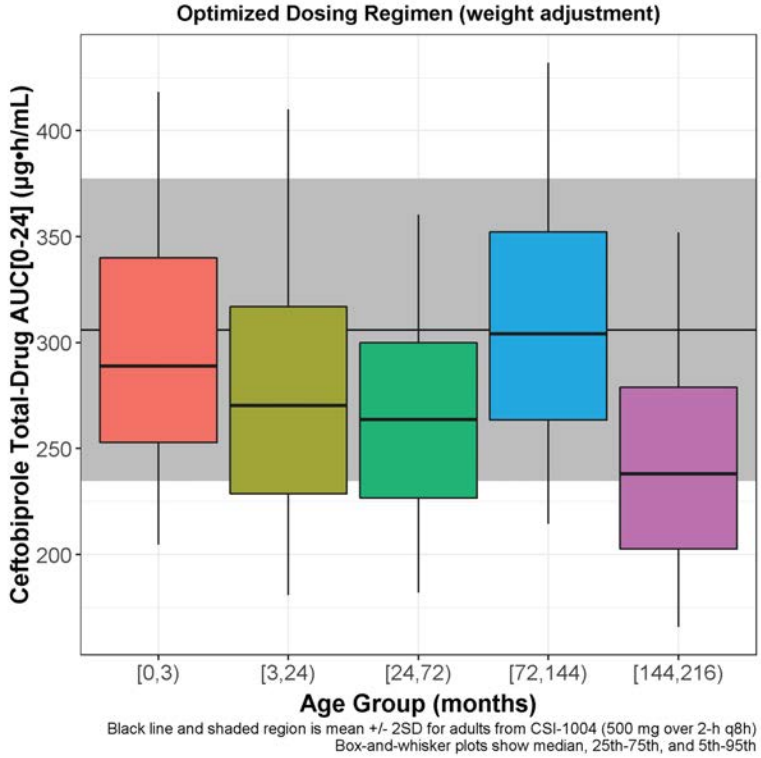
Model-based predictions of 24-hour AUC and C_{max} of ceftobiprole according to the weight-based dosing regimens (proposed by the Applicant) by age group are shown in Figure 60 and Figure 61 and are summarized in Table 277. Target attainment based on predicted exposures are summarized in Table 278. Because the submission includes study data for pediatric subjects under 3 months of age, this subgroup was evaluated and included in the technical reports by the Applicant. The analysis results of this pediatric subgroup are irrelevant to the proposed pediatric indication of 3 month to <18 years of age.

Figure 59. Characteristics of the Simulated Pediatric Population



Source: Applicant's revised PopPK report 00616-3A, Figure 11, page 52

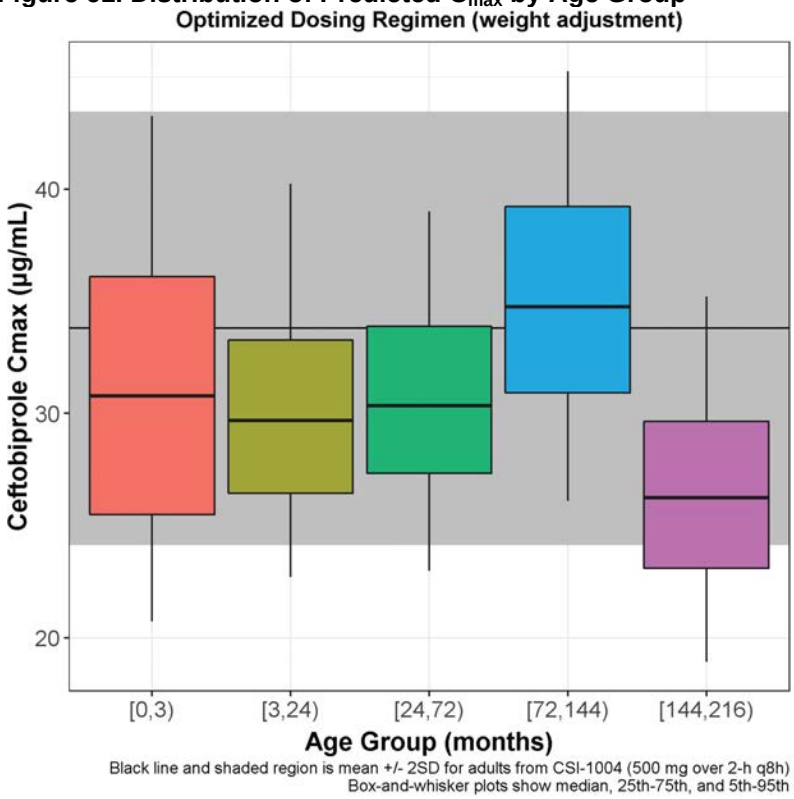
Figure 60. Distribution of Predicted 24-Hour AUC by Age Group



Source: Applicant's revised PopPK report 00616-3A, Figure 8, page 27

Note: 667 mg of ceftobiprole medocaril sodium is equivalent to 500 mg of ceftobiprole. For pediatric patients: 13.3 mg/kg is equivalent to 10 mg/kg of ceftobiprole. 26.7 mg/kg of ceftobiprole medocaril sodium is equivalent to 20 mg/kg of ceftobiprole. Dosing adjustments for each indication are based on renal function

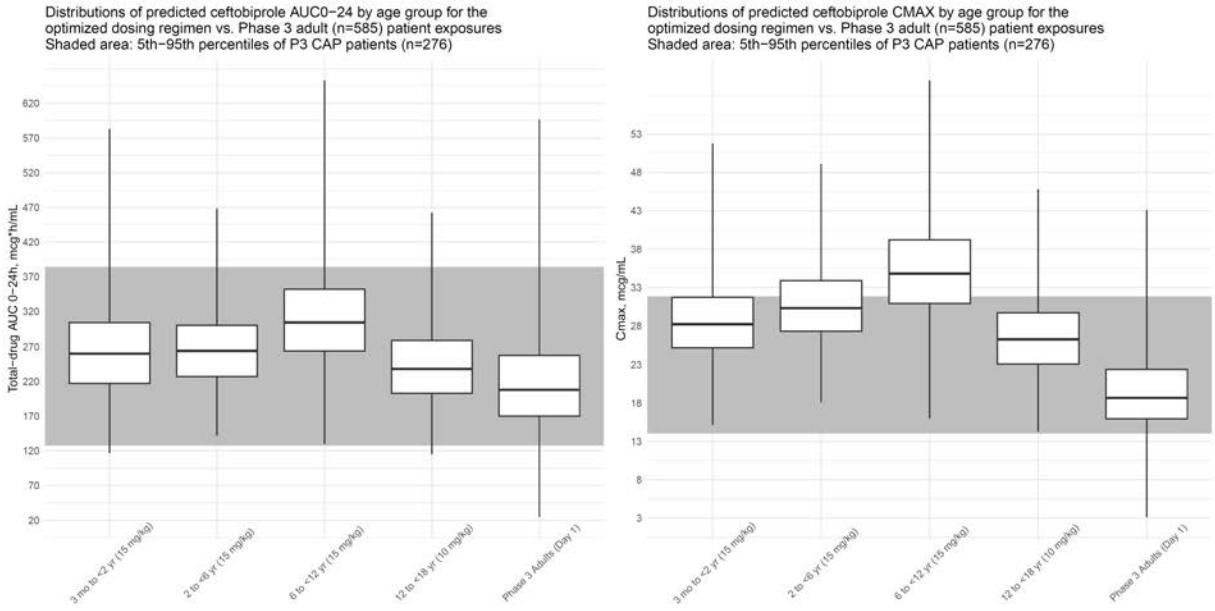
Figure 61. Distribution of Predicted C_{max} by Age Group



Source: Applicant's revised PopPK report 00616-3A, Figure 9, page 28

Note: 667 mg of ceftobiprole medocaril sodium is equivalent to 500 mg of ceftobiprole. For pediatric patients: 13.3 mg/kg is equivalent to 10 mg/kg of ceftobiprole. 26.7 mg/kg of ceftobiprole medocaril sodium is equivalent to 20 mg/kg of ceftobiprole. Dosing adjustments for each indication are based on renal function

Figure 62. Distribution of Predicted AUC and C_{max} by Age Group Compared Against Adult Subject Exposures



Source: reviewer's analysis based on Applicant's submitted dataset
Grey shaded area, 5th to 95th percentiles of the phase3 CAP adult subjects based on Bayesian posterior predictions; boxplot, median and 25th to 75th percentiles; whiskers, range within 1.5 * interquartile range of the distribution; Phase 3 Adults, exposure combining all Phase 3 subjects with ABSSSI and CAP

Table 277. Summary Statistics of Predicted Exposures by Age Group

Age Group	Dosing regimen	Mean	SD	Median	Min	25th	75th	Max
			AUC_{0-24} (µg•h/mL)					
Birth to <3 mo	15 mg/kg q12h[a]	298	66.4	289	141	253	340	638
3 mo to <2 yr	15 mg/kg q8h	278	69.9	270	129	229	317	624
2 to <6 yr	15 mg/kg q8h	266	55.3	264	142	227	300	468
6 to <12 yr	15 mg/kg q8h	312	68.7	304	130	264	352	653
12 to <18 yr	10 mg/kg q8h	245	56.9	238	115	203	279	462
Adults[b]	500 mg q8h	306	35.7	306	228	-	-	390
			C_{max} (µg/mL)					
Birth to <3 mo	15 mg/kg q12h[a]	31.1	7.05	30.8	13.9	25.5	36.1	54.6
3 mo to <2 yr	15 mg/kg q8h	30.3	5.32	29.7	15.4	26.5	33.3	53.4
2 to <6 yr	15 mg/kg q8h	30.8	4.98	30.3	18.1	27.3	33.9	49.1
6 to <12 yr	15 mg/kg q8h	35.2	5.94	34.8	16	30.9	39.2	60
12 to <18 yr	10 mg/kg q8h	26.6	4.92	26.3	14.3	23.1	29.7	45.8
Adults[b]	500 mg q8h	33.0	4.83	31.5	23.8	-	-	44.4

Source: Applicant's revised PopPK report 00616-3A, Table 4, page 29
All doses are infused over 2 hours; maximum dose was 500 mg regardless of weight.
[a]Not relevant for this NDA submission

Note: 667 mg of ceftobiprole medocaril sodium is equivalent to 500 mg of ceftobiprole. For pediatric patients: 13.3 mg/kg is equivalent to 10 mg/kg of ceftobiprole. 26.7 mg/kg of ceftobiprole medocaril sodium is equivalent to 20 mg/kg of ceftobiprole. Dosing adjustments for each indication are based on renal function

Table 278. Predicted PK/PD Target Attainment by Age Group

Target (%*f*T>MIC)	Birth to <3 mo 15 mg/kg q12h[a]	3 mo to <2 yr 15 mg/kg q8h	2 to <6 yr 15 mg/kg q8h	6 to <12 yr 15 mg/kg q8h	12 to 17 yr 10 mg/kg q8h
30%	100	100	100	100	100
40%	100	98.2	97.8	99.1	98.4
50%	98.5	88.3	85.1	93	87.2
60%	93.8	70.6	60.4	76.8	63.8

Source: Applicant's revised PopPK report 00616-3A, Table 5, page 30
All doses are infused over 2 hours; maximum dose was 500 mg regardless of weight;
[a]Not relevant for this NDA submission
Note: 667 mg of ceftobiprole medocaril sodium is equivalent to 500 mg of ceftobiprole. For pediatric patients: 13.3 mg/kg is equivalent to 10 mg/kg of ceftobiprole. 26.7 mg/kg of ceftobiprole medocaril sodium is equivalent to 20 mg/kg of ceftobiprole. Dosing adjustments for each indication are based on renal function

Reviewer Comments

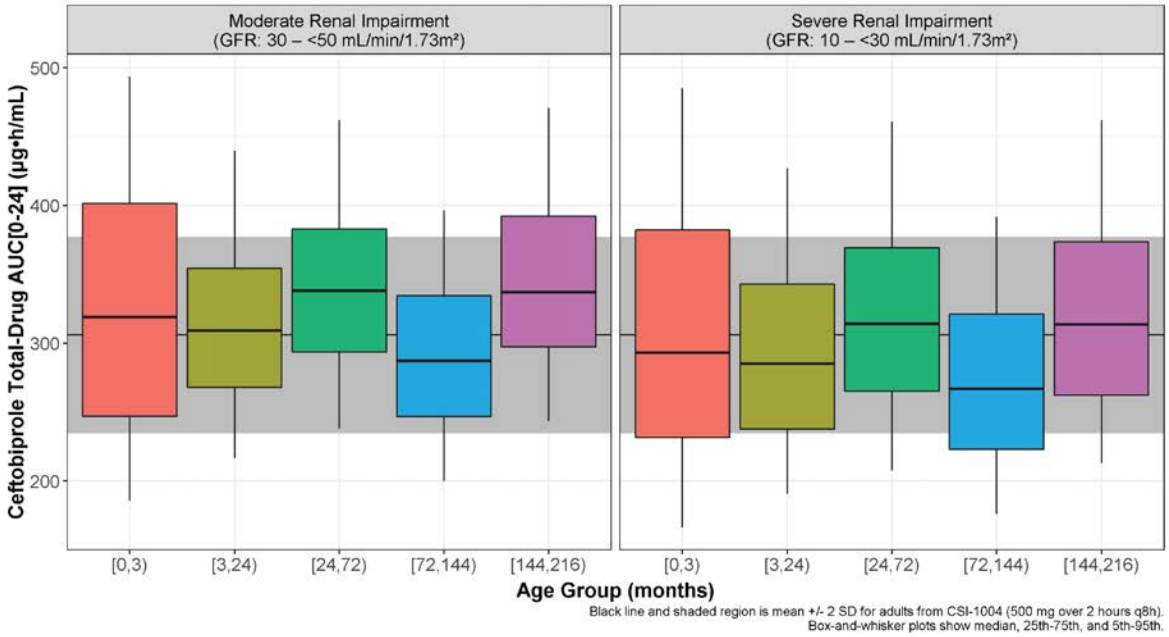
Based on model-predicted exposures, the AUC and C_{max} of the pediatric age subgroups generally align with those from the healthy adult subjects from Study CSI-1004. Because the healthy adult exposures are known to be higher than adult subjects from the phase 3 studies, an additional plot was generated by the reviewer to compare the exposures from pediatric subgroups to adult subjects. As shown in Figure 62, the AUCs of the pediatric subgroups generally fall within those of the adult subjects with CABP from phase 3. While the C_{max} may be slightly higher for the 2 to <6-year-old and 6 to <12-year-old groups, the C_{max} is contained within the healthy adult exposures for safety. The exposures in adolescent subjects (i.e., 12 to <18 year-olds) are numerically lower when compared to those in healthy adults (Figure 60 and Figure 61); however, most adolescents received 500 mg dosages based on body weight, and the exposures generally align with those in the adult subjects.

Overall, the predicted exposures in pediatric subgroups are comparable to those in adult subjects (from Phase 3 studies) while not exceeding those in healthy adults (i.e., safety consideration). Furthermore, the PTA results demonstrate appropriate target attainments across age groups, indicating that the dosing recommendations are acceptable for pediatric age groups.

14.5.2.4.1. Moderate or Severe Renal Impairment

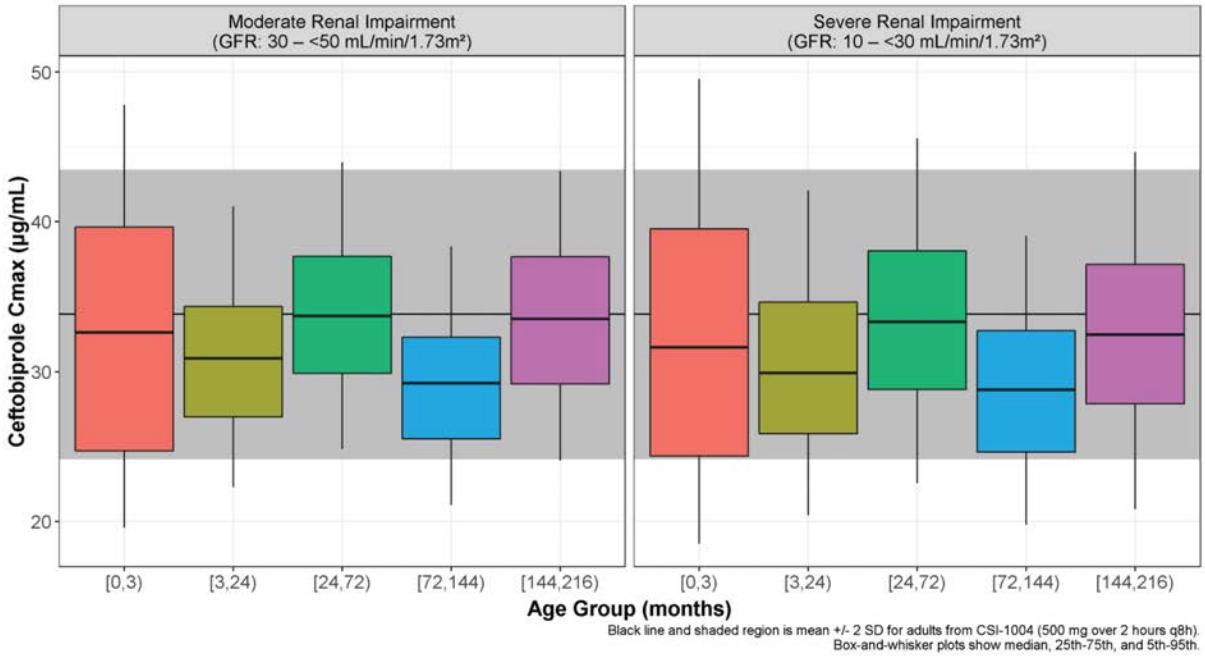
Dosing recommendations in renally impairment pediatric subjects was previously assessed and proposed with the original pediatrics only PopPK model. After modeling refitting with the pooled PK data, the Applicant re-evaluated the dosing regimen. Overall, the exposures of the pediatric renal impairment subgroups are predicted to be mostly within the reference healthy adults exposure range (Figure 63 and Figure 64), and the dosing regimens are supported by the PTA results as shown in Table 281. Of note, the dosing recommendation for adolescents with severe RI has been modified to be 7.5 mg q12h (up to 250 mg). This is further discussed in Section 14.5.2.5.

Figure 63. Distribution of Predicted 24-hour AUC by Age Group in Renal Impairment



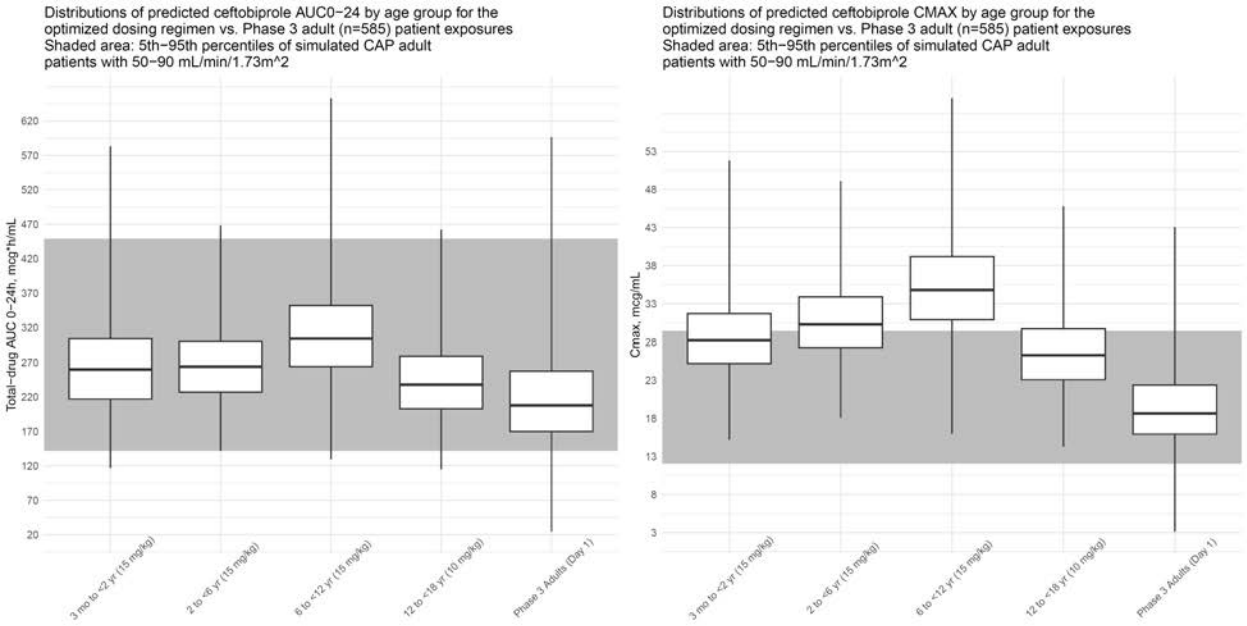
Source: Applicant's revised PopPK report 00616-3A, Figure 12, page 36
Note: 667 mg of ceftobiprole medocaril sodium is equivalent to 500 mg of ceftobiprole. For pediatric patients: 13.3 mg/kg is equivalent to 10 mg/kg of ceftobiprole. 26.7 mg/kg of ceftobiprole medocaril sodium is equivalent to 20 mg/kg of ceftobiprole. Dosing adjustments for each indication are based on renal function

Figure 64. Distribution of Predicted C_{max} by Age Group in Renal Impairment



Source: Applicant's revised PopPK report 00616-3A, Figure 13, page 37
Note: 667 mg of ceftobiprole medocaril sodium is equivalent to 500 mg of ceftobiprole. For pediatric patients: 13.3 mg/kg is equivalent to 10 mg/kg of ceftobiprole. 26.7 mg/kg of ceftobiprole medocaril sodium is equivalent to 20 mg/kg of ceftobiprole. Dosing adjustments for each indication are based on renal function

Figure 65. Distribution of Predicted AUC and C_{max} by Age Group Compared Against Exposures in Adult Subject With Mild Renal Impairment



Source: reviewer's analysis based on Applicant's submitted dataset
Grey shaded area, 5th to 95th percentiles of the Phase 3 CAP adult subjects with mild renal impairment (50-90 mL/min/1.73 m^2) based on Bayesian posterior predictions; boxplot, median and 25th to 75th percentiles; whiskers, range within 1.5 * interquartile range of the distribution; Phase 3 Adults, exposure combining all Phase 3 subjects with ABSSSI and CAP

Table 279. Summary Statistics of Ceftobiprole in Subjects With Moderate Renal Impairment

Age Group	Dosing regimen	Mean	SD	Median	Min	25th	75th	Max
			AUC_{0-24} (µg•h/mL)					
Birth to <3 mo	15 mg/kg q12h[a]	328	99.3	319	117	247	402	648
3 mo to <2 yr	10 mg/kg q12h	315	67.4	309	113	268	354	612
2 to <6 yr	10 mg/kg q12h	341	67.0	338	193	294	383	610
6 to <12 yr	7.5 mg/kg q12h	293	61	287	142	247	334	545
12 to <18 yr	7.5 mg/kg q12h	347	68.6	337	195	297	392	602
			C_{max} (µg/mL)					
Birth to <3 mo	15 mg/kg q12h[a]	32.7	9.14	32.6	13.8	24.7	39.6	59.9
3 mo to <2 yr	10 mg/kg q12h	31	5.7	30.9	14.7	27	34.3	53.4
2 to <6 yr	10 mg/kg q12h	34	5.81	33.7	20.2	29.9	37.7	55.1
6 to <12 yr	7.5 mg/kg q12h	29.2	5.15	29.2	14.6	25.5	32.3	49.5
12 to <18 yr	7.5 mg/kg q12h	33.6	5.96	33.5	18.4	29.2	37.7	52.7

Source: Applicant's revised PopPK report 00616-3A, Table 9, page 38
All doses are infused over 2 hours; maximum dose was 500 mg regardless of weight; grey shaded area highlights the modified regimen after refitting the model to pooled data
[a]Not relevant for this NDA submission
Note: 667 mg of ceftobiprole medocaril sodium is equivalent to 500 mg of ceftobiprole. For pediatric patients: 13.3 mg/kg is equivalent to 10 mg/kg of ceftobiprole. 26.7 mg/kg of ceftobiprole medocaril sodium is equivalent to 20 mg/kg of ceftobiprole. Dosing adjustments for each indication are based on renal function

Table 280. Summary Statistics of Ceftobiprole in Subjects With Severe Renal Impairment

Age Group	Dosing regimen	Mean	SD	Median	Min	25th	75th	Max
			AUC_{0-24} (µg•h/mL)					
Birth to <3 mo	15 mg/kg q24h[a]	308	101	293	107	232	382	654
3 mo to <2 yr	10 mg/kg q24h	295	74.9	285	95	238	343	582
2 to <6 yr	10 mg/kg q24h	321	78.0	314	165	265	369	636
6 to <12 yr	7.5 mg/kg q24h	275	67.7	267	126	223	321	522
12 to <18 yr	7.5 mg/kg q24h	322	76.8	314	164	262	374	562
			C_{max} (µg/mL)					
Birth to <3 mo	15 mg/kg q24h[a]	32.4	9.78	31.6	11.8	24.4	39.5	58.7
3 mo to <2 yr	10 mg/kg q24h	30.3	6.45	29.9	12.1	25.9	34.6	50.6
2 to <6 yr	10 mg/kg q24h	33.6	6.85	33.3	17.3	28.8	38	56.5
6 to <12 yr	7.5 mg/kg q24h	28.9	6.00	28.8	12.6	24.6	32.7	48.4
12 to <18 yr	7.5 mg/kg q24h	32.5	6.95	32.4	15.5	27.9	37.1	52.4

Source: Applicant's revised PopPK report 00616-3A, Table 10, page 39
All doses are infused over 2 hours; maximum dose was 500 mg regardless of weight; grey shaded area highlights the modified regimen after refitting the model to pooled data
[a]Not relevant for this NDA submission
Note: 667 mg of ceftobiprole medocaril sodium is equivalent to 500 mg of ceftobiprole. For pediatric patients: 13.3 mg/kg is equivalent to 10 mg/kg of ceftobiprole. 26.7 mg/kg of ceftobiprole medocaril sodium is equivalent to 20 mg/kg of ceftobiprole. Dosing adjustments for each indication are based on renal function

Table 281. Predicted PK/PD Target Attainment by Age Group in Subjects With Renal Impairment

Target (%*f*T>MIC)	Birth to <3 mo	3 mo to <2 yr	2 to <6 yr	6 to <12 yr	12 to <18 yr
	Moderate Renal Impairment (GFR: 30 to <50 mL/min/1.73 m^2)				
	15 mg/kg q12h[a]	10 mg/kg q12h	10 mg/kg q12h	7.5 mg/kg q12h	7.5 mg/kg q12h
30%	100	100	100	100	100
40%	99.9	99.9	100	99.9	100
50%	98.7	99.5	99.9	98.9	100
60%	93.8	97.6	98.0	95.6	99.3
	Severe Renal Impairment (GFR: 10 to <30 mL/min/1.73 m^2)				
	15 mg/kg q24h[a]	10 mg/kg q24h	10 mg/kg q24h	7.5 mg/kg q24h	7.5 mg/kg q24h
30%	100	99.9	100	100	100
40%	99.2	99.6	100	99.5	100
50%	94.3	97.2	97.7	95.8	99.3
60%	87.2	91.0	92.4	86.9	96.0

Source: Applicant's revised PopPK report 00616-3A, Table 11, page 40
All doses are infused over 2 hours; maximum dose was 500 mg regardless of weight;
[a]Not relevant for this NDA submission

Note: 667 mg of ceftobiprole medocaril sodium is equivalent to 500 mg of ceftobiprole. For pediatric patients: 13.3 mg/kg is equivalent to 10 mg/kg of ceftobiprole. 26.7 mg/kg of ceftobiprole medocaril sodium is equivalent to 20 mg/kg of ceftobiprole. Dosing adjustments for each indication are based on renal function

Reviewer Comments

While the C_{max} in Figure 65 may seem elevated in pediatric subgroups, the C_{max} across groups are comparable to those in healthy adult subjects (Figure 63 and Figure 64). The healthy adult exposure serves as the conservative reference exposure as they are higher than those who are infected (i.e., subjects in phase 3 studies).

14.5.2.5. Assessment of Severe Renal Impairment Dosing Regimen for Adolescents

Based on the submitted PK/PD report for pediatric subjects for the CABP indication (Report 00616-3), a dose of 7.5 mg/kg q24h (up to 500 mg) was recommended for adolescents 12 to <18 years of age; however, the Applicant proposes the same weight-based dosing at q12h dosing frequency (i.e., 7.5 mg/kg q12h, up to 250 mg) in the severe RI category. As such, an Information Request (dated 5 FEBRUARY 2024; link) was communicated to the Applicant. Briefly, the Applicant stated that the decision to modify from q24h to q12h was to align with adult dosing regimen for severe RI through interactions with the European Health Authorities. Additionally, the Applicant provided further simulations to support the q12h dosing regimen in this population as summarized in Table 282. At a dosing frequency of q12h (capped at 250 mg per dose), the exposures based on AUC would be slightly higher and the C_{max} slightly lower in adolescent subjects with severe RI (AUC = 259 µg*h/mL; C_{max} = 20.7 µg/mL) than the exposures predicted in subjects with q24h dosing frequency (AUC = 240 µg*h/mL; C_{max} = 24.6 µg/mL). Overall, the change in dosing frequency results in an improvement in PTA results.

Table 282. Summary of Predicted Ceftobiprole AUC and C_{max} for Q24H and Q12H Dosing Interval for Adolescents With Severe Renal Impairment

Age group	Dosing regimen	CrCL	C_{max} (µg/mL)	Daily AUC (h.µg/mL)	Probability of PK/PD target attainment (MIC = 4 µg/mL)			
					30%	40%	50%	60%
12 to < 18 years	7.5 mg/kg q24h (max 500 mg)	10 – 30	24.6	240	1	0.999	0.977	0.888
12 to < 18 years	7.5 mg/kg q12h (max 250 mg)	10 – 30	20.7	259	1	1	1	0.996
12 to < 18 years	15 mg/kg q8h (max 500 mg)	≥ 50	24.3	240	1	0.985	0.894	0.7

Note: All doses infused over 2 hours. The maximum allowable dose to be administered was 500 mg q24h or 250 mg q12h regardless of patient's weight. All values are arithmetic means.

Source: Applicant's response to Information Request [dated 5FEBRUARY2024; link], Table 1, page 4

Note: 667 mg of ceftobiprole medocaril sodium is equivalent to 500 mg of ceftobiprole. For pediatric patients: 13.3 mg/kg is equivalent to 10 mg/kg of ceftobiprole. 26.7 mg/kg of ceftobiprole medocaril sodium is equivalent to 20 mg/kg of ceftobiprole. Dosing adjustments for each indication are based on renal function

Reviewer's Comments

Considering an increase in dosing frequency, the PTA is expected to be similar or improved as shown in results above. Because the ceftobiprole dose is capped at 250 mg for the q12h dosing frequency (as opposed to 500 mg q24h), this dosing strategy likely will optimize the PK/PD target of %T>MIC given that the 250 mg single dose leads to an effective exposure for respective pathogens. Overall, the proposed 7.5 mg/kg q12h dosing for adolescents with severe RI is acceptable.

14.6. Pharmacogenetics

NA

15. Study/Trial Design

Not applicable. Please refer to Section 6

16. Efficacy

Not applicable. Please refer to Section 6.

17. Clinical Safety

17.1. Phase 1 Studies

The Applicant submitted eighteen adult phase 1 and two pediatric phase 1 studies for ceftobiprole. The population of these studies include healthy subjects, subjects on hemodialysis, subjects with impaired renal function and end-stage renal disease, morbidly obese subjects, subjects who underwent elective hip replacement surgery, and subjects who were hospitalized in intensive or intermediate care units. These studies covered a dose range of 125 mg to 1000 mg.

There were no deaths in the phase 1 healthy adult studies. However, there were two adult subjects in the intensive care unit phase 1 studies who died due to the unrelated adverse events (AEs) of septic shock and intracranial hemorrhage. SAEs were reported for eight subjects (none in healthy adults). The only SAE which was considered related to the study drug was acute kidney injury. The most common AEs experienced in this population were nausea (29.6%), taste disorder (21%), headache (16.6%), and vomiting (11.2%). Additional AEs that occurred in >2 % of the subjects include dysgeusia, infusion site pain, diarrhea, hypotension, abdominal pain, nasopharyngitis, feeling hot, phlebitis, pyrexia, constipation, dizziness, fatigue, and injection site pain. The AEs experienced in phase 1 studies were similar to the AEs seen in the subsequent phase 3 studies. There are no significant safety issues or concerns based on the phase 1 data.

The pediatric phase 1 studies BPR-PIP-001 and CSI-1006 were multicenter, open-label, single-dose, add-on studies of ceftobiprole in pediatric subjects undergoing treatment with IV antibacterial drugs with the aim of evaluating the single-dose PK and safety of ceftobiprole. Trial BPR-PIP-001 included 15 neonates and infants aged up to 3 months; 6 treatment-emergent adverse events (TEAEs) occurred in 6 subjects and only one TEAE of diaper dermatitis occurred in more than one subject. Neither the TEAEs nor the two SAEs of cerebral infarction and diaphragmatic hernia were considered to be related to the study drug. Study CSI-1006 included 64 subjects aged 3 months to less than 18 years. Eight subjects experienced 14 SAEs, none of which were considered treatment-related by the investigator. TEAEs were reported in 48.4% of subjects and vomiting was the most common (9.4%). TEAEs of vomiting, diaper dermatitis, pruritis, headache, increased eosinophil count, diarrhea, catheter-related site reaction, urine crystals, increased alanine aminotransferase (125 U/L), and increased aspartate aminotransferase (121 U/L) were considered potentially related to ceftobiprole; the latter two laboratory-based TEAEs occurred in the same subject. No deaths were reported and no subjects discontinued either Study due to a TEAE.

17.2. *Staphylococcus aureus* Bacteremia, Trial BPR-CS-009

The full list of TEAEs by either grouped queries created by the FDA reviewer or Food and Drug Administration Medical Dictionary for Regulatory Activities queries (FMQs) are noted below. For selected AESI, a grouped query was created instead of using the narrow FMQ or in instances where an FMQ was not available.

Table 283. Grouped Queries by Preferred Term, Safety Population, Trial BPR-CS-009

	Ceftobiprole	Daptomycin
Grouped Query **Preferred Term**	**N=191** **n (%)**	**N=198** **n (%)**
Anemia [GQ]	22 (11.5)	26 (13.1)
Anemia	21 (11.0)	24 (12.1)
Hypochromic anemia	1 (0.5)	0
Hemoglobin decreased	0	1 (0.5)
Normochromic normocytic anemia	0	2 (1.0)

Reference ID: 5357793

	Ceftobiprole	Daptomycin
Grouped Query **Preferred Term**	**N=191** **n (%)**	**N=198** **n (%)**
Bacterial Infection [FMQ]	22 (11.5)	33 (16.7)
Pyelonephritis acute	3 (1.6)	0
Cellulitis	2 (1.0)	1 (0.5)
Endocarditis staphylococcal	2 (1.0)	6 (3.0)
Abdominal abscess	1 (0.5)	3 (1.5)
Arthritis bacterial	1 (0.5)	1 (0.5)
Bacteremia	1 (0.5)	1 (0.5)
Bacterial infection	1 (0.5)	0
Cholecystitis chronic	1 (0.5)	0
Endotoxemia	1 (0.5)	0
Escherichia infection	1 (0.5)	0
Gangrene	1 (0.5)	1 (0.5)
Lung abscess	1 (0.5)	0
Pneumonia pseudomonal	1 (0.5)	0
Pneumonia staphylococcal	1 (0.5)	1 (0.5)
Pseudomonas infection	1 (0.5)	0
Psoas abscess	1 (0.5)	2 (1.0)
Sepsis	1 (0.5)	1 (0.5)
Skin bacterial infection	1 (0.5)	0
Staphylococcal bacteremia	1 (0.5)	3 (1.5)
Subcutaneous abscess	1 (0.5)	0
Urinary tract infection	1 (0.5)	3 (1.5)
Urosepsis	1 (0.5)	1 (0.5)
Wound infection	1 (0.5)	0
Abscess limb	0	3 (1.5)
Bacterial sepsis	0	1 (0.5)
Catheter site infection	0	1 (0.5)
Enterobacter bacteremia	0	1 (0.5)
Escherichia bacteremia	0	1 (0.5)
Extradural abscess	0	1 (0.5)
Genitourinary tract infection	0	1 (0.5)
Infected gouty tophus	0	1 (0.5)
Muscle abscess	0	1 (0.5)
Pancreatic abscess	0	1 (0.5)
Postoperative wound infection	0	1 (0.5)
Pseudomonal bacteremia	0	1 (0.5)
Pyelonephritis	0	1 (0.5)
Renal abscess	0	1 (0.5)
Superinfection bacterial	0	2 (1.0)
Nausea [FMQ]	20 (10.5)	8 (4.0)
Nausea	20 (10.5)	8 (4.0)
Hypokalemia [GQ]	17 (8.9)	5 (2.5)
Blood potassium decreased	17 (8.9)	5 (2.5)
Pneumonia [FMQ]	16 (8.4)	5 (2.5)
Pneumonia	11 (5.8)	3 (1.5)
Infectious pleural effusion	2 (1.0)	0
Pneumonia aspiration	2 (1.0)	0
Lung abscess	1 (0.5)	0
Pneumonia pseudomonal	1 (0.5)	0
Pneumonia staphylococcal	1 (0.5)	1 (0.5)
Pneumonia viral	1 (0.5)	1 (0.5)

	Ceftobiprole	Daptomycin
Grouped Query **Preferred Term**	**N=191** **n (%)**	**N=198** **n (%)**
Vomiting [FMQ]	16 (8.4)	4 (2.0)
Vomiting	16 (8.4)	4 (2.0)
Liver enzyme increased [GQ]	15 (7.9)	20 (10.1)
Gamma-glutamyltransferase increased	12 (6.3)	15 (7.6)
Alanine aminotransferase increased	5 (2.6)	6 (3.0)
Aspartate aminotransferase increased	5 (2.6)	5 (2.5)
Blood alkaline phosphatase increased	1 (0.5)	2 (1.0)
Blood bilirubin increased	1 (0.5)	0
Hyperbilirubinemia	0	1 (0.5)
Diarrhea [FMQ]	13 (6.8)	5 (2.5)
Diarrhea	13 (6.8)	5 (2.5)
Renal impairment [GQ]	13 (6.8)	11 (5.6)
Blood creatinine increased	5 (2.6)	4 (2.0)
Creatinine renal clearance decreased	4 (2.1)	5 (2.5)
Acute kidney injury	3 (1.6)	2 (1.0)
Renal impairment	3 (1.6)	1 (0.5)
Oliguria	2 (1.0)	0
Hemorrhage [FMQ]	11 (5.8)	9 (4.5)
Blood loss anemia	2 (1.0)	0
Hematuria	2 (1.0)	1 (0.5)
Epistaxis	1 (0.5)	0
Intra-abdominal hemorrhage	1 (0.5)	0
Esophageal varices hemorrhage	1 (0.5)	0
Petechia	1 (0.5)	0
Post procedural hemorrhage	1 (0.5)	0
Rectal hemorrhage	1 (0.5)	0
Renal hematoma	1 (0.5)	0
Respiratory tract hemorrhage	1 (0.5)	0
Retroperitoneal hematoma	1 (0.5)	0
Shock hemorrhagic	1 (0.5)	1 (0.5)
Arterial hemorrhage	0	1 (0.5)
Arteriovenous fistula site hemorrhage	0	1 (0.5)
Gastrointestinal hemorrhage	0	2 (1.0)
Hematoma infection	0	1 (0.5)
Lower gastrointestinal hemorrhage	0	1 (0.5)
Pancreatic hemorrhage	0	1 (0.5)
Respiratory Failure [FMQ]	10 (5.2)	4 (2.0)
Respiratory failure	4 (2.1)	3 (1.5)
Acute respiratory failure	3 (1.6)	0
Acute respiratory distress syndrome	2 (1.0)	0
Cyanosis	1 (0.5)	0
Oxygen saturation decreased	1 (0.5)	0
Hypoxia	0	1 (0.5)
Viral Infection [FMQ]	10 (5.2)	7 (3.5)
COVID-19	4 (2.1)	3 (1.5)
COVID-19 pneumonia	4 (2.1)	5 (2.5)
Herpes simplex reactivation	1 (0.5)	0
Herpes zoster	1 (0.5)	0
Herpes zoster reactivation	1 (0.5)	0
Human herpesvirus 6 infection	1 (0.5)	0
Pneumonia viral	1 (0.5)	1 (0.5)

Grouped Query Preferred Term	Ceftobiprole N=191 n (%)	Daptomycin N=198 n (%)
SARS-CoV-2 test positive	1 (0.5)	0
Hypertension [GQ]	10 (5.2)	4 (2.0)
Hypertension	7 (3.7)	3 (1.5)
Blood pressure increased	2 (1.0)	0
Hypertensive Crisis	2 (1.0)	1 (0.5)
Leukopenia [GQ]	8 (4.2)	5 (2.5)
Leukopenia	3 (1.6)	1 (0.5)
Lymphocyte count decreased	3 (1.6)	0
Neutropenia	1 (0.5)	1 (0.5)
White blood cell count decreased	1 (0.5)	1 (0.5)
Lymphopenia	0	2 (1.0)
Neutrophil count decreased	0	1 (0.5)
Pyrexia [GQ]	8 (4.2)	5 (2.5)
Pyrexia	6 (3.1)	5 (2.5)
Hyperthermia	2 (1.0)	0
Arthritis [FMQ]	7 (3.7)	7 (3.5)
Arthritis	2 (1.0)	0
Intervertebral discitis	2 (1.0)	4 (2.0)
Arthritis bacterial	1 (0.5)	1 (0.5)
Arthritis reactive	1 (0.5)	0
Spinal osteoarthritis	1 (0.5)	0
Synovitis	1 (0.5)	0
Osteoarthritis	0	2 (1.0)
Rheumatoid arthritis	0	1 (0.5)
Thrombosis [GQ]	7 (3.7)	2 (1.0)
Venous thrombosis limb	2 (1.0)	0
Arteriovenous fistula thrombosis	1 (0.5)	0
Atrial thrombosis	1 (0.5)	0
Deep vein thrombosis	1 (0.5)	1 (0.5)
Portal vein thrombosis	1 (0.5)	0
Thrombosis	1 (0.5)	0
Splenic infarction	0	1 (0.5)
Abdominal pain [GQ]	6 (3.1)	2 (1.0)
Abdominal pain upper	5 (2.6)	2 (1.0)
Abdominal tenderness	1 (0.5)	0
Constipation [FMQ]	6 (3.1)	7 (3.5)
Constipation	6 (3.1)	7 (3.5)
Cardiac failure [GQ]	5 (2.6)	9 (4.5)
Cardiac failure	2 (1.0)	4 (2.0)
Cardiac failure acute	2 (1.0)	1 (0.5)
Cardiopulmonary failure	1 (0.5)	1 (0.5)
Acute pulmonary edema	0	2 (1.0)
Cardiac failure congestive	0	1 (0.5)
Pulmonary edema	0	2 (1.0)
Fungal Infection [FMQ]	5 (2.6)	3 (1.5)
Oral candidiasis	2 (1.0)	1 (0.5)
Candida infection	1 (0.5)	0
Candida sepsis	1 (0.5)	0
Vulvovaginal candidiasis	1 (0.5)	0
Fungal test positive	0	1 (0.5)
Tinea pedis	0	1 (0.5)

