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APPLICATION NUMBER:

213972Orig1s000

INTEGRATED REVIEW

Clinical Addendum to the Integrated Review, NDA 213972

NDA 213972

Applicant: Iterum Therapeutics US Ltd

Drug: Sulopenem etzadroxil/probenecid

Date Addendum Completed: November 15, 2024

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The following is an addendum to the