	Ceftobiprole	Daptomycin
Grouped Query Preferred Term	**N=191 n (%)**	**N=198 n (%)**
Headache [FMQ]	5 (2.6)	6 (3.0)
Headache	5 (2.6)	6 (3.0)
Septic shock [PT]	5 (2.6)	8 (4.0)
Septic shock	5 (2.6)	8 (4.0)
Ascites [PT]	4 (2.1)	0
Ascites	4 (2.1)	0
Dyspnea [FMQ]	4 (2.1)	2 (1.0)
Dyspnea	4 (2.1)	1 (0.5)
Respiratory distress	0	1 (0.5)
Hydrothorax [PT]	4 (2.1)	5 (2.5)
Hydrothorax	4 (2.1)	5 (2.5)
Hypoglycemia [FMQ]	4 (2.1)	6 (3.0)
Hypoglycemia	4 (2.1)	6 (3.0)
Multiple organ dysfunction syndrome [PT]	4 (2.1)	2 (1.0)
Multiple organ dysfunction syndrome	4 (2.1)	2 (1.0)
Pleural effusion [PT]	4 (2.1)	2 (1.0)
Pleural effusion	4 (2.1)	2 (1.0)
Purulent Material [FMQ]	4 (2.1)	9 (4.5)
Abdominal abscess	1 (0.5)	3 (1.5)
Lung abscess	1 (0.5)	0
Psoas abscess	1 (0.5)	2 (1.0)
Subcutaneous abscess	1 (0.5)	0
Abscess limb	0	3 (1.5)
Extradural abscess	0	1 (0.5)
Muscle abscess	0	1 (0.5)
Pancreatic abscess	0	1 (0.5)
Renal abscess	0	1 (0.5)
Renal & Urinary Tract Infection [FMQ]	4 (2.1)	7 (3.5)
Pyelonephritis acute	3 (1.6)	0
Urinary tract infection	1 (0.5)	3 (1.5)
Urosepsis	1 (0.5)	1 (0.5)
Genitourinary tract infection	0	1 (0.5)
Pyelonephritis	0	1 (0.5)
Renal abscess	0	1 (0.5)
Anemia [FMQ]	3 (1.6)	0
Blood loss anemia	2 (1.0)	0
Iron deficiency anemia	1 (0.5)	0
Arrhythmia [FMQ]	3 (1.6)	1 (0.5)
Arrhythmia	1 (0.5)	0
Atrial fibrillation	1 (0.5)	1 (0.5)
Supraventricular extrasystoles	1 (0.5)	0
Hepatic Injury [FMQ]	3 (1.6)	5 (2.5)
Cholestasis	2 (1.0)	1 (0.5)
Esophageal varices hemorrhage	1 (0.5)	0
Hepatomegaly	0	1 (0.5)
Liver disorder	0	1 (0.5)
Pneumobilia	0	1 (0.5)
Portal hypertension	0	1 (0.5)
Hyperglycemia [FMQ]	3 (1.6)	4 (2.0)
Diabetes mellitus	1 (0.5)	2 (1.0)
Diabetic retinopathy	1 (0.5)	0

	Ceftobiprole	Daptomycin
Grouped Query Preferred Term	**N=191 n (%)**	**N=198 n (%)**
Hyperglycemia	1 (0.5)	2 (1.0)
Hypersensitivity [GQ]	3 (1.6)	1 (0.5)
Urticaria	2 (1.0)	0
Cutaneous vasculitis	1 (0.5)	0
Red man syndrome	0	1 (0.5)
Hypoalbuminemia [GQ]	3 (1.6)	2 (1.0)
Blood albumin decreased	3 (1.6)	2 (1.0)
Hypomagnesaemia [GQ]	3 (1.6)	2 (1.0)
Blood magnesium decreased	3 (1.6)	2 (1.0)
Hypotension [FMQ]	3 (1.6)	3 (1.5)
Hypotension	3 (1.6)	2 (1.0)
Orthostatic hypotension	0	1 (0.5)
Insomnia [FMQ]	3 (1.6)	0
Insomnia	3 (1.6)	0
Pancreatitis [FMQ]	3 (1.6)	3 (1.5)
Pancreatitis acute	2 (1.0)	1 (0.5)
Pancreatitis chronic	1 (0.5)	0
Obstructive pancreatitis	0	2 (1.0)
Pancreatic abscess	0	1 (0.5)
Pancreatic hemorrhage	0	1 (0.5)
Pancreatitis necrotizing	0	2 (1.0)
Pericardial effusion [GQ]	3 (1.6)	0
Pericardial effusion	3 (1.6)	0
Peripheral Edema [FMQ]	3 (1.6)	4 (2.0)
Edema peripheral	2 (1.0)	3 (1.5)
Peripheral swelling	1 (0.5)	1 (0.5)
Phlebitis [GQ]	3 (1.6)	1 (0.5)
Catheter site phlebitis	1 (0.5)	0
Infusion site phlebitis	1 (0.5)	1 (0.5)
Thrombophlebitis	1 (0.5)	0
Rash [GQ]	3 (1.6)	1 (0.5)
Dermatitis allergic	2 (1.0)	0
Rash	1 (0.5)	0
Rash macular	0	1 (0.5)
Seizure [GQ]	3 (1.6)	2 (1.0)
Generalized tonic-clonic seizure	1 (0.5)	0
Hypoglycemic seizure	1 (0.5)	0
Seizure	1 (0.5)	1 (0.5)
Status epilepticus	0	1 (0.5)
Activated partial thromboplastin time prolonged [PT]	2 (1.0)	1 (0.5)
Activated partial thromboplastin time prolonged	2 (1.0)	1 (0.5)
Aortic valve disease [GQ]	2 (1.0)	3 (1.5)
Aortic valve sclerosis	2 (1.0)	1 (0.5)
Aortic valve incompetence	1 (0.5)	2 (1.0)
Aortic valve calcification	0	1 (0.5)
Aortic valve disease	0	1 (0.5)
Aortic valve stenosis	0	1 (0.5)
Atelectasis [PT]	2 (1.0)	2 (1.0)
Atelectasis	2 (1.0)	2 (1.0)

	Ceftobiprole	Daptomycin
Grouped Query **Preferred Term**	**N=191** **n (%)**	**N=198** **n (%)**
Back Pain [FMQ]	2 (1.0)	3 (1.5)
Back pain	2 (1.0)	3 (1.5)
Cardiac Conduction Disturbance [FMQ]	2 (1.0)	1 (0.5)
Bundle branch block right	2 (1.0)	1 (0.5)
Cholelithiasis [PT]	2 (1.0)	1 (0.5)
Cholelithiasis	2 (1.0)	1 (0.5)
Coagulopathy [PT]	2 (1.0)	1 (0.5)
Coagulopathy	2 (1.0)	1 (0.5)
Decubitus ulcer [PT]	2 (1.0)	2 (1.0)
Decubitus ulcer	2 (1.0)	2 (1.0)
Dysgeusia [FMQ]	2 (1.0)	0
Dysgeusia	2 (1.0)	0
Erythema [FMQ]	2 (1.0)	2 (1.0)
Erythema	2 (1.0)	2 (1.0)
Gastritis [GQ]	2 (1.0)	2 (1.0)
Gastritis	1 (0.5)	2 (1.0)
Gastritis erosive	1 (0.5)	0
Infusion site reaction [GQ]	2 (1.0)	2 (1.0)
Catheter site hemorrhage	2 (1.0)	1 (0.5)
Catheter site erythema	0	1 (0.5)
Intervertebral disc protrusion [PT]	2 (1.0)	0
Intervertebral disc protrusion	2 (1.0)	0
Lymphadenopathy [PT]	2 (1.0)	0
Lymphadenopathy	2 (1.0)	0
Mediastinitis [PT]	2 (1.0)	0
Mediastinitis	2 (1.0)	0
Mitral valve disease [GQ]	2 (1.0)	4 (2.0)
Mitral valve incompetence	2 (1.0)	4 (2.0)
Mitral valve stenosis	1 (0.5)	0
Cardiac valve sclerosis	0	1 (0.5)
Myocardial injury [GQ]	2 (1.0)	1 (0.5)
Acute myocardial infarction	1 (0.5)	0
Myocardial infarction	1 (0.5)	1 (0.5)
Osteochondrosis [PT]	2 (1.0)	0
Osteochondrosis	2 (1.0)	0
Osteomyelitis [PT]	2 (1.0)	4 (2.0)
Osteomyelitis	2 (1.0)	4 (2.0)
Pleurisy [PT]	2 (1.0)	3 (1.5)
Pleurisy	2 (1.0)	3 (1.5)
Thrombocytopenia [GQ]	2 (1.0)	1 (0.5)
Platelet count decreased	1 (0.5)	1 (0.5)
Thrombocytopenia	1 (0.5)	0
Thrombocytosis [GQ]	2 (1.0)	1 (0.5)
Thrombocytosis	2 (1.0)	0
Platelet count increased	0	1 (0.5)
Acrodermatitis [PT]	1 (0.5)	0
Acrodermatitis	1 (0.5)	0
Affective disorder [PT]	1 (0.5)	0
Affective disorder	1 (0.5)	0
Alopecia [FMQ]	1 (0.5)	0
Madarosis	1 (0.5)	0

	Ceftobiprole	Daptomycin
Grouped Query **Preferred Term**	**N=191** **n (%)**	**N=198** **n (%)**
Angina [GQ]	1 (0.5)	1 (0.5)
Angina pectoris	1 (0.5)	0
Angina unstable	0	1 (0.5)
Anxiety [FMQ]	1 (0.5)	1 (0.5)
Anxiety	1 (0.5)	1 (0.5)
Arteriosclerotic retinopathy [PT]	1 (0.5)	0
Arteriosclerotic retinopathy	1 (0.5)	0
Asymptomatic bacteriuria [PT]	1 (0.5)	0
Asymptomatic bacteriuria	1 (0.5)	0
Back disorder [PT]	1 (0.5)	0
Back disorder	1 (0.5)	0
Benign neoplasm of prostate [PT]	1 (0.5)	0
Benign neoplasm of prostate	1 (0.5)	0
Blood creatine phosphokinase increased [PT]	1 (0.5)	3 (1.5)
Blood creatine phosphokinase increased	1 (0.5)	3 (1.5)
Blood electrolytes abnormal [PT]	1 (0.5)	0
Blood electrolytes abnormal	1 (0.5)	0
Blood fibrinogen decreased [PT]	1 (0.5)	0
Blood fibrinogen decreased	1 (0.5)	0
Blood fibrinogen increased [PT]	1 (0.5)	0
Blood fibrinogen increased	1 (0.5)	0
Blood folate decreased [PT]	1 (0.5)	0
Blood folate decreased	1 (0.5)	0
Blood lactate dehydrogenase increased [PT]	1 (0.5)	0
Blood lactate dehydrogenase increased	1 (0.5)	0
Blood uric acid increased [PT]	1 (0.5)	0
Blood uric acid increased	1 (0.5)	0
Breath sounds abnormal [PT]	1 (0.5)	0
Breath sounds abnormal	1 (0.5)	0
Candida test positive [PT]	1 (0.5)	1 (0.5)
Candida test positive	1 (0.5)	1 (0.5)
Cardiac arrest [PT]	1 (0.5)	1 (0.5)
Cardiac arrest	1 (0.5)	1 (0.5)
Cardiac discomfort [PT]	1 (0.5)	0
Cardiac discomfort	1 (0.5)	0
Cataract [PT]	1 (0.5)	0
Cataract	1 (0.5)	0
Cheilitis [PT]	1 (0.5)	0
Cheilitis	1 (0.5)	0
Chest discomfort [PT]	1 (0.5)	0
Chest discomfort	1 (0.5)	0
Chloroma [PT]	1 (0.5)	0
Chloroma	1 (0.5)	0
Cholecystitis [FMQ]	1 (0.5)	0
Cholecystitis chronic	1 (0.5)	0
Chondrocalcinosis [PT]	1 (0.5)	0
Chondrocalcinosis	1 (0.5)	0
Chronic obstructive pulmonary disease [PT]	1 (0.5)	0
Chronic obstructive pulmonary disease	1 (0.5)	0
Complication associated with device [PT]	1 (0.5)	0
Complication associated with device	1 (0.5)	0

	Ceftobiprole	Daptomycin
Grouped Query **Preferred Term**	**N=191** **n (%)**	**N=198** **n (%)**
Confusional State [FMQ]	1 (0.5)	3 (1.5)
Confusional state	1 (0.5)	1 (0.5)
Delirium	0	1 (0.5)
Disorientation	0	2 (1.0)
Cough [FMQ]	1 (0.5)	0
Cough	1 (0.5)	0
Deafness neurosensory [PT]	1 (0.5)	0
Deafness neurosensory	1 (0.5)	0
Death [PT]	1 (0.5)	0
Death	1 (0.5)	0
Diaphragmatic abnormal relaxation [PT]	1 (0.5)	0
Diaphragmatic abnormal relaxation	1 (0.5)	0
Dizziness [FMQ]	1 (0.5)	1 (0.5)
Dizziness	1 (0.5)	0
Presyncope	0	1 (0.5)
Drug withdrawal syndrome [PT]	1 (0.5)	0
Drug withdrawal syndrome	1 (0.5)	0
Dry eye [PT]	1 (0.5)	0
Dry eye	1 (0.5)	0
Dysbiosis [PT]	1 (0.5)	0
Dysbiosis	1 (0.5)	0
Encephalopathy [GQ]	1 (0.5)	2 (1.0)
Toxic encephalopathy	1 (0.5)	0
Encephalopathy	0	1 (0.5)
Metabolic encephalopathy	0	1 (0.5)
Extremity necrosis [PT]	1 (0.5)	1 (0.5)
Extremity necrosis	1 (0.5)	1 (0.5)
Fatigue [FMQ]	1 (0.5)	1 (0.5)
Malaise	1 (0.5)	0
Fatigue	0	1 (0.5)
Generalized edema [PT]	1 (0.5)	0
Generalized edema	1 (0.5)	0
Goiter [PT]	1 (0.5)	0
Goiter	1 (0.5)	0
Hemangioma of bone [PT]	1 (0.5)	0
Hemangioma of bone	1 (0.5)	0
Hemodialysis complication [PT]	1 (0.5)	0
Hemodialysis complication	1 (0.5)	0
Hepatic steatosis [PT]	1 (0.5)	1 (0.5)
Hepatic steatosis	1 (0.5)	1 (0.5)
Hydronephrosis [PT]	1 (0.5)	0
Hydronephrosis	1 (0.5)	0
Hyperkalemia [GQ]	1 (0.5)	2 (1.0)
Blood potassium increased	1 (0.5)	2 (1.0)
Hyperparathyroidism secondary [PT]	1 (0.5)	0
Hyperparathyroidism secondary	1 (0.5)	0
Hypertensive heart disease [PT]	1 (0.5)	0
Hypertensive heart disease	1 (0.5)	0
Hypophosphatemia [GQ]	1 (0.5)	1 (0.5)
Blood phosphorus decreased	1 (0.5)	1 (0.5)
Hypotony maculopathy [PT]	1 (0.5)	0

	Ceftobiprole	Daptomycin
Grouped Query **Preferred Term**	**N=191** **n (%)**	**N=198** **n (%)**
Hypotony maculopathy	1 (0.5)	0
Infective tenosynovitis [PT]	1 (0.5)	0
Infective tenosynovitis	1 (0.5)	0
International normalized ratio increased [PT]	1 (0.5)	0
International normalized ratio increased	1 (0.5)	0
Irritability [FMQ]	1 (0.5)	0
Agitation	1 (0.5)	0
Keratitis [PT]	1 (0.5)	0
Keratitis	1 (0.5)	0
Kidney rupture [PT]	1 (0.5)	0
Kidney rupture	1 (0.5)	0
Laryngeal disorder [PT]	1 (0.5)	0
Laryngeal disorder	1 (0.5)	0
Laryngopharyngitis [PT]	1 (0.5)	0
Laryngopharyngitis	1 (0.5)	0
Leg amputation [PT]	1 (0.5)	1 (0.5)
Leg amputation	1 (0.5)	1 (0.5)
Limb injury [PT]	1 (0.5)	0
Limb injury	1 (0.5)	0
Local Administration Reaction [FMQ]	1 (0.5)	0
Infusion site pain	1 (0.5)	0
Lymphadenitis [PT]	1 (0.5)	1 (0.5)
Lymphadenitis	1 (0.5)	1 (0.5)
Lymphostasis [PT]	1 (0.5)	1 (0.5)
Lymphostasis	1 (0.5)	1 (0.5)
Metabolic acidosis [PT]	1 (0.5)	0
Metabolic acidosis	1 (0.5)	0
Monoparesis [PT]	1 (0.5)	0
Monoparesis	1 (0.5)	0
Musculoskeletal chest pain [PT]	1 (0.5)	1 (0.5)
Musculoskeletal chest pain	1 (0.5)	1 (0.5)
Myalgia [FMQ]	1 (0.5)	0
Myalgia	1 (0.5)	0
Myocardial injury [GQ]	1 (0.5)	0
Myocardial ischemia	1 (0.5)	0
Myocardial fibrosis [PT]	1 (0.5)	0
Myocardial fibrosis	1 (0.5)	0
Neck pain [PT]	1 (0.5)	1 (0.5)
Neck pain	1 (0.5)	1 (0.5)
Non-cardiac chest pain [PT]	1 (0.5)	2 (1.0)
Non-cardiac chest pain	1 (0.5)	2 (1.0)
Esophageal disorder [PT]	1 (0.5)	0
Esophageal disorder	1 (0.5)	0
Optic neuropathy [PT]	1 (0.5)	0
Optic neuropathy	1 (0.5)	0
Otitis media [PT]	1 (0.5)	0
Otitis media	1 (0.5)	0
Otitis media acute [PT]	1 (0.5)	0
Otitis media acute	1 (0.5)	0
Pain in extremity [PT]	1 (0.5)	2 (1.0)
Pain in extremity	1 (0.5)	2 (1.0)

	Ceftobiprole	Daptomycin
Grouped Query **Preferred Term**	**N=191** **n (%)**	**N=198** **n (%)**
Paresthesia [FMQ]	1 (0.5)	1 (0.5)
Hypoesthesia	1 (0.5)	1 (0.5)
Parkinsonism [PT]	1 (0.5)	0
Parkinsonism	1 (0.5)	0
Penis disorder [PT]	1 (0.5)	0
Penis disorder	1 (0.5)	0
Pericarditis [PT]	1 (0.5)	1 (0.5)
Pericarditis	1 (0.5)	1 (0.5)
Personality disorder [PT]	1 (0.5)	0
Personality disorder	1 (0.5)	0
Pollakiuria [PT]	1 (0.5)	0
Pollakiuria	1 (0.5)	0
Postoperative wound complication [PT]	1 (0.5)	1 (0.5)
Postoperative wound complication	1 (0.5)	1 (0.5)
Prothrombin time prolonged [PT]	1 (0.5)	1 (0.5)
Prothrombin time prolonged	1 (0.5)	1 (0.5)
Psychomotor hyperactivity [PT]	1 (0.5)	1 (0.5)
Psychomotor hyperactivity	1 (0.5)	1 (0.5)
Pulmonary fibrosis [PT]	1 (0.5)	0
Pulmonary fibrosis	1 (0.5)	0
Purulent pericarditis [PT]	1 (0.5)	0
Purulent pericarditis	1 (0.5)	0
Renal adenoma [PT]	1 (0.5)	0
Renal adenoma	1 (0.5)	0
Renal hypoplasia [PT]	1 (0.5)	0
Renal hypoplasia	1 (0.5)	0
Restlessness [PT]	1 (0.5)	1 (0.5)
Restlessness	1 (0.5)	1 (0.5)
Secretion discharge [PT]	1 (0.5)	0
Secretion discharge	1 (0.5)	0
Skin ulcer [PT]	1 (0.5)	0
Skin ulcer	1 (0.5)	0
Spinal pain [PT]	1 (0.5)	1 (0.5)
Spinal pain	1 (0.5)	1 (0.5)
Systemic inflammatory response syndrome [PT]	1 (0.5)	0
Systemic inflammatory response syndrome	1 (0.5)	0
Tachycardia [GQ]	1 (0.5)	1 (0.5)
Sinus tachycardia	1 (0.5)	1 (0.5)
Testicular pain [PT]	1 (0.5)	0
Testicular pain	1 (0.5)	0
Tracheal stenosis [PT]	1 (0.5)	0
Tracheal stenosis	1 (0.5)	0
Tremor [FMQ]	1 (0.5)	0
Tremor	1 (0.5)	0
Upper gastrointestinal hemorrhage [PT]	1 (0.5)	0
Upper gastrointestinal hemorrhage	1 (0.5)	0
Varicose vein [PT]	1 (0.5)	0
Varicose vein	1 (0.5)	0
Vasodilatation [PT]	1 (0.5)	0
Vasodilatation	1 (0.5)	0
Wound [PT]	1 (0.5)	0

Grouped Query Preferred Term	Ceftobiprole N=191 n (%)	Daptomycin N=198 n (%)
Wound	1 (0.5)	0
Wound hemorrhage [PT]	1 (0.5)	0
Wound hemorrhage	1 (0.5)	0
Wound healing normal [PT]	1 (0.5)	1 (0.5)
Wound healing normal	1 (0.5)	1 (0.5)
Wound secretion [PT]	1 (0.5)	0
Wound secretion	1 (0.5)	0
Adrenal insufficiency [PT]	0	1 (0.5)
Adrenal insufficiency	0	1 (0.5)
Aortic arteriosclerosis [PT]	0	1 (0.5)
Aortic arteriosclerosis	0	1 (0.5)
Arachnoiditis [PT]	0	1 (0.5)
Arachnoiditis	0	1 (0.5)
Arteriosclerosis [PT]	0	1 (0.5)
Arteriosclerosis	0	1 (0.5)
Arthralgia [FMQ]	0	2 (1.0)
Arthralgia	0	2 (1.0)
Benign prostatic hyperplasia [PT]	0	1 (0.5)
Benign prostatic hyperplasia	0	1 (0.5)
Bursitis [PT]	0	1 (0.5)
Bursitis	0	1 (0.5)
Calyceal diverticulum [PT]	0	1 (0.5)
Calyceal diverticulum	0	1 (0.5)
Cardiac valve vegetation [PT]	0	1 (0.5)
Cardiac valve vegetation	0	1 (0.5)
Carotid arteriosclerosis [PT]	0	1 (0.5)
Carotid arteriosclerosis	0	1 (0.5)
Cerebral arteriosclerosis [PT]	0	1 (0.5)
Cerebral arteriosclerosis	0	1 (0.5)
Cerebral cyst [PT]	0	1 (0.5)
Cerebral cyst	0	1 (0.5)
Chordae tendinae rupture [PT]	0	1 (0.5)
Chordae tendinae rupture	0	1 (0.5)
Chronic kidney disease [PT]	0	1 (0.5)
Chronic kidney disease	0	1 (0.5)
Delayed recovery from anesthesia [PT]	0	1 (0.5)
Delayed recovery from anesthesia	0	1 (0.5)
Depression [FMQ]	0	1 (0.5)
Depression	0	1 (0.5)
Diverticulum intestinal [PT]	0	1 (0.5)
Diverticulum intestinal	0	1 (0.5)
Dry skin [PT]	0	1 (0.5)
Dry skin	0	1 (0.5)
Duodenogastric reflux [PT]	0	1 (0.5)
Duodenogastric reflux	0	1 (0.5)
Dysuria [PT]	0	1 (0.5)
Dysuria	0	1 (0.5)
Eczema [PT]	0	1 (0.5)
Eczema	0	1 (0.5)
Eosinophilic pneumonia [GQ]	0	2 (1.0)
Eosinophilic pneumonia	0	1 (0.5)

	Ceftobiprole	Daptomycin
Grouped Query **Preferred Term**	**N=191** **n (%)**	**N=198** **n (%)**
Eosinophilic pneumonia acute	0	1 (0.5)
Exostosis [PT]	0	1 (0.5)
Exostosis	0	1 (0.5)
Extensor plantar response [PT]	0	1 (0.5)
Extensor plantar response	0	1 (0.5)
Flatulence [PT]	0	1 (0.5)
Flatulence	0	1 (0.5)
Fluid overload [PT]	0	1 (0.5)
Fluid overload	0	1 (0.5)
Fracture [FMQ]	0	1 (0.5)
Foot fracture	0	1 (0.5)
Gout [FMQ]	0	1 (0.5)
Infected gouty tophus	0	1 (0.5)
Hematoma [GQ]	0	2 (1.0)
Subcapsular hepatic hematoma	0	1 (0.5)
Subcutaneous hematoma	0	1 (0.5)
Hydrocalyx [PT]	0	1 (0.5)
Hydrocalyx	0	1 (0.5)
Hydrocephalus [PT]	0	1 (0.5)
Hydrocephalus	0	1 (0.5)
Hypocalcemia [GQ]	0	1 (0.5)
Blood calcium decreased	0	1 (0.5)
Hypocoagulable state [PT]	0	1 (0.5)
Hypocoagulable state	0	1 (0.5)
Impaired healing [PT]	0	1 (0.5)
Impaired healing	0	1 (0.5)
Infection [PT]	0	1 (0.5)
Infection	0	1 (0.5)
Intra-abdominal fluid collection [PT]	0	3 (1.5)
Intra-abdominal fluid collection	0	3 (1.5)
Ischemic stroke [PT]	0	1 (0.5)
Ischemic stroke	0	1 (0.5)
Joint effusion [PT]	0	1 (0.5)
Joint effusion	0	1 (0.5)
Joint instability [PT]	0	1 (0.5)
Joint instability	0	1 (0.5)
Laryngitis [PT]	0	1 (0.5)
Laryngitis	0	1 (0.5)
Left ventricular dysfunction [PT]	0	1 (0.5)
Left ventricular dysfunction	0	1 (0.5)
Left ventricular hypertrophy [PT]	0	1 (0.5)
Left ventricular hypertrophy	0	1 (0.5)
Malignancy [FMQ]	0	1 (0.5)
Squamous cell carcinoma of skin	0	1 (0.5)
Mitra valve disease [GQ]	0	1 (0.5)
Mitral valve calcification	0	1 (0.5)
Myocarditis [PT]	0	1 (0.5)
Myocarditis	0	1 (0.5)
Myopathy [PT]	0	1 (0.5)
Myopathy	0	1 (0.5)
Nasopharyngitis [FMQ]	0	2 (1.0)

	Ceftobiprole	Daptomycin
Grouped Query **Preferred Term**	**N=191** **n (%)**	**N=198** **n (%)**
Nasopharyngitis	0	1 (0.5)
Pharyngitis	0	1 (0.5)
Nephrotic syndrome [PT]	0	1 (0.5)
Nephrotic syndrome	0	1 (0.5)
Osteoporosis [FMQ]	0	1 (0.5)
Osteoporosis	0	1 (0.5)
Pathogen resistance [PT]	0	1 (0.5)
Pathogen resistance	0	1 (0.5)
Pemphigoid [PT]	0	1 (0.5)
Pemphigoid	0	1 (0.5)
Peripheral ischemia [PT]	0	1 (0.5)
Peripheral ischemia	0	1 (0.5)
Pneumatosis [PT]	0	1 (0.5)
Pneumatosis	0	1 (0.5)
Polyserositis [PT]	0	1 (0.5)
Polyserositis	0	1 (0.5)
Polyuria [PT]	0	2 (1.0)
Polyuria	0	2 (1.0)
Portal vein stenosis [PT]	0	1 (0.5)
Portal vein stenosis	0	1 (0.5)
Pruritus [FMQ]	0	2 (1.0)
Eye pruritus	0	1 (0.5)
Pruritus	0	1 (0.5)
Pulmonary valve incompetence [PT]	0	1 (0.5)
Pulmonary valve incompetence	0	1 (0.5)
Rales [PT]	0	2 (1.0)
Rales	0	2 (1.0)
Renal cyst [PT]	0	2 (1.0)
Renal cyst	0	2 (1.0)
Reticuloendothelial dysfunction [PT]	0	1 (0.5)
Reticuloendothelial dysfunction	0	1 (0.5)
Septic necrosis [PT]	0	1 (0.5)
Septic necrosis	0	1 (0.5)
Skin mass [PT]	0	1 (0.5)
Skin mass	0	1 (0.5)
Somnolence [FMQ]	0	1 (0.5)
Somnolence	0	1 (0.5)
Stomatitis [PT]	0	1 (0.5)
Stomatitis	0	1 (0.5)
Stroke and TIA [FMQ]	0	1 (0.5)
Ischemic stroke	0	1 (0.5)
Study Agent Abuse Potential [FMQ]	0	1 (0.5)
Somnolence	0	1 (0.5)
Suspected COVID-19 [PT]	0	2 (1.0)
Suspected COVID-19	0	2 (1.0)
Syncope [FMQ]	0	2 (1.0)
Syncope	0	2 (1.0)
Thrombosis Arterial [FMQ]	0	1 (0.5)
Ischemic stroke	0	1 (0.5)
Tracheal disorder [PT]	0	1 (0.5)
Tracheal disorder	0	1 (0.5)

	Ceftobiprole	Daptomycin
Grouped Query **Preferred Term**	**N=191** **n (%)**	**N=198** **n (%)**
Tricuspid valve disease [GQ]	0	3 (1.5)
Tricuspid valve incompetence	0	3 (1.5)
Ulcer hemorrhage [PT]	0	1 (0.5)
Ulcer hemorrhage	0	1 (0.5)
Umbilical hernia [PT]	0	1 (0.5)
Umbilical hernia	0	1 (0.5)
Urinary Retention [FMQ]	0	2 (1.0)
Urinary retention	0	2 (1.0)
Vascular pseudoaneurysm [PT]	0	1 (0.5)
Vascular pseudoaneurysm	0	1 (0.5)
Visual impairment [PT]	0	1 (0.5)
Visual impairment	0	1 (0.5)
Volume Depletion [FMQ]	0	3 (1.5)
Dehydration	0	1 (0.5)
Hypovolemia	0	2 (1.0)
Wound dehiscence [PT]	0	3 (1.5)
Wound dehiscence	0	3 (1.5)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any adverse event which occurred between the start of the first dosing up to and including the scheduled last follow-up.
Duration is up to 42 days plus the follow-up period up to Day 70
Abbreviations: GQ, grouped query; N, number of subjects in treatment arm; n, number of subjects with adverse event

17.3. Acute Bacterial Skin/Soft Tissue Infection, Trial BPR-CS-008

The full list of TEAEs by either grouped queries created by the FDA reviewer or FMQs are noted below. For selected AESI, a grouped query was created instead of using the narrow FMQ or in instances where an FMQ was not available.

Table 284. Grouped Queries by Preferred Term, Safety Population, Trial BPR-CS-008

	Ceftobiprole	Vancomycin
Grouped Query **Preferred Term**	**N=334** **n (%)**	**N=342** **n (%)**
Nausea [FMQ]	36 (10.8)	19 (5.6)
Nausea	36 (10.8)	19 (5.6)
Bacterial Infection [FMQ]	25 (7.5)	32 (9.4)
Skin bacterial infection	14 (4.2)	17 (5.0)
Cellulitis	6 (1.8)	5 (1.5)
Abscess limb	3 (0.9)	4 (1.2)
Wound infection	2 (0.6)	1 (0.3)
Device related infection	1 (0.3)	0
Subcutaneous abscess	1 (0.3)	1 (0.3)
Abdominal abscess	0	1 (0.3)
Necrotising fasciitis	0	1 (0.3)
Pseudomonas infection	0	1 (0.3)
Sepsis	0	1 (0.3)
Urinary tract infection	0	1 (0.3)

	Ceftobiprole	Vancomycin
Grouped Query **Preferred Term**	**N=334** **n (%)**	**N=342** **n (%)**
Wound abscess	0	1 (0.3)
Diarrhea [FMQ]	21 (6.3)	16 (4.7)
Diarrhea	21 (6.3)	16 (4.7)
Headache [FMQ]	21 (6.3)	24 (7.0)
Headache	19 (5.7)	24 (7.0)
Migraine	2 (0.6)	0
Liver enzyme increased [GQ]	8 (2.4)	11 (3.2)
Alanine aminotransferase increased	8 (2.4)	10 (2.9)
Aspartate aminotransferase increased	7 (2.1)	10 (2.9)
Gamma-glutamyltransferase increased	2 (0.6)	3 (0.9)
Blood alkaline phosphatase increased	1 (0.3)	1 (0.3)
Nasopharyngitis [FMQ]	8 (2.4)	4 (1.2)
Upper respiratory tract infection	5 (1.5)	3 (0.9)
Nasopharyngitis	3 (0.9)	1 (0.3)
Dysgeusia [FMQ]	7 (2.1)	0
Dysgeusia	7 (2.1)	0
Injection site reaction [GQ]	7 (2.1)	9 (2.6)
Injection site reaction	7 (2.1)	8 (2.3)
Infusion related reaction	0	1 (0.3)
Rash [GQ]	7 (2.1)	9 (2.6)
Rash	5 (1.5)	7 (2.0)
Dermatitis	1 (0.3)	2 (0.6)
Drug eruption	1 (0.3)	0
Vomiting [FMQ]	7 (2.1)	7 (2.0)
Vomiting	7 (2.1)	7 (2.0)
Constipation [FMQ]	6 (1.8)	4 (1.2)
Constipation	6 (1.8)	4 (1.2)
Drug withdrawal syndrome [PT]	4 (1.2)	6 (1.8)
Drug withdrawal syndrome	4 (1.2)	6 (1.8)
Purulent Material [FMQ]	4 (1.2)	6 (1.8)
Abscess limb	3 (0.9)	4 (1.2)
Subcutaneous abscess	1 (0.3)	1 (0.3)
Abdominal abscess	0	1 (0.3)
Wound abscess	0	1 (0.3)
Chills [PT]	3 (0.9)	1 (0.3)
Chills	3 (0.9)	1 (0.3)
Hyperglycemia [FMQ]	3 (0.9)	5 (1.5)
Diabetes mellitus	2 (0.6)	1 (0.3)
Hyperglycemia	1 (0.3)	1 (0.3)
Type 2 diabetes mellitus	1 (0.3)	2 (0.6)
Type 1 diabetes mellitus	0	1 (0.3)
Hypertension [GQ]	3 (0.9)	5 (1.5)
Hypertension	2 (0.6)	4 (1.2)
Blood pressure increased	1 (0.3)	1 (0.3)
Leukopenia [GQ]	3 (0.9)	2 (0.6)
Leukopenia	2 (0.6)	2 (0.6)
Lymphopenia	1 (0.3)	0
Peripheral Edema [FMQ]	3 (0.9)	7 (2.0)
Edema peripheral	3 (0.9)	7 (2.0)
Phlebitis [GQ]	3 (0.9)	0
Phlebitis	2 (0.6)	0

	Ceftobiprole	Vancomycin
Grouped Query **Preferred Term**	**N=334** **n (%)**	**N=342** **n (%)**
Thrombophlebitis superficial	1 (0.3)	0
Pruritus [FMQ]	3 (0.9)	5 (1.5)
Pruritus	3 (0.9)	5 (1.5)
Pyrexia [FMQ]	3 (0.9)	8 (2.3)
Pyrexia	3 (0.9)	8 (2.3)
Thrombocytopenia [FMQ]	3 (0.9)	1 (0.3)
Thrombocytopenia	3 (0.9)	1 (0.3)
Abdominal pain [GQ]	2 (0.6)	8 (2.3)
Abdominal discomfort	1 (0.3)	0
Abdominal pain	1 (0.3)	8 (2.3)
Accidental overdose [PT]	2 (0.6)	0
Accidental overdose	2 (0.6)	0
Arthralgia [FMQ]	2 (0.6)	0
Arthralgia	2 (0.6)	0
Back Pain [FMQ]	2 (0.6)	1 (0.3)
Back pain	2 (0.6)	0
Flank pain	0	1 (0.3)
Bronchial obstruction [PT]	2 (0.6)	0
Bronchial obstruction	2 (0.6)	0
Dizziness [FMQ]	2 (0.6)	4 (1.2)
Dizziness	1 (0.3)	3 (0.9)
Vertigo	1 (0.3)	0
Dizziness postural	0	1 (0.3)
Dyspepsia [FMQ]	2 (0.6)	5 (1.5)
Dyspepsia	2 (0.6)	5 (1.5)
Dyspnea [FMQ]	2 (0.6)	1 (0.3)
Dyspnea	2 (0.6)	1 (0.3)
Hemorrhage [FMQ]	2 (0.6)	4 (1.2)
Ecchymosis	1 (0.3)	0
Post procedural hematoma	1 (0.3)	0
Contusion	0	1 (0.3)
Hematuria	0	1 (0.3)
Petechiae	0	1 (0.3)
Post procedural hemorrhage	0	1 (0.3)
Hypomagnesaemia [GQ]	2 (0.6)	2 (0.6)
Blood magnesium decreased	2 (0.6)	2 (0.6)
Insomnia [FMQ]	2 (0.6)	2 (0.6)
Insomnia	2 (0.6)	2 (0.6)
Nasal congestion [PT]	2 (0.6)	0
Nasal congestion	2 (0.6)	0
Pneumonia [FMQ]	2 (0.6)	0
Pneumonia	2 (0.6)	0
Renal impairment [GQ]	2 (0.6)	4 (1.2)
Blood creatinine increased	2 (0.6)	4 (1.2)
Acute kidney injury	0	1 (0.3)
Viral Infection [FMQ]	2 (0.6)	2 (0.6)
Acute hepatitis C	1 (0.3)	0
Hepatitis C virus test positive	1 (0.3)	0
Hepatitis A	0	1 (0.3)
Oral herpes	0	1 (0.3)

	Ceftobiprole	Vancomycin
Grouped Query **Preferred Term**	**N=334** **n (%)**	**N=342** **n (%)**
Acne [PT]	1 (0.3)	0
Acne	1 (0.3)	0
Anemia [GQ]	1 (0.3)	5 (1.5)
Anemia	1 (0.3)	5 (1.5)
Anxiety [GQ]	1 (0.3)	1 (0.3)
Feeling jittery	1 (0.3)	0
Anxiety	0	1 (0.3)
Arthritis [FMQ]	1 (0.3)	0
Polyarthritis	1 (0.3)	0
Blood lactate dehydrogenase increased [PT]	1 (0.3)	2 (0.6)
Blood lactate dehydrogenase increased	1 (0.3)	2 (0.6)
Burn [GQ]	1 (0.3)	0
Thermal burn	1 (0.3)	0
Cachexia [FMQ]	1 (0.3)	1 (0.3)
Abnormal loss of weight	1 (0.3)	1 (0.3)
Chronic obstructive pulmonary disease [PT]	1 (0.3)	0
Chronic obstructive pulmonary disease	1 (0.3)	0
Cough [FMQ]	1 (0.3)	2 (0.6)
Cough	1 (0.3)	2 (0.6)
Dry skin [PT]	1 (0.3)	0
Dry skin	1 (0.3)	0
Eczema [PT]	1 (0.3)	0
Eczema	1 (0.3)	0
Face edema [PT]	1 (0.3)	0
Face edema	1 (0.3)	0
Fatigue [FMQ]	1 (0.3)	2 (0.6)
Asthenia	1 (0.3)	0
Fatigue	0	1 (0.3)
Malaise	0	1 (0.3)
Flatulence [PT]	1 (0.3)	0
Flatulence	1 (0.3)	0
Fungal Infection [FMQ]	1 (0.3)	2 (0.6)
Candida infection	1 (0.3)	1 (0.3)
Tinea pedis	0	1 (0.3)
Glossodynia [PT]	1 (0.3)	0
Glossodynia	1 (0.3)	0
Hematocrit increased [PT]	1 (0.3)	0
Hematocrit increased	1 (0.3)	0
Hematoma [GQ]	1 (0.3)	1 (0.3)
Hematoma	1 (0.3)	0
Vessel puncture site hematoma	0	1 (0.3)
Heart Failure [FMQ]	1 (0.3)	0
Edema due to cardiac disease	1 (0.3)	0
Hyperkalemia [GQ]	1 (0.3)	2 (0.6)
Blood potassium increased	1 (0.3)	2 (0.6)
Infusion site pain [GQ]	1 (0.3)	2 (0.6)
Infusion site pain	1 (0.3)	0
Catheter site pain	0	2 (0.6)
Lacrimation increased [PT]	1 (0.3)	0
Lacrimation increased	1 (0.3)	0
Lip swelling [PT]	1 (0.3)	0

	Ceftobiprole	Vancomycin
Grouped Query **Preferred Term**	**N=334** **n (%)**	**N=342** **n (%)**
Lip swelling	1 (0.3)	0
Lymphostasis [PT]	1 (0.3)	0
Lymphostasis	1 (0.3)	0
Pain [PT]	1 (0.3)	0
Pain	1 (0.3)	0
Pain in extremity [PT]	1 (0.3)	0
Pain in extremity	1 (0.3)	0
Paresthesia [FMQ]	1 (0.3)	0
Sensory loss	1 (0.3)	0
Psychosis [FMQ]	1 (0.3)	0
Reactive psychosis	1 (0.3)	0
Skin abrasion [PT]	1 (0.3)	0
Skin abrasion	1 (0.3)	0
Skin laceration [PT]	1 (0.3)	0
Skin laceration	1 (0.3)	0
Skin lesion [PT]	1 (0.3)	1 (0.3)
Skin lesion	1 (0.3)	1 (0.3)
Thrombosis [GQ]	1 (0.3)	1 (0.3)
Deep vein thrombosis	1 (0.3)	1 (0.3)
Tonsillitis [PT]	1 (0.3)	0
Tonsillitis	1 (0.3)	0
Toothache [PT]	1 (0.3)	2 (0.6)
Toothache	1 (0.3)	2 (0.6)
Vaginal infection [PT]	1 (0.3)	0
Vaginal infection	1 (0.3)	0
Vertigo [FMQ]	1 (0.3)	0
Vertigo	1 (0.3)	0
Vulvovaginal candidiasis [GQ]	1 (0.3)	4 (1.2)
Vulvovaginal mycotic infection	1 (0.3)	1 (0.3)
Vulvovaginal candidiasis	0	3 (0.9)
Wheezing [PT]	1 (0.3)	3 (0.9)
Wheezing	1 (0.3)	3 (0.9)
Wound complication [PT]	1 (0.3)	0
Wound complication	1 (0.3)	0
Abdominal lymphadenopathy [PT]	0	1 (0.3)
Abdominal lymphadenopathy	0	1 (0.3)
Arrhythmia [FMQ]	0	4 (1.2)
Atrial fibrillation	0	1 (0.3)
Atrial flutter	0	1 (0.3)
Bradycardia	0	1 (0.3)
Tachycardia	0	1 (0.3)
Arthropod bite [PT]	0	1 (0.3)
Arthropod bite	0	1 (0.3)
Breath sounds abnormal [PT]	0	1 (0.3)
Breath sounds abnormal	0	1 (0.3)
Bronchitis [PT]	0	1 (0.3)
Bronchitis	0	1 (0.3)
Cardiac arrest [PT]	0	1 (0.3)
Cardiac arrest	0	1 (0.3)
Cholelithiasis [PT]	0	1 (0.3)
Cholelithiasis	0	1 (0.3)

	Ceftobiprole	Vancomycin
Grouped Query **Preferred Term**	**N=334** **n (%)**	**N=342** **n (%)**
Decreased Appetite [FMQ]	0	1 (0.3)
Decreased appetite	0	1 (0.3)
Erythema [FMQ]	0	4 (1.2)
Erythema	0	4 (1.2)
Fall [FMQ]	0	1 (0.3)
Fall	0	1 (0.3)
Fracture [FMQ]	0	1 (0.3)
Clavicle fracture	0	1 (0.3)
Hepatic Injury [FMQ]	0	1 (0.3)
Hepatitis A	0	1 (0.3)
Hyperhidrosis [PT]	0	3 (0.9)
Hyperhidrosis	0	3 (0.9)
Hypersensitivity [GQ]	0	3 (0.9)
Angioedema	0	1 (0.3)
Drug hypersensitivity	0	1 (0.3)
Urticaria	0	2 (0.6)
Hypoalbuminemia [GQ]	0	1 (0.3)
Blood albumin decreased	0	1 (0.3)
Hypocalcemia [GQ]	0	1 (0.3)
Blood calcium decreased	0	1 (0.3)
Hypokalemia [GQ]	0	2 (0.6)
Blood potassium decreased	0	2 (0.6)
Influenza like illness [PT]	0	2 (0.6)
Influenza like illness	0	2 (0.6)
Ingrowing nail [PT]	0	1 (0.3)
Ingrowing nail	0	1 (0.3)
Joint swelling [PT]	0	1 (0.3)
Joint swelling	0	1 (0.3)
Leukocytosis [GQ]	0	2 (0.6)
Leukocytosis	0	1 (0.3)
White blood cell count increased	0	1 (0.3)
Localized infection [PT]	0	1 (0.3)
Localized infection	0	1 (0.3)
Lymphadenopathy [PT]	0	1 (0.3)
Lymphadenopathy	0	1 (0.3)
Malignancy [FMQ]	0	1 (0.3)
Leukemia	0	1 (0.3)
Multiple allergies [PT]	0	1 (0.3)
Multiple allergies	0	1 (0.3)
Multiple organ dysfunction syndrome [PT]	0	1 (0.3)
Multiple organ dysfunction syndrome	0	1 (0.3)
Muscle spasms [PT]	0	1 (0.3)
Muscle spasms	0	1 (0.3)
Myalgia [FMQ]	0	1 (0.3)
Myalgia	0	1 (0.3)
Neuropathy peripheral [PT]	0	1 (0.3)
Neuropathy peripheral	0	1 (0.3)
Non-cardiac chest pain [PT]	0	2 (0.6)
Non-cardiac chest pain	0	2 (0.6)
Post-traumatic stress disorder [PT]	0	1 (0.3)
Post-traumatic stress disorder	0	1 (0.3)

	Ceftobiprole	Vancomycin
Grouped Query Preferred Term	**N=334 n (%)**	**N=342 n (%)**
Protein total decreased [PT]	0	1 (0.3)
Protein total decreased	0	1 (0.3)
Renal & Urinary Tract Infection [FMQ]	0	1 (0.3)
Urinary tract infection	0	1 (0.3)
Respiratory Failure [FMQ]	0	3 (0.9)
Respiratory failure	0	2 (0.6)
Sleep apnea syndrome	0	1 (0.3)
Rhabdomyolysis [FMQ]	0	2 (0.6)
Rhabdomyolysis	0	2 (0.6)
Septic shock [PT]	0	1 (0.3)
Septic shock	0	1 (0.3)
Skin necrosis [PT]	0	1 (0.3)
Skin necrosis	0	1 (0.3)
Somnolence [FMQ]	0	1 (0.3)
Somnolence	0	1 (0.3)
Study Agent Abuse Potential [FMQ]	0	1 (0.3)
Somnolence	0	1 (0.3)
Syncope [FMQ]	0	1 (0.3)
Syncope	0	1 (0.3)
Tachycardia [FMQ]	0	1 (0.3)
Tachycardia	0	1 (0.3)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any adverse event which occurred between the start of the first dosing up to and including the scheduled last follow-up.
Duration of treatment is up to 14 days.

Abbreviations: GQ, grouped query; N, number of subjects in treatment arm; n, number of subjects with adverse event

17.4. Community-Acquired Bacterial Pneumonia, Trial CAP-3001

The full list of TEAEs by either grouped queries created by the FDA reviewer or FMQs are noted below. For selected AESI, a grouped query was created instead of using the narrow FMQ or in instances where an FMQ was not available.

Table 285. Full Listing of TEAEs by Preferred Term, Group Term, and FMQ, Safety Population, Trial CAP-3001

	Ceftobiprole	Ceftriaxone
Grouped Query **Preferred Term**	**N=310** **n (%)**	**N=322** **n (%)**
Liver enzyme increased [GQ]	30 (9.7)	34 (10.6)
Gamma-glutamyltransferase increased	9 (2.9)	4 (1.2)
Alanine aminotransferase increased	8 (2.6)	10 (3.1)
Transaminases increased	8 (2.6)	13 (4.0)
Aspartate aminotransferase increased	7 (2.3)	7 (2.2)
Hepatic enzyme increased	3 (1.0)	5 (1.6)
Liver function test increased	3 (1.0)	4 (1.2)
Blood alkaline phosphatase increased	2 (0.6)	1 (0.3)
Alanine aminotransferase	1 (0.3)	0
Nausea [FMQ]	30 (9.7)	13 (4.0)
Nausea	30 (9.7)	13 (4.0)
Vomiting [FMQ]	27 (8.7)	9 (2.8)
Vomiting	27 (8.7)	9 (2.8)
Diarrhea [FMQ]	22 (7.1)	28 (8.7)
Diarrhea	22 (7.1)	28 (8.7)
Headache [FMQ]	21 (6.8)	23 (7.1)
Headache	21 (6.8)	23 (7.1)
Bacterial Infection [FMQ]	19 (6.1)	15 (4.7)
Urinary tract infection	5 (1.6)	0
Empyema	4 (1.3)	1 (0.3)
Pulmonary tuberculosis	2 (0.6)	1 (0.3)
Abscess limb	1 (0.3)	0
Cellulitis	1 (0.3)	1 (0.3)
Cholecystitis chronic	1 (0.3)	1 (0.3)
Hordeolum	1 (0.3)	0
Pneumonia chlamydial	1 (0.3)	0
Pseudomonas infection	1 (0.3)	0
Tuberculosis	1 (0.3)	0
Urethritis	1 (0.3)	2 (0.6)
Appendicitis	0	1 (0.3)
Borrelia test positive	0	1 (0.3)
Cholecystitis	0	1 (0.3)
Clostridium difficile colitis	0	2 (0.6)
Infected bite	0	1 (0.3)
Lung abscess	0	2 (0.6)
Sepsis	0	1 (0.3)
Hypokalemia [GQ]	14 (4.5)	19 (5.9)
Hypokalemia	14 (4.5)	19 (5.9)
Insomnia [FMQ]	14 (4.5)	13 (4.0)
Insomnia	14 (4.5)	13 (4.0)
Pneumonia [FMQ]	14 (4.5)	14 (4.3)
Pneumonia	6 (1.9)	10 (3.1)
Empyema	4 (1.3)	1 (0.3)
Pulmonary tuberculosis	2 (0.6)	1 (0.3)
Pneumonia chlamydial	1 (0.3)	0
Pneumonia necrotizing	1 (0.3)	0
Tuberculosis	1 (0.3)	0
Lung abscess	0	2 (0.6)
Rash [GQ]	14 (4.5)	6 (1.9)

	Ceftobiprole	Ceftriaxone
Grouped Query **Preferred Term**	**N=310** **n (%)**	**N=322** **n (%)**
Rash	12 (3.9)	4 (1.2)
Dermatitis allergic	1 (0.3)	1 (0.3)
Dermatitis contact	1 (0.3)	0
Rash pruritic	0	1 (0.3)
Hemorrhage [FMQ]	13 (4.2)	7 (2.2)
Hemoptysis	4 (1.3)	1 (0.3)
Hematoma	2 (0.6)	0
Ecchymosis	1 (0.3)	0
Epistaxis	1 (0.3)	1 (0.3)
Gastrointestinal haemorrhage	1 (0.3)	2 (0.6)
Hematochezia	1 (0.3)	1 (0.3)
Hematuria	1 (0.3)	0
Melena	1 (0.3)	0
Rectal hemorrhage	1 (0.3)	0
Blood urine present	0	1 (0.3)
Conjunctival hemorrhage	0	1 (0.3)
Phlebitis [GQ]	13 (4.2)	7 (2.2)
Phlebitis	12 (3.9)	7 (2.2)
Injection site phlebitis	1 (0.3)	0
Hypertension [GQ]	12 (3.9)	14 (4.3)
Hypertension	11 (3.5)	12 (3.7)
Hypertensive crisis	1 (0.3)	0
Blood pressure increased	0	2 (0.6)
Abdominal pain [GQ]	11 (3.5)	10 (3.1)
Abdominal pain	9 (2.9)	4 (1.2)
Abdominal discomfort	2 (0.6)	2 (0.6)
Abdominal pain upper	0	5 (1.6)
Constipation [FMQ]	11 (3.5)	8 (2.5)
Constipation	11 (3.5)	8 (2.5)
Dizziness [FMQ]	10 (3.2)	8 (2.5)
Dizziness	9 (2.9)	8 (2.5)
Vertigo	1 (0.3)	0
Viral Infection [FMQ]	10 (3.2)	4 (1.2)
Oral herpes	4 (1.3)	3 (0.9)
Gastroenteritis viral	1 (0.3)	0
Genital herpes	1 (0.3)	0
Hepatitis C	1 (0.3)	0
Herpes simplex	1 (0.3)	0
Influenza	1 (0.3)	0
Viral infection	1 (0.3)	0
HIV infection	0	1 (0.3)
Hyperglycemia [FMQ]	8 (2.6)	10 (3.1)
Hyperglycemia	4 (1.3)	7 (2.2)
Diabetes mellitus	3 (1.0)	2 (0.6)
Diabetic foot	1 (0.3)	0
Type 2 diabetes mellitus	1 (0.3)	0
Diabetic complication	0	1 (0.3)
Cough [FMQ]	7 (2.3)	6 (1.9)
Hemoptysis	4 (1.3)	1 (0.3)
Cough	2 (0.6)	4 (1.2)
Productive cough	1 (0.3)	3 (0.9)

	Ceftobiprole	Ceftriaxone
Grouped Query **Preferred Term**	**N=310** **n (%)**	**N=322** **n (%)**
Cardiac failure [GQ]	6 (1.9)	3 (0.9)
Cardiac failure congestive	3 (1.0)	2 (0.6)
Cardiac failure	1 (0.3)	1 (0.3)
Cardiac failure acute	1 (0.3)	0
Cardiogenic shock	1 (0.3)	0
Dysgeusia [FMQ]	6 (1.9)	1 (0.3)
Dysgeusia	6 (1.9)	1 (0.3)
Fatigue [FMQ]	6 (1.9)	3 (0.9)
Malaise	3 (1.0)	0
Asthenia	2 (0.6)	2 (0.6)
Lethargy	1 (0.3)	1 (0.3)
Injection site reaction [GQ]	6 (1.9)	10 (3.1)
Infusion site extravasation	2 (0.6)	2 (0.6)
Infusion site reaction	2 (0.6)	4 (1.2)
Infusion site irritation	1 (0.3)	0
Infusion site oedema	1 (0.3)	2 (0.6)
Infusion site erythema	0	1 (0.3)
Injection site erythema	0	1 (0.3)
Lipid Disorder [FMQ]	6 (1.9)	6 (1.9)
Hypertriglyceridemia	6 (1.9)	5 (1.6)
Blood cholesterol increased	1 (0.3)	0
Hypocholesterolemia	0	1 (0.3)
Renal & Urinary Tract Infection [FMQ]	6 (1.9)	3 (0.9)
Urinary tract infection	5 (1.6)	0
Urethritis	1 (0.3)	2 (0.6)
Urinary tract candidiasis	0	1 (0.3)
Anxiety [GQ]	5 (1.6)	5 (1.6)
Anxiety	4 (1.3)	5 (1.6)
Feeling jittery	1 (0.3)	0
Arrhythmia [FMQ]	5 (1.6)	8 (2.5)
Arrhythmia	2 (0.6)	4 (1.2)
Atrial fibrillation	2 (0.6)	4 (1.2)
Ventricular fibrillation	1 (0.3)	0
Chest pain [PT]	5 (1.6)	8 (2.5)
Chest pain	5 (1.6)	8 (2.5)
Fungal Infection [FMQ]	5 (1.6)	6 (1.9)
Candida infection	3 (1.0)	1 (0.3)
Oral candidiasis	2 (0.6)	3 (0.9)
Genital candidiasis	1 (0.3)	0
Fungal infection	0	1 (0.3)
Urinary tract candidiasis	0	1 (0.3)
Infusion site pain [GQ]	5 (1.6)	3 (0.9)
Infusion site pain	5 (1.6)	3 (0.9)
Peripheral Edema [FMQ]	5 (1.6)	6 (1.9)
Edema peripheral	5 (1.6)	5 (1.6)
Peripheral swelling	0	1 (0.3)
Purulent Material [FMQ]	5 (1.6)	3 (0.9)
Empyema	4 (1.3)	1 (0.3)
Abscess limb	1 (0.3)	0
Lung abscess	0	2 (0.6)
Respiratory Failure [FMQ]	5 (1.6)	10 (3.1)

	Ceftobiprole	Ceftriaxone
Grouped Query **Preferred Term**	**N=310** **n (%)**	**N=322** **n (%)**
Respiratory failure	3 (1.0)	5 (1.6)
Hypoxia	2 (0.6)	4 (1.2)
Acute respiratory failure	1 (0.3)	0
Acute respiratory distress syndrome	0	2 (0.6)
Thrombocytosis [PT]	5 (1.6)	10 (3.1)
Thrombocytosis	5 (1.6)	10 (3.1)
Back Pain [FMQ]	4 (1.3)	3 (0.9)
Back pain	3 (1.0)	3 (0.9)
Flank pain	1 (0.3)	0
Bronchospasm [FMQ]	4 (1.3)	9 (2.8)
Bronchospasm	4 (1.3)	7 (2.2)
Asthma	0	3 (0.9)
Chronic obstructive pulmonary disease [PT]	4 (1.3)	3 (0.9)
Chronic obstructive pulmonary disease	4 (1.3)	3 (0.9)
Dyspepsia [FMQ]	4 (1.3)	5 (1.6)
Dyspepsia	4 (1.3)	5 (1.6)
Hepatic Injury [FMQ]	4 (1.3)	4 (1.2)
Hepatic cirrhosis	1 (0.3)	0
Hepatic function abnormal	1 (0.3)	2 (0.6)
Hepatitis C	1 (0.3)	0
Liver disorder	1 (0.3)	0
Hepatomegaly	0	1 (0.3)
Liver injury	0	1 (0.3)
Hypomagnesaemia [PT]	4 (1.3)	1 (0.3)
Hypomagnesaemia	4 (1.3)	1 (0.3)
Hyponatraemia [PT]	4 (1.3)	9 (2.8)
Hyponatraemia	4 (1.3)	9 (2.8)
Malignancy [FMQ]	4 (1.3)	3 (0.9)
Lung neoplasm malignant	4 (1.3)	2 (0.6)
Neoplasm malignant	0	1 (0.3)
Nasopharyngitis [FMQ]	4 (1.3)	2 (0.6)
Upper respiratory tract infection	2 (0.6)	0
Nasopharyngitis	1 (0.3)	1 (0.3)
Pharyngitis	1 (0.3)	0
Rhinitis	0	1 (0.3)
Abdominal distension [PT]	3 (1.0)	3 (0.9)
Abdominal distension	3 (1.0)	3 (0.9)
Arthralgia [FMQ]	3 (1.0)	2 (0.6)
Arthralgia	3 (1.0)	2 (0.6)
Decreased Appetite [FMQ]	3 (1.0)	2 (0.6)
Decreased appetite	3 (1.0)	2 (0.6)
Hypophosphatemia [PT]	3 (1.0)	2 (0.6)
Hypophosphatemia	3 (1.0)	2 (0.6)
Oropharyngeal pain [PT]	3 (1.0)	0
Oropharyngeal pain	3 (1.0)	0
Pleural effusion [PT]	3 (1.0)	2 (0.6)
Pleural effusion	3 (1.0)	2 (0.6)
Pruritus [FMQ]	3 (1.0)	4 (1.2)
Pruritus	2 (0.6)	4 (1.2)
Vulvovaginal pruritus	1 (0.3)	0
Pyrexia [FMQ]	3 (1.0)	8 (2.5)

	Ceftobiprole	Ceftriaxone
Grouped Query **Preferred Term**	**N=310** **n (%)**	**N=322** **n (%)**
Pyrexia	3 (1.0)	8 (2.5)
Tachycardia [GQ]	3 (1.0)	2 (0.6)
Tachycardia	2 (0.6)	2 (0.6)
Supraventricular tachycardia	1 (0.3)	0
Toothache [PT]	3 (1.0)	0
Toothache	3 (1.0)	0
Anemia [GQ]	2 (0.6)	11 (3.4)
Anemia	2 (0.6)	11 (3.4)
Angina [GQ]	2 (0.6)	0
Angina pectoris	2 (0.6)	0
Arthritis [FMQ]	2 (0.6)	1 (0.3)
Gouty arthritis	1 (0.3)	0
Spinal osteoarthritis	1 (0.3)	0
Osteoarthritis	0	1 (0.3)
Asymptomatic bacteriuria [PT]	2 (0.6)	0
Asymptomatic bacteriuria	2 (0.6)	0
Blood lactate dehydrogenase increased [PT]	2 (0.6)	3 (0.9)
Blood lactate dehydrogenase increased	2 (0.6)	3 (0.9)
Chest discomfort [PT]	2 (0.6)	2 (0.6)
Chest discomfort	2 (0.6)	2 (0.6)
Confusional State [FMQ]	2 (0.6)	3 (0.9)
Delirium	2 (0.6)	0
Confusional state	0	1 (0.3)
Disorientation	0	2 (0.6)
Dysphagia [PT]	2 (0.6)	0
Dysphagia	2 (0.6)	0
Dyspnea [GQ]	2 (0.6)	2 (0.6)
Dyspnea	2 (0.6)	1 (0.3)
Dyspnea exertional	0	1 (0.3)
Erythema [FMQ]	2 (0.6)	3 (0.9)
Erythema	1 (0.3)	2 (0.6)
Flushing	1 (0.3)	1 (0.3)
Fall [FMQ]	2 (0.6)	0
Fall	2 (0.6)	0
Gastritis [GQ]	2 (0.6)	0
Chronic gastritis	1 (0.3)	0
Gastritis	1 (0.3)	0
Hepatic steatosis [PT]	2 (0.6)	2 (0.6)
Hepatic steatosis	2 (0.6)	2 (0.6)
Hypersensitivity [GQ]	2 (0.6)	1 (0.3)
Anaphylactic shock	1 (0.3)	0
Hypersensitivity	1 (0.3)	0
Urticaria	0	1 (0.3)
Hypocalcemia [PT]	2 (0.6)	4 (1.2)
Hypocalcemia	2 (0.6)	4 (1.2)
Hypochloremia [PT]	2 (0.6)	0
Hypochloremia	2 (0.6)	0
Hypoglycemia [FMQ]	2 (0.6)	5 (1.6)
Hypoglycemia	2 (0.6)	5 (1.6)
Hypotension [FMQ]	2 (0.6)	3 (0.9)
Hypotension	2 (0.6)	3 (0.9)

	Ceftobiprole	Ceftriaxone
Grouped Query **Preferred Term**	**N=310** **n (%)**	**N=322** **n (%)**
Muscle spasms [PT]	2 (0.6)	0
Muscle spasms	2 (0.6)	0
Myocardial injury [GQ]	2 (0.6)	4 (1.2)
Acute myocardial infarction	1 (0.3)	1 (0.3)
Myocardial infarction	1 (0.3)	0
Myocardial ischemia	0	3 (0.9)
Night sweats [PT]	2 (0.6)	0
Night sweats	2 (0.6)	0
Esophagitis [PT]	2 (0.6)	0
Esophagitis	2 (0.6)	0
Pain [PT]	2 (0.6)	2 (0.6)
Pain	2 (0.6)	2 (0.6)
Pain in extremity [PT]	2 (0.6)	3 (0.9)
Pain in extremity	2 (0.6)	3 (0.9)
Phlebotomy [PT]	2 (0.6)	0
Phlebotomy	2 (0.6)	0
Pleurisy [PT]	2 (0.6)	3 (0.9)
Pleurisy	2 (0.6)	3 (0.9)
Renal cyst [PT]	2 (0.6)	1 (0.3)
Renal cyst	2 (0.6)	1 (0.3)
Renal impairment [GQ]	2 (0.6)	6 (1.9)
Acute kidney injury	1 (0.3)	1 (0.3)
Creatinine renal clearance decreased	1 (0.3)	2 (0.6)
Blood creatinine increased	0	1 (0.3)
Renal failure	0	1 (0.3)
Renal impairment	0	1 (0.3)
Rhinorrhea [PT]	2 (0.6)	2 (0.6)
Rhinorrhea	2 (0.6)	2 (0.6)
Somnolence [FMQ]	2 (0.6)	2 (0.6)
Lethargy	1 (0.3)	1 (0.3)
Sedation	1 (0.3)	0
Somnolence	0	1 (0.3)
Study Agent Abuse Potential [FMQ]	2 (0.6)	1 (0.3)
Euphoric mood	1 (0.3)	0
Sedation	1 (0.3)	0
Somnolence	0	1 (0.3)
Thrombosis Arterial [FMQ]	2 (0.6)	0
Cerebral infarction	1 (0.3)	0
Infarction	1 (0.3)	0
Urine odor abnormal [PT]	2 (0.6)	0
Urine odor abnormal	2 (0.6)	0
Vision impairment [GQ]	2 (0.6)	0
Vision blurred	2 (0.6)	0
Volume Depletion [FMQ]	2 (0.6)	0
Dehydration	2 (0.6)	0
Acne [PT]	1 (0.3)	0
Acne	1 (0.3)	0
Alcohol abuse [PT]	1 (0.3)	0
Alcohol abuse	1 (0.3)	0
Amenorrhea [FMQ]	1 (0.3)	0
Amenorrhea	1 (0.3)	0

	Ceftobiprole	Ceftriaxone
Grouped Query **Preferred Term**	**N=310** **n (%)**	**N=322** **n (%)**
Ascites [PT]	1 (0.3)	0
Ascites	1 (0.3)	0
Blister [PT]	1 (0.3)	0
Blister	1 (0.3)	0
Blood albumin decreased [PT]	1 (0.3)	0
Blood albumin decreased	1 (0.3)	0
Blood creatine phosphokinase increased [PT]	1 (0.3)	2 (0.6)
Blood creatine phosphokinase increased	1 (0.3)	2 (0.6)
Blood thyroid stimulating hormone increased [PT]	1 (0.3)	0
Blood thyroid stimulating hormone increased	1 (0.3)	0
Blood uric acid increased [PT]	1 (0.3)	0
Blood uric acid increased	1 (0.3)	0
Bradycardia [GQ]	1 (0.3)	2 (0.6)
Bradycardia	1 (0.3)	1 (0.3)
Sinus bradycardia	0	1 (0.3)
Bronchitis [PT]	1 (0.3)	0
Bronchitis	1 (0.3)	0
Bursitis [PT]	1 (0.3)	0
Bursitis	1 (0.3)	0
Cardiac hypertrophy [PT]	1 (0.3)	0
Cardiac hypertrophy	1 (0.3)	0
Cerebral infarction [PT]	1 (0.3)	0
Cerebral infarction	1 (0.3)	0
Chills [PT]	1 (0.3)	1 (0.3)
Chills	1 (0.3)	1 (0.3)
Cholecystitis [FMQ]	1 (0.3)	2 (0.6)
Cholecystitis chronic	1 (0.3)	1 (0.3)
Cholecystitis	0	1 (0.3)
Circulatory collapse [PT]	1 (0.3)	0
Circulatory collapse	1 (0.3)	0
Conjunctivitis [PT]	1 (0.3)	0
Conjunctivitis	1 (0.3)	0
Decreased Menstrual Bleeding [FMQ]	1 (0.3)	0
Amenorrhea	1 (0.3)	0
Decubitus ulcer [PT]	1 (0.3)	0
Decubitus ulcer	1 (0.3)	0
Dry Mouth [FMQ]	1 (0.3)	1 (0.3)
Dry mouth	1 (0.3)	0
Dry throat	0	1 (0.3)
Duodenal ulcer [PT]	1 (0.3)	1 (0.3)
Duodenal ulcer	1 (0.3)	1 (0.3)
Dysphonia [PT]	1 (0.3)	0
Dysphonia	1 (0.3)	0
Ear discomfort [PT]	1 (0.3)	0
Ear discomfort	1 (0.3)	0
Ear disorder [PT]	1 (0.3)	0
Ear disorder	1 (0.3)	0
Ear pain [PT]	1 (0.3)	1 (0.3)
Ear pain	1 (0.3)	1 (0.3)

	Ceftobiprole	Ceftriaxone
Grouped Query **Preferred Term**	**N=310** **n (%)**	**N=322** **n (%)**
Electrocardiogram abnormal [PT]	1 (0.3)	0
Electrocardiogram abnormal	1 (0.3)	0
Epidermolysis [PT]	1 (0.3)	0
Epidermolysis	1 (0.3)	0
Eye pain [PT]	1 (0.3)	0
Eye pain	1 (0.3)	0
Feeling hot [PT]	1 (0.3)	0
Feeling hot	1 (0.3)	0
Fracture [FMQ]	1 (0.3)	3 (0.9)
Rib fracture	1 (0.3)	2 (0.6)
Patella fracture	0	1 (0.3)
Gastric ulcer [PT]	1 (0.3)	0
Gastric ulcer	1 (0.3)	0
Gastroenteritis [PT]	1 (0.3)	1 (0.3)
Gastroenteritis	1 (0.3)	1 (0.3)
Gastroesophageal reflux disease [PT]	1 (0.3)	0
Gastroesophageal reflux disease	1 (0.3)	0
Gout [FMQ]	1 (0.3)	0
Gouty arthritis	1 (0.3)	0
Hemangioma [PT]	1 (0.3)	0
Hemangioma	1 (0.3)	0
Hemorrhoids [PT]	1 (0.3)	0
Hemorrhoids	1 (0.3)	0
Heart Failure [FMQ]	1 (0.3)	1 (0.3)
Acute pulmonary edema	1 (0.3)	0
Pulmonary edema	0	1 (0.3)
Hepatic cyst [PT]	1 (0.3)	0
Hepatic cyst	1 (0.3)	0
Hepatitis [GQ]	1 (0.3)	1 (0.3)
Hepatitis	1 (0.3)	1 (0.3)
Hyperemia [PT]	1 (0.3)	2 (0.6)
Hyperemia	1 (0.3)	2 (0.6)
Hyperhidrosis [PT]	1 (0.3)	2 (0.6)
Hyperhidrosis	1 (0.3)	2 (0.6)
Hypervolemia [PT]	1 (0.3)	0
Hypervolemia	1 (0.3)	0
Hypothyroidism [PT]	1 (0.3)	0
Hypothyroidism	1 (0.3)	0
Infarction [PT]	1 (0.3)	0
Infarction	1 (0.3)	0
Influenza like illness [PT]	1 (0.3)	0
Influenza like illness	1 (0.3)	0
Intervertebral disc protrusion [PT]	1 (0.3)	0
Intervertebral disc protrusion	1 (0.3)	0
Irritability [FMQ]	1 (0.3)	0
Irritability	1 (0.3)	0
Jaundice [PT]	1 (0.3)	0
Jaundice	1 (0.3)	0
Leukemoid reaction [PT]	1 (0.3)	0
Leukemoid reaction	1 (0.3)	0
Leukocytosis [GQ]	1 (0.3)	3 (0.9)

	Ceftobiprole	Ceftriaxone
Grouped Query **Preferred Term**	**N=310** **n (%)**	**N=322** **n (%)**
Leukocytosis	1 (0.3)	3 (0.9)
Leukopenia [GQ]	1 (0.3)	2 (0.6)
Leukopenia	1 (0.3)	1 (0.3)
Neutropenia	0	1 (0.3)
Ligament rupture [PT]	1 (0.3)	0
Ligament rupture	1 (0.3)	0
Mania [FMQ]	1 (0.3)	0
Euphoric mood	1 (0.3)	0
Mouth ulceration [PT]	1 (0.3)	2 (0.6)
Mouth ulceration	1 (0.3)	2 (0.6)
Muscle contracture [PT]	1 (0.3)	0
Muscle contracture	1 (0.3)	0
Myalgia [FMQ]	1 (0.3)	0
Myalgia	1 (0.3)	0
Nicotine dependence [PT]	1 (0.3)	0
Nicotine dependence	1 (0.3)	0
Obstruction [PT]	1 (0.3)	0
Obstruction	1 (0.3)	0
Organizing pneumonia [PT]	1 (0.3)	0
Organizing pneumonia	1 (0.3)	0
Pain of skin [PT]	1 (0.3)	0
Pain of skin	1 (0.3)	0
Panic attack [PT]	1 (0.3)	0
Panic attack	1 (0.3)	0
Parasomnia [FMQ]	1 (0.3)	0
Nightmare	1 (0.3)	0
Pericarditis [PT]	1 (0.3)	0
Pericarditis	1 (0.3)	0
Pollakiuria [PT]	1 (0.3)	0
Pollakiuria	1 (0.3)	0
Protein total increased [PT]	1 (0.3)	0
Protein total increased	1 (0.3)	0
Prothrombin time prolonged [PT]	1 (0.3)	0
Prothrombin time prolonged	1 (0.3)	0
Pulmonary mass [PT]	1 (0.3)	0
Pulmonary mass	1 (0.3)	0
Respiratory tract infection [PT]	1 (0.3)	1 (0.3)
Respiratory tract infection	1 (0.3)	1 (0.3)
Restlessness [PT]	1 (0.3)	0
Restlessness	1 (0.3)	0
Seizure [FMQ]	1 (0.3)	1 (0.3)
Seizure	1 (0.3)	1 (0.3)
Sinusitis [PT]	1 (0.3)	1 (0.3)
Sinusitis	1 (0.3)	1 (0.3)
Skin laceration [PT]	1 (0.3)	1 (0.3)
Skin laceration	1 (0.3)	1 (0.3)
Small intestinal obstruction [PT]	1 (0.3)	0
Small intestinal obstruction	1 (0.3)	0
Stroke and TIA [FMQ]	1 (0.3)	0
Cerebral infarction	1 (0.3)	0
Swelling face [PT]	1 (0.3)	0

	Ceftobiprole	Ceftriaxone
Grouped Query **Preferred Term**	**N=310** **n (%)**	**N=322** **n (%)**
Swelling face	1 (0.3)	0
Thrombocytopenia [GQ]	1 (0.3)	2 (0.6)
Thrombocytopenia	1 (0.3)	2 (0.6)
Tinnitus [PT]	1 (0.3)	0
Tinnitus	1 (0.3)	0
Tonsillitis [PT]	1 (0.3)	0
Tonsillitis	1 (0.3)	0
Tremor [FMQ]	1 (0.3)	1 (0.3)
Tremor	1 (0.3)	1 (0.3)
Urine abnormality [PT]	1 (0.3)	0
Urine abnormality	1 (0.3)	0
Vertigo [FMQ]	1 (0.3)	0
Vertigo	1 (0.3)	0
Vulvovaginal inflammation [PT]	1 (0.3)	0
Vulvovaginal inflammation	1 (0.3)	0
Wheezing [PT]	1 (0.3)	0
Wheezing	1 (0.3)	0
Alopecia [FMQ]	0	1 (0.3)
Alopecia	0	1 (0.3)
Amylase increased [PT]	0	1 (0.3)
Amylase increased	0	1 (0.3)
Anemia [FMQ]	0	1 (0.3)
Pancytopenia	0	1 (0.3)
Anosmia [PT]	0	1 (0.3)
Anosmia	0	1 (0.3)
Atelectasis [PT]	0	1 (0.3)
Atelectasis	0	1 (0.3)
Barrett's esophagus [PT]	0	1 (0.3)
Barrett's esophagus	0	1 (0.3)
Blood creatinine decreased [PT]	0	1 (0.3)
Blood creatinine decreased	0	1 (0.3)
Blood gases abnormal [PT]	0	1 (0.3)
Blood gases abnormal	0	1 (0.3)
Blood urea abnormal [PT]	0	1 (0.3)
Blood urea abnormal	0	1 (0.3)
Blood urea increased [PT]	0	2 (0.6)
Blood urea increased	0	2 (0.6)
Bradypnea [PT]	0	1 (0.3)
Bradypnea	0	1 (0.3)
Bronchiectasis [PT]	0	1 (0.3)
Bronchiectasis	0	1 (0.3)
Bronchitis chronic [PT]	0	1 (0.3)
Bronchitis chronic	0	1 (0.3)
C-reactive protein increased [PT]	0	1 (0.3)
C-reactive protein increased	0	1 (0.3)
Cardiomegaly [PT]	0	1 (0.3)
Cardiomegaly	0	1 (0.3)
Cholelithiasis [PT]	0	2 (0.6)
Cholelithiasis	0	2 (0.6)
Coronary artery disease [PT]	0	1 (0.3)
Coronary artery disease	0	1 (0.3)

	Ceftobiprole	Ceftriaxone
Grouped Query **Preferred Term**	**N=310** **n (%)**	**N=322** **n (%)**
CSF test abnormal [PT]	0	1 (0.3)
CSF test abnormal	0	1 (0.3)
Death [GQ]	0	2 (0.6)
Sudden death	0	2 (0.6)
Depression [FMQ]	0	1 (0.3)
Depression	0	1 (0.3)
Dry skin [PT]	0	1 (0.3)
Dry skin	0	1 (0.3)
Emphysema [PT]	0	1 (0.3)
Emphysema	0	1 (0.3)
Excessive cerumen production [PT]	0	1 (0.3)
Excessive cerumen production	0	1 (0.3)
Flatulence [PT]	0	4 (1.2)
Flatulence	0	4 (1.2)
Fluid retention [PT]	0	1 (0.3)
Fluid retention	0	1 (0.3)
Gallbladder polyp [PT]	0	1 (0.3)
Gallbladder polyp	0	1 (0.3)
Glossitis [PT]	0	1 (0.3)
Glossitis	0	1 (0.3)
Hiccups [PT]	0	1 (0.3)
Hiccups	0	1 (0.3)
Hot flush [PT]	0	2 (0.6)
Hot flush	0	2 (0.6)
Hyperchloremia [PT]	0	1 (0.3)
Hyperchloremia	0	1 (0.3)
Hyperkalemia [GQ]	0	4 (1.2)
Hyperkalemia	0	4 (1.2)
Hyperuricemia [PT]	0	1 (0.3)
Hyperuricemia	0	1 (0.3)
Hypoalbuminemia [PT]	0	1 (0.3)
Hypoalbuminemia	0	1 (0.3)
Hypoproteinemia [PT]	0	1 (0.3)
Hypoproteinemia	0	1 (0.3)
Hyporeflexia [PT]	0	1 (0.3)
Hyporeflexia	0	1 (0.3)
Hypotonia [PT]	0	1 (0.3)
Hypotonia	0	1 (0.3)
Hypouricemia [PT]	0	1 (0.3)
Hypouricemia	0	1 (0.3)
Impaired gastric emptying [PT]	0	1 (0.3)
Impaired gastric emptying	0	1 (0.3)
Inappropriate antidiuretic hormone secretion [PT]	0	1 (0.3)
Inappropriate antidiuretic hormone secretion	0	1 (0.3)
Incontinence [PT]	0	1 (0.3)
Incontinence	0	1 (0.3)
Inflammation [PT]	0	1 (0.3)
Inflammation	0	1 (0.3)
Laryngitis [PT]	0	1 (0.3)
Laryngitis	0	1 (0.3)

Grouped Query Preferred Term	Ceftobiprole N=310 n (%)	Ceftriaxone N=322 n (%)
Limb discomfort [PT]	0	1 (0.3)
Limb discomfort	0	1 (0.3)
Lymphadenopathy [GQ]	0	1 (0.3)
Lymphadenopathy	0	1 (0.3)
Lymphocyte morphology abnormal [PT]	0	1 (0.3)
Lymphocyte morphology abnormal	0	1 (0.3)
Mental impairment [PT]	0	1 (0.3)
Mental impairment	0	1 (0.3)
Muscle injury [PT]	0	1 (0.3)
Muscle injury	0	1 (0.3)
Muscle twitching [PT]	0	1 (0.3)
Muscle twitching	0	1 (0.3)
Neck pain [PT]	0	3 (0.9)
Neck pain	0	3 (0.9)
Neuralgia [PT]	0	1 (0.3)
Neuralgia	0	1 (0.3)
Neutrophilia [PT]	0	2 (0.6)
Neutrophilia	0	2 (0.6)
Edema [PT]	0	3 (0.9)
Edema	0	3 (0.9)
Esophageal disorder [PT]	0	1 (0.3)
Esophageal disorder	0	1 (0.3)
Overdose [PT]	0	1 (0.3)
Overdose	0	1 (0.3)
Pancytopenia [PT]	0	1 (0.3)
Pancytopenia	0	1 (0.3)
Paresthesia [FMQ]	0	1 (0.3)
Paresthesia	0	1 (0.3)
Pericardial effusion [PT]	0	1 (0.3)
Pericardial effusion	0	1 (0.3)
Pneumothorax [PT]	0	2 (0.6)
Pneumothorax	0	2 (0.6)
Proteinuria [PT]	0	1 (0.3)
Proteinuria	0	1 (0.3)
Psychomotor hyperactivity [PT]	0	1 (0.3)
Psychomotor hyperactivity	0	1 (0.3)
Pulmonary congestion [PT]	0	1 (0.3)
Pulmonary congestion	0	1 (0.3)
Pulmonary hypertension [PT]	0	1 (0.3)
Pulmonary hypertension	0	1 (0.3)
Renal pain [PT]	0	1 (0.3)
Renal pain	0	1 (0.3)
Scrotal edema [PT]	0	1 (0.3)
Scrotal edema	0	1 (0.3)
Septic shock [PT]	0	2 (0.6)
Septic shock	0	2 (0.6)
Skin abrasion [PT]	0	1 (0.3)
Skin abrasion	0	1 (0.3)
Skin exfoliation [PT]	0	1 (0.3)
Skin exfoliation	0	1 (0.3)
Sleep disorder [PT]	0	1 (0.3)

Grouped Query Preferred Term	Ceftobiprole N=310 n (%)	Ceftriaxone N=322 n (%)
Sleep disorder	0	1 (0.3)
Spinal fusion surgery [PT]	0	1 (0.3)
Spinal fusion surgery	0	1 (0.3)
Sputum abnormal [PT]	0	1 (0.3)
Sputum abnormal	0	1 (0.3)
Strabismus [PT]	0	1 (0.3)
Strabismus	0	1 (0.3)
Subcutaneous emphysema [PT]	0	1 (0.3)
Subcutaneous emphysema	0	1 (0.3)
Swelling [PT]	0	1 (0.3)
Swelling	0	1 (0.3)
Thrombosis [GQ]	0	1 (0.3)
Deep vein thrombosis	0	1 (0.3)
Treatment failure [PT]	0	1 (0.3)
Treatment failure	0	1 (0.3)
Urinary incontinence [PT]	0	1 (0.3)
Urinary incontinence	0	1 (0.3)
Urinary Retention [FMQ]	0	1 (0.3)
Urinary retention	0	1 (0.3)
Urine analysis abnormal [PT]	0	1 (0.3)
Urine analysis abnormal	0	1 (0.3)
Vulvovaginal candidiasis [GQ]	0	1 (0.3)
Vulvovaginal mycotic infection	0	1 (0.3)
Vulvovaginal discomfort [PT]	0	1 (0.3)
Vulvovaginal discomfort	0	1 (0.3)
Weight decreased [PT]	0	1 (0.3)
Weight decreased	0	1 (0.3)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as an AE that is new in onset or aggravated in severity after the first dose treatment.
Duration is 4-day minimum study drug treatment period with prolonged treatment period of up to 10 days.
Abbreviations: CSF, cerebrospinal fluid; GQ, grouped query; N, number of subjects in treatment arm; n, number of subjects with adverse event

17.5. Community-Acquired Bacterial Pneumonia, Trial BPR-PIP-002 (Pediatric)

A full list of treatment-emergent AEs recorded in Trial BPR-PIP-002 is provided below.

Table 286. Full Listing of Treatment-Emergent Adverse Events, Safety Population, Trial BPR-PIP-002

Preferred Term	Ceftobiprole N=94 n (%)	Cephalosporin ± Vancomycin N=44 n (%)
Any AE	30 (31.9)	13 (29.5)
Vomiting	7 (7.4)	1 (2.3)
Viral infection	4 (4.3)	0
Headache	3 (3.2)	0

Preferred Term	Ceftobiprole N=94 n (%)	Cephalosporin ± Vancomycin N=44 n (%)
Pneumonia	3 (3.2)	0
Alanine aminotransferase increased	3 (3.2)	0
Infusion site reaction	2 (2.1)	0
Aphthous ulcer	1 (1.1)	0
Aspartate aminotransferase increased	1 (1.1)	0
Dehydration	1 (1.1)	0
Dermatitis allergic	1 (1.1)	0
Functional gastrointestinal disorder	1 (1.1)	0
Hyperkalemia	1 (1.1)	0
Hypersensitivity	1 (1.1)	0
Laryngitis	1 (1.1)	0
Nasopharyngitis	1 (1.1)	0
Pharyngitis streptococcal	1 (1.1)	0
Phlebitis	2 (2.1)	0
Pleural effusion	1 (1.1)	0
Pleurisy	1 (1.1)	0
Pyrexia	1 (1.1)	0
Tonsillitis streptococcal	1 (1.1)	0
Upper respiratory tract infection	1 (1.1)	0
Wheezing	1 (1.1)	0
Neutropenia	1 (1.1)	1 (2.3)
Otitis media	1 (1.1)	1 (2.3)
Urticaria	1 (1.1)	1 (2.3)
Abdominal pain	0	1 (2.3)
Gastroenteritis	0	1 (2.3)
Pain in extremity	0	1 (2.3)
Rhinitis	0	1 (2.3)
Seizure like phenomena	0	1 (2.3)
Thrombocytopenia	0	1 (2.3)
Bronchitis	0	2 (4.5)
Diarrhea	2 (2.1)	4 (9.1)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as any adverse event that began after treatment began.
Duration of treatment is 7-14 days including a minimum of 3 days of study drug treatment and subsequent switch to defined age-appropriate oral antibacterial drug.
Coded as MedDRA preferred terms.
Abbreviations: AE, adverse event; N, number of patients in treatment arm; n, number of patients with adverse event

17.6. HABP/VABP, Trial BAP 248/307

The full list of TEAEs by either grouped queries (created by the FDA reviewer) or FMQs are noted below. For selected AESI, a grouped query was created instead of using the narrow FMQ or in instances where an FMQ was not available.

Reference ID: 5357793

Table 287. Full Listing of TEAEs by Preferred Term, Group Term, and FMQ, Safety Population, Trial BAP248/307

Grouped Query Preferred Term	Ceftobiprole N=386 n (%)	Linezolid/ Ceftazidime N=386 n (%)
Bacterial Infection [FMQ]	70 (18.1)	55 (14.2)
Urinary tract infection	18 (4.7)	17 (4.4)
Sepsis	15 (3.9)	11 (2.8)
Bacteremia	5 (1.3)	6 (1.6)
Clostridium difficile colitis	5 (1.3)	2 (0.5)
Cholecystitis	3 (0.8)	0
Device related sepsis	3 (0.8)	0
Postoperative wound infection	3 (0.8)	2 (0.5)
Empyema	2 (0.5)	3 (0.8)
Lung abscess	2 (0.5)	1 (0.3)
Pyelonephritis	2 (0.5)	0
Staphylococcal bacteremia	2 (0.5)	0
Abdominal abscess	1 (0.3)	1 (0.3)
Abscess	1 (0.3)	2 (0.5)
Cholecystitis acute	1 (0.3)	1 (0.3)
Conjunctivitis bacterial	1 (0.3)	0
Device related infection	1 (0.3)	3 (0.8)
Fournier's gangrene	1 (0.3)	0
Implant site infection	1 (0.3)	0
Incision site cellulitis	1 (0.3)	0
Meningitis tuberculous	1 (0.3)	0
Pneumonia legionella	1 (0.3)	0
Pseudomonas infection	1 (0.3)	1 (0.3)
Psoas abscess	1 (0.3)	0
Pulmonary tuberculosis	1 (0.3)	0
Pustule	1 (0.3)	0
Staphylococcal infection	1 (0.3)	1 (0.3)
Subdiaphragmatic abscess	1 (0.3)	0
Wound abscess	1 (0.3)	0
Wound infection	1 (0.3)	2 (0.5)
Abdominal sepsis	0	1 (0.3)
Breast abscess	0	1 (0.3)
Bronchitis bacterial	0	2 (0.5)
Cholangitis	0	1 (0.3)
Clostridial infection	0	2 (0.5)
Cystitis	0	1 (0.3)
Endocarditis bacterial	0	1 (0.3)
Erysipelas	0	1 (0.3)
Pyopneumothorax	0	1 (0.3)
Staphylococcal sepsis	0	2 (0.5)
Stenotrophomonas infection	0	1 (0.3)
Urethritis	0	1 (0.3)
Diarrhea [FMQ]	43 (11.1)	60 (15.5)
Diarrhea	43 (11.1)	60 (15.5)

Grouped Query Preferred Term	Ceftobiprole N=386 n (%)	Linezolid/ Ceftazidime N=386 n (%)
Respiratory Failure [FMQ]	42 (10.9)	37 (9.6)
Respiratory failure	19 (4.9)	16 (4.1)
Hypoxia	7 (1.8)	2 (0.5)
Acute respiratory distress syndrome	5 (1.3)	5 (1.3)
Respiratory acidosis	3 (0.8)	1 (0.3)
Acute respiratory failure	2 (0.5)	4 (1.0)
Respiratory arrest	2 (0.5)	0
Tracheostomy	2 (0.5)	4 (1.0)
Asphyxia	1 (0.3)	2 (0.5)
Cardiopulmonary failure	1 (0.3)	2 (0.5)
Cyanosis	1 (0.3)	0
Carbon dioxide increased	0	1 (0.3)
Endotracheal intubation	0	1 (0.3)
Hypoventilation	0	1 (0.3)
Mechanical ventilation	0	1 (0.3)
Sleep apnea syndrome	0	1 (0.3)
Pyrexia [FMQ]	41 (10.6)	33 (8.5)
Pyrexia	40 (10.4)	33 (8.5)
Hyperthermia	1 (0.3)	0
Hypokalemia [GQ]	40 (10.4)	33 (8.5)
Hypokalemia	40 (10.4)	33 (8.5)
Hyponatremia [PT]	38 (9.8)	26 (6.7)
Hyponatremia	38 (9.8)	26 (6.7)
Vomiting [FMQ]	28 (7.3)	12 (3.1)
Vomiting	28 (7.3)	12 (3.1)
Arrhythmia [FMQ]	27 (7.0)	29 (7.5)
Bradycardia	8 (2.1)	6 (1.6)
Atrial fibrillation	7 (1.8)	8 (2.1)
Tachycardia	5 (1.3)	8 (2.1)
Arrhythmia	4 (1.0)	6 (1.6)
Sinus tachycardia	2 (0.5)	2 (0.5)
Supraventricular tachycardia	2 (0.5)	0
Ventricular fibrillation	2 (0.5)	1 (0.3)
Ventricular extrasystoles	1 (0.3)	1 (0.3)
Ventricular tachycardia	1 (0.3)	0
Supraventricular extrasystoles	0	2 (0.5)
Tachyarrhythmia	0	1 (0.3)
Anemia [GQ]	26 (6.7)	24 (6.2)
Anemia	24 (6.2)	23 (6.0)
Hemoglobin decreased	1 (0.3)	1 (0.3)
Normocytic anemia	1 (0.3)	0
Hemorrhage [FMQ]	26 (6.7)	30 (7.8)
Hematuria	4 (1.0)	7 (1.8)
Epistaxis	3 (0.8)	2 (0.5)
Gastrointestinal hemorrhage	3 (0.8)	6 (1.6)

Grouped Query Preferred Term	Ceftobiprole N=386 n (%)	Linezolid/ Ceftazidime N=386 n (%)
Hematoma	2 (0.5)	2 (0.5)
Petechiae	2 (0.5)	0
Duodenal ulcer hemorrhage	1 (0.3)	0
Ecchymosis	1 (0.3)	2 (0.5)
Gastric hemorrhage	1 (0.3)	2 (0.5)
Gastric ulcer hemorrhage	1 (0.3)	1 (0.3)
Gastritis hemorrhagic	1 (0.3)	0
Hematochezia	1 (0.3)	0
Hematoma evacuation	1 (0.3)	0
Hemoptysis	1 (0.3)	4 (1.0)
Hemorrhage	1 (0.3)	1 (0.3)
Hemothorax	1 (0.3)	1 (0.3)
Intraventricular hemorrhage	1 (0.3)	0
Melena	1 (0.3)	0
Post procedural hemorrhage	1 (0.3)	0
Splenic hemorrhage	1 (0.3)	0
Vaginal hemorrhage	1 (0.3)	0
Cerebral hemorrhage	0	1 (0.3)
Ear hemorrhage	0	1 (0.3)
Hemorrhage subcutaneous	0	1 (0.3)
Small intestinal hemorrhage	0	1 (0.3)
Liver enzyme increased [GQ]	25 (6.5)	23 (6.0)
Liver function test abnormal	8 (2.1)	1 (0.3)
Alanine aminotransferase increased	6 (1.6)	10 (2.6)
Aspartate aminotransferase increased	5 (1.3)	9 (2.3)
Gamma-glutamyltransferase increased	5 (1.3)	4 (1.0)
Blood alkaline phosphatase increased	4 (1.0)	4 (1.0)
Hepatic enzyme increased	4 (1.0)	2 (0.5)
Transaminases increased	2 (0.5)	3 (0.8)
Hepatic enzyme abnormal	1 (0.3)	0
Blood bilirubin increased	0	1 (0.3)
Gamma-glutamyltransferase abnormal	0	1 (0.3)
Hyperbilirubinemia	0	1 (0.3)
Pneumonia [FMQ]	25 (6.5)	21 (5.4)
Pneumonia	17 (4.4)	16 (4.1)
Empyema	2 (0.5)	3 (0.8)
Lung abscess	2 (0.5)	1 (0.3)
Pneumonia aspiration	2 (0.5)	2 (0.5)
Pneumonia legionella	1 (0.3)	0
Pulmonary tuberculosis	1 (0.3)	0

Grouped Query Preferred Term	Ceftobiprole N=386 n (%)	Linezolid/ Ceftazidime N=386 n (%)
Fungal Infection [FMQ]	22 (5.7)	29 (7.5)
Oral candidiasis	7 (1.8)	4 (1.0)
Candida infection	6 (1.6)	5 (1.3)
Fungal skin infection	3 (0.8)	6 (1.6)
Fungal infection	2 (0.5)	3 (0.8)
Systemic candida	2 (0.5)	3 (0.8)
Fungemia	1 (0.3)	1 (0.3)
Vulvovaginal candidiasis	1 (0.3)	0
Fungal test positive	0	1 (0.3)
Oropharyngeal candidiasis	0	2 (0.5)
Urinary tract candidiasis	0	5 (1.3)
Renal & Urinary Tract Infection [FMQ]	22 (5.7)	24 (6.2)
Urinary tract infection	18 (4.7)	17 (4.4)
Culture urine positive	2 (0.5)	2 (0.5)
Pyelonephritis	2 (0.5)	0
Cystitis	0	1 (0.3)
Urethritis	0	1 (0.3)
Urinary tract candidiasis	0	5 (1.3)
Renal impairment [GQ]	21 (5.4)	13 (3.4)
Blood creatinine increased	7 (1.8)	4 (1.0)
Renal failure	7 (1.8)	3 (0.8)
Acute kidney injury	5 (1.3)	5 (1.3)
Renal impairment	3 (0.8)	1 (0.3)
Creatinine renal clearance decreased	1 (0.3)	2 (0.5)
Cardiac failure [GQ]	19 (4.9)	10 (2.6)
Cardiac failure	10 (2.6)	7 (1.8)
Cardiac failure congestive	7 (1.8)	1 (0.3)
Cardiac failure acute	1 (0.3)	2 (0.5)
Right ventricular failure	1 (0.3)	0
Cardiac failure chronic	0	1 (0.3)
Hypertension [GQ]	18 (4.7)	20 (5.2)
Hypertension	16 (4.1)	19 (4.9)
Blood pressure increased	1 (0.3)	0
Hypertensive crisis	1 (0.3)	1 (0.3)
Phlebitis [GQ]	18 (4.7)	16 (4.1)
Phlebitis	17 (4.4)	12 (3.1)
Thrombophlebitis	1 (0.3)	3 (0.8)
Infusion site phlebitis	0	1 (0.3)
Injection site phlebitis	0	1 (0.3)
Hypotension [FMQ]	17 (4.4)	14 (3.6)
Hypotension	17 (4.4)	14 (3.6)
Constipation [FMQ]	16 (4.1)	24 (6.2)
Constipation	16 (4.1)	24 (6.2)
Dyspnea [FMQ]	16 (4.1)	11 (2.8)
Dyspnea	10 (2.6)	10 (2.6)

Grouped Query Preferred Term	Ceftobiprole N=386 n (%)	Linezolid/ Ceftazidime N=386 n (%)
Respiratory distress	7 (1.8)	1 (0.3)
Hyperglycemia [FMQ]	16 (4.1)	24 (6.2)
Hyperglycemia	11 (2.8)	19 (4.9)
Diabetes mellitus	2 (0.5)	1 (0.3)
Diabetes mellitus inadequate control	2 (0.5)	2 (0.5)
Hyperglycemic hyperosmolar nonketotic syndrome	1 (0.3)	0
Type 2 diabetes mellitus	1 (0.3)	1 (0.3)
Steroid diabetes	0	1 (0.3)
Nausea [FMQ]	15 (3.9)	13 (3.4)
Nausea	15 (3.9)	13 (3.4)
Rash [GQ]	15 (3.9)	17 (4.4)
Rash	11 (2.8)	12 (3.1)
Rash erythematous	2 (0.5)	1 (0.3)
Dermatitis allergic	1 (0.3)	0
Rash vesicular	1 (0.3)	0
Dermatitis	0	4 (1.0)
Dermatitis contact	0	1 (0.3)
Abdominal pain [GQ]	14 (3.6)	13 (3.4)
Abdominal pain	7 (1.8)	12 (3.1)
Abdominal pain upper	4 (1.0)	1 (0.3)
Abdominal discomfort	3 (0.8)	0
Abdominal tenderness	1 (0.3)	0
Decubitus ulcer [PT]	14 (3.6)	17 (4.4)
Decubitus ulcer	14 (3.6)	17 (4.4)
Septic shock [PT]	14 (3.6)	6 (1.6)
Septic shock	14 (3.6)	6 (1.6)
Insomnia [FMQ]	12 (3.1)	10 (2.6)
Insomnia	12 (3.1)	10 (2.6)
Seizure [GQ]	12 (3.1)	4 (1.0)
Seizure	12 (3.1)	4 (1.0)
Acute Kidney Injury [FMQ]	11 (2.8)	5 (1.3)
Oliguria	7 (1.8)	5 (1.3)
Anuria	2 (0.5)	0
Nephropathy toxic	1 (0.3)	0
Tubulointerstitial nephritis	1 (0.3)	0
Peripheral Edema [FMQ]	11 (2.8)	17 (4.4)
Edema peripheral	11 (2.8)	15 (3.9)
Peripheral swelling	0	2 (0.5)
Pleural effusion [PT]	11 (2.8)	10 (2.6)
Pleural effusion	11 (2.8)	10 (2.6)
Purulent Material [FMQ]	11 (2.8)	9 (2.3)
Empyema	2 (0.5)	3 (0.8)
Lung abscess	2 (0.5)	1 (0.3)
Abdominal abscess	1 (0.3)	1 (0.3)

Reference ID: 5357793

Grouped Query Preferred Term	Ceftobiprole N=386 n (%)	Linezolid/ Ceftazidime N=386 n (%)
Abscess	1 (0.3)	2 (0.5)
Liver abscess	1 (0.3)	0
Psoas abscess	1 (0.3)	0
Pustule	1 (0.3)	0
Subdiaphragmatic abscess	1 (0.3)	0
Wound abscess	1 (0.3)	0
Breast abscess	0	1 (0.3)
Pyopneumothorax	0	1 (0.3)
Confusional State [FMQ]	10 (2.6)	9 (2.3)
Confusional state	5 (1.3)	6 (1.6)
Delirium	4 (1.0)	3 (0.8)
Disorientation	1 (0.3)	0
Headache [FMQ]	10 (2.6)	11 (2.8)
Headache	9 (2.3)	11 (2.8)
Migraine	1 (0.3)	0
Heart Failure [FMQ]	10 (2.6)	13 (3.4)
Pulmonary edema	7 (1.8)	7 (1.8)
Cardiogenic shock	1 (0.3)	3 (0.8)
Cardiopulmonary failure	1 (0.3)	2 (0.5)
Cor pulmonale acute	1 (0.3)	0
Acute pulmonary edema	0	1 (0.3)
Pain [PT]	10 (2.6)	3 (0.8)
Pain	10 (2.6)	3 (0.8)
Tachycardia [FMQ]	10 (2.6)	10 (2.6)
Tachycardia	5 (1.3)	8 (2.1)
Sinus tachycardia	2 (0.5)	2 (0.5)
Supraventricular tachycardia	2 (0.5)	0
Ventricular tachycardia	1 (0.3)	0
Tachyarrhythmia	0	1 (0.3)
Anxiety [FMQ]	9 (2.3)	8 (2.1)
Anxiety	8 (2.1)	8 (2.1)
Panic attack	1 (0.3)	0
Bronchospasm [FMQ]	9 (2.3)	10 (2.6)
Bronchospasm	9 (2.3)	9 (2.3)
Asthma	0	1 (0.3)
Cardiac arrest [GQ]	9 (2.3)	11 (2.8)
Cardiac arrest	7 (1.8)	8 (2.1)
Cardio-respiratory arrest	2 (0.5)	3 (0.8)
Cough [FMQ]	9 (2.3)	7 (1.8)
Cough	6 (1.6)	4 (1.0)
Productive cough	2 (0.5)	0
Hemoptysis	1 (0.3)	4 (1.0)
Fatigue [FMQ]	9 (2.3)	4 (1.0)
Asthenia	7 (1.8)	2 (0.5)
Fatigue	3 (0.8)	0
Lethargy	1 (0.3)	2 (0.5)

Grouped Query Preferred Term	Ceftobiprole N=386 n (%)	Linezolid/ Ceftazidime N=386 n (%)
Hypoglycemia [FMQ]	9 (2.3)	11 (2.8)
Hypoglycemia	9 (2.3)	11 (2.8)
Irritability [FMQ]	9 (2.3)	13 (3.4)
Agitation	8 (2.1)	11 (2.8)
Irritability	1 (0.3)	2 (0.5)
Edema [PT]	9 (2.3)	7 (1.8)
Edema	9 (2.3)	7 (1.8)
Polyuria [PT]	9 (2.3)	0
Polyuria	9 (2.3)	0
Erythema [FMQ]	8 (2.1)	9 (2.3)
Erythema	8 (2.1)	7 (1.8)
Flushing	0	2 (0.5)
Leukocytosis [PT]	8 (2.1)	6 (1.6)
Leukocytosis	8 (2.1)	6 (1.6)
Myocardial injury [GQ]	8 (2.1)	4 (1.0)
Myocardial infarction	6 (1.6)	1 (0.3)
Acute myocardial infarction	2 (0.5)	1 (0.3)
Myocardial ischemia	0	2 (0.5)
Pain in extremity [PT]	8 (2.1)	7 (1.8)
Pain in extremity	8 (2.1)	7 (1.8)
Pneumothorax [PT]	8 (2.1)	6 (1.6)
Pneumothorax	8 (2.1)	6 (1.6)
Multiple organ dysfunction syndrome [PT]	7 (1.8)	10 (2.6)
Multiple organ dysfunction syndrome	7 (1.8)	10 (2.6)
Stroke and TIA [FMQ]	7 (1.8)	6 (1.6)
Ischemic stroke	3 (0.8)	1 (0.3)
Cerebral infarction	2 (0.5)	0
Cerebral ischemia	1 (0.3)	0
Cerebrovascular accident	1 (0.3)	2 (0.5)
Intraventricular hemorrhage	1 (0.3)	0
Cerebral hemorrhage	0	1 (0.3)
Stroke in evolution	0	2 (0.5)
Chest pain [PT]	6 (1.6)	6 (1.6)
Chest pain	6 (1.6)	6 (1.6)
Depression [FMQ]	6 (1.6)	4 (1.0)
Depression	6 (1.6)	4 (1.0)
Hypernatremia [PT]	6 (1.6)	3 (0.8)
Hypernatremia	6 (1.6)	3 (0.8)
Hypomagnesemia [PT]	6 (1.6)	6 (1.6)
Hypomagnesemia	6 (1.6)	6 (1.6)
Urinary Retention [FMQ]	6 (1.6)	3 (0.8)
Urinary retention	6 (1.6)	3 (0.8)
Arthralgia [FMQ]	5 (1.3)	2 (0.5)
Arthralgia	5 (1.3)	2 (0.5)

Grouped Query Preferred Term	Ceftobiprole N=386 n (%)	Linezolid/ Ceftazidime N=386 n (%)
Back Pain [FMQ]	5 (1.3)	3 (0.8)
Back pain	5 (1.3)	3 (0.8)
Blister [PT]	5 (1.3)	1 (0.3)
Blister	5 (1.3)	1 (0.3)
Brain edema [PT]	5 (1.3)	3 (0.8)
Brain edema	5 (1.3)	3 (0.8)
Dysgeusia [FMQ]	5 (1.3)	0
Dysgeusia	5 (1.3)	0
Fracture [FMQ]	5 (1.3)	2 (0.5)
Femoral neck fracture	1 (0.3)	0
Femur fracture	1 (0.3)	0
Hip fracture	1 (0.3)	0
Internal fixation of fracture	1 (0.3)	2 (0.5)
Wrist fracture	1 (0.3)	0
Generalized oedema [PT]	5 (1.3)	2 (0.5)
Generalized oedema	5 (1.3)	2 (0.5)
Hyperkalemia [GQ]	5 (1.3)	2 (0.5)
Hyperkalemia	5 (1.3)	2 (0.5)
Shock [PT]	5 (1.3)	3 (0.8)
Shock	5 (1.3)	3 (0.8)
Thrombocytopenia [GQ]	5 (1.3)	9 (2.3)
Thrombocytopenia	4 (1.0)	9 (2.3)
Platelet count decreased	1 (0.3)	0
Thrombosis [GQ]	5 (1.3)	3 (0.8)
Deep vein thrombosis	3 (0.8)	2 (0.5)
Venous thrombosis	2 (0.5)	0
Thrombosis	0	1 (0.3)
Thrombosis Arterial [FMQ]	5 (1.3)	2 (0.5)
Ischemic stroke	3 (0.8)	1 (0.3)
Cerebral infarction	2 (0.5)	0
Intestinal infarction	0	1 (0.3)
Atelectasis [PT]	4 (1.0)	3 (0.8)
Atelectasis	4 (1.0)	3 (0.8)
Cholecystitis [FMQ]	4 (1.0)	1 (0.3)
Cholecystitis	3 (0.8)	0
Cholecystitis acute	1 (0.3)	1 (0.3)
Coma [PT]	4 (1.0)	0
Coma	4 (1.0)	0
Conjunctivitis [PT]	4 (1.0)	0
Conjunctivitis	4 (1.0)	0
General physical health deterioration [PT]	4 (1.0)	2 (0.5)
General physical health deterioration	4 (1.0)	2 (0.5)
Hypersensitivity [GQ]	4 (1.0)	5 (1.3)
Urticaria	2 (0.5)	3 (0.8)

Grouped Query Preferred Term	Ceftobiprole N=386 n (%)	Linezolid/ Ceftazidime N=386 n (%)
Anaphylactic shock	1 (0.3)	0
Hypersensitivity	1 (0.3)	2 (0.5)
Hypoalbuminemia [PT]	4 (1.0)	4 (1.0)
Hypoalbuminemia	4 (1.0)	4 (1.0)
Hypocalcemia [PT]	4 (1.0)	4 (1.0)
Hypocalcemia	4 (1.0)	4 (1.0)
Hypothermia [PT]	4 (1.0)	0
Hypothermia	4 (1.0)	0
Intracranial pressure increased [PT]	4 (1.0)	2 (0.5)
Intracranial pressure increased	4 (1.0)	2 (0.5)
Metabolic acidosis [PT]	4 (1.0)	1 (0.3)
Metabolic acidosis	4 (1.0)	1 (0.3)
Paresthesia [FMQ]	4 (1.0)	1 (0.3)
Paresthesia	4 (1.0)	1 (0.3)
Pulmonary congestion [PT]	4 (1.0)	2 (0.5)
Pulmonary congestion	4 (1.0)	2 (0.5)
Somnolence [FMQ]	4 (1.0)	3 (0.8)
Somnolence	3 (0.8)	1 (0.3)
Lethargy	1 (0.3)	2 (0.5)
Thrombocytosis [GQ]	4 (1.0)	7 (1.8)
Thrombocytosis	4 (1.0)	6 (1.6)
Platelet count increased	0	1 (0.3)
Visual impairment [GQ]	4 (1.0)	3 (0.8)
Vision blurred	2 (0.5)	1 (0.3)
Visual acuity reduced	1 (0.3)	1 (0.3)
Visual impairment	1 (0.3)	1 (0.3)
Abdominal distension [PT]	3 (0.8)	10 (2.6)
Abdominal distension	3 (0.8)	10 (2.6)
Adverse drug reaction [PT]	3 (0.8)	1 (0.3)
Adverse drug reaction	3 (0.8)	1 (0.3)
Chronic obstructive pulmonary disease [PT]	3 (0.8)	0
Chronic obstructive pulmonary disease	3 (0.8)	0
Circulatory collapse [PT]	3 (0.8)	2 (0.5)
Circulatory collapse	3 (0.8)	2 (0.5)
Diabetes insipidus [PT]	3 (0.8)	0
Diabetes insipidus	3 (0.8)	0
Dizziness [FMQ]	3 (0.8)	6 (1.6)
Dizziness	3 (0.8)	6 (1.6)
Dysbiosis [PT]	3 (0.8)	0
Dysbiosis	3 (0.8)	0
Dyspepsia [FMQ]	3 (0.8)	2 (0.5)
Dyspepsia	3 (0.8)	2 (0.5)
Hepatic Injury [FMQ]	3 (0.8)	11 (2.8)
Cholestasis	1 (0.3)	1 (0.3)

Grouped Query Preferred Term	Ceftobiprole N=386 n (%)	Linezolid/ Ceftazidime N=386 n (%)
Hepatic function abnormal	1 (0.3)	2 (0.5)
Hepatomegaly	1 (0.3)	0
Acute hepatic failure	0	1 (0.3)
Hepatic cirrhosis	0	1 (0.3)
Hepatic encephalopathy	0	1 (0.3)
Hepatic failure	0	2 (0.5)
Hepatotoxicity	0	1 (0.3)
Liver disorder	0	3 (0.8)
Hiccups [PT]	3 (0.8)	3 (0.8)
Hiccups	3 (0.8)	3 (0.8)
Hyperemia [PT]	3 (0.8)	0
Hyperemia	3 (0.8)	0
Hyperchloremia [PT]	3 (0.8)	0
Hyperchloremia	3 (0.8)	0
Hypophosphatemia [PT]	3 (0.8)	2 (0.5)
Hypophosphatemia	3 (0.8)	2 (0.5)
Ileus [PT]	3 (0.8)	4 (1.0)
Ileus	3 (0.8)	4 (1.0)
Impaired gastric emptying [PT]	3 (0.8)	1 (0.3)
Impaired gastric emptying	3 (0.8)	1 (0.3)
Ischemic stroke [PT]	3 (0.8)	1 (0.3)
Ischemic stroke	3 (0.8)	1 (0.3)
Leukocyturia [PT]	3 (0.8)	2 (0.5)
Leukocyturia	3 (0.8)	2 (0.5)
Lipid Disorder [FMQ]	3 (0.8)	1 (0.3)
Hypercholesterolemia	2 (0.5)	0
Hypertriglyceridemia	2 (0.5)	0
Hypocholesterolemia	0	1 (0.3)
Local Administration Reaction [FMQ]	3 (0.8)	2 (0.5)
Infusion site reaction	2 (0.5)	1 (0.3)
Infusion site inflammation	1 (0.3)	0
Infusion site extravasation	0	1 (0.3)
Procedural complication [PT]	3 (0.8)	3 (0.8)
Procedural complication	3 (0.8)	3 (0.8)
Proteinuria [PT]	3 (0.8)	1 (0.3)
Proteinuria	3 (0.8)	1 (0.3)
Pruritus [FMQ]	3 (0.8)	2 (0.5)
Pruritus	3 (0.8)	2 (0.5)
Scar [PT]	3 (0.8)	0
Scar	3 (0.8)	0
Study Agent Abuse Potential [FMQ]	3 (0.8)	1 (0.3)
Somnolence	3 (0.8)	1 (0.3)
Tachypnea [PT]	3 (0.8)	3 (0.8)
Tachypnea	3 (0.8)	3 (0.8)
Viral Infection [FMQ]	3 (0.8)	3 (0.8)
Cytomegalovirus test positive	1 (0.3)	0

Grouped Query Preferred Term	Ceftobiprole N=386 n (%)	Linezolid/ Ceftazidime N=386 n (%)
Herpes zoster	1 (0.3)	1 (0.3)
Oral herpes	1 (0.3)	1 (0.3)
Influenza	0	1 (0.3)
Volume Depletion [FMQ]	3 (0.8)	0
Dehydration	3 (0.8)	0
Angina [GQ]	2 (0.5)	0
Angina pectoris	2 (0.5)	0
Aspiration pleural cavity [PT]	2 (0.5)	0
Aspiration pleural cavity	2 (0.5)	0
Blood urea increased [PT]	2 (0.5)	2 (0.5)
Blood urea increased	2 (0.5)	2 (0.5)
Brain herniation [PT]	2 (0.5)	1 (0.3)
Brain herniation	2 (0.5)	1 (0.3)
Breath sounds abnormal [PT]	2 (0.5)	0
Breath sounds abnormal	2 (0.5)	0
Cerebral infarction [PT]	2 (0.5)	0
Cerebral infarction	2 (0.5)	0
Cerebral vasoconstriction [PT]	2 (0.5)	0
Cerebral vasoconstriction	2 (0.5)	0
Coagulopathy [GQ]	2 (0.5)	1 (0.3)
Coagulopathy	1 (0.3)	1 (0.3)
Disseminated intravascular coagulation	1 (0.3)	0
Complication associated with device [PT]	2 (0.5)	1 (0.3)
Complication associated with device	2 (0.5)	1 (0.3)
Craniocerebral injury [PT]	2 (0.5)	0
Craniocerebral injury	2 (0.5)	0
Cystostomy [PT]	2 (0.5)	0
Cystostomy	2 (0.5)	0
Decreased Appetite [FMQ]	2 (0.5)	5 (1.3)
Decreased appetite	2 (0.5)	5 (1.3)
Epilepsy [PT]	2 (0.5)	0
Epilepsy	2 (0.5)	0
Fall [FMQ]	2 (0.5)	2 (0.5)
Fall	2 (0.5)	2 (0.5)
Gastrointestinal hypomotility [PT]	2 (0.5)	0
Gastrointestinal hypomotility	2 (0.5)	0
Gastroesophageal reflux disease [PT]	2 (0.5)	1 (0.3)
Gastroesophageal reflux disease	2 (0.5)	1 (0.3)
General physical condition abnormal [PT]	2 (0.5)	0
General physical condition abnormal	2 (0.5)	0
Hepatitis [GQ]	2 (0.5)	3 (0.8)

Grouped Query Preferred Term	Ceftobiprole N=386 n (%)	Linezolid/ Ceftazidime N=386 n (%)
Hepatitis	1 (0.3)	2 (0.5)
Ischaemic hepatitis	1 (0.3)	0
Hepatitis toxic	0	1 (0.3)
Hydrothorax [PT]	2 (0.5)	1 (0.3)
Hydrothorax	2 (0.5)	1 (0.3)
Hyperhidrosis [PT]	2 (0.5)	7 (1.8)
Hyperhidrosis	2 (0.5)	7 (1.8)
Hypothyroidism [PT]	2 (0.5)	0
Hypothyroidism	2 (0.5)	0
Leukopenia [FMQ]	2 (0.5)	2 (0.5)
Leukopenia	1 (0.3)	2 (0.5)
Pancytopenia	1 (0.3)	0
Malignancy [FMQ]	2 (0.5)	3 (0.8)
Carcinoid syndrome	1 (0.3)	0
Metastases to liver	1 (0.3)	0
Adenocarcinoma of colon	0	1 (0.3)
Cancer pain	0	1 (0.3)
Lung neoplasm malignant	0	1 (0.3)
Metabolic alkalosis [PT]	2 (0.5)	2 (0.5)
Metabolic alkalosis	2 (0.5)	2 (0.5)
Muscle contracture [PT]	2 (0.5)	0
Muscle contracture	2 (0.5)	0
Nasopharyngitis [FMQ]	2 (0.5)	4 (1.0)
Nasopharyngitis	1 (0.3)	0
Pharyngitis	1 (0.3)	2 (0.5)
Rhinitis	0	3 (0.8)
Upper respiratory tract infection	0	1 (0.3)
Neurogenic bladder [PT]	2 (0.5)	0
Neurogenic bladder	2 (0.5)	0
Oropharyngeal pain [PT]	2 (0.5)	3 (0.8)
Oropharyngeal pain	2 (0.5)	3 (0.8)
Osteoporosis [FMQ]	2 (0.5)	0
Femoral neck fracture	1 (0.3)	0
Hip fracture	1 (0.3)	0
Prothrombin time shortened [PT]	2 (0.5)	0
Prothrombin time shortened	2 (0.5)	0
Psychomotor hyperactivity [PT]	2 (0.5)	1 (0.3)
Psychomotor hyperactivity	2 (0.5)	1 (0.3)
Pulmonary embolism [PT]	2 (0.5)	6 (1.6)
Pulmonary embolism	2 (0.5)	6 (1.6)
Pulmonary fibrosis [PT]	2 (0.5)	0
Pulmonary fibrosis	2 (0.5)	0
Pyuria [PT]	2 (0.5)	4 (1.0)
Pyuria	2 (0.5)	4 (1.0)
Rales [PT]	2 (0.5)	0
Rales	2 (0.5)	0

Grouped Query Preferred Term	Ceftobiprole N=386 n (%)	Linezolid/ Ceftazidime N=386 n (%)
Respiratory Depression [FMQ]	2 (0.5)	0
Respiratory arrest	2 (0.5)	0
Secretion discharge [PT]	2 (0.5)	1 (0.3)
Secretion discharge	2 (0.5)	1 (0.3)
Skin abrasion [PT]	2 (0.5)	1 (0.3)
Skin abrasion	2 (0.5)	1 (0.3)
Skin irritation [PT]	2 (0.5)	2 (0.5)
Skin irritation	2 (0.5)	2 (0.5)
Skin ulcer [PT]	2 (0.5)	0
Skin ulcer	2 (0.5)	0
Sputum increased [PT]	2 (0.5)	0
Sputum increased	2 (0.5)	0
Subcutaneous emphysema [PT]	2 (0.5)	1 (0.3)
Subcutaneous emphysema	2 (0.5)	1 (0.3)
Therapy non-responder [PT]	2 (0.5)	0
Therapy non-responder	2 (0.5)	0
Thrombosis Venous [FMQ]	2 (0.5)	6 (1.6)
Pulmonary embolism	2 (0.5)	6 (1.6)
Tracheitis [PT]	2 (0.5)	0
Tracheitis	2 (0.5)	0
Tracheoesophageal fistula [PT]	2 (0.5)	0
Tracheoesophageal fistula	2 (0.5)	0
Upper gastrointestinal hemorrhage [PT]	2 (0.5)	3 (0.8)
Upper gastrointestinal hemorrhage	2 (0.5)	3 (0.8)
Urethral haemorrhage [PT]	2 (0.5)	0
Urethral hemorrhage	2 (0.5)	0
Urinary incontinence [PT]	2 (0.5)	0
Urinary incontinence	2 (0.5)	0
Urine odor abnormal [PT]	2 (0.5)	1 (0.3)
Urine odor abnormal	2 (0.5)	1 (0.3)
Weight decreased [PT]	2 (0.5)	2 (0.5)
Weight decreased	2 (0.5)	2 (0.5)
Wheezing [PT]	2 (0.5)	2 (0.5)
Wheezing	2 (0.5)	2 (0.5)
Wound [PT]	2 (0.5)	1 (0.3)
Wound	2 (0.5)	1 (0.3)
Abnormal Uterine Bleeding [FMQ]	1 (0.3)	0
Vaginal hemorrhage	1 (0.3)	0
Acrodermatitis [PT]	1 (0.3)	1 (0.3)
Acrodermatitis	1 (0.3)	1 (0.3)
Adrenal insufficiency [PT]	1 (0.3)	0
Adrenal insufficiency	1 (0.3)	0
Anal incontinence [PT]	1 (0.3)	1 (0.3)
Anal incontinence	1 (0.3)	1 (0.3)
Anal injury [PT]	1 (0.3)	0

Grouped Query Preferred Term	Ceftobiprole N=386 n (%)	Linezolid/ Ceftazidime N=386 n (%)
Anal injury	1 (0.3)	0
Anemia [FMQ]	1 (0.3)	0
Pancytopenia	1 (0.3)	0
Angioedema [FMQ]	1 (0.3)	1 (0.3)
Laryngeal edema	1 (0.3)	1 (0.3)
Apnea [PT]	1 (0.3)	1 (0.3)
Apnea	1 (0.3)	1 (0.3)
Ataxia [PT]	1 (0.3)	0
Ataxia	1 (0.3)	0
Benign prostatic hyperplasia [PT]	1 (0.3)	0
Benign prostatic hyperplasia	1 (0.3)	0
Biliary colic [PT]	1 (0.3)	0
Biliary colic	1 (0.3)	0
Bladder catheterization [PT]	1 (0.3)	0
Bladder catheterization	1 (0.3)	0
Blood albumin decreased [PT]	1 (0.3)	4 (1.0)
Blood albumin decreased	1 (0.3)	4 (1.0)
Blood lactate dehydrogenase abnormal [PT]	1 (0.3)	0
Blood lactate dehydrogenase abnormal	1 (0.3)	0
Blood lactate dehydrogenase increased [PT]	1 (0.3)	2 (0.5)
Blood lactate dehydrogenase increased	1 (0.3)	2 (0.5)
Brain death [PT]	1 (0.3)	1 (0.3)
Brain death	1 (0.3)	1 (0.3)
Bronchial obstruction [PT]	1 (0.3)	0
Bronchial obstruction	1 (0.3)	0
Bronchitis chronic [PT]	1 (0.3)	0
Bronchitis chronic	1 (0.3)	0
C-reactive protein increased [PT]	1 (0.3)	2 (0.5)
C-reactive protein increased	1 (0.3)	2 (0.5)
Capillary permeability increased [PT]	1 (0.3)	0
Capillary permeability increased	1 (0.3)	0
Cardiac Conduction Disturbance [FMQ]	1 (0.3)	5 (1.3)
Electrocardiogram QT prolonged	1 (0.3)	5 (1.3)
Cardiac output decreased [PT]	1 (0.3)	0
Cardiac output decreased	1 (0.3)	0
Cardiac pacemaker insertion [PT]	1 (0.3)	0
Cardiac pacemaker insertion	1 (0.3)	0
Central nervous system infection [PT]	1 (0.3)	0
Central nervous system infection	1 (0.3)	0
Central venous catheterization [PT]	1 (0.3)	2 (0.5)
Central venous catheterization	1 (0.3)	2 (0.5)

Grouped Query Preferred Term	Ceftobiprole N=386 n (%)	Linezolid/ Ceftazidime N=386 n (%)
Cerebral salt-wasting syndrome [PT]	1 (0.3)	0
Cerebral salt-wasting syndrome	1 (0.3)	0
Chest discomfort [PT]	1 (0.3)	1 (0.3)
Chest discomfort	1 (0.3)	1 (0.3)
Chills [PT]	1 (0.3)	2 (0.5)
Chills	1 (0.3)	2 (0.5)
Chromaturia [PT]	1 (0.3)	0
Chromaturia	1 (0.3)	0
Chronic kidney disease [PT]	1 (0.3)	0
Chronic kidney disease	1 (0.3)	0
CNS ventriculitis [PT]	1 (0.3)	1 (0.3)
CNS ventriculitis	1 (0.3)	1 (0.3)
Colitis [PT]	1 (0.3)	0
Colitis	1 (0.3)	0
Color blindness [PT]	1 (0.3)	3 (0.8)
Color blindness	1 (0.3)	3 (0.8)
Complication of device insertion [PT]	1 (0.3)	0
Complication of device insertion	1 (0.3)	0
Coronary artery disease [PT]	1 (0.3)	1 (0.3)
Coronary artery disease	1 (0.3)	1 (0.3)
Crepitations [PT]	1 (0.3)	0
Crepitations	1 (0.3)	0
Cystic lymphangioma [PT]	1 (0.3)	0
Cystic lymphangioma	1 (0.3)	0
Device malfunction [PT]	1 (0.3)	0
Device malfunction	1 (0.3)	0
Diverticulum [PT]	1 (0.3)	0
Diverticulum	1 (0.3)	0
Drooling [PT]	1 (0.3)	0
Drooling	1 (0.3)	0
Dry gangrene [PT]	1 (0.3)	0
Dry gangrene	1 (0.3)	0
Dyskinesia [PT]	1 (0.3)	0
Dyskinesia	1 (0.3)	0
Dysphonia [PT]	1 (0.3)	0
Dysphonia	1 (0.3)	0
Dysuria [PT]	1 (0.3)	2 (0.5)
Dysuria	1 (0.3)	2 (0.5)
Ear infection [PT]	1 (0.3)	0
Ear infection	1 (0.3)	0
Ear pain [PT]	1 (0.3)	2 (0.5)
Ear pain	1 (0.3)	2 (0.5)
Electrocardiogram T wave inversion [PT]	1 (0.3)	0
Electrocardiogram T wave inversion	1 (0.3)	0

Grouped Query Preferred Term	Ceftobiprole N=386 n (%)	Linezolid/ Ceftazidime N=386 n (%)
Electrolyte imbalance [PT]	1 (0.3)	0
Electrolyte imbalance	1 (0.3)	0
Embolism [PT]	1 (0.3)	1 (0.3)
Embolism	1 (0.3)	1 (0.3)
Encephalopathy [PT]	1 (0.3)	1 (0.3)
Encephalopathy	1 (0.3)	1 (0.3)
Enterocutaneous fistula [PT]	1 (0.3)	0
Enterocutaneous fistula	1 (0.3)	0
Eosinophilia [PT]	1 (0.3)	1 (0.3)
Eosinophilia	1 (0.3)	1 (0.3)
Epiglottic edema [PT]	1 (0.3)	0
Epiglottic edema	1 (0.3)	0
Eschar [PT]	1 (0.3)	0
Eschar	1 (0.3)	0
Eye irritation [PT]	1 (0.3)	1 (0.3)
Eye irritation	1 (0.3)	1 (0.3)
Eye pain [PT]	1 (0.3)	0
Eye pain	1 (0.3)	0
Fecalith [PT]	1 (0.3)	0
Fecalith	1 (0.3)	0
Feeling cold [PT]	1 (0.3)	0
Feeling cold	1 (0.3)	0
Flatulence [PT]	1 (0.3)	0
Flatulence	1 (0.3)	0
Fluid overload [PT]	1 (0.3)	3 (0.8)
Fluid overload	1 (0.3)	3 (0.8)
Gastritis [GQ]	1 (0.3)	1 (0.3)
Gastritis	1 (0.3)	0
Gastritis erosive	0	1 (0.3)
Gastrointestinal necrosis [PT]	1 (0.3)	0
Gastrointestinal necrosis	1 (0.3)	0
Glossitis [PT]	1 (0.3)	0
Glossitis	1 (0.3)	0
Groin pain [PT]	1 (0.3)	0
Groin pain	1 (0.3)	0
Hematology test abnormal [PT]	1 (0.3)	0
Hematology test abnormal	1 (0.3)	0
Hemorrhoids [PT]	1 (0.3)	0
Hemorrhoids	1 (0.3)	0
Hallucination [PT]	1 (0.3)	1 (0.3)
Hallucination	1 (0.3)	1 (0.3)
Heart sounds abnormal [PT]	1 (0.3)	0
Heart sounds abnormal	1 (0.3)	0
Hemiplegia [PT]	1 (0.3)	0
Hemiplegia	1 (0.3)	0
Hip arthroplasty [PT]	1 (0.3)	0

Grouped Query Preferred Term	Ceftobiprole N=386 n (%)	Linezolid/ Ceftazidime N=386 n (%)
Hip arthroplasty	1 (0.3)	0
Hypertonia [PT]	1 (0.3)	0
Hypertonia	1 (0.3)	0
Hypertonic bladder [PT]	1 (0.3)	0
Hypertonic bladder	1 (0.3)	0
Hypervolemia [PT]	1 (0.3)	0
Hypervolemia	1 (0.3)	0
Hypoprothrombinemia [PT]	1 (0.3)	0
Hypoprothrombinemia	1 (0.3)	0
Hypotonia [PT]	1 (0.3)	0
Hypotonia	1 (0.3)	0
Inappropriate antidiuretic hormone secretion [PT]	1 (0.3)	0
Inappropriate antidiuretic hormone secretion	1 (0.3)	0
Incisional drainage [PT]	1 (0.3)	0
Incisional drainage	1 (0.3)	0
Increased bronchial secretion [PT]	1 (0.3)	1 (0.3)
Increased bronchial secretion	1 (0.3)	1 (0.3)
Inflammation [PT]	1 (0.3)	0
Inflammation	1 (0.3)	0
Injection site reaction [GQ]	1 (0.3)	0
Catheter site related reaction	1 (0.3)	0
Injury [PT]	1 (0.3)	0
Injury	1 (0.3)	0
International normalized ratio increased [PT]	1 (0.3)	2 (0.5)
International normalized ratio increased	1 (0.3)	2 (0.5)
Intestinal ischaemia [PT]	1 (0.3)	0
Intestinal ischaemia	1 (0.3)	0
Ketonuria [PT]	1 (0.3)	0
Ketonuria	1 (0.3)	0
Laboratory test abnormal [PT]	1 (0.3)	0
Laboratory test abnormal	1 (0.3)	0
Laryngitis [PT]	1 (0.3)	0
Laryngitis	1 (0.3)	0
Limb discomfort [PT]	1 (0.3)	0
Limb discomfort	1 (0.3)	0
Livedo reticularis [PT]	1 (0.3)	0
Livedo reticularis	1 (0.3)	0
Lumbar puncture [PT]	1 (0.3)	0
Lumbar puncture	1 (0.3)	0
Lung infiltration [PT]	1 (0.3)	1 (0.3)
Lung infiltration	1 (0.3)	1 (0.3)
Lymphadenopathy [PT]	1 (0.3)	1 (0.3)

Grouped Query Preferred Term	Ceftobiprole N=386 n (%)	Linezolid/ Ceftazidime N=386 n (%)
Lymphadenopathy	1 (0.3)	1 (0.3)
Malnutrition [PT]	1 (0.3)	1 (0.3)
Malnutrition	1 (0.3)	1 (0.3)
Mediastinitis [PT]	1 (0.3)	0
Mediastinitis	1 (0.3)	0
Medical device site reaction [PT]	1 (0.3)	0
Medical device site reaction	1 (0.3)	0
Meningism [PT]	1 (0.3)	0
Meningism	1 (0.3)	0
Meningitis [PT]	1 (0.3)	1 (0.3)
Meningitis	1 (0.3)	1 (0.3)
Metabolic disorder [PT]	1 (0.3)	0
Metabolic disorder	1 (0.3)	0
Mouth ulceration [PT]	1 (0.3)	0
Mouth ulceration	1 (0.3)	0
Muscle spasms [PT]	1 (0.3)	0
Muscle spasms	1 (0.3)	0
Myalgia [FMQ]	1 (0.3)	2 (0.5)
Myalgia	1 (0.3)	2 (0.5)
Nephrolithiasis [PT]	1 (0.3)	0
Nephrolithiasis	1 (0.3)	0
Neuralgia [PT]	1 (0.3)	0
Neuralgia	1 (0.3)	0
Neuropathy peripheral [PT]	1 (0.3)	1 (0.3)
Neuropathy peripheral	1 (0.3)	1 (0.3)
Otitis media [PT]	1 (0.3)	0
Otitis media	1 (0.3)	0
Otorrhea [PT]	1 (0.3)	0
Otorrhea	1 (0.3)	0
Pallor [PT]	1 (0.3)	0
Pallor	1 (0.3)	0
Pancreatitis [FMQ]	1 (0.3)	5 (1.3)
Pancreatitis necrotizing	1 (0.3)	2 (0.5)
Pancreatic pseudocyst	0	1 (0.3)
Pancreatitis	0	2 (0.5)
Pancytopenia [PT]	1 (0.3)	0
Pancytopenia	1 (0.3)	0
Parkinson's disease [PT]	1 (0.3)	0
Parkinson's disease	1 (0.3)	0
Parosmia [PT]	1 (0.3)	0
Parosmia	1 (0.3)	0
Penile exfoliation [PT]	1 (0.3)	0
Penile exfoliation	1 (0.3)	0
Peripheral coldness [PT]	1 (0.3)	0
Peripheral coldness	1 (0.3)	0

Grouped Query Preferred Term	Ceftobiprole N=386 n (%)	Linezolid/ Ceftazidime N=386 n (%)
Peripheral vascular disorder [PT]	1 (0.3)	0
Peripheral vascular disorder	1 (0.3)	0
Photophobia [PT]	1 (0.3)	0
Photophobia	1 (0.3)	0
Pleuritic pain [PT]	1 (0.3)	0
Pleuritic pain	1 (0.3)	0
Pneumothorax spontaneous [PT]	1 (0.3)	0
Pneumothorax spontaneous	1 (0.3)	0
Postoperative wound complication [PT]	1 (0.3)	2 (0.5)
Postoperative wound complication	1 (0.3)	2 (0.5)
Protein total increased [PT]	1 (0.3)	0
Protein total increased	1 (0.3)	0
Pulmonary mass [PT]	1 (0.3)	0
Pulmonary mass	1 (0.3)	0
Pulseless electrical activity [PT]	1 (0.3)	0
Pulseless electrical activity	1 (0.3)	0
Respiratory alkalosis [PT]	1 (0.3)	0
Respiratory alkalosis	1 (0.3)	0
Respiratory tract infection [PT]	1 (0.3)	0
Respiratory tract infection	1 (0.3)	0
Restlessness [PT]	1 (0.3)	3 (0.8)
Restlessness	1 (0.3)	3 (0.8)
Rhinorrhea [PT]	1 (0.3)	0
Rhinorrhea	1 (0.3)	0
Salivary hypersecretion [PT]	1 (0.3)	1 (0.3)
Salivary hypersecretion	1 (0.3)	1 (0.3)
Scab [PT]	1 (0.3)	0
Scab	1 (0.3)	0
Sensorimotor disorder [PT]	1 (0.3)	0
Sensorimotor disorder	1 (0.3)	0
Short-bowel syndrome [PT]	1 (0.3)	0
Short-bowel syndrome	1 (0.3)	0
Sinusitis [PT]	1 (0.3)	2 (0.5)
Sinusitis	1 (0.3)	2 (0.5)
Skin warm [PT]	1 (0.3)	0
Skin warm	1 (0.3)	0
Sleep disorder [PT]	1 (0.3)	2 (0.5)
Sleep disorder	1 (0.3)	2 (0.5)
Spinal operation [PT]	1 (0.3)	0
Spinal operation	1 (0.3)	0
Sputum retention [PT]	1 (0.3)	0
Sputum retention	1 (0.3)	0
Stress urinary incontinence [PT]	1 (0.3)	0
Stress urinary incontinence	1 (0.3)	0
Stridor [PT]	1 (0.3)	0

Grouped Query Preferred Term	Ceftobiprole N=386 n (%)	Linezolid/ Ceftazidime N=386 n (%)
Stridor	1 (0.3)	0
Suprapubic pain [PT]	1 (0.3)	0
Suprapubic pain	1 (0.3)	0
Swelling [PT]	1 (0.3)	0
Swelling	1 (0.3)	0
Thermal burn [PT]	1 (0.3)	1 (0.3)
Thermal burn	1 (0.3)	1 (0.3)
Toe amputation [PT]	1 (0.3)	0
Toe amputation	1 (0.3)	0
Tracheal stenosis [PT]	1 (0.3)	0
Tracheal stenosis	1 (0.3)	0
Tremor [FMQ]	1 (0.3)	3 (0.8)
Tremor	1 (0.3)	3 (0.8)
Troponin increased [PT]	1 (0.3)	0
Troponin increased	1 (0.3)	0
Ulcer [PT]	1 (0.3)	0
Ulcer	1 (0.3)	0
Ulcerative keratitis [PT]	1 (0.3)	1 (0.3)
Ulcerative keratitis	1 (0.3)	1 (0.3)
Urinary casts [PT]	1 (0.3)	0
Urinary casts	1 (0.3)	0
Vaginal infection [PT]	1 (0.3)	0
Vaginal infection	1 (0.3)	0
Vascular device infection [PT]	1 (0.3)	0
Vascular device infection	1 (0.3)	0
Vascular fragility [PT]	1 (0.3)	0
Vascular fragility	1 (0.3)	0
Vasculitis [PT]	1 (0.3)	0
Vasculitis	1 (0.3)	0
Vitamin K decreased [PT]	1 (0.3)	0
Vitamin K decreased	1 (0.3)	0
Vocal cord paresis [PT]	1 (0.3)	0
Vocal cord paresis	1 (0.3)	0
Volvulus [PT]	1 (0.3)	0
Volvulus	1 (0.3)	0
White blood cell count abnormal [PT]	1 (0.3)	0
White blood cell count abnormal	1 (0.3)	0
Wound decomposition [PT]	1 (0.3)	0
Wound decomposition	1 (0.3)	0
Wound evisceration [PT]	1 (0.3)	0
Wound evisceration	1 (0.3)	0
Wound treatment [PT]	1 (0.3)	0
Wound treatment	1 (0.3)	0
Acidosis [PT]	0	1 (0.3)
Acidosis	0	1 (0.3)
Amylase increased [PT]	0	1 (0.3)

Grouped Query Preferred Term	Ceftobiprole N=386 n (%)	Linezolid/ Ceftazidime N=386 n (%)
Amylase increased	0	1 (0.3)
Aortic arteriosclerosis [PT]	0	1 (0.3)
Aortic arteriosclerosis	0	1 (0.3)
Apathy [PT]	0	1 (0.3)
Apathy	0	1 (0.3)
Aphasia [PT]	0	1 (0.3)
Aphasia	0	1 (0.3)
Biliary dyskinesia [PT]	0	1 (0.3)
Biliary dyskinesia	0	1 (0.3)
Blepharospasm [PT]	0	1 (0.3)
Blepharospasm	0	1 (0.3)
Blindness unilateral [PT]	0	1 (0.3)
Blindness unilateral	0	1 (0.3)
Blood bicarbonate increased [PT]	0	1 (0.3)
Blood bicarbonate increased	0	1 (0.3)
Blood lactic acid increased [PT]	0	1 (0.3)
Blood lactic acid increased	0	1 (0.3)
Blood urea [PT]	0	1 (0.3)
Blood urea	0	1 (0.3)
Blood urea decreased [PT]	0	1 (0.3)
Blood urea decreased	0	1 (0.3)
Brain injury [PT]	0	1 (0.3)
Brain injury	0	1 (0.3)
Bronchial fistula [PT]	0	1 (0.3)
Bronchial fistula	0	1 (0.3)
Bronchitis [PT]	0	2 (0.5)
Bronchitis	0	2 (0.5)
Cachexia [FMQ]	0	1 (0.3)
Cachexia	0	1 (0.3)
Cardiac murmur [PT]	0	2 (0.5)
Cardiac murmur	0	2 (0.5)
Cardiomyopathy [PT]	0	3 (0.8)
Cardiomyopathy	0	3 (0.8)
Cataract [PT]	0	1 (0.3)
Cataract	0	1 (0.3)
Cheilosis [PT]	0	1 (0.3)
Cheilosis	0	1 (0.3)
Clonus [PT]	0	1 (0.3)
Clonus	0	1 (0.3)
Colonic fistula [PT]	0	1 (0.3)
Colonic fistula	0	1 (0.3)
Conjunctival oedema [PT]	0	1 (0.3)
Conjunctival oedema	0	1 (0.3)
Corneal erosion [PT]	0	1 (0.3)
Corneal erosion	0	1 (0.3)
Corneal lesion [PT]	0	1 (0.3)

Grouped Query Preferred Term	Ceftobiprole N=386 n (%)	Linezolid/ Ceftazidime N=386 n (%)
Corneal lesion	0	1 (0.3)
Deafness neurosensory [PT]	0	1 (0.3)
Deafness neurosensory	0	1 (0.3)
Death [PT]	0	2 (0.5)
Death	0	2 (0.5)
Debridement [PT]	0	1 (0.3)
Debridement	0	1 (0.3)
Device occlusion [PT]	0	1 (0.3)
Device occlusion	0	1 (0.3)
Drug intolerance [PT]	0	1 (0.3)
Drug intolerance	0	1 (0.3)
Dry Mouth [FMQ]	0	2 (0.5)
Dry mouth	0	1 (0.3)
Lip dry	0	1 (0.3)
Duodenal ulcer [PT]	0	1 (0.3)
Duodenal ulcer	0	1 (0.3)
Dysphagia [PT]	0	1 (0.3)
Dysphagia	0	1 (0.3)
Dystonia [PT]	0	1 (0.3)
Dystonia	0	1 (0.3)
Eating disorder [PT]	0	1 (0.3)
Eating disorder	0	1 (0.3)
ECG signs of myocardial ischaemia [PT]	0	1 (0.3)
ECG signs of myocardial ischaemia	0	1 (0.3)
Eczema [PT]	0	1 (0.3)
Eczema	0	1 (0.3)
Emphysema [PT]	0	2 (0.5)
Emphysema	0	2 (0.5)
Extubation [PT]	0	1 (0.3)
Extubation	0	1 (0.3)
Face injury [PT]	0	1 (0.3)
Face injury	0	1 (0.3)
Fistula [PT]	0	1 (0.3)
Fistula	0	1 (0.3)
Gastric ulcer [PT]	0	1 (0.3)
Gastric ulcer	0	1 (0.3)
Gastrointestinal motility disorder [PT]	0	2 (0.5)
Gastrointestinal motility disorder	0	2 (0.5)
Gastrointestinal sounds abnormal [PT]	0	1 (0.3)
Gastrointestinal sounds abnormal	0	1 (0.3)
Gastrointestinal tube insertion [PT]	0	1 (0.3)
Gastrointestinal tube insertion	0	1 (0.3)
Gastrostomy [PT]	0	1 (0.3)
Gastrostomy	0	1 (0.3)

Grouped Query Preferred Term	Ceftobiprole N=386 n (%)	Linezolid/ Ceftazidime N=386 n (%)
Hepatic Failure [FMQ]	0	3 (0.8)
Acute hepatic failure	0	1 (0.3)
Hepatic encephalopathy	0	1 (0.3)
Hepatic failure	0	2 (0.5)
Hepatic steatosis [PT]	0	1 (0.3)
Hepatic steatosis	0	1 (0.3)
Hydrocephalus [PT]	0	1 (0.3)
Hydrocephalus	0	1 (0.3)
Hypercalcemia [PT]	0	2 (0.5)
Hypercalcemia	0	2 (0.5)
Hyperphosphatasemia [PT]	0	1 (0.3)
Hyperphosphatasemia	0	1 (0.3)
Hyperuricosuria [PT]	0	1 (0.3)
Hyperuricosuria	0	1 (0.3)
Hypochloremia [PT]	0	1 (0.3)
Hypochloremia	0	1 (0.3)
Hypokinesia [PT]	0	1 (0.3)
Hypokinesia	0	1 (0.3)
Illness [PT]	0	1 (0.3)
Illness	0	1 (0.3)
Intertrigo [PT]	0	1 (0.3)
Intertrigo	0	1 (0.3)
Intestinal infarction [PT]	0	1 (0.3)
Intestinal infarction	0	1 (0.3)
Intestinal perforation [PT]	0	1 (0.3)
Intestinal perforation	0	1 (0.3)
Jaundice [PT]	0	1 (0.3)
Jaundice	0	1 (0.3)
Ketoacidosis [PT]	0	1 (0.3)
Ketoacidosis	0	1 (0.3)
Limb injury [PT]	0	1 (0.3)
Limb injury	0	1 (0.3)
Lipase increased [PT]	0	2 (0.5)
Lipase increased	0	2 (0.5)
Lymphocyte morphology abnormal [PT]	0	1 (0.3)
Lymphocyte morphology abnormal	0	1 (0.3)
Mediastinum neoplasm [PT]	0	1 (0.3)
Mediastinum neoplasm	0	1 (0.3)
Metamyelocyte count increased [PT]	0	1 (0.3)
Metamyelocyte count increased	0	1 (0.3)
Metastases to meninges [PT]	0	1 (0.3)
Metastases to meninges	0	1 (0.3)
Mood altered [PT]	0	1 (0.3)
Mood altered	0	1 (0.3)
Muscle spasticity [PT]	0	1 (0.3)

Grouped Query Preferred Term	Ceftobiprole N=386 n (%)	Linezolid/ Ceftazidime N=386 n (%)
Muscle spasticity	0	1 (0.3)
Muscle strain [PT]	0	1 (0.3)
Muscle strain	0	1 (0.3)
Muscular weakness [PT]	0	1 (0.3)
Muscular weakness	0	1 (0.3)
Musculoskeletal chest pain [PT]	0	2 (0.5)
Musculoskeletal chest pain	0	2 (0.5)
Musculoskeletal disorder [PT]	0	1 (0.3)
Musculoskeletal disorder	0	1 (0.3)
Musculoskeletal pain [PT]	0	1 (0.3)
Musculoskeletal pain	0	1 (0.3)
Mydriasis [PT]	0	1 (0.3)
Mydriasis	0	1 (0.3)
Myelocyte count increased [PT]	0	1 (0.3)
Myelocyte count increased	0	1 (0.3)
Myoclonus [PT]	0	2 (0.5)
Myoclonus	0	2 (0.5)
Nasal congestion [PT]	0	1 (0.3)
Nasal congestion	0	1 (0.3)
Neck pain [PT]	0	2 (0.5)
Neck pain	0	2 (0.5)
Neutropenia [PT]	0	2 (0.5)
Neutropenia	0	2 (0.5)
Neutrophilia [PT]	0	1 (0.3)
Neutrophilia	0	1 (0.3)
Nosocomial infection [PT]	0	1 (0.3)
Nosocomial infection	0	1 (0.3)
Oesophageal rupture [PT]	0	1 (0.3)
Oesophageal rupture	0	1 (0.3)
Esophagitis [PT]	0	1 (0.3)
Esophagitis	0	1 (0.3)
Opportunistic Infection [FMQ]	0	2 (0.5)
Oropharyngeal candidiasis	0	2 (0.5)
Orchitis [PT]	0	1 (0.3)
Orchitis	0	1 (0.3)
Overdose [PT]	0	1 (0.3)
Overdose	0	1 (0.3)
Palpitations [FMQ]	0	1 (0.3)
Palpitations	0	1 (0.3)
Paraplegia [PT]	0	1 (0.3)
Paraplegia	0	1 (0.3)
Penile edema [PT]	0	1 (0.3)
Penile edema	0	1 (0.3)
Phantom limb syndrome [PT]	0	1 (0.3)
Phantom limb syndrome	0	1 (0.3)
Plasma cell disorder [PT]	0	1 (0.3)

Grouped Query Preferred Term	Ceftobiprole N=386 n (%)	Linezolid/ Ceftazidime N=386 n (%)
Plasma cell disorder	0	1 (0.3)
Pleurisy [PT]	0	1 (0.3)
Pleurisy	0	1 (0.3)
Post-traumatic epilepsy [PT]	0	1 (0.3)
Post-traumatic epilepsy	0	1 (0.3)
Post concussion syndrome [PT]	0	1 (0.3)
Post concussion syndrome	0	1 (0.3)
Protein total decreased [PT]	0	1 (0.3)
Protein total decreased	0	1 (0.3)
Psychosis [FMQ]	0	1 (0.3)
Delusion	0	1 (0.3)
Purulent discharge [PT]	0	1 (0.3)
Purulent discharge	0	1 (0.3)
Respiratory disorder [PT]	0	1 (0.3)
Respiratory disorder	0	1 (0.3)
Scrotal edema [PT]	0	1 (0.3)
Scrotal edema	0	1 (0.3)
Self-Harm [FMQ]	0	1 (0.3)
Suicidal ideation	0	1 (0.3)
Skin disorder [PT]	0	1 (0.3)
Skin disorder	0	1 (0.3)
Skin exfoliation [PT]	0	1 (0.3)
Skin exfoliation	0	1 (0.3)
Skin laceration [PT]	0	2 (0.5)
Skin laceration	0	2 (0.5)
Skin maceration [PT]	0	1 (0.3)
Skin maceration	0	1 (0.3)
Speech disorder [PT]	0	1 (0.3)
Speech disorder	0	1 (0.3)
Sputum culture positive [PT]	0	3 (0.8)
Sputum culture positive	0	3 (0.8)
Sputum purulent [PT]	0	1 (0.3)
Sputum purulent	0	1 (0.3)
Stomatitis [PT]	0	1 (0.3)
Stomatitis	0	1 (0.3)
Stroke in evolution [PT]	0	2 (0.5)
Stroke in evolution	0	2 (0.5)
Subdural hemorrhage [PT]	0	1 (0.3)
Subdural hemorrhage	0	1 (0.3)
Swelling face [PT]	0	2 (0.5)
Swelling face	0	2 (0.5)
Therapeutic procedure [PT]	0	1 (0.3)
Therapeutic procedure	0	1 (0.3)
Tobacco withdrawal symptoms [PT]	0	1 (0.3)
Tobacco withdrawal symptoms	0	1 (0.3)
Tracheal aspiration procedure [PT]	0	1 (0.3)

Grouped Query Preferred Term	Ceftobiprole N=386 n (%)	Linezolid/ Ceftazidime N=386 n (%)
Tracheal aspiration procedure	0	1 (0.3)
Tracheobronchitis [PT]	0	2 (0.5)
Tracheobronchitis	0	2 (0.5)
Urine analysis abnormal [PT]	0	1 (0.3)
Urine analysis abnormal	0	1 (0.3)
Urobilinogen urine increased [PT]	0	1 (0.3)
Urobilinogen urine increased	0	1 (0.3)
Vasodilatation [PT]	0	1 (0.3)
Vasodilatation	0	1 (0.3)
Weight increased [PT]	0	1 (0.3)
Weight increased	0	1 (0.3)
White blood cell disorder [PT]	0	1 (0.3)
White blood cell disorder	0	1 (0.3)
Wound dehiscence [PT]	0	1 (0.3)
Wound dehiscence	0	1 (0.3)
Wound secretion [PT]	0	1 (0.3)
Wound secretion	0	1 (0.3)
Xeroderma [PT]	0	1 (0.3)
Xeroderma	0	1 (0.3)

Source: adae.xpt; Software: R
Treatment-emergent adverse events defined as an AE that is new in onset or aggravated in severity after the first dose treatment. Duration of treatment is 7 to 14 days.
Abbreviations: GQ, grouped query; N, number of subjects in treatment arm; n, number of subjects with adverse event

18. Clinical Virology

Not applicable.

19. Clinical Microbiology

19.1. In Vitro Activity

The in vitro ceftobiprole MIC range and concentrations required to inhibit 90% of isolates (MIC_{90}) against the target pathogen isolates collected in the JMI SENTRY surveillance studies from 2016 to 2020 and isolates collected in the European Union surveillance studies from 2016 to 2019 is shown in Table 288. Ceftobiprole is active against MSSA (MIC_{90} = 0.5 mcg/mL), MRSA (MIC_{90} = 2 mcg/mL), *S. pneumoniae* (MIC_{90} = 0.25-0.5 mcg/mL), *S. pyogenes* (MIC_{90} = 0.015 mcg/mL), *S. agalactiae* (MIC_{90} = 0.03 mcg/mL), *H. influenzae* (MIC_{90} = 0.12 mcg/mL), and *H. parainfluenzae* (MIC_{90} = 0.25 mcg/mL). The ceftobiprole MIC_{90}s for the penicillin-resistant *S. pneumoniae* subset was higher (MIC_{90} = 0.5 mcg/mL) than for the penicillin-susceptible subset (MIC_{90} = 0.015 mcg/mL) but were within the proposed susceptible breakpoint of ≤0.5 mcg/mL for ceftobiprole.

The ceftobiprole MIC_{90} for *E. faecalis* and *E. faecium* were 2 mcg/mL and >4 mcg/mL, respectively. The ceftobiprole MIC_{90} against *M. catarrhalis* was 0.25 mcg/mL. Against 12 vancomycin-resistant/ampicillin-susceptible *E. faecalis*, the ceftobiprole MIC_{90} was 2 mcg/mL.

Ceftobiprole is active against some gram-negative bacteria producing AmpC cephalosporinases or non-ESBL Class A enzymes with MIC_{90} values of ≤1 mcg/mL. Ceftobiprole has limited activity against *Pseudomonas aeruginosa* and *Acinetobacter* species with MIC_{90} values of ≥16 mcg/mL. The ceftobiprole MIC_{90} values against *P. aeruginosa* are above the PK-PD target achievable by proposed dosing regimen. Ceftobiprole is not active against ESBL or metallo β-lactamases producing bacteria. The ceftobiprole MIC_{90}s for key pathogens, *S. aureus, S. pneumoniae, E. coli,* and *K. pneumoniae* isolates from the European Union surveillance were similar to that observed for the US isolates. Ceftobiprole, like other cephalosporins, is not active against the atypical intracellular bacterial CABP pathogens, *Mycoplasma pneumoniae* or *Chlamydophila pneumoniae*. The ceftobiprole MIC against 30 *Legionella pneumophila* isolates by broth microdilution ranged from 0.03 – 0.12 mcg/mL (MIC_{90} = 0.06 mcg/mL) (Sahm 2007a). Ceftobiprole activity against intracellular forms of *L. pneumophila* has not been investigated. Ceftobiprole has limited activity against anaerobes.

Table 288. Ceftobiprole Antimicrobial Activity In Vitro Against Relevant Pathogens From Surveillance Studies

Organism	US Surveillance (2016-2020)		EU Surveillance (2016-2019)	
	MIC range (mcg/mL)	MIC_{90} in mcg/mL (no. of isolates)	MIC range (mcg/mL)	MIC_{90} in mcg/mL (no. of isolates)
Gram positive				
Staphylococcus aureus	0.03 - 4	2 (13868)	0.015-4	2 (5241)
MSSA	0.03 - 1	0.5 (7962)	0.015 – 1.0	0.5 (2772)
MRSA	0.12 -4	2 (5906)	0.015-4	2 (2469)
Staphylococcus epidermidis	0.03 -2	1 (885)		
Staphylococcus haemolyticus	0.03 - >4	4 (72)		
Staphylococcus hominis	0.03 - 2	2 (115)		
Staphylococcus lugdunensis	0.03 - 2	1 (191)		
Viridans group streptococci[a]	0.004 – 4	0.25 (611)		
Streptococcus anginosus group	0.004 – 0.25	0.12 (175)		
Streptococcus mitis group	0.008 - > 2	0.25 (183)		
β-hemolytic streptococci	0.004 – 0.12	0.03 (1830)		
Streptococcus pyogenes	0.008 – 0.12	0.015 (804)		
Streptococcus agalactiae	0.008 – 0.06	0.03 (744)		
Streptococcus dysgalactiae	0.004 - 0.015	0.015 (94)		
Streptococcus pneumoniae	0.001 - 2	0.5 (3248)	0.015-4	0.5 (2146)
Penicillin-susceptible[b]	0.001 – 0.5	0.12 (2104)		
Penicillin-resistant[c]	0.008 – 1	0.5 (1144)		
Enterococcus faecalis	0.03 - >16	2 (1837)		
Enterococcus faecium	0.12 - >16	>4 (812)		
Gram negative				
Acinetobacter spp.	0.008 - >16	>16 (720)		
Citrobacter freundii complex	0.015 - >16	4 (461)		
Citrobacter koseri	0.015 - >16	0.12 (264)		
Enterobacter spp.	0.008 ->16	4 (1872)		
Enterobacter cloacae species complex	0.015 - >16	4 (1841)		
Escherichia coli	0.008 ->16	>16 (9302)	0.015 - >64	>64 (1466)
ESBL-phenotype	0.03 - >16	>16 (1733)		
Non-ESBL-phenotype	0.008 -8	0.06 (7569)		
Haemophilus influenzae	0.008 - 1	0.12 (2248)		
β-lactamase positive	0.008 - 1	0.12 (669)		
β-lactamase negative	0.008 - 1	0.12(1579)		
Haemophilus parainfluenzae	0.008 – 0.25	0.25 (26)		
Klebsiella aerogenes	0.008 - >16	0.12 (711)		
Klebsiella oxytoca	0.015 ->16	>16 (1294)		
ESBL-phenotype	0.25 ->16	>16 (220)		
Non-ESBL-phenotype	0.015 ->16	0.5 (1074)		
Klebsiella pneumoniae	0.008 ->16	>16 (4055)	0.015 - >64	>64 (1672)
ESBL-phenotype	0.03 - >16	>16 (751)		
Non-ESBL-phenotype	0.008 - 8	0.06 (3304)		

Organism	US Surveillance (2016-2020)		EU Surveillance (2016-2019)	
	MIC range (mcg/mL)	MIC_{90} in mcg/mL (no. of isolates)	MIC range (mcg/mL)	MIC_{90} in mcg/mL (no. of isolates)
Moraxella catarrhalis	0.008 – >1	0.25 (1119)		
Morganella morganii	0.008 - >16	0.06 (330)		
Proteus mirabilis	0.015 - >16	0.06 (1369)		
Pseudomonas aeruginosa	0.12 ->16	16 (5317)		
Serratia marcescens	0.015 - 16	0.5 (1289)		
Stenotrophomonas maltophilia	8 ->16	>16 (869)		

Source: (Flamm 2016; Flamm 2017; Flamm 2018; Duncan 2019; Duncan 2020; Hawser et al. 2020; Hawser et al. 2021; Hawser et al. 2022)
ESBL = extended spectrum β-lactamase; MIC = minimum inhibitory concentration; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *Staphylococcus aureus*; EU = European Union
[a] Includes *Streptococcus anginosus*
[b] From meningitis infections (penicillin susceptible ≤ 0.06 mcg/mL).
[c] From meningitis infections (penicillin resistant ≥ 0.12 mcg/mL).

Other individual studies showed that MRSA isolates with reduced susceptibility to vancomycin, daptomycin, or linezolid had ceftobiprole MICs ranging from 0.25 to 4 mcg/mL (Table 289).

Table 289. Activity of Ceftobiprole Against Staphylococcal Clinical Isolates With Reduced Susceptibility to Vancomycin or Daptomycin, or Resistance to Linezolid or Tigecycline

Resistance phenotype	Number of Isolates	Program/ investigator	Ceftobiprole MIC (mcg/mL)	Additional Information
VISA/VICoNS[a]	7	JMI surveillance 2007-2008	1 – 4 (mode = 2)	Included 4 *S.s aureus* (incl. 1 DAP-NSd), and 3 coagulase-negative staphylococci (incl. 1 DAP-NS[d])
Linezolid-resistant[b]	38	JMI surveillance 2007-2010	1 – 4 (mode = 1)	Included 5 *S. aureus*. All isolates were susceptible to vancomycin.
Daptomycin-NS	32	Farrell 2014	0.25 - 2	–
VISA	3	Lin 2008	1 - 2	–
VRSA[c]	2	Lin 2008	1 - 2	–
VISA	20	Saravolatz 2010	1 - 2	15/20 were DAP-NS[d]
VRSA	10	Saravolatz 2010	1	Included 1 tigecycline-resistant isolate
DAP-NS[d]	7	Saravolatz 2010	1	–
hVISA	12	Borbone 2010	1 - 4	–

Source: (Fritsche 2007; Lin and Appelbaum 2008; Castanheira 2009; Borbone et al. 2010; Farrell 2010; Saravolatz et al. 2010; Farrell 2011)
DAP-NS = daptomycin-non-susceptible; MIC = minimum inhibitory concentration; VICoNS = vancomycin-intermediate coagulase-negative staphylococci; VISA = vancomycin-intermediate *Staphylococcus aureus*; VRSA = vancomycin-resistant *Staphylococcus aureus;* VSSA = vancomycin-susceptible *Staphylococcus aureus*.
[a] Vancomycin MIC > 2 mcg/mL for *S. aureus* and > 4 mcg/mL for CoNS (CLSI and EUCAST)
[b] Linezolid MIC > 4 mcg/mL
[c] Vancomycin MIC > 8 mcg/mL
[d] Daptomycin MIC > 1 mcg/mL

19.2. Interaction With Other Antimicrobials

In the *in vitro* checkboard broth and/or time kill assays, ceftobiprole was tested in combination with daptomycin, vancomycin, gentamicin, or rifampin against 20 MRSA strains with varying degrees of vancomycin susceptibility. Ceftobiprole was also tested in combination with doripenem, levofloxacin or colistin against strains of *P. aeruginosa* (N = 24), *A. baumannii* (N = 19) or fluoroquinolone-resistant *E. coli* (N = 19). Ceftobiprole in combination with ciprofloxacin, levofloxacin, amikacin, and tobramycin was evaluated in 61 clinical *P. aeruginosa* isolates. No antagonism was observed in these studies. Majority of the combination were indifferent.

19.3. In Vivo Activity

The in vivo activity of ceftobiprole was evaluated in multiple animal models of infection. These include the murine septicemia model, the murine peritonitis model, the neutropenic thigh infection model (PK-PD studies), the murine acute pneumonia model, the rat and rabbit endocarditis model, the rabbit meningitis model, the rat and rabbit osteomyelitis model, and the murine urinary tract infection model.

Murine Septicemia Model

Ceftobiprole (ED_{50} values <5 mg/kg) was effective in treating experimental septicemia in mice due to *S. aureus* strains (ceftobiprole MIC values ≤2 mcg/mL) (Table 290). Against MRSA I-6 and MRSA 8525, ceftobiprole was more active than vancomycin (vancomycin ED_{50} = 6.7 mg/kg and 12.1 mg/kg). Ceftobiprole also demonstrated activity against three penicillin-resistant strains of *S. pneumoniae*, including a strain *S. pneumoniae* 23 F-CTR (ceftobiprole MIC 1 mg/mL), however, the ceftobiprole ED_{50} for the *S. pneumoniae* penicillin resistant strains were higher than the *S. pneumoniae* penicillin sensitive strain. Similar ceftobiprole doses (ED_{50} <5 mg/kg) were effective against *E. coli, K. pneumoniae, C. freundii, S. marcescens* and *P. mirabilis*. Against the TEM-1 containing *E. coli* OC4367, the ceftobiprole ED_{50} was higher (2.7 mg/kg/day) than against the parent *E. coli* strain (0.5 mg/kg/day) but ceftobiprole was more active than ceftazidime or cefepime and as active as meropenem. The presence of the ACT-1 AmpC cephalosporinase did not affect the in vivo activity of the ceftobiprole and comparators in this animal model. The strain *Proteus vulgaris* 1028 with *in vitro* resistance to ceftobiprole was also resistant in vivo (ED_{50} >12 mg/kg). Cefepime (ED_{50} = 1 mg/kg) and meropenem (ED_{50} <0.4 mg/kg) had greater activity against the *P. aeruginosa* BA strain compared to ceftobiprole (ED_{50} = 4 mg/kg).

Table 290. Activity of Ceftobiprole Against Target Pathogens in Murine Septicemia Model

Model	Organisms (CFU/Mouse)	Ceftobiprole MIC (mcg/mL)	Resistance/ Genotype	Ceftobiprole Dose/Duration	Result
Murine septicemia model	MSSA Smith (2 x10^7)	0.25	Methicillin sensitive	SC,1 and 3 hours after infection	ED_{50} = <0.2 mg/kg[a]
	MSSA Smith (4 x10^5)	0.25	Methicillin sensitive	SC,1 and 3 hours after infection	ED_{50} = 0.19 mg/kg[a,b]
	MRSA 1-6 (5 x 10^7)	2	Methicillin resistant	SC,1 and 3 hours after infection	ED_{50} = 2.4 mg/kg[a]
	CA-MRSA OC8525 (1 x10^7)	1	Methicillin resistant	SC,1 and 3 hours after infection	ED_{50} = 4.9 mg/kg[a,b]
	S. pyogenes b-15 (1 x 10^6)	≤0.06	-	SC,1 and 3 hours after infection	ED_{50} = <0.2 mg/kg[a]
	S. pneumoniae 4241 (2 x 10^2)	≤0.06	Penicillin sensitive	SC,1 and 3 hours after infection	ED_{50} = <0.2 mg/kg[a]
	S. pneumoniae 1/37 (1 x 10^6)	0.5	Penicillin resistant	SC,1 and 3 hours after infection	ED_{50} = 1.1 mg/kg[a]
	S. pneumoniae 536 (1x 10^6)	1	Penicillin resistant	SC,1 and 3 hours after infection	ED_{50} = 0.6 mg/kg[a]
	S. pneumoniae 23F-CTR (5 x 10^4)	1	Penicillin resistant	SC,1 and 3 hours after infection	ED_{50} = 1.0 mg/kg[a]
	E. coli 29522 (5 x 10^3)	≤0.06	-	SC,1 and 3 hours after infection	ED_{50} = <0.2 mg/kg[a]
	E. coli 9040 (1 x 10^6)	0.03	Wild type	SC,1 and 3 hours after infection	ED_{50} = 0.5 mg/kg[a,b]
	E. coli 4367 (6–8 x 10^5)	0.06	TEM-1	SC,1 and 3 hours after infection	ED_{50} = 2.7 mg/kg[a,b]
	E. coli 4368 (1–4 x 10^6)	0.03	ACT-1	SC,1 and 3 hours after infection	ED_{50} = 0.5 mg/kg[a,b]
	K. pneumoniae 418 (1 x10^3)	≤0.06	-	SC,1 and 3 hours after infection	ED_{50} = <0.4 mg/kg[a]
	E. cloacae MRW (2 x 106)	4	Ceftriaxone resistant	SC,1 and 3 hours after infection	ED_{50} = 3.8 mg/kg[a]
	C. freundii 1982 (1 x 10^7)	1	Ceftriaxone resistant	SC,1 and 3 hours after infection	ED_{50} = 1.5 mg/kg[a]
	S. marcescens 69438 (5 x 103)	0.25	-	SC,1 and 3 hours after infection	ED_{50} = 0.68 mg/kg[a]
	P. vulgaris 1028 (1x10^6)	>32	Ceftobiprole resistant	SC,1 and 3 hours after infection	ED_{50} >12 mg/kg[a]
	P. mirabilis 2117 (2 x 10^6)	≤0.06		SC,1 and 3 hours after infection	ED_{50} = 0.35 mg/kg[a]

	P. aeruginosa BA (1 x10^6)	8	Ceftobiprole and ceftriaxone resistant	SC,1, 3 and 5 hours after infection	ED_{50} = 4 mg/kg[a]
	P. aeruginosa 4351 (5 x 10^5)	4	-	SC,1, and 3 hours after infection	100% survival at 24 hours post-infection with 10 mg/kg/day dose of ceftobiprole medocaril sodium

Source: Study Report DD07014, (Hebeisen et al. 2001; Hilliard 2006b; Hilliard 2007b-a; Hilliard 2007b-b)
[a]ED50 = effective dose for 50% survival based on survival rates by day 4
[b] ceftobiprole medocaril sodium was used
SC = subcutaneously; MIC = minimum inhibitory concentration; CFU = colony forming units; MSSA = methicillin sensitive *Staphylococcus aureus*; MRSA = methicillin resistant *Staphylococcus aureus;* CA-MRSA = community-acquired MRSA

Murine Peritonitis Model

In the murine peritonitis model, female mice were infected intraperitoneally with *E. faecalis* (10X the 50% lethal dose) and then immediately treated subcutaneously with ceftobiprole medocaril sodium or ampicillin. Against the rare β-lactamase-producing strain TX0921, ceftobiprole was more active than ampicillin (Table 291). It is likely that the activity of ceftobiprole against β–lactamase-producing *E. faecalis* is due to the inherent stability of the drug to hydrolysis by this enzyme (similar to class A staphylococcal penicillinase PC1). Ceftobiprole PD_{50} (dose that protects 50% of the animals) values at 96 hours were lower than ampicillin for *E. faecalis* strains TX2484, and OG1RF, respectively.

Table 291. Efficacy of Ceftobiprole Medocaril Sodium and Ampicillin Against *Enterococcus Faecalis* in a Murine Peritonitis Model

Model	Organisms (CFU/Mouse)	Ceftobiprole MIC (mcg/mL)	Resistance/Genotype	Ceftobiprole Dose/Duration	Result
Murine peritonitis model	*E. faecalis* TX0921 (1 x10^9)	<0.5 mcg/mL	b-lactamase positive similar to class A staphylococcal penicillinase PC1; gentamicin resistant	Various single SC dose administered immediately after infection	PD_{50} = 2 mg/kg[a, b]
	E. faecalis TX2484 (0.1 – 2 x 109)	<0.5 mcg/mL	Vancomycin resistant; *vanB*	Various single SC dose administered immediately after infection	PD_{50} = 7.67 mg/kg[a, b]
	E. faecalis OG1RF (1 x 10^9)	<0.5 mcg/mL	Laboratory strain fusidic acid resistant	Various single SC dose administered immediately after infection	PD_{50} = 4.17 mg/kg[a, b]

Source: (Arias et al. 2007)
CFU = colony forming unit
[a]PD50 = protective dose for 50% animals
b ceftobiprole medocaril was used
SC = subcutaneously; MIC = minimum inhibitory concentration.

Murine Acute Pneumonia Model

In the immunocompromised murine model of acute pneumonia, the ten-day cumulative survival rates for infected mice (all strains) receiving ceftobiprole medocaril sodium (total daily doses of ceftobiprole equivalents, 2.1 to 75 mg/kg) ranged from 57 to 100%, whereas with ceftriaxone (total daily doses, 10 to 400 mg/kg), the survival rates varied between 13 and 100% (Table 292). In the immunocompetent murine model of acute pneumonia, ceftobiprole medocaril sodium reduced bacterial burden in the lungs. Against the wildtype strain ATCC 6301, and the two macrolide-resistant isolates, the ceftobiprole ED_{50} was 2.5- to 4-fold lower than that determined for ceftriaxone. Against *H. influenzae*, *E. cloacae* and the non-ESBL producing *K. pneumoniae* ceftobiprole, ceftriaxone and cefepime all reduced bacterial burden in the lungs compared to no treatment. The reason for the activity of ceftriaxone (MIC=16 mcg/mL; Intermediate susceptibility) against the non-ESBL producing *K. pneumoniae* is not clear. For the ESBL-positive *K. pneumoniae* strain where the MICs were all greater than or equal to 128 mcg/mL, there was no difference between treated and untreated animals. Emergence of resistance studies conducted on bacteria recovered after therapy (except for ESBL-positive *K. pneumoniae*) found post-treatment MIC values within 2-fold of pre-treatment MIC values.

Table 292. Activity of Ceftobiprole in a Murine Model of Acute Pneumonia

Model	Organisms (CFU/Mouse)	Ceftobiprole MIC (mcg/mL)	Resistance/Genotype	Ceftobiprole Medocaril Sodium Dose/Duration	Result
Leukopenic murine model of acute pneumonia (intratracheal inoculation)	*S. pneumoniae* P-52181 (10^7)	0.008	Penicillin sensitive Ceftriaxone susceptible Ceftotaxime susceptible	2.1 mg/kg q12 h for 3 days administered SC 3 hours post infection	100% survival
	S. pneumoniae P-15986 (10^7)	0.25	Penicillin resistant Ceftriaxone susceptible Ceftotaxime susceptible	4.2 mg/kg q12 h for 3 days administered SC 3 hours post infection	93% survival
	S. pneumoniae P-40422 (10^7)	1	Penicillin resistant Ceftriaxone resistant Ceftotaxime resistant	17 mg/kg q8 h for 3 days administered SC 3 hours post infection	80% survival
	S. pneumoniae P-40984 (10^7)	1	Penicillin resistant Ceftriaxone resistant Ceftotaxime resistant	25 mg/kg q8 h for 3 days administered SC 3 hours post infection	80% survival
Immunocompetent murine model of lethal pneumonia (intranasal inoculation)	*S. pneumoniae* ATCC 6301 ($2x10^7$)	0.015	Macrolide susceptible Penicillin susceptible	Various doses administered SC	ED_{50} = 0.04 mg/kg/day
	S. pneumoniae OC6263 ($2x10^7$)	0.015	Macrolide susceptible Penicillin susceptible	Various doses administered SC	ED_{50} = 0.17 mg/kg/day

Model	Organisms (CFU/Mouse)	Ceftobiprole MIC (mcg/mL)	Resistance/Genotype	Ceftobiprole Medocaril Sodium Dose/Duration	Result
	S. pneumoniae OC6235 ($2x10^7$)	0.008	Macrolide resistant; *ermB* Penicillin susceptible	Various doses administered SC	ED_{50} = 0.07 mg/kg/day
	S. pneumoniae OC6236 ($2x10^7$)	0.008	Macrolide resistant; *mefB* Penicillin susceptible	Various doses administered SC	ED_{50} = 0.07 mg/kg/day
Immunocompetent murine model of lethal pneumonia (intratracheal inoculation)	*H. influenzae* (10^8)	≤0.012	β-lactamase negative	71 mg/kg q6h for 2 days, SC	2 $\log_{10}$ CFU reduction/g lung 9/15 animals sterile
	E. cloacae (10^7)	≤0.012	Non ESBL producing	71 mg/kg q6h for 2 days, SC	2 $\log_{10}$ CFU reduction/g lung 4/16 animals sterile
	K pneumoniae (10^7)	0.5	Non ESBL producing	71 mg/kg q6h for 2 days, SC	4 $\log_{10}$ reduction in CFU/g lung 2/15 animals sterile
	K. pneumoniae (10^7)	128	ESBL producing; TEM-1, SHV-1, CTX-M-2	71 mg/kg q6h for 2 days, SC	Median 6.36 $\log_{10}$ CFU/g lung same as untreated 0/16 animals sterile

Source: (Azoulay-Dupuis et al. 2004)
ED_{50} = effective dose for 50% survival based on survival rates at 48 hours post-infection
SC = subcutaneously; MIC = minimum inhibitory concentration; CFU = colony forming units

Neutropenic murine thigh infection model

The neutropenic murine thigh infection model was used for PK-PD assessments and ceftobiprole exposures for a 1 log kill for *S. aureus* (MRSA and MSSA), *S. pneumoniae*, *E. coli*, *K. pneumoniae*, *E. cloacae* were determined (see section 19.4).

Endocarditis Model

The activity of ceftobiprole medocaril sodium against *S. aureus* was examined in a rat and rabbit model of endocarditis (Table 293). In the rat model of endocarditis, the three ceftobiprole medocaril sodium dosing regimens (72 mg/kg, 144 mg/kg, and 288 mg/kg that achieved steady-state levels in serum of 2.5, 5, and 10 times the MIC for the test organisms) cleared >90% of vegetations in rats with experimental endocarditis caused by penicillinase-producing MRSA COL (Bla+) and the MRSA P8-Hom strain. Blood and spleen cultures from all animals were negative. No resistant mutants were isolated from infected vegetations from any group of treated

animals. In another study, treatment with standard dose-ceftobiprole simulating human kinetics of 500 mg every 12 hours (q12h) cleared 93% and 77% of vegetations infected with strains PC3 and Mu50, respectively, and reduced the vegetation counts by >6 $\log_{10}$ CFU/g compared to those in untreated controls. In general, spleens remained infected even after effective antibacterial therapy of the valves with some decrease in the bacterial burden. After 3 days of treatment, rats were followed for an additional three days without drug for relapse. In the relapse subset, regrowth of bacteria was observed with all treatment groups.

In the rabbit model of endocarditis, the activity of ceftobiprole medocaril sodium (25 mg/kg (equivalent to 19 mg of ceftobiprole per kg) intramuscularly every 8 hours for 4 days) was equivalent to that of vancomycin (30 mg/kg intravenously every 12 hours for 4 days) in rabbits infected with MRSA 76, and superior to that of vancomycin for rabbits infected with the vancomycin-intermediate *Staphylococcus aureus* strain HIP5836. Ceftobiprole medocaril sodium (25 mg/kg intramuscular q8h for 4 days) cleared the vegetations, spleen and kidneys of MRSA in 6/7, 5/7, and 7/7 rabbits with aortic catheter infected with 1.5 x 10^7 CFU of MRSA strain COL. In contrast, vancomycin (30 mg/kg intravenous q12h for 4 days) and daptomycin (18 mg/kg intravenous q24h for 4 days) cleared MRSA from these tissues in fewer animals.

Table 293. Efficacy of Ceftobiprole in Experimental Endocarditis

Model	Organisms (CFU/Mouse)	Ceftobiprole MIC (mcg/mL)	Resistance/Genotype	Ceftobiprole Medocaril Sodium Dose/Duration	Result
Rat model of endocarditis	MRSA COL Bla+ (10^5)	2	Penicillinase producing	72 mg/kg IV for 3 days, 12 hours after bacterial challenge	6 $\log_{10}$ reduction in vegetation Blood and spleen culture negative
	MRSA P-8_Hom (10^5)	2	Penicillinase producing	72 mg/kg IV for 3 days, 12 hours after bacterial challenge	6 $\log_{10}$ reduction in vegetation Blood and spleen culture negative
	S. aureus Xen 29 (10^6)	0.25	Methicillin susceptible	20 mg/kg IV for 3 days, 3 days after bacterial challenge	6 $\log_{10}$ reduction in vegetation 4.5 $\log_{10}$ reduction in kidneys and spleen; Relapse observed 3 days after treatment discontinuation
	S. aureus PC3 (10^6)	2	Vancomycin intermediate	500 mg twice a day IV for 3 days, 12 hours after bacterial challenge	13 out of 14 vegetation sterile and 6 $\log_{10}$ reduction in vegetation
	S. aureus Mu50 (10^6)	1	Vancomycin intermediate	500 mg twice a day IV for 3 days, 12 hours after bacterial challenge	10 out of 13 vegetation sterile and 6 $\log_{10}$ reduction in vegetation

	MRSA ATCC43300 (10^6)	1	Methicillin resistant	100 mg/kg twice daily IV for 3 days; 3 days after bacterial challenge	4.5 $\log_{10}$ reduction in vegetation; Relapse observed 3 days after treatment discontinuation
New Zealand White Rabbit Model of endocarditis	MRSA 76 (10^6)	2	Methicillin resistant	25 mg/kg q8h, IM for 4 days, 16-18 hours post-infection	4 $\log_{10}$ CFU reduction in vegetation
	MRSA HIP5836 (10^6)	0.5	Methicillin resistant Vancomycin intermediate	25 mg/kg q8h, IM for 4 days, 16-18 hours post-infection	4 $\log_{10}$ CFU reduction in vegetation
	MRSA COL (1.5×10^7)	4	Methicillin resistant	25 mg/kg q8h, IM for 4 days, 16-18 hours post-infection	6 $\log_{10}$ CFU reduction in vegetation

Source: (Entenza et al. 2002; Chambers 2005; Xiong 2009; Tattevin et al. 2010; Entenza et al. 2011; Fernandez et al. 2012)
Abbreviations: ATCC, American type culture collection; CFU = colony forming unit; MRSA = methicillin-resistant *Staphylococcus aureus*
IV = intravenous; IM = intramuscular

Rabbit Meningitis Model

In the rabbit model of experimental meningitis, the activity of ceftobiprole (40 mg/kg IV once) was similar to cefepime (100 mg/kg at 0 and 4 hours) against *E. coli*, *K. pneumoniae* and the β-lactamase-negative and positive *H. influenzae* strains (Table 294). Ceftobiprole reduced the bacterial burden in the CSF of animals infected with the β-lactamase-positive *H. influenzae* strain to a greater extent than cefepime.

Table 294. Efficacy of Ceftobiprole in Experimental Meningitis and Osteomyelitis Models

Model	Organisms (CFU/Mouse)	Ceftobiprole MIC (mcg/mL)	Resistance/Genotype	Ceftobiprole Medocaril Sodium Dose/Duration	Result
Rabbit model of meningitis	*K. pneumoniae* strain 1173687 (10^5)	1	-	40 mg/kg iv, 24 hours post infection	4 $\log_{10}$ reduction in CSF CFU at 8 hours
	E.coli strain QK-9 (10^5)	0.25	-	40 mg/kg iv, 24 hours post infection	2 $\log_{10}$ reduction CSF CFU at 8 hours
	H. influenzae (10^7)	0.5	β lactamase positive	40 mg/kg iv, 24 hours post infection	2 $\log_{10}$ reduction in CSF CFU at 8 hours
	H. influenzae (10^7)	0.5	β lactamase negative	40 mg/kg iv, 24 hours post infection	4 $\log_{10}$ reduction in CSF CFU at 8 hours
Rat model of Osteomyelitis	MRSA strain 3020 (10^7)	1	Methicillin resistant	70 mg/kg q8h IP for 5 or 14 days; 24 hours post-infection	1 $\log_{10}$ reduction after 5 days of therapy and 2 $\log_{10}$ reduction in CFU in sternal bones after 14 days of therapy
				100 mg/kgq8h IP for 5 or 14 days; 24 hours post-infection	1.4- 2 $\log_{10}$ reduction in CFU in sternal bones after 5-14 days of therapy
Rabbit model of osteomyelitis	MRSA 168-1 (10^6)	0.39	Methicillin resistant	40 mg/kg q8H for 4 weeks	100% clearance

Source: (Yin 2005; Navon-Venezia 2009; Stucki et al. 2012; Barnea et al. 2014)
IV = intravenous; CSF = cerebrospinal fluid; CFU = colony forming units; IP = intraperitoneally

Rat and Rabbit Osteomyelitis Model

In the rat model of MRSA mediastinitis and sternal osteomyelitis (Table 294), ceftobiprole (70 and 100 mg/kg for 5 days) decreased the MRSA load in the sternum by 1 $\log_{10}$ and 1.4 $\log_{10}$ compared with untreated controls and the vancomycin-treated group. MRSA was recovered from the spleen in 5/7 saline-treated animals but in none of the antibacterial drug-treated animals. Following 14 days therapy, 5/8 ceftobiprole-treated rats and 6/8 vancomycin-treated rats cleared MRSA from the sternum compared with none of the saline-treated animals. In those animals that did not clear MRSA, only rare colonies were recovered. In rabbits with localized osteomyelitis due to MRSA 168-1, ceftobiprole medocaril sodium (40 mg/kg ceftobiprole equivalent, q8h, 4 weeks) administered subcutaneously was more active than vancomycin (30 mg/kg, q12h, 4 weeks, subcutaneous) or oral linezolid (60 mg/kg, q8h, 4 weeks) at 2 weeks after end of treatment.

Murine Urinary Tract Infection Model

In the murine urinary tract infection model, mice were treated with single doses of ceftobiprole medocaril sodium (equivalent to 4.3 to 34.2 mg/kg of ceftobiprole and concentrations achievable in humans with standard human dosing) or vancomycin (2-fold range from 6.25 to 50 mg/kg of body weight), 1-hour post-infection. Two doses of ampicillin (2-fold range from 12.5 to 200 mg/kg) were administered subcutaneously 1- and 2-hour post-infection (previously shown to simulate ampicillin human doses of 3 gm). The minimum detection limit of bacteria in these experiments was 10^2 CFU/gm. Protection was defined as no recovery of bacteria from kidney or bladder homogenates at 48 hours post-infection. The authors state that ceftobiprole was active against the Bla^+ and Bla^- *E. faecalis* OG1 strains, while ampicillin (depending on the inoculum) was less effective against Bla^+ than Bla^- OG1 strains in this murine urinary tract infection model based on 50% protective dose (Table 295). However, it should be noted that treatment was initiated 1-2 hours post-infection making it difficult to assess if urinary tract infection was established. Hence, data from this Study should be interpreted with caution.

Table 295. PD50s of Ceftobiprole and Other Antibiotics Against *Enterococcus Faecalis* Bla+ OG1 and Bla- OG1 Strains in a Mouse UTI Model

Strain	Inoculum (CFU)	Antibiotic	MIC (mcg/mL)	No. of Doses (Time [h] Post Inoculation)	PD_{50} (mg/kg)	
					Kidney	Bladder
Bla^- OG1	10^5	Ceftobiprole[a]	1	1 (1)	10	18
		Ampicillin	1	2 (1,2)	7	19
		Vancomycin	1	1 (1)	31	36
Bla^+ OG1	10^5	Ceftobiprole[a]	0.5	1 (1)	7	15
		Ampicillin	4	2 (1,2)	44	66
		Vancomycin	1	1 (1)	27	38
Bla^+ OG1	10^7	Ceftobiprole[a]	1	1 (1)	33	31
		Ampicillin	>128	2 (1,2)	>200	>200
		Vancomycin[b]				

Source: Singh and Murray (2012)
[a] Ceftobiprole was used for in vitro MIC determinations, and ceftobiprole medocaril sodium was used for in vivo experiments.
[b] Vancomycin was not tested at the higher inoculum, since it is not known to be affected by E. faecalis Bla and the purpose was to evaluate an in vivo effect of Bla on ampicillin and test the stability of ceftobiprole.

In summary, ceftobiprole was shown to be active against MSSA and MRSA in the murine septicemia model and rat and rabbit endocarditis and osteomyelitis models. Ceftobiprole was active against *S. pneumoniae,* including penicillin resistant strains in the murine septicemia and the murine acute pneumonia models. Ceftobiprole was also shown to be active against *E. coli* expressing TEM-1 and Act-1 AmpC cephalosporinase, *K. pneumoniae, C. freundii, S. marcescens,* and *P. mirabilis* in the murine septicemia model. In a rabbit model of meningitis ceftobiprole was effective at reducing bacterial burden in the CSF in rabbits infected with strains of *E. coli*, *K. pneumoniae* and β-lactamase positive and negative *H. influenzae*. In both a rat and rabbit model of endocarditis, ceftobiprole did not sterilize but was effective in reducing cardiac vegetations of MRSA including a vancomycin intermediate strain. Similarly, in both a rat and rabbit model of osteomyelitis, ceftobiprole was effective in reducing bacterial burden in MRSA infected sternal bones.

19.4. PK/PD Studies

Pharmacokinetic/pharmacodynamic studies in the neutropenic mouse thigh infection model identified %fT>MIC as the PK/PD index that correlated with *in vivo* activity. An exposure target of %fT>MIC = 30% for 1-log kill was selected based on the animal studies with gram-positive bacteria (Table 296 and Table 297).

Table 296. Exposure Targets Required for a 1-Log Kill in Neutropenic Murine Thigh Infection Models (Gram-Positive Bacteria)

Bacteria	Phenotype	Ceftobiprole MIC mcg/mL	Model	Ceftobiprole %*f*T>MIC		Reference
				Stasis	1-log kill	
Staphylococcus aureus	Two MSSA and four MRSA. Low inoculum infection $10^{4.5\text{-}5.7}$ CFU	0.5 – 2	Neutropenic murine thigh infection	11.4%	15.3%	Lee 2013[a]
Staphylococcus aureus	Two MSSA and four MRSA. High inoculum infection $10^{6.4\text{-}7.2}$ CFU	0.5 – 2	Neutropenic murine thigh Infection	16.1%	19.8%	Lee 2013[a]
Streptococcus pneumoniae	Two penicillin-susceptible and two penicillin-resistant strains. Low inoculum infection $10^{4.5\text{-}5.7}$ CFU	0.015 – 0.5	Neutropenic murine thigh infection	8.4%	13.8%	Lee 2013[a]
Streptococcus pneumoniae	Two penicillin-susceptible and two penicillin-resistant strains. High inoculum infection $10^{6.4\text{-}7.2}$ CFU	0.015 – 0.5	Neutropenic murine thigh infection	16.7%	18.4%	Lee 2013[a]
Staphylococcus aureus	Eight *Staphylococcus aureus*, including five MRSA	0.5 – 2	Neutropenic murine thigh infection	21.1%	25.8%	Craig 2008[b]
Streptococcus pneumoniae	Six *Streptococcus pneumoniae*, including 4 penicillin-resistant strains	0.03 – 1	Neutropenic murine thigh infection	18.8%	22.3%	Craig 2008[b]

Source: Referenced in the table
[a].(Lee et al. 2013)
[b] (Craig and Andes 2008)
CFU = colony forming unit; CA-MRSA = community-acquired methicillin-resistant Staphylococcus aureus; HA-MRSA = hospital-acquired methicillin-resistant Staphylococcus aureus; MIC = minimal inhibitory concentration; MRSA = methicillin-resistant Staphylococcus aureus; MSSA = methicillin-susceptible Staphylococcus aureus; SD = standard deviation; T>MIC = Time (hours) above the minimal inhibitory concentration.

Table 297. Exposure Targets Required for a 1-Log Kill in Murine Pneumonia Models (Gram-Positive Bacteria)

Bacteria	Phenotype	Ceftobiprole MIC mcg/mL	Model	Ceftobiprole %*f*T>MIC		Reference
				Stasis	1-log kill	
Staphylococcus aureus	Two MSSA, three HA-MRSA and three CA-MRSA	0.25 – 2	Neutropenic murine pneumonia	8.8%	13.5%	Laohavaleeson 2008[a], Rodvold 2009[b]
Streptococcus pneumoniae	Two *Streptococcus pneumoniae*, including one Penicillin-resistant strain and two Penicillin-, Ceftriaxone- and Cefotaxime-resistant strains	0.008 – 1	Murine pneumonia		12.5%	Azoulay- Dupuis 2004[c]

Source: Referenced in the Table
[a] (Laohavaleeson et al. 2008)
[b] (Rodvold et al. 2009)
[c] (Azoulay-Dupuis et al. 2004)

CFU = colony forming unit; CA-MRSA = community-acquired methicillin-resistant *Staphylococcus aureus*; HA-MRSA = hospital-acquired methicillin-resistant *Staphylococcus aureus*; MIC = minimal inhibitory concentration; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *Staphylococcus aureus*; SD = standard deviation; T>MIC = Time (hours) above the minimal inhibitory concentration.

The %fT>MIC required for bactericidal (1-log kill) activity against gram-negative organisms was greater than for the gram-positive organisms. An exposure target of %fT>MIC = 60% for 1-log kill was selected based on the animal studies with gram-negative bacteria (Table 298).

Table 298. Exposure Targets Required for a 1-Log Kill in Neutropenic Murine Thigh Infection and Neutropenic Lung Infection Models (Gram-Negative Bacteria)

Bacteria	Ceftobiprole MIC mcg/mL	Model	Ceftobiprole %*f*T>MIC		Reference
			Stasis	1-log kill	
Escherichia coli	0.06	Neutropenic murine-thigh infection	41.9%	47.4%	Craig 2008[c]
Klebsiella pneumoniae	0.06		41.2%	46.5%	
Enterobacter cloacae	2.0		44.6%	60.4%	
Enterobacter cloacae	0.5		35.6%	35%	
Pseudomonas aeruginosa	2.0		46.7%	56.9%	
*Enterobacter cloacae (*non-ESBL)	≤0.125	Murine lung infection	–	44.3%[a]	Rouse 2007[d]
*Klebsiella pneumoniae (*non-ESBL)	0.5		–	35.2%[b]	

Source: Referenced in the Table
[a] Lung CFU following ceftobiprole treatment was 3.59 log10 CFU/g, compared to untreated control of 6.04 log10 CFU/g.
[b] Lung CFU following ceftobiprole treatment was <2.50 log10 CFU/g (below limit of detection), compared to untreated control of 6.80 log10 CFU/g
[c.](Craig and Andes 2008)
[d.](Rouse et al. 2007)
ESBL = extended spectrum β-lactamase; MIC = minimal inhibitory concentration; SD = standard deviation; T>MIC = Time (hours) above the minimal inhibitory concentration.

PK/PD target attainment analysis was conducted using data from the completed phase 1, 2 and 3 studies. These analyses suggest that the PK-PD cutoff for breakpoint determination is MIC of 4 mcg/mL for *S. aureus, S. pneumoniae*, and *Streptococcus* species with exposures from proposed dosing while the PK-PD cutoff is MIC of 2 mcg/mL for *Enterobacterales* (see Clinical Pharmacology Section 14.5.2.1.3).

19.5. Clinical Studies

***Staphylococcus aureus* Bacteremia**

BPR-CS-009 was a randomized, double-blind, multicenter trial conducted to establish the efficacy and safety of ceftobiprole medocaril sodium compared to daptomycin in the treatment of SAB, including infective endocarditis. The trial assessed microbiological eradication rates (negative blood culture for *S. aureus*) at Day 4, Day 8, and the EOT and PTE visits in the mITT population. The mITT population comprised of 387 subjects (ceftobiprole: n = 189; comparator: n = 198). In the ceftobiprole group, 74.6% of subjects (141/189) had an MSSA infection at baseline, and 23.8% of subjects (45/189) had an MRSA infection at baseline. In the comparator group, 73.7% of subjects (146/198) had an MSSA infection, and 24.7% of subjects (49/198) had an MRSA infection.

The microbiological eradication rates at various visits in the mITT population in subjects with SAB due to MSSA and MRSA are shown in Table 299. The microbiological eradication rates appear to be slightly lower in the MRSA subgroup compared to the MSSA subgroup but could be due to the small number of subjects with MRSA.

Table 299. Microbiological Eradication Rates in the mITT and CE Populations for Subject With Baseline *Staphylococcus aureus* Bacteremia

	mITT Population	
	Microbiological Eradication, n/N (%)	
Baseline Blood Pathogen	**Ceftobiprole N = 189**	**Daptomycin N = 198**
Day 4		
Staphylococcus aureus, MSSA	82/141 (58.2)	84/146 (57.5)
Staphylococcus aureus, MRSA	18/45 (40.0)	23/49 (47.9)
Day 8		
Staphylococcus aureus, MSSA	121/141 (85.8)	124/146 (84.9)
Staphylococcus aureus, MRSA	38/45 (84.4)	46/49 (93.9)
EOT		
Staphylococcus aureus, MSSA	127/141 (90.1)	130/146 (89.0)
Staphylococcus aureus, MRSA	38/45 (84.4)	44/49 (89.8)
PTE		
Staphylococcus aureus, MSSA	117/141 (83.0)	112/146 (76.7)
Staphylococcus aureus, MRSA	36/45 (80.0)	40/49 (81.6)

Source Table 14.2.2.3.2.6 Trial BPR-CS-009 CSR
n/N = number of subjects with microbiological eradication/ total number of patents with the pathogen

Relapse of *S. aureus* bacteremia was assessed by the data review committee in two subjects (1%), treated with ceftobiprole, both with MSSA, and in four subjects (3%) treated in the daptomycin ± aztreonam group, two with MSSA and two with MRSA. Three subjects (1.5%), two with MSSA and one with MRSA, in the daptomycin ± aztreonam group had non-susceptible isolates with MICs that were four-fold higher than the baseline MICs and were clinical failures. No development of resistance on therapy was observed in subjects treated with ceftobiprole.

In the ceftobiprole group, MICs were determined for 141 baseline MSSA isolates and 43 baseline MRSA isolates (Table 300). For the MSSA isolates, the ceftobiprole MIC range was 0.12 – 1 mcg/mL with an MIC_{90} of 0.5 mcg/mL. For the MRSA isolates, the ceftobiprole MIC range was 0.5 – 2 mcg/mL with an MIC_{90} of 2 mcg/mL. There was no apparent correlation between baseline ceftobiprole MICs and clinical failure.

Table 300. Overall Success and Microbiological Eradication at PTE by Ceftobiprole MIC (mITT and CE Populations; DRC Assessment)

Ceftobiprole MIC (mcg/mL)	Ceftobiprole (mITT = 189)			Ceftobiprole (CE = 163)		
	Total n	Overall Success n (%)	Microbiological Eradication n (%)	Total n	Overall Success n (%)	Microbiological Eradication n (%)
MRSA	43	30 (69.8)	35 (81.4)	37	29 (78.4)	32 (86.5)
0.5	6	2 (33.3)	3 (50.0)	4	2 (50.0)	2 (50.0)
1	25	19 (76.0)	22 (88.0)	23	18 (78.3)	20 (87.0)
2	12	9 (75.0)	10 (83.3)	10	9 (90.0)	10 (100)
MSSA	141	100 (70.9)	117 (83.0)	123	96 (78.0)	107 (87.0)
0.12	1	1 (100)	1 (100)	1	1 (100)	1 (100)
0.25	72	54 (75.0)	60 (83.3)	64	51 (79.7)	54 (84.4)
0.5	67	44 (65.7)	55 (82.1)	57	43 (75.4)	51 (89.5)
1	1	1 (100)	1 (100)	1	1 (100)	1 (100)

Source: BPR-CS-009 CSR Table 14.2.1.2.8a and Table 14.2.2.1.1.2.8a
n = number of subjects with a response; N = total number of subjects in the respective category with susceptibility results from the CML.
Note: 3 subjects in each treatment arm did not have MRSA/MSSA designations and therefore are not included. Baseline pathogens were identified based on isolates from blood collected within 80 hours prior to randomization date and time up to first dose date and time.

Characterization of the clonal strain type of the baseline MRSA isolates (ceftobiprole n = 43, daptomycin n = 47) was performed using Multi-Locus Sequence Testing, spa typing, and SCCmec typing. These results identified the presence of several pandemic MRSA lineages and a global representation. U.S. strains such as USA30, USA100, USA300, and USA1100 were identified in this strain set. Of the strains identified from U.S. subjects, 75% belonged to the USA300 clonal complex. Clinical outcome per treatment group for the pooled U.S. and U.S. LAV clonal types, representing 49% of strains typed, was assessed. Overall success at the PTE visits was observed in 76.2% of subjects (16/21) in the ceftobiprole group, and 69.6% (16/23) in the comparator group (Table 301) for the US strain type.

Table 301. Overall Success Based on DRC Assessment at the PTE Visit by MRSA Clonal Strain Type (mITT Population)

Clonal strain type	Ceftobiprole n/N (%)	Daptomycin n/N (%)	Difference (95% CI)[a]
USA or Latin American strain types (pooled)	**16/21 (76.2)**	**16/23 (69.6)**	**3.9 (−20.6, 28.4)**
USA 300 LAV	7/8 (87.5)	10/11 (90.9)	
USA 800	3/4 (75.0)	4/4 (100.0)	
USA 100	4/4 (100.0)	0/3 (0.0)	
USA 300	0/2 (0.0)	1/2 (50.0)	
USA 400	1/1 (100.0)	1/2 (50.0)	
USA 1100	1/2 (50.0)	0/0 (NE)	
USA 700	0/0 (NE)	0/1 (0.0)	
Other strain types (pooled)	**14/21 (66.7)**	**19/22 (86.4)**	**−12.3 (−33.4, 8.9)**
UK-EMRSA-15	5/8 (62.5)	10/11 (90.9)	
Hungarian/Brazilian	5/7 (71.4)	4/5 (80.0)	
Taiwan	1/3 (33.3)	2/2 (100.0)	
ST398-LA-MRSA	1/1 (100.0)	2/3 (66.7)	
Berlin	1/1 (100.0)	0/0 (NE)	
Iberian	1/1 (100.0)	0/0 (NE)	
ST1-LA-MRSA	0/0 (NE)	1/1 (100.0)	

Source: Table 14.4.1.4
CI = confidence interval; CMH = Cochran-Mantel-Haenszel; DRC = Data Review Committee; LAV: Latin-American variant; mITT = Modified Intent-to-Treat; MRSA = methicillin-resistant *S. aureus*; NE = not evaluable; PTE = post-treatment evaluation visit; LA-MRSA = Livestock-associated MRSA.
[a] Proportion difference of ceftobiprole minus daptomycin. Computed using CMH weights method adjusted for actual stratum (dialysis status and prior antibacterial treatment use

Source: Source: BPR-CS-009 Clinical study Report Table 14.4.1.4

The trial demonstrates that ceftobiprole is effective in the treatment of SAB due to methicillin-resistant and methicillin-sensitive *S. aureus*.

ABSSSIs

Trial BPR-CS-008 was a double-blind, non-inferiority, active-controlled trial, which randomized 679 adult subjects with qualifying ABSSSI and who fulfilled the requirement to receive intravenous antibacterial drugs in a hospital setting. The mITT population consisted of 506 subjects (ceftobiprole N= 244; vancomycin plus aztreonam N =262) and was a subset of subjects in the ITT population who had causative pathogens identified by the central microbiology laboratory from skin lesions or blood cultures. Local laboratory results were included only if isolate could not be cultured at the central laboratory. Nine gram-negative and 27 gram-positive baseline pathogens isolated from subjects in the mITT population were only analyzed by local laboratories. The ME population consisted of 426 subjects (ceftobiprole N= 203; vancomycin plus aztreonam N =223) and was the subset of subjects in the mITT population who were also in the clinically evaluable population. Gram- positive pathogens were isolated at Baseline in 442 subjects while gram-negative pathogens were isolated in 34 subjects and mixed gram positive and gram-negative pathogens were isolated in 30 subjects at Baseline. The early clinical response and investigator's assessment of overall clinical success at TOC by Baseline pathogen are shown in Table 302. Ceftobiprole was active against *S. aureus* (methicillin sensitive and methicillin resistant), *Streptococcus pyogenes*, and *K. pneumoniae*. There were no ABSSSI subjects with baseline *E. coli* in the mITT population. It should be noted that the number of subjects with *Enterobacter cloacae* was small (n = 3), but all 3 subjects were a clinical success, including a subject with *E. cloacae* isolate with MIC>64 mcg/mL (Table 303).

Table 302. Primary Efficacy Outcome by Pathogen From the Adult Phase 3 ABSSSI Trial

	Early Clinical Response at 48–72 Hours After Start of Treatment* (mITT)		Investigator-Assessed Clinical Success at the TOC Visit† (mITT)	
Pathogen	**ZEVTERA n/N (%)**	**Vancomycin Plus Aztreonam n/N (%)**	**ZEVTERA n/N (%)**	**Vancomycin Plus aztreonam n/N (%)**
Any gram-positive pathogen	213/228 (93.4)	220/244 (90.2)	203/228 (89.0)	217/244 (88.9)
Staphylococcus aureus	186/197 (94.4)	185/205 (90.2)	174/197 (88.3)	180/205 (87.8)
Methicillin-susceptible	102/108 (94.3)	112/124 (90.3)	95/108 (88.0)	107/124 (86.3)
Methicillin-resistant	81/86 (94.2)	67/73 (91.8)	76/86 (88.4)	66/73 (90.4)
Streptococcus agalactiae	4/4 (100.0)	6/6 (100.0)	4/4 (100.0)	6/6 (100.0)
Streptococcus pyogenes	17/20 (85.0)	23/24 (95.8)	17/20 (85.0)	22/24 (91.7)
Streptococcus anginosus	4/6 (66.7%)	5/6 (83.3)	5/6 (83.3)	4/6 (66.7)
Streptococcus constellatus	2/2 (100.0)	6/6 (100.0)	2/2 (100.0)	6/6 (100.0)
Streptococcus intermedius	7/8 (87.5)	4/4 (100.0)	7/8 (87.5)	4/4 (100.0)
Any gram-negative pathogen	26/27 (96.3)	33/37 (89.2)	24/27 (88.9)	34/37 (91.9)
Enterobacterales spp.	16/16 (100.0)	24/27 (88.9)	15/16 (93.8)	25/27 (92.6)
Klebsiella pneumoniae	8/8 (100.0)	5/5 (100.0)	7/8 (87.5)	5/5 (100.0)
Enterobacter cloacae	3/3 (100.0)	4/6 (66.7)	3/3 (100.0)	4/6 (66.7)
Escherichia coli	0	8/9 (88.9)	0	9/9 (100.0)
Serratia marcescens	3/3 (100.0)	4/4 (100.0)	3/3 (100.0)	4/4 (100.0)
Pseudomonas aeruginosa	4/4 (100.0)	2/3 (66.7)	4/4 (100.0%)	3/3 (100.0)

Source: Reviewer generated
* Early clinical response based on at least 20% reduction from baseline in the area of the primary lesion, survival for ≥ 72 hours from the time of administration of the first dose of study drug, no use of concomitant systemic antibacterial treatments, or topical antibacterial administration on the primary lesion and no additional unplanned surgical procedure for the ABSSSI after the start of study treatment.
† Clinical success was defined as complete (cured) or nearly complete (improved) resolution of baseline signs and symptoms of the primary infection such that no further antibacterial treatment was needed.
Data are the number of responders out of the number of subjects in the category.

Table 303. Investigator-Assessed Early Clinical Response by 48 to 72 Hours and Investigator Assessed Clinical Success at TOC by Baseline Pathogen Susceptibility of Infection-Site Specimens in the Ceftobiprole Arm (mITT Population)

Pathogen/Ceftobiprole MIC (mcg/mL)	**Early Clinical Responder n/N(%)**	**Clinical Success at TOC n/N (%)**
Gram-positive		
Staphylococcus aureus		
MRSA	77/82 (93.9)	72/82 (87.8)
0.25	3/3 (100.0)	3/3(100.0)
0.5	11/11 (100.0)	11/11 (100.0)
1	63/68 (92.6)	58/68 (85.3)
MSSA	100/106 (94.3)	95/106 (89.6)
≤0.015	1/1	1/1
0.12	3/3 (100.0)	2/3 (66.7)
0.25	53/57 (93.0)	54/57 (94.7)
0.5	43/45 (95.6)	38/45 (84.4)
β-hemolytic streptococci		
Streptococcus agalactiae	3/3 (100.0)	3/3 (100.0)
≤0.015	2/2 (100.0)	2/2 (100.0)
0.03	1/1	1/1
Streptococcus pyogenes	16 /19 (84.2)	17/19 (89.5)
≤0.015	13/16 (81.3)	14/16 (87.5)
0.03	3/3 (100.0)	3/3 (100.0)
Staphylococcus lugdunensis	1/1	1/1

Pathogen/Ceftobiprole MIC (mcg/mL)	Early Clinical Responder n/N(%)	Clinical Success at TOC n/N (%)
0.25	1/1	1/1
Enterococcus faecalis	3/3 (100.0)	3/3 (100.0)
0.25	2/2(100.0)	2/2 (100.0)
4	1/1	1/1
Gram-negative		
Acinetobacter baumannii	2/2 (100.0)	1/2 (50.0)
>64	2/2 (100.0)	½ (50.0)
Prevotella bivia	1/1	1/1
>8	1/1	1/1
Proteus mirabilis	1/1	1/1
≤0.015	1/1	1/1
Pseudomonas aeruginosa	3/3 (100.0)	3/3 (100.0)
1	1/1	1/1
4	1/1	1/1
>64	1/1	1/1
Pseudomonas oryzihabitans	1/1	1/1
0.06	1/1	1/1
Pseudomonas, non-speciated	1/1	1/1
2	1/1	1/1
Enterobacter asburiae	1/1	1/1
≤0.015	1/1	1/1
Enterobacter cloacae	3/3 (100.0)	3/3 (100.0)
≤0.015	2/2(100.0)	2/2(100.0)
>64	1/1	1/1
Klebsiella oxytoca	1/1	1/1
0.12	1/1	1/1
Klebsiella pneumoniae	7/7 (100.0)	7/7 (100.0)
≤0.015	4/4 (100.0)	4/4 (100.0)
0.03	1/1	1/1
>64	2/2 (100.0)	2/2 (100.0)
Serratia marcescens	2/2 (100.0)	2/2 (100.0)
≤0.015	2/2 (100.0)	2/2 (100.0)

Source: BPR-CS-008 CSR Table 14.2.1.3.7.1.2. and Table 14.2.2.3.7.1.2.
n = number of subjects with a response; N = total number of subjects in the respective category.
mITT= microbiological Intent-to-Treat, MIC = minimal inhibitory concentration, MRSA = methicillin-resistant *Staphylococcus aureus*, MSSA = methicillin-susceptible *Staphylococcus aureus*.
Note: MIC data are from the CML only.

Bacteremia Subjects

Of the 506 subjects in the mITT population, 17 (3.4%) had concomitant bacteremia and had pathogens isolated from baseline blood cultures. Of the 17 subjects with positive blood cultures, 7 were in the ceftobiprole arm and 10 were in the comparator arm). All subjects with positive blood cultures in the ceftobiprole arm (n = 7) were responders, while 9 out of 10 subjects were responders in the comparator arm (Table 304).

Table 304. Subjects With Baseline Pathogens Isolated From Blood Cultures (mITT Population)

Baseline Blood Pathogen	Ceftobiprole (N=244) n (%)	Vancomycin Plus Aztreonam (N=262) n (%)	Total (N=506) n (%)
Gram-positive	4 (1.6)	10 (3.8)	14 (2.8)
Staphylococcus aureus[1]	3 (1.2)	6 (2.3)	9 (1.8)
S. aureus, unspecified[2]	2 (0.8)	1 (0.4)	3 (0.6)
S. aureus, MSSA	2 (0.8)	6 (2.3)	8 (1.6)
Staphylococcus epidermidis	0	1 (0.4)	1 (0.2)
Viridans group streptococci[2]	1 (0.4)	4 (1.5)	5 (1.0)
Streptococcus constellatus	0	1 (0.4)	1 (0.2)
Streptococcus intermedius	0	1 (0.4)	1 (0.2)
Streptococcus mitis	0	2 (0.8)	2 (0.4)
Streptococcus oralis	0	1 (0.4)	1 (0.2)
Streptococcus parasanguinis	1 (0.4)	0	1 (0.2)
Streptococcus sanguinis	0	1 (0.4)	1 (0.2)
Streptococcus vestibularis	0	1 (0.4)	1 (0.2)
Gram-negative	3 (1.2)	0	3 (0.6)
Klebsiella pneumoniae	1 (0.4)	0	1 (0.2)
Serratia marcescens	1 (0.4)	0	1 (0.2)
Pseudomonas aeruginosa	1 (0.4)	0	1 (0.2)

Source: Table 14.1.5.2.1.2, Listing 16.2.6.11.
Note: A subject could have more than one baseline pathogen.
[1]Subject numbers are presented; subjects could have more than 1 pathogen. 1 subject had 3 streptococci species identified, while 1 subject had both S. intermedius and an MSSA baseline pathogen. 2 subjects had both an unspecified S. aureus and an MSSA in the final dataset.
[2]Unspecified indicates that the methicillin susceptibility is not known.

The MIC_{90} of baseline isolates in the mITT population is shown in Table 305. The MICs of baseline isolates from blood culture are shown in Table 306. The MIC_{90s} for *K. pneumoniae*, MRSA, MSSA and *S. pyogenes* were the same or within one-dilution of the MIC_{90s} observed in surveillance studies.

Table 305. In Vitro Ceftobiprole Susceptibility of Baseline Pathogens From Infection-Site Specimens Isolated From Ceftobiprole-Treated Subjects (mITT Population)

Baseline Pathogen	n	MIC_{50} (mcg/mL)	Ceftobiprole MIC_{90} (mcg/mL)	Range
Gram-negative	23	0.06	>64	≤0.015 – >64
Enterobacterales	14	≤0.015	>64	≤0.015 – >64
Klebsiella pneumoniae	7	–	–	>64
Gram-positive	215	0.5	1.0	≤0.015 – 4
Staphylococcus aureus, all	188	0.5	1.0	≤0.015 – 1
S. aureus, MRSA	82	1	1	0.25 – 1
S. aureus, MSSA	106	0.25	0.5	≤0.015 – 0.5
Beta-hemolytic streptococci	22	≤0.015	0.03	≤0.015 – 0.03
Streptococcus pyogenes	19	≤0.015	0.03	≤0.015 – 0.03

Source: Table 14.2.3.5.4.1.2.
Note: $MIC_{50/90}$ was only calculated when n ≥ 10. n = baseline pathogens isolated from infection-site specimens tested for study-drug susceptibility at the CML.

Table 306. In Vitro Susceptibility of Baseline Pathogens Isolated From Blood Cultures–mITT Population

Baseline pathogen / Treatment Arm	n	MIC Range (mcg/mL)
Ceftobiprole		Ceftobiprole
Staphylococcus aureus, MSSA	2	0.25 – 0.50
Pseudomonas aeruginosa	1	4
Klebsiella pneumoniae	1	≤0.015
Serratia marcescens		0.06
Vancomycin plus aztreonam	1	Vancomycin[1]
Staphylococcus aureus, MSSA	6	0.50 – 1

Source: Table 14.2.3.5.4.1.1.
Note: $MIC_{50/90}$ was only calculated when n ≥ 10.
[1]As there were no gram-negative baseline pathogens from blood cultures in the comparator arm, there are no data for aztreonam.
n = number of baseline pathogens isolated from blood cultures tested for study-drug susceptibility at the CML.

Increase in MIC (≥4 Fold)

Only one subject in the ceftobiprole arm, Subject (b) (6), had a pathogen with a ≥ 4-fold increase in the ceftobiprole MIC. The pathogen was *E. faecalis* with a baseline ceftobiprole MIC of 0.25 mcg/mL that increased to 8 mcg/mL at EOT. Even though this subject had a microbiological persistence at EOT, the subject met the definition of clinical cure. The isolate was not further characterized.

CABP

Common typical bacterial pathogens that cause CABP include *Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus,* and *Moraxella catarrhalis*. Atypical bacterial pathogens such as *Chlamydophila pneumoniae, Mycoplasma pneumoniae,* and *Legionella pneumophila* also cause CABP. Data from two multiregional phase 3 trials, CAP-3001 and BPR-PIP-002 were included to support the CABP indication. Evidence of efficacy and safety in HABP from trial BPR 248/307 was included to provide additional information on the pneumonia population. The Applicant is not requesting an indication for the treatment of HABP and data from this trial were not reviewed for efficacy.

Reference ID: 5357793

CAP-3001

Please refer to section 6.2.3.1 for study design and section 6.2.3.3 for efficacy analysis populations.

Only 29.3% of the Day 3-ITT population had a valid pathogen at baseline (Table 307).

Table 307. Baseline Characteristics of Trial CAP3001 Subjects Reanalyzed Per 2020 FDA CABP Guidance Document

Baseline Pathogen Characteristics	Day 3 ITT population			Day 3-modified ITT population		
	Ceftobiprole N=307	Ceftriaxone N=311	Total N=618	Ceftobiprole N = 97	Ceftriaxone N = 90	Total N=187
Subjects with any valid baseline pathogen, n(%)	85 (27.7)	96 (30.9)	181 (29.3)	32 (33.0)	27 (30.0)	59 (31.6)
Gram positive pathogen, n(%)	46 (15.0)	52 (16.7)	98 (15.9)	18 (18.6)	14 (15.6)	32 (17.1)
Gram negative pathogen, n(%)	49 (16.0)	51 (16.4)	100 (16.2)	19 (19.6)	14 (15.6)	33 (17.6)
Monomicrobial, n(%)	69 (22.5)	88 (28.3)	157 (25.4)	25 (25.8)	26 (28.9)	51 (27.3)
Polymicrobial, n(%)	16 (5.2)	8 (2.6)	24 (3.9)	7 (7.2)	1 (1.1)	8 (4.3)

Source: Reviewer generated

The analysis of clinical success by pathogen in the Day3-mITT population suggests that ceftobiprole has similar activity as ceftriaxone except that ceftobiprole appears to have greater efficacy against *S. pneumoniae* (Table 45). The analysis of microbiological eradication by pathogen, and clinical success by pathogen, per the original prespecified analysis is shown in Table 308. Microbiological Eradication at the TOC Visit by Causative Pathogen (mITT and ME Populations, Pre-Specified Analysis), CAP-3001 and Table 309, respectively. For the majority of the subjects, microbiological outcome at TOC was presumed eradication or presumed persistence and derived from clinical outcome. Ceftobiprole was active against methicillin sensitive *Staphylococcus aureus, Streptococcus pneumoniae, E. coli, K. pneumoniae, H. influenzae* and *H. parainfluenzae*. Although both subjects with CABP due to MRSA were a clinical success, only one of the two subjects had eradication of MRSA. The number of subjects with CABP due to MRSA was small (n = 2). Similarly, only one subject had *E. cloacae* but was a clinical success. No microbiological relapse was noted in either treatment arm at the late follow-up visit. The analysis of clinical outcome by baseline pathogen and ceftobiprole MIC is shown in Table 311. Clinical Cure at the TOC Visit, Early Clinical Response at Day 3, and Modified Early Clinical Response at Day 3 by Ceftobiprole MIC for Causative Pathogen (mITT Population), CAP-3001.

Table 308. Microbiological Eradication at the TOC Visit by Causative Pathogen (mITT and ME Populations, Pre-Specified Analysis), CAP-3001

	mITT Population		ME Population	
Pathogen	**Ceftobiprole (N = 87)**	**Ceftriaxone* (N = 97)**	**Ceftobiprole (N = 68)**	**Ceftriaxone* (N = 76)**
Any gram-positive, n/N (%)	37/48 (77.1)	41/53 (77.4)	31/34 (91.2)	39/43 (90.7)
Streptococcus pneumoniae	29/35 (82.9)	33/41 (80.5)	26/28 (92.9)	32/36 (88.9)
Staphylococcus aureus	10/14 (71.4)	7/10 (70.0)	7/7 (100.0)	6/6 (100.0)
MRSA	1/2 (50.0)	0/0 (NA)	1/1 (100.0)	0/0 (NA)
MSSA	9/12 (75.0)	7/10 (70.0)	6/6 (100.0)	6/6 (100.0)
Any gram-negative, n/N (%)	39/49 (79.6)	43/51 (84.3)	33/38 (86.8)	35/38 (92.1)
Enterobacterales	14/18 (77.8)	11/16 (68.8)	12/14 (85.7)	9/10 (90.0)
Enterobacter cloacae	1/1 (100.0)	2/3 (66.7)	1/1 (100.0)	1/1 (100.0)
Escherichia coli	6/6 (100.0)	1/4 (25.0)	6/6 (100.0)	0/1 (0.0)
Klebsiella pneumoniae	6/8 (75.0)	7/8 (87.5)	4/5 (80.0)	7/7 (100.0)
Haemophilus influenzae	9/10 (90.0)	15/16 (93.8)	7/7 (100.0)	13/14 (92.9)
Haemophilus parainfluenzae	7/9 (77.8)	7/8 (87.5)	7/9 (77.8)	6/7 (85.7)
Moraxella catarrhalis	4/4 (100.0)	5/5 (100.0)	4/4 (100.0)	4/4 (100.0)
Pseudomonas aeruginosa	1/2 (50.0)	4/4 (100.0)	0/1 (0.0)	2/2 (100.0)
Acinetobacter baumannii	2/3 (66.7)	1/1 (100.0)	2/2 (100.0)	1/1 (100.0)

Source: CSR Addendum 2, Post-text Table 7.
n = number of subjects with a response; N = total number of subjects in the respective category.
mITT = microbiological Intent-to-Treat; ME = Microbiologically evaluable; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *Staphylococcus aureus.*
* Ceftriaxone with or without linezolid.

Table 309. Clinical Cure at the TOC Visit by Causative Pathogen (Pre-Specified analysis), CAP-3001

		Clinical Cure at the TOC Visit (mITT)		Clinical Cure at the TOC Visit (ME)	
Pathogen		**Ceftobiprole (N=87)**	**Ceftriaxone[a] (N=97)**	**Ceftobiprole (N=68)**	**Ceftriaxone[a] (N=76)**
Any gram-positive, n/N (%)		37/48 (77.1)	40/53 (75.5)	31/34 (91.2)	38/43 (88.4)
Streptococcus pneumoniae		29/35 (82.9)	33/41 (80.5)	26/28 (92.9)	32/36 (88.9)
Staphylococcus aureus		10/14 (71.4)	6/10 (60.0)	7/7 (100.0)	5/6 (83.3)
MRSA		1/2 (50.0)	0/0 (NA)	1/1 (100.0)	0/0 (NA)
MSSA		9/12 (75.0)	6/10 (60.0)	6/6 (100.0)	5/6 (83.3)

Pathogen		Clinical Cure at the TOC Visit (mITT)		Clinical Cure at the TOC Visit (ME)	
		Ceftobiprole (N=87)	Ceftriaxone[a] (N=97)	Ceftobiprole (N=68)	Ceftriaxone[a] (N=76)
Any gram-negative, n/N (%)		39/49 (79.6)	43/51 (84.3)	32/38 (84.2)	35/38 (92.1)
Enterobacterales		14/18 (77.8)	11/16 (68.8)	12/14 (85.7)	9/10 (90.0)
Citrobacter koseri		0/1	0	0/1	0
Enterobacter cloacae		1/1 (100.0)	2/3 (66.7)	1/1 (100.0)	1/1 (100.0)
Escherichia coli		6/6 (100.0)	1/4 (25.0)	6/6 (100.0)	0/1 (0.0)
Klebsiella oxytoca		1/1 (100.0)	0	1/1	0
Klebsiella pneumoniae		6/8 (75.0)	7/8 (87.5)	4/5 (80.0)	7/7 (100.0)
Haemophilus influenzae		9/10 (90.0)	15/16 (93.8)	7/7 100.0)	13/14 (92.9)
Haemophilus parainfluenzae		6/9 (66.7)	7/8 (87.5)	6/9 (66.7)	6/7 (85.7)
Moraxella catarrhalis		4/4 (100.0)	5/5 (100.0)	4/4 (100.0)	4/4 (100.0)
Pseudomonas aeruginosa		1/2 (50.0)	4/4 (100.0)	0/1 (0.0)	2/2 (100.0)
Acinetobacter baumannii		2/3 (66.7)	1/1 (100.0)	2/2 (100.0)	1/1 (100.0)

Source: CAP-3001 CSR Attachment 3.3.3, Table 29, CSR Addendum 1 Table 29a Note: N is the number of subjects with susceptibility data for pathogens isolated at baseline. n is the number of pathogen isolates at baseline. ME: microbiologically evaluable, mITT = microbiological Intent-to-Treat; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-susceptible *Staphylococcus aureus*. TOC = test of cure.
[a] Ceftriaxone with or without linezolid

There was one subject (b) (6)) in the ceftriaxone arm with superinfection due to MRSA at the test of cure visit and one subject in the ceftobiprole arm ((b) (6)) had superinfections with *A. baumannii* during treatment and *S. marcescens* at TOC. The ceftobiprole MIC for the *A. baumannii* isolate was 16 mcg/mL and that of the *S. marcescens* isolate was >16 mcg/mL and the subject was a clinical failure. Two subjects (b) (6) in the ceftobiprole arm and 2 subjects (b) (6)) in the ceftriaxone arm were reported as having relapsed clinically at the late follow-up visit. These subjects were in the clinically evaluable population but did not have a pathogen at baseline.

Baseline bacteremia was observed in 11 subjects (3.4%) in the ceftobiprole group and 17 subjects (5.2%) in the comparator group in the ITT population (Table 310). The clinical cure rate at the TOC visit for subjects with a positive blood culture for *S. pneumoniae* was 55.6% (5/9) in the ceftobiprole arm vs. 71.4% (10/14) in the ceftriaxone arm.

Table 310. Clinical Cure at TOC by Blood Culture Pathogens at Baseline (Pre-Specified Analysis; mITT and ME Populations), CAP-3001

	Clinical Cure at TOC mITT Population		Clinical Cure at TOC ME Population	
Pathogen	**Ceftobiprole (N=87)**	**Ceftriaxone[a] (N=97)**	**Ceftobiprole (N=68)**	**Ceftriaxone[a] (N=76)**
Any gram-positive, n/N (%)	5/9 (55.6)	11/15 (73.3)	5/6 (83.3)	11/13 (84.6)
Streptococcus pneumoniae	5/9 (55.6)	10/14 (71.4)	5/6 (83.3)	10/12 (83.3)
Staphylococcus aureus	0/0 (NA)	1/1 (100.0)	0/0 (NA)	1/1 (100.0)
MSSA	0/0 (NA)	1/1 (100.0)	0/0 (NA)	1/1 (100.0)
Any gram-negative, n/N (%)	1/2 (50.0)	1/2 (50.0)	1/1 (100.0)	1/1 (100.0)
Acinetobacter baumannii	1/2 (50.0)	0/0 (NA)	1/1 (100.0)	0/0 (NA)
Escherichia coli	0/0 (NA)	0/1 (0.0)	0/0 (NA)	0/0 (NA)
Haemophilus influenzae	0/0 (NA)	1/1 (100.0)	0/0 (NA)	1/1 (100.0)

Source: CAP-3001 CSR Addendum 2, Table 9
Note: N is the number of subjects with susceptibility data for pathogens isolated at baseline. n is the number of pathogen isolates at baseline.
ME = Microbiologically Evaluable, mITT = microbiological Intent-to-Treat; MSSA = methicillin-susceptible *Staphylococcus aureus*; n = number of subjects with a response; NA = not applicable; TOC = test of cure.
[a] Ceftriaxone with or without linezolid

Table 311. Clinical Cure at the TOC Visit, Early Clinical Response at Day 3, and Modified Early Clinical Response at Day 3 by Ceftobiprole MIC for Causative Pathogen (mITT Population), CAP-3001

Pathogen Ceftobiprole MIC (mcg/mL)	**Clinical Cure at TOC mITT population Ceftobiprole (N = 87)**	**Early Clinical Response at Day 3 mITT Population Ceftobiprole (N = 85)**	**Early Clinical Response at Modified Day 3 mITT Population Ceftobiprole (N = 32)**
Any gram-positive, n/N (%)	37/48 (77.1)	36/46 (78.3)	13/18 (72.2)
Staphylococcus aureus	10/14 (71.4)	10/14 (71.4)	3/4 (75.0)
MRSA	1/2 (50.0)	2/2 (100.0)	-
0.5	1/1 (100.0)	1/1 (100.0)	-
1	-	-	-
2	0/1 (0.0)	1/1 (100.0)	-
MSSA	9/12 (75.0)	8/12 (66.7)	3/4 (75.0)
0.25	6/8 (75.0)	5/8 (62.5)	3/3 (100.0)
0.5	3/3 (100.0)	3/3 (100.0)	-
unknown	0/1 (0.0)	0/1 (0.0)	0/1 (0.0)
Streptococcus pneumoniae	29/35 (82.9)	27/33 (81.8)	11/14 (78.6)
0.008	10/10 (100.0)	8/9 (88.9)	1/1 (100.0)
0.015	7/12 (58.3)	8/11 (72.7)	3/5 (60.0)
0.03	2/2 (100.0)	1/2 (50.0)	1/1 (100.0)
0.06	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
0.12	3/4 (75.0)	4/4 (100.0)	2/2 (100.0)
0.25	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
0.5	-	-	-
1	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
unknown	-	3/4 (75.0)	1/2 (50.0)
Any gram-negative, n/N (%)	39/49 (78.6)	35/49 (71.4)	13/19 (68.4)
Enterobacterales	14/18 (77.8)	14/18 (77.8)	5/7 (71.4)
Enterobacter cloacae	1/1 (100.0)	0/1 (0.0)	0/1 (0.0)
8	1/1 (100.0)	0/1 (0.0)	0/1 (0.0)
Escherichia coli	6/6 (100.0)	6/6 (100.0)	2/3 (66.7)
0.03	3/3 (100.0)	3/3 (100.0)	1/1 (100.0)
0.06	2/2 (100.0)	2/2 (100.0)	-
0.12	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)

Klebsiella pneumoniae	6/8 (75.0)	7/8 (87.5)	2/3 (66.7)
0.03	1/1 (100.0)	1/1 (100.0)	-
0.06	-	-	-
0.12	3/5 (60.0)	5/5 (100.0)	2/2 (100.0)
unknown	2/2 (100.0)	1/2 (50.0)	0/1 (0.0)
Proteus mirabilis	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
unknown	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Pseudomonas aeruginosa	1/2 (50.0)	2/2 (100.0)	1/1 (100.0)
4	0/1 (0.0)	1/1 (100.0)	-
>16	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
Acinetobacter baumannii	2/3 (66.7)	2/3 (66.7)	1/2 (50.0)
0.25	1/1 (100.0)	1/1 (100.0)	-
0.5	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)
8	0/1 (0.0)	0/1 (0.0)	0/1 (0.0)
Haemophilus influenzae	9/10 (90.0)	4/10 (40.0)	2/3 (66.7)
0.015	0/1 (0.0)	0/1 (0.0)	-
0.03	2/2 (100.0)	1/2 (50.0)	1/1 (100.0)
0.06	5/5 (100.0)	2/5 (40.0)	1/2 (50.0)
0.12	2/2 (100.0)	1/2 (50.0)	-
Haemophilus parainfluenzae	6/9 (66.7)	8/9 (88.9)	2/2 (100.0)
0.004	0/1 (0.0)	0/1 (0.0)	-
0.015	-	-	-
0.03	-	-	-
0.06	0/1 (0.0)	1/1 (100.0)	-
0.12	3/3 (100.0)	3/3 (100.0)	-
0.25	1/2 (50.0)	2/2 (100.0)	1/1 (100.0)
1	1/1 (100.0)	1/1 (100.0)	-
unknown	1/1 (100.0)	1/1 (100.0)	1/1 (100.0)

Source: CAP-3001 CSR Appendix Attachment 3.3.9; CAP-3001 Addendum 2 Table 5a
Note: N is the number of subjects with susceptibility data for pathogens isolated at baseline. n is the number of pathogen isolates at baseline.
mITT = microbiological Intent-to-Treat; TOC = test of cure.

Increase in MIC

In the mITT analysis set, 1 subject in the ceftobiprole group had a pathogen isolated after baseline that had a ceftobiprole MIC value ≥4-fold higher than the MIC value at Baseline. Subject (b) (6) had an isolate of *K. pneumoniae* that was negative for an ESBL and had a ceftobiprole MIC of 0.12 mcg/mL at baseline. At TOC, the isolate had acquired a TEM-4 β-lactamase and was ESBL positive with an MIC of 16 mcg/mL. The subject was a clinical failure at TOC. No mITT subjects in the ceftriaxone with or without linezolid group had a pathogen isolated after baseline that had a ceftriaxone MIC value ≥4-fold higher than the value at Baseline.

BPR-PIP-002

This was a phase 3 investigator-blind trial which enrolled pediatric subjects with CABP or HABP requiring intravenous antibacterial treatment in a hospital setting. The BPR-PIP-002 phase 3 trial evaluated the safety and efficacy of ceftobiprole versus standard-of-care cephalosporin treatments, with or without vancomycin, in pediatric subjects (3 months to 17 years) with HABP or CABP requiring hospitalization. The mITT population comprised of only six subjects: five in the ceftobiprole arm and one in the comparator arm. Table 312. Microbiological Outcomes at TOC and LFU – mITT Population in Trial BPR-PIP-002 shows the microbiological outcomes of these six subjects at TOC and last follow-up. Five subjects in the ceftobiprole arm had a diagnosis of CABP with baseline pathogens as follows: *S. aureus* (n = 3,

MSSA), *H. influenzae* (n = 1), and *H. parainfluenzae* (n = 1). Due to limited microbiology data from this Trial, it was not included in breakpoint analysis.

Table 312. Microbiological Outcomes at TOC and LFU – mITT Population in Trial BPR-PIP-002

	Ceftobiprole			IV Standard-of-Care Cephalosporin	
Pathogen	**n**	**Screening TOC Ceftobiprole Outcome MIC (mg/L)***	**LFU Outcome**	**n**	**TOC LFU Outcome**
Haemophilus parainfluenzae	1	NT presumed eradication	presumed eradication maintained	1	presumed eradication maintained
Haemophilus influenzae	1	0.015 presumed eradication	not evaluable	0	
Staphylococcus aureus	3	0.25 presumed eradication 0.25 presumed persistence NT not evaluable	presumed eradication maintained presumed persistence maintained not evaluable	0	

Source: Appendix 16.2, Listing 8.2 and Listing 8.6. BPR-PIP-002 study report
Abbreviations: IV, intravenous; LFU, last follow-up; MIC, minimum inhibitory concentration; mITT, modified intent-to-treat; TOC, test-of-cure, NT, not tested

19.6. In Vitro Susceptibility Test Method

The MIC values for ceftobiprole were determined by broth microdilution method in accordance with the Clinical and Laboratory Standards Institute (CLSI) guidelines (M07-A6). Tier 1 studies evaluated the effect of media (cation-adjusted Mueller-Hinton broth, Iso-Sensitest broth), media supplementation (25 mg/L calcium, 0.002% Tween 80), temperature (30°C or 35°C), presence of 2% NaCl, inoculum size, incubation conditions (5%CO_2), pH, and serum. A 2-fold increase in ceftobiprole MICs against the two *P. aeruginosa* strains occurred with increase of inoculum density from 10^4 to 10^5 to 10^6 CFU/mL Increases in ceftobiprole MIC were also made when high inoculum β-lactamase-positive strains were tested. Ceftobiprole MIC values from dry-form broth microdilution MIC panels were within $1\log_2$ dilution of the reference frozen-form MIC values. Overall, the ceftobiprole MIC obtained under various of testing conditions were within $1\log_2$ dilution of the standard CLSI broth microdilution method.

Quality Control for Reference Broth Microdilution

Tier 2 studies were conducted in 8 laboratories and utilized the frozen-form reference broth microdilution panels prepared by [redacted] (b) (4)) and four lots of cation-adjusted Mueller-Hinton broth. The quality control (QC) strains and ranges for broth microdilution susceptibility testing of ceftobiprole have been published (CLSI 2005) (Table 313).

Table 313. Broth Microdilution Quality Control Results From an Eight-Laboratory Tier 2 QC Study as Specified by CLSI Document M23

Quality Control Strain	MIC Mode (mcg/mL)	% of Results at Mode	Proposed MIC Range (mcg/mL)	% of Results in Range
Staphylococcus aureus ATCC 29213	0.5	62.8	0.25 - 1	100
Enterococcus faecalis ATCC 29212	0.12	46.2	0.06 - 0.5	100
Escherichia coli ATCC 25922	0.06	84.7	0.03 - 0.12	100
Pseudomonas aeruginosa ATCC 27853	2	63.1	1 - 4	97.8
Streptococcus pneumoniae ATCC 49619	0.008, 0.015	49.2, 43.8	0.004 - 0.03	100
Haemophilus influenzae ATCC 49247	0.25	49.4	0.12 - 1	100
Haemophilus influenzae ATCC 49766	0.03	75	0.015 - 0.06	100

Source: (Anderegg et al. 2004)(Issa et al. 2004; CLSI 2006a)
Abbreviations: ATCC, American type culture collection; CLSI, Clinical and Laboratory Standards Institute; MIC, minimum inhibitory concentration; QC, quality control.

Ceftobiprole Disk Diffusion Method

The 30 mcg ceftobiprole disk, similar to other cephalosporin disk masses, was originally developed according to CLSI M23 guidelines and QC ranges were established by CLSI (CLSI M23). Since the original disk development studies, a new 5 mcg ceftobiprole disk was found to reduce the size of the inhibition zones and was commercialized in the European regions.

Disk Optimization

The activity of the 5 (lot#322789), 10 (lot# 322790), and 30 (lot# 322793) mcg ceftobiprole disks against seven QC strains (*E. coli* ATCC® 25922, *H. influenzae* ATCC® 49247, *H. influenzae* NCTC 8468, *P. aeruginosa* ATCC® 27853, *S. aureus* ATCC® 25923, *S. aureus* ATCC® 29213, *S. pneumoniae* ATCC® 49619) was examined using (b) (4) disk (Technical report CT-041). All 3 disk masses resulted in an acceptable zone size range (i.e., a variation of not more than 3 mm) for all QC strains tested. A study conducted by the EUCAST laboratory examined 5 mcg (from (b) (4)) and 30 mcg ceftobiprole disks against 40 – 42 clinical isolates each of *S. aureus*, *S. pneumoniae* (including a penicillin non-susceptible subset), and different species of the *Enterobacterales*. Scatterplots comparing the 30 mcg and 5 mcg disks using the raw data provided by the EUCAST laboratory was submitted. The 5 mcg ceftobiprole disks was stated to result in a better differentiation for non-wildtype isolates than the 30 mcg disks.

Disk Stability

Stability study was conducted using (b) (4) 5 mcg ceftobiprole disk (Study 9294). Three batches were tested (Batches 011321087, 101421109 and 111221068). The data suggests that the (b) (4) 5 mcg ceftobiprole disks were stable for 21 months at -20 ± 5°C / 5 ± 3°C and under in-use condition of 5 ± 3°C for 7 days. The disk stability study performed by (b) (4) suggest that their 5 mcg ceftobiprole disk (lot #322793) was stable for 4 weeks at -20°C and 4°C (Technical report CT-041).

Disk Diffusion QC Strains And Ranges

A study ([(b) (4)] 3422 2020) was conducted in seven laboratories using three media lots (different manufacturers: [(b) (4)], two disk lots ([(b) (4)] lot# 435540 ([(b) (4)]), [(b) (4)] lot#90319080 ([(b) (4)] and 420 test points to establish disk diffusion QC ranges for a 5 mcg ceftobiprole disk against two QC organisms recommended by CLSI: *E. coli* ATCC 25922 and *S. aureus* ATCC 25923. The QC ranges were approved by CLSI is August 2020 (Table 314).

Table 314. CLSI-Approved Disk Diffusion Quality Control Ranges for Ceftobiprole 5 mcg Disk

Organism	Range (mm)	Size of Range (mm)	Percentage in Range (%)
Escherichia coli ATCC 25922	25-31	7	97.5 (509/522)
Staphylococcus aureus ATCC 25923	20-27	8	99.3 (536/540)

Source: ([(b) (4)] 3422 2020) ([(b) (4)] 2020)
Abbreviations: ATCC, American type culture collection; CLSI, Clinical and Laboratory Standards Institute.

19.7. In Vitro Susceptibility Test Interpretive Criteria/Breakpoints

Proposed ceftobiprole clinical breakpoints based on nonclinical data, wildtype MIC distribution and epidemiological cut-off analysis, identified preclinical PD targets, clinical PK/PD analyses of phase 3 trial data, and clinical and microbiological outcomes for *S. aureus* (including MSSA and MRSA), *Streptococcus* spp., species of the *Enterobacterales* order, *H. influenzae*, and *H. parainfluenzae* are shown in Table 315.

Table 315. Proposed Ceftobiprole Clinical Breakpoints and Disk Diffusion Zones

	MIC Values (mcg/mL)			Zone Diameter in mm		
Primary Pathogen	**S**	**I**	**R**	**S**	**I**	**R**
SAB				[(b) (4)]		
Staphylococcus aureus (including both MSSA and MRSA)	≤2	4	≥8			
ABSSSI						
Staphylococcus aureus (including both MSSA and MRSA)	≤2	4	≥ 8			
Streptococcus pyogenes	≤0.5	[(b) (4)]				
Enterobacter cloacae	≤0.25	0.5	≥1			
Escherichia coli	≤0.25	0.5	≥1			
Klebsiella pneumoniae	≤0.25	0.5	≥1			
CABP						
Staphylococcus aureus (including both MSSA and MRSA)	≤2	4	≥8			
Streptococcus pneumoniae	≤0.5	1	≥2	NP	NP	NP
Enterobacter cloacae	≤0.25	0.5	≥1			[(b) (4)]
Escherichia coli	≤0.25	0.5	≥1			
Klebsiella pneumoniae	≤0.25	0.5	≥1			
Haemophilus influenzae	≤0.25	0.5	≥1	NP	NP	NP
Haemophilus parainfluenzae	≤0.25	0.5	≥1	NP	NP	NP

Source: NDA application/submission Section 2.7.2 Table 145
Abbreviations: ABSSSI, acute bacterial skin and skin structure infection; CABP, community-acquired bacterial pneumonia; I, intermediate; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; NP, not proposed; R, resistant; S, susceptible; SAB, *Staphylococcus aureus* bacteremia

Breakpoint Assessment

The *in vitro* surveillance, PK-PD cut-off and clinical outcome data were used to arrive at breakpoints for the target pathogen.

Staphylococcus aureus (Methicillin Sensitive and Methicillin Resistant)

The assessment supports a ceftobiprole susceptible breakpoint of 2 mcg/mL for *S. aureus* (methicillin-susceptible and methicillin-resistant) based on MIC_{90} values, PK-PD cut-off, overall success or clinical cure rates in the clinical studies for SAB, ABSSSI, and CABP (Table 316). Note that there is insufficient clinical data from CABP subjects with MRSA. The intermediate (4 mcg/mL) and resistant (8 mcg/mL) breakpoints are set as 2-fold and 4-fold dilution higher than the susceptible breakpoint as the maximum MIC observed for *S. aureus* in surveillance studies was 4 mcg/mL. The corresponding ceftobiprole 5 mcg disk breakpoints are S ≥16 mm; I = 14-15 mm; R ≥13 mm based on acceptable error rates.

Table 316. Data for Ceftobiprole Breakpoint Determination for *Staphylococcus aureus*

		Ceftobiprole MIC (mcg/mL)	
Parameter		**MSSA**	**MRSA**
Surveillance MIC_{90}		0.5	2
SAB trial MIC_{90}		0.5	2
ABSSSI trial MIC_{90}		0.5	1
CABP trial MIC_{90}		0.5	-
PK-PD cut-off		4	4
Clinical Outcome	**Ceftobiprole MIC (mcg/mL)**	**MSSA n/N (%)**	**MRSA n/N (%)**
Overall success at PTE (SAB)	≤0.015	0	0
Clinical success at TOC (ABSSSI)		1/1	0
Clinical cure at TOC (CABP)		0	0
Overall success at PTE (SAB)	0.12	1/1	0
Clinical success at TOC (ABSSSI)		2/3 (66.7%)	0
Clinical cure at TOC (CABP)		0	0
Overall success at PTE (SAB)	0.25	54/72 (75.0%)	0
Clinical success at TOC (ABSSSI)		54/57 (94.7%)	3/3 (100.0%)
Clinical cure at TOC (CABP)		6/8 (75.0%)	0
Overall success at PTE (SAB)	0.5	44/67 (65.7%)	2/6 (33.3%)
Clinical success at TOC (ABSSSI)		38/45 (84.4%)	11/11 (100.0%)
Clinical cure at TOC (CABP)		3/3 (100.0%)	1/1
Overall success at PTE (SAB)	1	1/1	19/25 (76.0%)
Clinical success at TOC (ABSSSI)		0	58/68 (85.3%)
Clinical cure at TOC (CABP)		0	0
Overall success at PTE (SAB)	2	0	9/12 (75.0%)
Clinical success at TOC (ABSSSI)		0	0
Clinical cure at TOC (CABP)		0	0/1
Overall success at PTE (SAB)	4	0	0
Clinical success at TOC (ABSSSI)		0	0
Clinical cure at TOC (CABP)		0	0

Source: Reviewer generated
Abbreviations: ABSSSI, acute bacterial skin and skin structure infection; CABP, community-acquired bacterial pneumoniae; HABP, hospital-acquired bacterial pneumoniae; MIC, Minimum inhibitory concentration; MIC_{90}, concentration required to inhibit 90% of isolates; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*; N, number of subjects in the specific category; n, number of subjects with response; PD, pharmacodynamic; PK, pharmacokinetic; PTE, post-treatment evaluation; SAB, *Staphylococcus aureus* bacteremia; TOC, test-of-cure

Reference ID: 5357793

Streptococcus pneumoniae

The assessment supports a ceftobiprole susceptible breakpoint of 0.5 mcg/mL for *S. pneumoniae* based on MIC_{90} values, animal studies with isolates with MIC of 1 mcg/mL, PK-PD target attainment, clinical cure rates in the CABP trial (Table 317). Limited clinical data at MIC of 1 mcg/mL. The intermediate (1 mcg/mL) and resistant (2 mcg/mL) breakpoints are set as 2-fold and 4-fold dilution higher than the susceptible breakpoint as the maximum MIC observed for *S. pneumoniae* in surveillance studies was 2 mcg/mL, while the maximum MIC in CABP trial was 1 mcg/mL. No disk breakpoints are proposed by the Applicant as clinical isolates from CABP trial were not tested with the 5 mcg ceftobiprole disk.

Table 317. Data for Ceftobiprole Breakpoint Determination for *Streptococcus pneumoniae*

Parameter		Ceftobiprole MIC (mcg/mL) *S. pneumoniae*
Surveillance MIC_{90}		0.5
CABP trial MIC_{90}		0.12
PK-PD cut-off		4
Clinical Outcome	**Ceftobiprole MIC (mcg/mL)**	***S. pneumoniae* n/N (%)**
Clinical cure at TOC (CABP)	≤0.015	17/22 (77.3%)
	0.03	2/2 (100.0%)
	0.06	1/1
	0.12	3/4 (75.0%)
	0.25	1/1
	0.5	0
	1	1/1

Source: Reviewer generated
Abbreviations: CABP, community-acquired bacterial pneumoniae; HABP, hospital-acquired bacterial pneumoniae; MIC, minimum inhibitory concentration; MIC_{90}, concentration required to inhibit 90% of isolates; N, number of subjects in the specific category; n, number of subjects with response; PD, pharmacodynamic; PK, pharmacokinetic; TOC, test-of-cure

Streptococcus pyogenes

The assessment supports a ceftobiprole susceptible only breakpoint of ≤ 0.5 mcg/mL for *S. pyogenes* based on MIC range and MIC_{90} values, PK-PD cut-off, clinical cure rates in the ABSSSI trial (Table 318). No clinical data is available for isolates with MIC > 0.03 mcg/mL. A susceptible only breakpoint of ≤0.5 mcg/ml is acceptable based on the Applicant's rationale and MICs observed with other *Streptococcus* species that are susceptible to ceftobiprole, ceftaroline and ceftriaxone. No intermediate or resistant breakpoints are set as the maximum MIC observed for *S. pyogenes* in surveillance studies was 0.12 mcg/mL. The corresponding ceftobiprole 5 mcg disk susceptible only breakpoint is ≥ 24 mm.

Table 318. Data for Ceftobiprole Breakpoint Determination for *Streptococcus pyogenes*

Parameter	Ceftobiprole MIC (mcg/mL) *S. pyogenes*
Surveillance MIC_{90}	0.015
ABSSSI trial MIC_{90}	0.03
PK-PD cut-off	4

Clinical Outcome	Ceftobiprole MIC (mcg/mL)	*S. pyogenes* n/N (%)
Clinical success at TOC (ABSSSI)	≤0.015	14/16 (87.5)
	0.03	3/3 (100.0)

Source: Reviewer generated
Abbreviations: ABSSSI, acute bacterial skin and skin structure infection; MIC, minimum inhibitory concentration; MIC_{90}, concentration required to inhibit 90% of isolates; N, number of subjects in the specific category; n, number of subjects with response; PD, pharmacodynamic; PK, pharmacokinetic; TOC, test-of-cure

Enterobacterales (*Escherichia coli, Klebsiella pneumoniae*)

The assessment supports a ceftobiprole susceptible breakpoint of 0.25 mcg/mL for *Enterobacterales* based on MIC_{90} values, animal studies performed with ceftobiprole MICs of 0.5 mcg/mL, PK-PD cut-off, clinical cure rates in the ABSSSI and CABP studies (Table 319). A HABP subject with baseline *K. pneumoniae* with ceftobiprole MIC of 0.25 mcg/mL had a successful clinical outcome. Limited clinical data is available for MIC ≥ 0.25 mcg/mL. The intermediate (0.5 mcg/mL) and resistant (1 mcg/mL) breakpoints are set as 2-fold and 4-fold dilution higher than the susceptible breakpoint as the maximum MIC observed for *Enterobacterales* in surveillance studies was >16 mcg/mL. The corresponding ceftobiprole 5 mcg disk breakpoints are S ≥23 mm; I = 21-22 mm; R ≥20 mm based on acceptable error rates.

Table 319. Data for Ceftobiprole Breakpoint Determination for *Enterobacterales*

		Ceftobiprole MIC (mcg/mL)		
Parameter		***E. cloacae***	***E.coli***	***K. pneumoniae***
Surveillance MIC_{90}		4*	>16*	>16*
ABSSSI trial MIC_{90}		-	-	-
CABP trial MIC_{90}		-	-	-
PK-PD target		2	2	2
Clinical Outcome	**Ceftobiprole MIC (mcg/mL)**	***E. cloacae* n/N (%)**	***E.coli* n/N (%)**	***K. pneumoniae* n/N (%)**
Clinical success at TOC (ABSSSI)	≤0.015	2/2 (100.0%)	0	4/4 (100.0%)
Clinical cure at TOC (CABP)		0	0	0
Clinical success at TOC (ABSSSI)	0.03	0	0	1/1
Clinical cure at TOC (CABP)		0	3/3 (100.0%)	1/1
Clinical success at TOC (ABSSSI)	0.06	0	0	0
Clinical cure at TOC (CABP)		0	2/2 (200.0%)	0
Clinical success at TOC (ABSSSI)	0.12	0	0	0
Clinical cure at TOC (CABP)		0	1/1	3/5 (60.0%)
Clinical success at TOC (ABSSSI)	0.25	0	0	0
Clinical cure at TOC (CABP)		0	0	0
Clinical success at TOC (ABSSSI)	2	0	0	0
Clinical cure at TOC (CABP)		0	0	0
Clinical success at TOC (ABSSSI)	4	0	0	0
Clinical cure at TOC (CABP)		0	0	0
Clinical success at TOC (ABSSSI)	8	0	0	0
Clinical cure at TOC (CABP)		1/1	0	0
Clinical success at TOC (ABSSSI)	16	0	0	0
Clinical cure at TOC (CABP)		0	0	0
Clinical success at TOC (ABSSSI)	>16	0	0	0
Clinical cure at TOC (CABP)		0	0	0
Clinical success at TOC (ABSSSI)	>64	1/1	0	2/2 (100.0%)
Clinical cure at TOC (CABP)		0	0	0

Source: Reviewer generated
* For non-ESBL isolates from surveillance studies, MIC_{90} = 0.06 mcg/mL.
Abbreviations: ABSSSI, acute bacterial skin and skin structure infection; CABP, community-acquired bacterial pneumoniae; MIC, minimum inhibitory concentration; MIC_{90}, concentration required to inhibit 90% of isolates; N, number of subjects in the specific category; n, number of subjects with response; PD, pharmacodynamic; PK, pharmacokinetic; TOC, test-of-cure

Haemophilus influenzae* and *Haemophilus parainfluenzae

The assessment supports a ceftobiprole susceptible breakpoint of 0.25 mcg/mL for *H, influenzae* and *H. parainfluenzae* based on MIC_{90} values, clinical cure rates in the CABP trial (Table 320). Limited clinical data is available for MIC >0.12 mcg/mL. The wildtype *H. influenzae* β-lactamase positive and negative populations have an epidemiological cut-off of 0.25 mcg/mL. The *H. parainfluenzae* population is similar to the *H. influenzae* population. A susceptible breakpoint of 0.25 mcg/mL would not cut the MIC distribution for *H. influenzae* and cover the wildtype population. The intermediate (0.5 mcg/mL) and resistant (1 mcg/mL) breakpoints are set as 2-fold and 4-fold dilution higher than the susceptible breakpoint, as the maximum MIC observed for *H. influenzae* in surveillance studies was 1 mcg/mL. No disk breakpoints are proposed by the Applicant as *H. influenzae* and *H. parainfluenzae* clinical isolates were not tested using the 5mcg ceftobiprole disks.

Table 320. Data for Ceftobiprole Breakpoint Determination for *Haemophilus influenzae* and *Haemophilus parainfluenzae*

	Ceftobiprole MIC (mcg/mL)	
Parameter	***H. influenzae***	***H. parainfluenzae***
Surveillance MIC_{90}	0.25	0.5
CABP trial MIC_{90}	0.12	-
PK-PD cut-off	-	-

Clinical Outcome	**Ceftobiprole MIC (mcg/mL)**	***H. influenzae* n/N (%)**	***H. parainfluenzae* n/N (%)**
Clinical cure at TOC (CABP)	≤0.015	0/1	0/1
	0.03	2/2 (100.0%)	0
	0.06	5/5 (100.0%)	0/1
	0.12	2/2 (100.0%)	3/3 (100.0%)
	0.25	0	1/2 (50.0%)
	1	0	1/1

Source: Reviewer generated
Abbreviations: CABP, community-acquired bacterial pneumoniae; MIC, minimum inhibitory concentration; MIC_{90}, concentration required to inhibit 90% of isolates; N, number of subjects in the specific category; n, number of subjects with response; PD, pharmacodynamic; PK, pharmacokinetic; TOC, test-of-cure

The breakpoints established by FDA based on available surveillance, PK-PD, and clinical data is shown in Table 321.

Table 321. FDA Established Ceftobiprole Breakpoints

Pathogen	Minimum Inhibitory Concentrations (mcg/mL)			Disk Diffusion (Zone Diameters in mm)		
	S	I	R	S	I	R
Staphylococcus aureus (includes methicillin resistant isolates)	≤2	4	≥8	≥16	14-15	≤13
Streptococcus pneumoniae	≤0.5	1	≥2	NP	NP	NP
Streptococcus pyogenes [a]	≤0.5	-	-	≥24	-	-
Enterobacterales[b]	≤0.25	0.5	≥1	≥23	21-22	≤20
Haemophilus influenzae and *parainfluenzae*	≤0.25	0.5	≥1	NP	NP	NP

Source: Reviewer generated
Note: Limited clinical data is available on ceftobiprole medocaril sodium for injection to treat community-acquired bacterial pneumoniae due to methicillin resistant Staphylococcus aureus (MRSA).
[a] The absence of resistant isolates precludes defining any results other than "Susceptible". Isolates yielding MIC results other than "Susceptible" should be submitted to a reference laboratory for further testing.
[b] Clinical efficacy was shown for *Klebsiella pneumoniae* in subjects with ABSSSI and for *Escherichia coli* and *Klebsiella pneumoniae* in subjects with CABP.
For disk diffusion, use paper disks impregnated with 5 mcg ceftobiprole.
Abbreviations: ABSSSI, acute bacterial skin and skin structure infection; CABP, community-acquired bacterial pneumoniae; I, intermediate; NP, Not proposed; R, resistant; S, susceptible

20. Mechanism of Action/Drug Resistance

20.1. Mechanism of Action

Ceftobiprole exerts its antibacterial activity by binding to multiple penicillin-binding proteins (PBPs) and inhibiting their transpeptidase activity, which is essential for the synthesis of the bacterial cell wall. The concentrations required to inhibit 50% binding to PBPs (IC_{50s}) from various gram-positive and gram-negative bacteria were determined using fluorescein-labeled penicillin, [H^3}-penicillin, biocillin fluorescein-labeled, or fluorescein isothiocyanate labeled ampicillin (Table 322 and Table 323). The studies showed that ceftobiprole has a high affinity for *S. aureus* PBPs 1 – 4, including PBP2a in methicillin-resistant *S. aureus* (Table 322). Ceftobiprole has high affinity for all six *S. pneumoniae* PBPs in penicillin-susceptible strains, including PBP2b. Ceftobiprole's PBP binding affinity is reduced for PBP1b and PBP2b in penicillin-resistant strains, but ceftobiprole still has good affinity for PBP1a, PBP2a, PBP2x, and PBP3 in these strains. Ceftobiprole has a high affinity for *S. epidermidis* PBP 2', compared to all other β-lactams measured. Ceftobiprole has good affinity for wildtype PBPs 1-5 of *E. faecium* but does not have measurable affinity for the mutated PBP5 from ampicillin-resistant *E. faecium*, resulting in elevated β-lactam MICs in *E. faecium* strains that have these variants of PBP5.

Table 322. Ceftobiprole Penicillin-Binding Proteins in Gram-Positive Bacterial Strains

Strain	PBP	IC_{50} (mcg/mL)[a]						Source/Reference
		Ceftobiprole	CRO	CAZ	MET	IPM	PEN	
Staphylococcus aureus ATCC 29213 (MSSA)	1	0.1	0.5	ND	ND	ND	ND	Davies 2007a[d]
	2	0.5	0.1	ND	ND	ND	ND	
	3	0.05	1	ND	ND	ND	ND	
	4	1	10	ND	ND	ND	ND	
Staphylococcus aureus 3,726 (MRSA)	2a	0.9	>50	>50	ND	ND	ND	Davies 2007a[d]
Staphylococcus aureus COL (MRSA)	2a[b]	1.7	ND	ND	320	ND	ND	Chung 2008[e]
Staphylococcus aureus COL Bla+ (MRSA)	2a	0.31	ND	ND	39	ND	ND	Entenza 2002[f]
Staphylococcus aureus P8-Hom (MRSA)	2a	0.47	ND	ND	78	ND	ND	Entenza 2002[f]
S. epidermidis (MRSE)	2a[b]	0.47	70	ND	>190	>160	ND	Hebeisen 2001[g]
Streptococcus pneumoniae 8865 (Pen-S)	1a	0.03	0.01	ND	ND	0.015	ND	Davies 2007a[d]
	1b	0.05	0.03	ND	ND	0.005	ND	
	2x	0.01	0.03	ND	ND	0.013	ND	
	2a	0.03	0.1	ND	ND	0.015	ND	
	2b	0.06	>1	ND	ND	0.008	≤0.015	
	3	0.02	0.02	ND	ND	0.004	ND	
Streptococcus pneumoniae	2x[b]	0.14	0.096	ND	0.019	0.05	ND	Hebeisen 2001[g]
Streptococcus pneumoniae 8819 (Pen-R)	1a	0.1	0.02	ND	ND	0.04	ND	Davies 2006[h] Davies 2007a[d] Davies 2010[i]
	1b	>8	0.02	ND	ND	0.06	ND	
	2x	1	8	ND	ND	8	ND	
	2a	0.1	0.5	ND	ND	0.015	ND	
	2b	>8	>8	ND	ND	2	>8	
	3	0.01	0.01	ND	ND	<0.015	ND	
Streptococcus pneumoniae 8882 (Pen-I)	2b	1.2	>8	ND	ND	ND	2.5	Davies 2010[i]
Streptococcus pneumoniae 8009 (Pen-I)	2b	0.9	>8	ND	ND	ND	2.5	Davies 2010[i]
Enterococcus faecium D63 (Pen-I)	1	0.6	ND	0.9	ND	ND	0.9	Henry 2010[j]
	2	0.2	ND	0.5	ND	ND	0.1	
	3	0.6	ND	0.04	ND	ND	1.3	
	4	1.5	ND	>200	ND	ND	10	
	5	0.7	ND	>200	ND	ND	75	
	6	>16	ND	>50	ND	ND	1.5	
Enterococcus faecium (Pen-R)	5[b,c]	>270	>300	ND	>190	350	300	Hebeisen 2001[g] Hujer 2005[k]

Source: Source referenced in Table
[a] Concentration of drug that inhibited binding of Bocillin FL or [3H]-penicillin by 50%.
[b] Cloned and purified PBP tested.

[c] Mutant form of PBP5 with several amino acid substitutions (Hujer et al. 2005)
[d.].(Davies et al. 2007)
[e.] (Chung et al. 2008)
[f.] (Entenza et al. 2002)
[g.] (Hebeisen et al. 2001)
[h.] (Davies et al. 2006)
[i.] (Davies et al. 2010)
[j.](Henry et al. 2010)
[k.] (Hujer et al. 2005)
Abbreviations: ATCC, American type culture collection; CAZ, ceftazidime; CRO, ceftriaxone; IC_{50}, concentration required to inhibit 50% of the activity; IPM, imipenem; MET, methicillin (oxacillin used in the study of (Chung 2008); MRSA, methicillin-resistant *S. aureus*; MRSE, methicillin-resistant *S. epidermidis*; MSSA, methicillin-susceptible *S. aureus* ND, not determined; PBP, penicillin-binding protein; PEN, benzylpenicillin; Pen-I, penicillin-intermediate; Pen-R, penicillin-resistant; Pen-S, penicillin-susceptible

In *E.coli*, ceftobiprole has good affinity for PBP3 and PBP2. The ceftobiprole IC_{50s} for PBP1a and PBP4 were similar to ceftriaxone and imipenem (Table 323). In *P. aeruginosa*, ceftobiprole, ceftazidime, and imipenem had comparable binding affinities for PBP1a and PBP3. Incubation of *P. aeruginosa* strain PAO-1 or *E. coli* MC4100 for 2 hours in the presence of 1x MIC of ceftobiprole led to filamentation (Davies 2007a, Glen 2021). The IC_{50} and filamentation data, indicate that PBP3 is the preferred target in gram-negative bacilli. Ceftobiprole has high affinity for purified PBP1b from *C. freundii*, which is comparable to ceftriaxone.

Table 323. Penicillin-Binding Protein in Gram-Negative Bacteria

Strain	PBP	IC_{50} (mcg/mL)[a]					Reference
		Ceftobiprole	CRO	CAZ	IMP	AZT	
Escherichia coli MC4100	1a	0.3	0.2	1.1	0.5	>8	Davies 2007a[c]
	1b	8	0.5	1.1	0.5	>8	
	2	0.2	0.2	4	0.01	>8	
	3	0.2	<0.01	0.07	8	0.03	
	4	0.5	0.4	>4	0.01	>8	
	5	>8	6	>4	0.5	>8	
	6	3	>8	>4	0.1	>8	
Pseudomonas aeruginosa PAO1	1a	0.1	ND	0.2	0.5	2	Davies 2007a[c]
	1b	0.5	ND	5	0.5	2	
	2	3	ND	>32	0.1	16	
	3	0.1	ND	0.1	0.1	0.03	
	4	0.2	ND	2	0.01	16	
	5/6	>32	ND	>32	2	>16	
Pseudomonas aeruginosa ATCC 27853	1a	0.1	ND	0.3	0.1	2	Davies 2007a[c]
	1b	0.2	ND	1.7	0.1	2	
	2	1.1	ND	4	0.1	4	
	3	0.1	ND	0.1	0.3	<0.02	
	4	0.2	ND	2	<0.008	>4	
	5/6	>4	ND	>4	2	>4	
Citrobacter freundii	1b[b]	0.085	0.11	ND	0.67	ND	Hebeisen 2001[d]

Source: Referenced in Table
[a] Concentration of drug that inhibited binding of Bocillin FL (Davies 2007a) or fluorescein isothiocyanate-labeled ampicillin (Hebeisen 2001) by 50%.
[b] Cloned and purified PBP tested.
[c] (Davies et al. 2007)
[d] (Hebeisen et al. 2001)
Abbreviations: ATCC, American type culture collection; AZT, aztreonam; CAZ, ceftazidime; CRO, ceftriaxone; IC_{50}, concentration required to inhibit 50% of the activity; IMP, imipenem; ND, not determined; PBP, penicillin-binding protein

Ceftobiprole is a poor substrate for class C β-lactamases and is hydrolyzed at very low rates (Table 324). Ceftobiprole is also a poor substrate for class A enzymes, particularly penicillinases (e.g., *S. aureus* PC1). It is readily hydrolyzed by the class A cephalosporinase from *P. vulgaris* 1028 and by ESBLs (TEM derivatives).

Table 324. Rates of Hydrolysis by Purified β-Lactamases

Compound	Mol of substrate hydrolyzed/mol of enzyme/min						
	Class C		Class A				
	Citrobacter freundii 1203	*Pseudomonas aeruginosa* 18SH	*Proteus vulgaris* 1028	*Staphylococcus aureus* PC 1	*Escherichia coli*		
					TEM1	TEM3	TEM4
Ro 63-9141	7.1	3.6	540	0.93	17	290	460
Ceftriaxone	4.1	6.8	900	19	900	4,900	640
Cephalothin	10,000	11,000	10,000	200	1,500	6,000	4,000
Penicillin G	900	760	1,000	10,000	12,000	9,000	15,000

Source: (Hebeisen et al. 2001)
Note: Ro 63-9141 = ceftobiprole
Abbreviations: TEM, transmission electron microscopy

Ceftobiprole was hydrolyzed slowly by the common staphylococcal PC1 β-lactamase, the class A TEM-1 β-lactamase, and the class C AmpC β-lactamase but was labile to hydrolysis by class B, class D, and class A extended-spectrum β-lactamases (Table 325). Ceftobiprole and cefepime generally had lower MICs than ceftazidime for AmpC producing organisms, particularly AmpC-overexpressing *Enterobacter cloacae* organisms. However, all three cephalosporins were hydrolyzed very slowly by AmpC cephalosporinases. Strains producing derepressed AmpC or rare class A cephalosporinases or strains producing ESBLs have higher ceftobiprole MICs, confirming that ceftobiprole is hydrolyzed by these enzymes.

Table 325. β-Lactamase Hydrolysis Parameters for Ceftobiprole and Comparator Antibacterial Drugs

β-Lactamase, strain	Substrate	k_{cat} (s^{-1})	Relative k_{cat}	K_m (μM)	k_{cat}/K_m (s^{-1} μM^{-1})	Relative k_{cat}/K_m
PC1	Cephaloridine	0.14	100	110	0.0013	100
	Benzylpenicillin	65	46,000	3.4[a]	19	1,500,000
	Ceftobiprole	0.024	17	78[b]	0.00031	24
	Cefepime	0.0020	1.4	61	0.000033	2.5
	Ceftazidime	0.00035	0.25	29[c]	0.000012	0.92
TEM-1	Cephaloridine	980	100	560	1.8	100
	Benzylpenicillin	1,200	122	12	100	5,600
	Ceftobiprole	8.8	0.90	300	0.029	1.6
	Cefepime	4.4	0.45	650	0.0068	0.38
	Ceftazidime	0.0023	0.00023	200	0.000012	0.00067
SHV-1	Cephaloridine	500	100	160	3.1	100
	Benzylpenicillin	1,300	260	16	81	2,600
	Ceftobiprole	30	6.0	130	0.23	7.4
	Cefepime	2.1	0.42	81	0.025	0.81
	Ceftazidime	0.013[d]	0.0026	500	0.000026	0.00084
CTX-M-15	Cephaloridine	190	100	39	4.9	100
	Benzylpenicillin	47	25	8.7[e]	5.4	110
	Ceftobiprole	270	140	19	14	290
	Cefepime	45[f]	24	180	0.25	5.1
	Ceftazidime	4.4	2.3	240	0.018	0.37
	Cefotaxime	180	95	26	6.9	140
K1	Cephaloridine	700	100	100	7.0	100
	Benzylpenicillin	1,100	160	40	28	400
	Ceftobiprole	230	33	32	7.2	100
	Cefepime	59	8.5	1,000	0.059	0.84
	Ceftazidime	0.018	0.0026	140	0.00013	0.0018
	Cefotaxime	88	13	550	0.16	2.3
TEM-26	Cephaloridine	37	100	66	0.56	100
	Benzylpenicillin	76	210	5.0	15	2,700
	Ceftobiprole	6.9	19	63	0.11	20
	Cefepime	20	54	65	0.31	55
	Ceftazidime	95	260	130	0.73	130
	Cefotaxime	2.9	7.8	15	0.19	34
KPC-2	Cephaloridine	390	100	510	0.77	100
	Benzylpenicillin	60	15	30	2.0	260
	Ceftobiprole	110[g]	28	340[h]	0.32	42
	Cefepime	12	3.1	540	0.022	2.9
	Ceftazidime	0.38	0.097	230	0.0017	0.22
SME-3	Cephaloridine	1,200	100	400	3.0	100
	Benzylpenicillin	8.8	0.73	2.2[i]	4.0	130
	Ceftobiprole	5.9	0.49	270	0.022	0.73
	Cefepime	1.5	0.13	280	0.0054	0.18
	Ceftazidime	0.16[j]	0.013	170[k]	0.00094	0.031
IMP-1	Cephaloridine	ND[l]	ND	ND	0.075	100
	Benzylpenicillin	ND	ND	ND	0.56	750
	Ceftobiprole	ND	ND	ND	0.74	990
	Cefepime	ND	ND	ND	0.15	200
	Ceftazidime	ND	ND	ND	0.090	120
VIM-2	Cephaloridine	120	100	1,400	0.086	100
	Benzylpenicillin	73	61	150	0.49	570
	Ceftobiprole	15	13	46	0.33	380
	Cefepime	0.38	0.32	110	0.0035	4.1
	Ceftazidime	0.23	0.19	150	0.0015	1.7
AmpC (E2), *E. cloacae*	Cephaloridine	690	100	480	1.5	100
	Benzylpenicillin	65	9.4	8.3	7.8	520
	Ceftobiprole[m]	≤0.057	≤0.0083	26	≤0.0022	≤0.15
	Cefepime[m]	≤0.021	≤0.0030	>630	≤0.000033	≤0.0022
	Ceftazidime	0.16[n]	0.023	110	0.0015	0.10
	Nitrocefin	570	83	56	10	670
AmpC (P99), *E. cloacae*	Cephaloridine	2,500[o]	100	330	7.6	100
	Benzylpenicillin	32	1.3	4.7	6.8	89
	Ceftobiprole	0.21	0.0084	9.4	0.022	0.29
	Cefepime	0.27	0.011	67	0.0040	0.053
	Ceftazidime	0.021	0.00084	2.9	0.0072	0.095
AmpC (908R), *E. cloacae*	Cephaloridine	3,200	100	360	8.9	100
	Benzylpenicillin	53	1.7	6.0	8.8	99
	Ceftobiprole	0.45	0.014	12	0.038	0.43
	Cefepime	0.82	0.025	16	0.075	0.84
	Ceftazidime	2.3	0.072	3.5	0.66	7.4

β-Lactamase, strain	Substrate	k_{cat} (s^{-1})	Relative k_{cat}	K_m (μM)	k_{cat}/K_m (s^{-1} μM^{-1})	Relative k_{cat}/K_m
AmpC, *M. morganii*	Cephaloridine	740	100	260	2.8	100
	Benzylpenicillin	190	26	7.9	24	860
	Ceftobiprole[m]	≤0.047	≤0.0064	23	≤0.0020	≤0.071
	Cefepime[m]	≤0.35	≤0.047	690	≤0.00051	≤0.018
	Ceftazidime[m]	≤1.0	≤0.14	14	≤0.071	≤2.5
	Nitrocefin	1,200	160	31	39	1,400
AmpC,[p] *P. stuartii*	Cephaloridine	530	100	920	0.58	100
	Benzylpenicillin	3.3	0.62	14	0.25	43
	Ceftobiprole	0.16	0.030	260	0.00062	0.11
	Cefepime	3.0	0.57	780	0.0038	0.66
	Ceftazidime	0.19	0.036	26	0.0073	1.3
AmpC, *P. aeruginosa* 4352	Cephaloridine	100	100	320	0.31	100
	Benzylpenicillin	37	37	11	3.4	1,100
	Ceftobiprole[m]	≤0.024[q]	≤0.024	55	≤0.00044	0.14
	Cefepime[m]	≤0.012	≤0.012	370	≤0.000033	0.011
	Ceftazidime[m]	≤0.010	≤0.010	8.0	≤0.0013	0.42
	Nitrocefin	68	68	12	5.7	1,800
AmpC, *P. aeruginosa* 18SH	Cephaloridine	130	100	71	1.8	100
	Benzylpenicillin	45	35	40	1.1	61
	Ceftobiprole	3.6	0.028	280	0.013	0.71
	Cefepime	≤0.10	≤0.10	210	0.0090	0.50
	Ceftazidime	≤0.10	≤0.10	20	0.015	0.83
AmpC, *P. aeruginosa* MK1184	Cephaloridine	22	100	21	1.1	100
	Benzylpenicillin	20	91	3.0	6.7	670
	Ceftobiprole	0.45	2.0	42	0.011	1.0
	Cefepime	0.33	1.5	38	0.0086	0.78
	Ceftazidime	0.69	3.1	12	0.058	5.3
AmpC, *S. marcescens*	Cephaloridine	2,000	100	680	3.1	100
	Benzylpenicillin	19	0.95	2.1[r]	9.0	290
	Ceftobiprole[m]	≤2.7	≤0.14	320	≤0.0084	≤0.27
	Cefepime[m]	≤0.55	≤0.028	>800	≤0.00069	≤0.022
	Ceftazidime[m]	≤0.050	≤0.0025	570	≤0.000088	≤0.0028
	Nitrocefin	840	42	14	60	19
OXA-10[p,s]	Cephaloridine	16	100	200	0.080	100
	Benzylpenicillin	86	540	7.9	11	14,000
	Ceftobiprole	230	1400	29	7.9	9,900
	Cefepime	3.1	19	230	0.0013	1.6
	Ceftazidime	≤0.0095	≤0.059	ND	ND	ND

Source: (Queenan et al. 2007)
[a] Standard deviation 20%, 1.3μM.
[b] Standard deviation 20%, 17μM.
[c] Standard deviation 20%, 8.8μM.
[d] Standard deviation 20%, 0.0042 s-1.
[e] Standard deviation 20%, 3.1μM.
[f] Standard deviation 20%, 11 s-1.
[g] Standard deviation 20%, 27 s-1.
[h] Standard deviation 20%, 79μM.
[i] Standard deviation 20%, 0.85μM.
[j] Standard deviation 20%, 0.045 s-1.
[k] Standard deviation 20%, 0.06 s-1.
[l] ND, not determined; kinetics were determined at five concentrations between 0.001 and 0.1mM, and the apparent k_{cat}/K_m value was calculated from the slope of the fitted line.
[m] The rates were too slow to determine the values of the parameters. V_{max} was estimated as two times the highest rate obtained, K_i and k_{cat}/K_i are reported. Nitrocefin data were added because K_i was determined by inhibition of nitrocefin hydrolysis.
[n] Standard deviation 20%, 44μM.
[o] Standard deviation 20%, 560 s-1.
[p] The yield of purified enzyme was only enough to test each substrate once.
[q] Standard deviation 20%, 0.006 s-1.
[r] Standard deviation 20%, 1.5μM.
[s] V_{max} is reported because the enzyme preparation was not pure enough to calculate a k_{cat} value; the rates were too slow to determine the values of the parameters for ceftazidime.
Abbreviations: k_{cat}, catalytic constant; K_i, inhibition constant; K_m, Michaelis constant; V_{max}, Maximum rate of reaction

20.2. Mechanism of Resistance

Single-step resistance frequencies were determined for 10 *S. aureus* strains using agar plates containing ceftobiprole at 2x to 8x MIC and an inoculum of 5 x 10^8 to 5 x 10^9 CFU. Resistance frequencies observed for ceftobiprole were low in *S. aureus* and ranged from ~9.6 x 10^{-8} at 2x MIC to <1.5 x 10^{-10} at 8X MIC (Table 326). In serial passage studies, a 4-fold increase in MIC was observed in 3 out of 5 *S. aureus* isolates after 50 passages. In the case of coagulase negative

staphylococci, the ceftobiprole resistance frequencies were 1.1 x 10^{-8} to <7.7 x 10^{-10} and 4 of the 5 strains had a 4-fold increase in MIC after 50 passages. In most cases, the transiently elevated ceftobiprole MICs decreased when the strains were cultured in the absence of drug, suggesting the resistance mutations were not stable.

When a high inoculum of *S. aureus* strains (10^9 CFU/mL) was serially passaged in subinhibitory concentrations of ceftobiprole for 28 days, resistance due to rare mutations developed in 20-21 days. For the strain carrying mutated *mecA* gene on a plasmid with an initial ceftobiprole MIC of 16 mcg/mL, the MIC increased to 256 mcg/mL after 20 passages. For the strain carrying wildtype *mecA* gene on a plasmid in a *mecA*– background, ceftobiprole MIC increased from 4 mcg/mL to 128 mcg/mL after 21 passages. In the third strain that lacked the *mecA* gene, ceftobiprole MIC increased from 1 mcg/mL to 256 mcg/mL after 20 passages. The *mecA* gene acquired mutations which lie close to the ceftobiprole binding site (Banerjee et al. 2008). The mutations in the *mecA*– strain that led to an increased ceftobiprole MIC were in three genes: two substitutions were in the gene encoding the low molecular weight PBP4, one in a gene encoding a predicted signaling protein, GdpP, and one in the gene encoding an efflux protein, AcrB, which is implicated in resistance to cationic compounds.

Single-step resistance frequencies for ceftobiprole in 10 *S. pneumoniae* (including penicillin sensitive and penicillin resistant) strains ranged from 2 x 10^{-7} at 2x MIC to <6.7 x 10^{-9} at 8X MIC. Three strains showed a 2-fold increase in MIC after 50 passages.

Single-step resistance frequencies for ceftobiprole in 8 *H. influenzae* (including β lactamase positive and β lactamase negative) and 2 *M. catarrhalis* strains resulted in very low resistance frequencies of <4.3 x 10^{-11} to 1.3 x 10^{-10} at 2x MIC and 8x MIC. A 4-fold increase in MIC was seen in one strain after 50 passages.

Single-step mutants were obtained by exposing clinical isolates of *Morganella morganii, Citrobacter freundii, Providencia stuartii, Enterobacter cloacae, Serratia marcescens, Escherichia coli,* and *Pseudomonas aeruginosa* to 2x-, 4x- and 8x- ceftobiprole MICs. Single-step resistance frequencies for five *Enterobacterales* strains and one *P. aeruginosa* strain were 10^{-6} to 10^{-8} at 2x MIC for ceftobiprole and comparable to the values obtained for cefepime and ceftazidime. The resistant mutants in *C. freundii* and *E. cloacae* occurred at frequencies of 10^{-6} at 2x MIC and 4x MIC of ceftobiprole. The mutants appeared to have become resistant through over-expression of the chromosomal Class C β-lactamase. Mutants of *P. aeruginosa* were obtained at a frequency of 10^{-6} and <10^{-9} at 2x MIC and 4x MIC, respectively. None of the mutants over-expressed the chromosomal Class C β-lactamase but were found to over-express the MexXY efflux pump (Queenan et al. 2010). The mutation frequencies for *Enterobacterales* and *P. aeruginosa* were higher than those observed for *S. aureus* and *S. pneumoniae*.

Reference ID: 5357793

Table 326. Ceftobiprole Single Step Resistance Frequencies in Bacteria

Organism, Strain	No of Strains Tested (Initial MIC Range in mcg/mL)	Resistance Frequencies at			Change in MIC After 50 Passages in the Presence of Ceftobiprole
		2X MIC	4x MIC	8x MIC	
S. aureus	5 (0.25 -2)	9.6 x 10-8 to 9.2 x 10-10	<0.9 x 10-10 to 2.8 x 10-10	<1.5 x 10-10	3 strains with 4-fold increase in MIC
CoNS	5 (0.25-1)	1.1 x 10-8 to <7.7 x 10-10	1.1 x 10-8 to <7.7 x 10-10	< 7.7 x10-10	4 strains with 4- fold increase in MIC
S. pneumoniae	10 (0.015 – 1)	2,0 x 10-7 to <5.0 x 10-9	1.1 x 10-8 to <6.7 x 10-9	1.1 x 10-8 to <6.7 x 10-9	3 strains with 2-fold increase in MIC
H. influenzae	8 (0.06-1)	1.3 x 10-10 to <5 x 10-10	1.3 x 10-10 to <5 x 10-10	1.3 x 10-10 to <5 x 10-10	1 strain with 4-fold increase in MIC
M. catarrhalis	2 (0.5 -1)	<4.3 x 10-11	<4.3 x 10-11	<4.3 x 10-11	No strain with increase in MIC
E. coli	0.06	5.1 x 10-7	<1 x 10-8	<1 x 10-8	ND
M. morganii	0.06	<5 x 10-9	<5 x 10-9	<5 x 10-9	ND
C. freundii	0.03	1.7 x 10-6	1.6 x 10-6	5.0 x 10-7	ND
E. cloacae	0.12	5.6 x 10-6	4.9 x 10-6	1.3 x 10-6	ND
S. marcescens	0.12	4.5 x 10-7	1.6 x 10-7	<7 x 10-9	ND
P. aeruginosa	4	6.4 x 10-7	<3 x 10-9	<3 x 10-9	ND

Source: (Bogdanovich et al. 2005; Kosowska et al. 2005; Queenan 2008b)
Abbreviations: CoNS, coagulase-negative staphylococci; MIC, minimum inhibitory concentration; ND, not done

Resistance in Isolates From Ceftobiprole Clinical Trials

In the CAP-3001 (CABP) trial, *K. pneumoniae* isolates from 1 subject had a ≥ 4-fold increase in the ceftobiprole MICs between baseline (0.12 mcg/mL) and post-baseline (>16 mcg/mL). The organism acquired an ESBL (TEM-4 with 4 amino acid changes) (Queenan 2009d). The Applicant concluded that ceftobiprole resistance did not develop over the course of therapy and the subject was infected with a new strain of *K. pneumoniae* which had a higher ceftobiprole MICs and expressed more resistance mechanisms.

Subject isolates from the BAP248/307 HABP clinical trial with a ≥4-fold increase in ceftobiprole MIC values were characterized by pulsed-field gel electrophoresis (Queenan 2009b). Eleven subjects had related or identical isolates post-baseline with increased ceftobiprole MICs analysis. All 11 baseline isolates were gram-negative (*P. aeruginosa*, n=4; *A. baumannii*, n=2; E. cloacae, n = 2; *E. coli*, n = 1; *S. marcescens*, n = 1; and *K. pneumoniae*, n = 1). The pulsed-field gel electrophoresis results suggest that resistance to ceftobiprole developed while on therapy for these isolates. Subject isolates from the BAP248/307 HABP clinical trial with ceftobiprole MIC values ≥16 mcg/mL were evaluated for the expression of β-lactamases. Three principal resistance profiles were discovered: (1) ESBL-positive, with CTX-M or SHV family Class A extended-spectrum β-lactamases, (2) ESBL-positive, combined with an AmpC Class C β-lactamase, (3) ESBL-negative, having an AmpC Class C β-lactamase, either plasmid-encoded or chromosomally located. Ceftobiprole is not active against gram-negative bacteria producing ESBLs from TEM, SHV or CTX-M families, serine carbapenemases (such as KPC), class B metallo-β-lactamases, or class C (AmpC cephalosporinases) expressed at high levels and Ambler class D β-lactamases including carbapenemases.

In summary, resistance in some bacteria is due to poor binding to PBPs, expression of β lactamases including AmpC β lactamases, and expression of efflux pumps. In *E. faecium*, β-lactam resistance is mediated by low affinity binding to PBP5, which may be expressed at higher levels in ampicillin-resistant isolates. Ceftobiprole is resistant to hydrolysis by *S. aureus* penicillinases and is hydrolyzed slowly by some Class C and Class A β-lactamases found in gram- negative bacteria. Like most cephalosporins, ceftobiprole is hydrolyzed by ESBLs, serine carbapenemases and metallo-β-lactamases. It is also hydrolyzed by the Class A cephalosporinases from *Proteus vulgaris*, which has inherent resistance to ceftobiprole.

Cross-Resistance

Analysis of drug-resistant *Staphylococcus aureus* subset of the 2016-2020 SENTRY surveillance isolates demonstrated that ceftobiprole was active against isolates non-susceptible to clindamycin, daptomycin, erythromycin, gentamicin, levofloxacin, linezolid, tetracycline, tigecycline, or trimethoprim-sulfamethoxazole (ceftobiprole susceptibility ranged from 97.7%–100.0% based on the proposed ceftobiprole breakpoint of S ≤2 mcg/mL for *S. aureus*). Ceftobiprole $MIC_{50/90}$ values (e.g., 0.5/2 mcg/mL) were identical for the *S. aureus* subsets with vancomycin MIC values of ≤1 mcg/mL and >1 mcg/mL. Ceftobiprole maintained activity against 88.0% of the ceftaroline non-susceptible isolates.

21. Other Drug Development Considerations

Not applicable

22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

Refer to Section 10 for a discussion on clinical site and Applicant inspections. In addition, the Office of Scientific Investigations completed a separate review dated February 7, 2024, in DARRTS.

23. Labeling: Key Changes and Considerations

This prescribing information (PI) review includes a high-level summary of the rationale for major changes to the finalized PI as compared to the Applicant's draft PI submitted on August 3, 2023 (see Table 327 below). The PI was reviewed to ensure that the PI meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

Table 327. Key Labeling Changes and Considerations

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI
BOXED WARNING	Not Applicable
1 INDICATIONS AND USAGE	Deletion of (b) (4) (b) (4) from the acute bacterial skin and skin structure infections (ABSSSI) indication statement (in subsection 1.2 of the PI) (b) (4) Refer to Section 19 of the IA for additional information. Deletion of (b) (4) (b) (4) from the community-acquired bacterial pneumonia (CABP) indication statement (in subsection 1.3 of the PI) (b) (4) Refer to Section 19 and Section 14 of the IA for data supporting the change.
2 DOSAGE AND ADMINISTRATION	The Dosage Regimen tables were modified to reflect dosing based on the sodium salt (667 mg ceftobiprole medocaril sodium) with a footnote that states that 667 mg ceftobiprole medocaril sodium is equivalent to 500 mg of ceftobiprole. In addition, pediatric dosing tables were modified to reflect dosing based on the sodium salt (667 mg ceftobiprole medocaril sodium) with a footnote that states that 13.3 mg/kg of ceftobiprole medocaril sodium is equivalent to 10 mg/kg of ceftobiprole; 20 mg/kg

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI
	ceftobiprole medocaril sodium is equivalent to 15 mg/kg of ceftobiprole. Footnotes were also added to describe duration and concentration of infusion solutions. Revised recommended dosage for pediatric patients with impaired renal function to specify that the dosing for renal impairment applies to pediatric patients 2 years of age and older (in subsection 2.4 of the PI). Renal function (b) (4) eGFR (mL/min/1.73 m^2) in the pediatric renal dosing table. Refer to Section 8.1.4 of the IA for additional information. (b) (4) CL_{CR} less than 15 mL/min. Refer to Section 8.1.2 of the IA for additional information.
4 CONTRAINDICATIONS	Deleted the statement (b) (4)" from the contraindication statement regarding hypersensitivity. The (b) (4)
5 WARNINGS AND PRECAUTIONS	Addition of warning regarding increased mortality in ventilator-associated bacterial pneumonia (VABP) patients, an unapproved use (in subsection 5.1 of the PI). Added a statement to the warning description indicating that safety and effectiveness have not been established in VABP patients and that the use of ceftobiprole medocaril sodium for injection is not approved for VABP as per the Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling [5]. Refer to Section 7.6.5 and 7.7.1 of the IA for more information. (b) (4) Addition of other adverse CNS reactions reported with cephalosporins (nonconvulsive status epilepticus (NCSE), encephalopathy, coma, asterixis, neuromuscular, and myoclonia) particularly in patients with history of seizures or when dosages were exceeded due to renal impairment.
6 ADVERSE REACTIONS	Addition of section on hospital-acquired bacterial pneumonia (HABP)/VABP (Trial 4), an unapproved indication, with corresponding trial information, adverse reactions (ARs), and deaths. Refer to Section 7.6.5 of the IA for more information. Modification of demographics in phase 3 clinical trials to reflect addition of HABP/VABP trial. Modification of demographics in Trials 1-3 and 5 to reflect demographics of ceftobiprole medocaril sodium for injection-treated patients only.

[5] (https://www.fda.gov/media/71866/download)

Trial 1 (SAB) – Refer to Section 7.6.1 of the IA for more information:

1. Added sentence regarding data on deaths and that the most common ARs leading to discontinuation were nausea, vomiting, rash, and urticaria.
2. Added hypokalemia and fungal infection as ARs to Table 8.
3. Added PT of blood bilirubin increased and hyperbilirubinemia to hepatic enzyme increased and updated data in Table 8 listing selected ARs in Trial 1.
4. Added PTs of acute kidney injury, blood creatinine increased, oliguria, and renal impairment to blood creatinine increased and updated data in Table 8in the PI.
5. Added hypertension, pyrexia, and thrombosis to the selected AR of Zevtera in Adult Patients section. The Applicant moved hypertension and pyrexia to Table 8 as these were considered ARs in ≥ 2%. We further added PT of hypertensive crisis to the hypertension grouping as it is a similar AR.

Trial 2 (ABSSSI) – Refer to Section 7.6.2 of the IA for more information:

1. Added sentence regarding data on deaths and that the most common ARs leading to discontinuation were dysgeusia and both pruritus and rash.
2. Changed the AR of “infusion site reaction” to “injection site reaction” and deleted (b) (4) from this AR in Table 9.

Trial 3 (CABP in adults): Refer to Section 7.6.3 of the IA for more information:

1. Added sentence regarding data on deaths and that the most common AR leading to discontinuation was vomiting.
2. Added insomnia and hypertension as ARs in Table 10.
3. Removed “injection site phlebitis” from grouped term (b) (4) as the former was grouped with phlebitis.
4. Regrouped PTs under rash and hepatic enzyme increased and updated data in Table 10. Added hypertensive crisis to the hypertension grouping.

Removed footnotes in Selected Adverse Reactions of Zevtera in Adult Patients section and revised AR PTs to provide additional clarity and brevity.

Trial 5 (CABP in pediatrics): Refer to Section 7.6.4 of the IA for more information:

1. (b) (4)
2. The (b) (4) (b) (4) to reflect that the trial study population consisted of patients with both HABP and CABP.
3. A statement was included to note the absence of deaths in the pediatric trial.
4. Added vomiting, headache, hepatic enzymes increased, diarrhea, infusion site reaction, phlebitis, and pyrexia as additional ARs occurring at a frequency of ≥2% of treated subjects.

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI
	5. Added a description of the comparator arm. (b) (4) moved the information to post-marketing experience (subsection 6.2 in the PI). This revision was supported by the labeling recommendations in 21 CFR 201.57(c)(7)(i) that require that Section 6 lists the adverse reactions that occurred with the subject drug (in this case, ceftobiprole medocaril sodium for injection) and with drugs in the same pharmacologically active and chemically related class, if applicable (in this case, other cephalosporin-class antibacterial drugs). Added myoclonus as case was reported in literature (Refer to Section 7.3 of the IA for more information).
7 DRUG INTERACTIONS	Revised drug interaction related to OATP1B1 and OATP1B3 substrates to include specific instructions for preventing this clinically significant drug interaction as per 21 CFR.201.57 (c)(8). Refer to Section 14.1.5 of the IA for additional information.
8 USE IN SPECIFIC POPULATIONS	The Division included PLR/PLLR compliant language on the absence of clinical safety data on use of ceftobiprole medocaril sodium for injection during pregnancy in subsection 8.1 Pregnancy of the PI. Refer to the Division of Pediatrics and Maternal Health (DPMH) review in DARRTS dated 03/29/2024 for additional details. Revised description of the results of the embryofetal development toxicity studies in rats and monkeys. Added description of results of a pre- and postnatal development toxicity study with ceftobiprole in rats to the Risk Summary. Updated the calculated safety margins (b) (4) to the maximum recommended human dose (MRHD) based on BSA comparison and included timing of exposure. Refer to Section 13 of the IA for additional information. Included PLR/PLLR compliant language for a lack of data on presence of ceftobiprole in human milk and detection of ceftobiprole in rat milk in subsection 8.2 Lactation of the PI. Refer to Section 13 of the IA for additional information. Added a statement that safety and effectiveness have not been established for treatment of CABP in pediatric patients less than 3 months of age or for treatment of ABSSSI and SAB in pediatric patients in subsection 8.4 Pediatric Use of the PI (see Section 8.3 of the IA for additional information)
9 DRUG ABUSE AND DEPENDENCE	Not Applicable
10 OVERDOSAGE	Added a specific statement to indicate that Zevtera can be removed by hemodialysis as per the labeling regulations in 21CFR 201.57(c)(11).
12 CLINICAL PHARMACOLOGY	Reformatted subsection 12.3 Pharmacokinetics of the PI to streamline the contents of this subsection. Under subsection 12.4 Microbiology of the PI: Clarification of ceftobiprole mechanism of action, in vitro activity, cross-resistance, interactions with other antimicrobials, data from animal models. Modified second pathogen list to include (b) (4)

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI
	(b) (4) (*Enterobacter cloacae*) (see above) (b) (4) The first pathogen list was modified to reflect the edits to the microorganisms specified in the Indication and Usage. See Section 19 and 20 of the IA for data supporting the changes.
13 NONCLINICAL TOXICOLOGY	Added more detailed description of results from the in vitro and in vivo genotoxicity assays with ceftobiprole medocaril sodium and ceftobiprole. Refer to Section 13 of the IA for additional information. Proposed revision to description of the results of the fertility studies in male and female rats including recalculation of margins based on BSA comparison. Refer to Section 13 of the IA for additional information. Proposed addition of new subsection 13.2 Animal Toxicology and/or Pharmacology of the PI that includes a description of the toxicity findings of concern in the 13-week rat and dog toxicology studies with ceftobiprole medocaril sodium. Refer to Section 13 of the IA for additional information.
14 CLINICAL STUDIES	Proposed modification to limit the number of subgroup analyses and secondary endpoint analyses displayed for Trial 1 (SAB) as they generally did not control for multiple comparisons and were based on small sample sizes. Refer to Section 6.2.1 of the IA for additional information. The Applicant proposed the addition of median time of SAB clearance in the MSSA and MRSA subgroups as these were considered clinically important. We agreed to add these median times without percentage achieving clearance because the very high percentages may be confusing given the lower rates presented for microbiological eradication at the PTE visit. (b) (4) we recommended to add the number of subjects with failure of treatment due to relapse by treatment arm and a statement that no increase in ceftobiprole MIC was observed. Clarified why Trial 1 was performed in two cohorts (Refer to Section 6 and 7 of the IA for additional information). Proposed modification to (b) (4) . Refer to Section 6.2.2 of the IA for additional information. Proposed modification to (b) (4) Refer to Section 6.2.2 of the IA for additional information. (b) (4) . In

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI
	addition, such information was generally not included on other labels for the CABP indication. Refer to Sections 6.2.3 and 6.3 of the IA for additional information. Proposed moving results for 'Clinical success at Day 3' to a newly created table. This move was made since the Day 3 results for the CABP study were not planned but rather based on part of a post-hoc re-analysis which considers different analysis populations (Day 3-ITT population and Day 3-modified ITT population). Additional text was added to better explain these analyses and analysis populations in referencing table 16. Refer to Section 6.2.3and 6.3 of the IA for additional information. Proposed modification of table 17 to better describe the analysis populations and types of analyses considered. In addition, only pathogens included in the CABP indication were included. Added a statement that Trial 5 (pediatric CABP) was not powered for comparative inferential efficacy analysis; included point estimates and confidence intervals for results in the ITT population (Refer to Section 6.2.4 of the IA for additional information). Added a disclaimer statement to the description of pediatric Trial 5 to note that the 26.7 mg/kg dose administered during the clinical trial is higher than the highest recommended dose (i.e., 20 mg/kg) in the Dosage and Administration section of the PI, to avoid implying or suggesting an unapproved dose. This statement was also added to subsection 6.1 of the PI. This statement is based on the regulatory requirements in 21 CFR 201. 57 (c)(3) and (c) (15).
17 PATIENT COUNSELING INFORMATION	Revised the statement required by 21 CFR 201.24 (d) under the "Antibacterial Resistance" subheading to remove clearly inapplicable information as follows: 1) ceftobiprole medocaril sodium for injection will only be prescribed to treat bacterial infection. (b) (4) 2) ceftobiprole medocaril sodium for injection is an intravenously administered drug that will typically be administered by health care practitioners, especially early in the treatment course. (b) (4) The revised statement added states "Patients should be counseled that antibacterial drugs, including ZEVTERA, should (b) (4) be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). Patients should be told that the medication should be administered exactly as directed *[see Warnings and Precautions (5.5)]*." This revision to the regulatory required statement was supported by the Office of New Drugs, Labeling Policy Team.

Full PI Sections[1]	Rationale for Major Changes to Finalized PI[2] Compared to Applicant's Draft PI
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	In the Dosage Forms and Strengths Section (3) of the PI, the strength was presented in terms of the salt (ceftobiprole medocaril sodium instead of the prodrug (ceftobiprole medocaril) and the active metabolite (ceftobiprole). This was an exception to the salt policy in the Guidance for Industry: Naming of Drug Products Containing Salt Drug Substances. This strength presentation was also included in Section 11 Description and Section 16 How Supplied/Storage and Handling of the PI. In the Description Section (11) of the PI, the sodium content stated as "Each vial of ZEVTERA contains approximately 32 mg of sodium" was added as per the labeling recommendations in the Draft Guidance for Industry: Quantitative Labeling of Sodium, Potassium, and Phosphorus for Human Over-the -Counter and Prescription Drug Products. Refer to the Office of Product Quality Assessment (in DARRTS dated 3/28/2024) for additional details regarding the labeling changes to the product quality sections.

[1] Product quality sections (Sections 3, 11, and 16) are pooled under the last row in this table; Section 15 (REFERENCES) is not included in this table.
[2] For the purposes of this document, the finalized PI is the PI that will be approved or is close to being approved.
Abbreviation(s): ABSSSI, acute bacterial skin and skin structure infections; BSA, body surface area; CABP, community-acquired bacterial pneumonia; CE, clinically evaluable; CFR, Code of Federal Regulations; CLcr, creatinine clearance; CNS, central nervous system; DARRTS, ESRD, end-stage renal disease; FDA's Document Archiving, Reporting and Regulatory Tracking System; IA, Integrated Assessment; ITT, intent-to-treat; IV, intravenous; NOAEL, no-observed adverse effect level; PI, Prescribing Information; PLR. Physician Labeling Rule; PLLR, Pregnancy and Lactation Labeling Rule' PORT, Pneumonia Outcomes Research Team; PT, preferred term; SAB, *Staphylococcus aureus* Bacteremia; TEAE, treatment-emergent adverse event; VABP, ventilator-associated bacterial pneumonia

23.1. Approved Labeling Types

Upon approval of this application, the following labeling documents will be FDA-approved:

- Prescribing Information
- Carton labeling
- Container labeling

24. Postmarketing Requirements and Commitments

The following postmarketing requirements (PMR)/postmarketing commitments (PMC) have been requested by FDA and agreed to by the Applicant. Please refer to the approval letter for the final PMR/PMC language and timelines.

PMRs:

Required pediatric assessments:

Reference ID: 5357793

- Conduct a randomized, controlled study to evaluate the safety, tolerability and efficacy of ceftobiprole medocaril sodium for injection in pediatric subjects from birth to less than 18 years of age with acute bacterial skin and skin structure infections (ABSSSI) requiring intravenous antibacterial drugs.

Draft Protocol Submission:	10/2024
Final Protocol Submission:	02/2025
Study Completion:	10/2027
Final Report Submission:	04/2028

- Conduct a randomized, controlled study to evaluate the safety, tolerability and efficacy of ceftobiprole medocaril sodium for injection in pediatric subjects from birth to less than 18 years of age with *Staphylococcus aureus* bacteremia (SAB).

Draft Protocol Submission:	04/2025
Final Protocol Submission:	08/2025
Study Completion:	10/2028
Final Report Submission:	04/2029

PMR under 505(o):

- Conduct a US surveillance study for a five-year period after the introduction of ceftobiprole medocaril sodium for injection to the market to determine if bacterial resistance to ceftobiprole has developed in those organisms specific to the indications in the labeling.

Draft Protocol Submission:	09/2024
Final Protocol Submission:	01/2025
Interim Report:	06/2026
Interim Report:	06/2027
Interim Report:	06/2028
Interim Report:	06/2029
Interim Report:	06/2030
Final Report Submission:	03/2031

- Conduct an in vivo drug interaction study evaluating ceftobiprole medocaril sodium for injection as an inhibitor of OATP1B1 and OATB1B3 transporters in healthy subjects.

Draft Protocol Submission:	05/2024
Final Protocol Submission:	09/2024
Study Completion:	06/2025
Final Report Submission:	12/2025

Postmarketing commitments:

PMC # 1:

Conduct studies to establish additional controls in the finished drug product specification and adequate in-process controls in the manufacturing process to demonstrate that the labeled vial

content can be withdrawn at the lower end of the fill weight variation range following reconstitution.

Final Protocol Submission: 8/2024
Final Report Submission: 8/2025

PMC # 2:

Conduct stability studies on three drug product batches manufactured by basing the weight of the drug substance [redacted](b) (4), and propose appropriately revised acceptance criteria for assay and impurities.

Interim Report Submission: 1/2026
Final Report Submission: 07/2026

25. Financial Disclosure

Table 328. Covered Clinical Studies: BPR-CS-009, BPR-CS-008, CAP-3001, BAP-248/307, BPR-PIP-002

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: BPR-CS-009: 117, BPR-CS-008: 34, CAP-3001: 612, BAP 248/307: 1142, BPR-PIP-002: 23		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Enter text here. Significant payments of other sorts: Enter text here. Proprietary interest in the product tested held by investigator: Enter text here. Significant equity interest held by investigator: Enter text here. Sponsor of covered study: Enter text here.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): Enter text here.		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Abbreviation: FDA, Food and Drug Administration

26. References

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27. Review Team

Table 329. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory project manager	Christopher Davi
Nonclinical reviewer	Ines Pagan
Nonclinical team leader	Terry Miller
OCP reviewer	Cristina Miglis
OCP team leader	Dakshina Chilukuri
Clinical reviewers	Joseph Chang, Gregory Mak, Roya Gordji
Clinical team leaders	Shabnam Naseer, Mukil Natarajan, Ramya Gopinath
Biometrics reviewer	Christopher Kadoorie
Biometrics secondary reviewer	Daniel Rubin
Cross-disciplinary team leader	Shabnam Naseer
Division director (pharm/tox)	Hanan Ghantous
Division director (OCP)	Kellie Reynolds
Division director (OB)	Nie Lei
Division director (clinical)	Peter Kim
Deputy division director (clinical)	Dmitri Iarikov
Office director (or designated signatory authority)	John Farley

Abbreviations: OCP, Office of Clinical Pharmacology; OB, Office of Biostatistics

Table 330. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	George Lunn, Dorota Matecka
Microbiology	Kalavati Suvarna, Avery Goodwin
OPDP	Qumerunissa Syed, Sam Skariah
OSI	John Lee, Philip Kronstein
OSE/DMEPA	Deborah Myers, Valerie Vaughn
Associate Director of Labeling	Abimbola Adebowale

Abbreviations: OPQ, Office of Pharmaceutical Quality; OPDP, Office of Prescription Drug Promotion; OSI, Office of Scientific Investigations; OSE, Office of Surveillance and Epidemiology; DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DRISK, Division of Risk Management

27.1. Reviewer Signatures

Table 27-331 Signatures of Reviewers

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Secondary Reviewer	Daniel Rubin OB DBIV	Sections: 6.2, 6.3, 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Daniel Rubin

Digitally signed by Daniel Rubin

Date: 4/1/2024 12:49 PM EDT
GUID: 202441164957

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Primary Reviewer	Joseph Davi ORO DROID	Sections: 12	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Joseph Davi

Digitally signed by Joseph Davi

Date: 4/1/2024 12:50 PM EDT
GUID: 202441165023

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Primary Reviewer	Dmitri Iarikov OID DAI	Sections: 1-27	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Dmitri Iarikov

Digitally signed by Dmitri Iarikov

Date: 4/1/2024 12:51 PM EDT
GUID: 202441165130

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Microbiology Discipline Secondary Reviewer	Avery Goodwin OID DAI	Sections: 19; 20;	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Avery Goodwin

Digitally signed by Avery Goodwin

Date: 4/1/2024 12:53 PM EDT
GUID: 202441165350

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Secondary Reviewer	Dakshina Chilukuri OCP DIDP	Sections: 5, 6, 8,14 and 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Dakshina Chilukuri

Digitally signed by Dakshina Chiluku

Date: 4/1/2024 12:54 PM EDT
GUID: 202441165421

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Secondary Reviewer	Terry Miller OID DPTID	Sections: 7.1, 8.4, 13, 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Terry Miller

Digitally signed by Terry Miller

Date: 4/1/2024 12:57 PM EDT
GUID: 202441165745

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Secondary Reviewer	Justin Earp OCP DPM	Sections: 6, 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Justin Earp

Digitally signed by Justin Earp

Date: 4/1/2024 1:00 PM EDT
GUID: 2024411707

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Primary Reviewer	Gregory Mak OID DAI	Sections: 2, 3, 7, 17, 23, 24, 25	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Gregory Mak

Digitally signed by Gregory Mak

Date: 4/1/2024 1:01 PM EDT
GUID: 2024411712

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Primary Reviewer	Christopher Kadoorie OB DBIV	Sections: 2,16,23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: **Christopher Kadoorie**

Digitally signed by Christopher Kado

Date: 4/1/2024 1:01 PM EDT
GUID: 20244117159

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Supervisor / Team Lead	Mukilan Natarajan OID DAI	Sections: 2, 3, 7, 10, 17, 23, 25, 26	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: **Mukilan Natarajan**

Digitally signed by Mukilan Natarajan

Date: 4/1/2024 1:02 PM EDT
GUID: 20244117219

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Microbiology Discipline Primary Reviewer	Kalavati Suvarna OID DAI	Sections: 19, 20 and 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: **Kalavati Suvarna**

Digitally signed by Kalavati Suvarna

Date: 4/1/2024 1:03 PM EDT
GUID: 2024411731

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Primary Reviewer	Joseph Chang OID DAI	Sections: 2, 3, 7, 17, 23, 24, 25	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: **Joseph Chang**

Digitally signed by Joseph Chang

Date: 4/1/2024 1:03 PM EDT
GUID: 20244117334

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Safety Discipline Other	Mukilan Natarajan OID DAI	Sections: 24	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Mukilan Natarajan

Digitally signed by Mukilan Natarajan

Date: 4/1/2024 1:03 PM EDT
GUID: 20244117347

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Labeling Discipline Associate Director for Labeling	Abimbola Adebowale OID DAI	Sections: 23 and 23.1	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Abimbola Adebowale

Digitally signed by Abimbola Adebow

Date: 4/1/2024 1:04 PM EDT
GUID: 2024411744

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Labeling Discipline Associate Director for Labeling	Abimbola Adebowale OID DAI	Sections: 23 and 23.1	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: **Abimbola Adebowale**

Digitally signed by Abimbola Adebow

Date: 4/1/2024 1:04 PM EDT
GUID: 20244117455

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Primary Reviewer	Roya Gordji OID DAI	Sections: 2, 3, 7, 17, 23, 24, 25	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: **Roya Gordji**

Digitally signed by Roya Gordji

Date: 4/1/2024 1:05 PM EDT
GUID: 2024411753

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Labeling Discipline Tertiary Reviewer	Abimbola Adebowale OID DAI	Sections: 23 and 23.1	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: **Abimbola Adebowale**

Digitally signed by Abimbola Adebow

Date: 4/1/2024 1:05 PM EDT
GUID: 20244117537

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Secondary Reviewer	Shabnam Naseer OID DAI	Sections: 1, 2, 3, 4, 6, 7, 8.3, 10, 11, 12, 15, 16, 17, 18, 19.5, 21, 22, 23, 24, 25, 26, 27	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: **Shabnam Naseer**

Digitally signed by Shabnam Naseer

Date: 4/1/2024 1:22 PM EDT
GUID: 202441172216

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Tertiary Reviewer	Lei Nie OB DBIV	Sections: 6, 15-16	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Lei Nie

Digitally signed by Lei Nie

Date: 4/1/2024 1:23 PM EDT
GUID: 202441172340

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Cristina Miglis OCP DIDP	Sections: 5, 6, 8, 14, 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Cristina Miglis

Digitally signed by Cristina Miglis

Date: 4/1/2024 1:23 PM EDT
GUID: 202441172357

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Primary Reviewer	Ines Pagan OID DPTID	Sections: 7.1, 8.4, 13, 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Ines Pagan

Digitally signed by Ines Pagan

Date: 4/1/2024 1:36 PM EDT
GUID: 202441173614

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Dakshina Chilukuri OCP DIDP	Sections: 5, 8, 14 and 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Dakshina Chilukuri

Digitally signed by Dakshina Chiluku
Sign on behalf of Signing on behalf o
Date: 4/1/2024 1:43 PM EDT
GUID: 202441174327

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Cristina Miglis OCP DIDP	Sections: 5, 6, 8, 14 and 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Cristina Miglis

Digitally signed by Cristina Miglis

Date: 4/1/2024 1:46 PM EDT
GUID: 202441174615

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Tertiary Reviewer	Maureen Dillon Parker ORO DRO-ID	Sections: 12	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Maureen Dillon Parker

Digitally signed by Maureen Dillon P

Date: 4/1/2024 1:54 PM EDT
GUID: 202441175412

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Tertiary Reviewer	Hanan Ghantous OID DPTID	Sections: 7.1, 8.4, 13, 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Hanan Ghantous

Digitally signed by Hanan Ghantous

Date: 4/1/2024 2:00 PM EDT
GUID: 20244118027

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
CMC (OPQ/ONDP) Discipline Primary Reviewer	David Claffey OPQAI DPQAIII	Sections: 9, 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: David Claffey

Digitally signed by David Claffey
Sign on behalf of Signing for Dorota
Date: 4/1/2024 2:08 PM EDT
GUID: 20244118859

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
CMC (OPQ/ONDP) Discipline Secondary Reviewer	David Claffey OPQAI DPQAIII	Sections: 9, 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: **David Claffey**

Digitally signed by David Claffey
Sign on behalf of Signing for Dorota
Date: 4/1/2024 2:09 PM EDT
GUID: 20244118957

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Secondary Reviewer	Gregory Dibernardo ORO DROID	Sections: 12	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: **Gregory Dibernardo**

Digitally signed by Gregory Dibernar

Date: 4/1/2024 2:35 PM EDT
GUID: 20244118354

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Tertiary Reviewer	Kellie Reynolds OCP DIDP	Sections: 5, 6, 8, 14, 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Kellie Reynolds

Digitally signed by Kellie Reynolds

Date: 4/1/2024 4:14 PM EDT
GUID: 202441201414

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Secondary Reviewer	Ramya Gopinath OID DAI	Sections: 2.1, 2.2, 3.2, 6.2.4, 7.2, 7.4, 7.6.4, 8.3, 17.1, 17.5, 23, 24, 25	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Signature: Ramya Gopinath

Digitally signed by Ramya Gopinath

Date: 4/2/2024 8:20 AM EDT
GUID: 202442122025

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SHABNAM N NASEER
04/01/2024 01:26:34 PM

PETER W KIM
04/01/2024 03:22:21 PM

JOHN J FARLEY
04/02/2024 06:12:37 PM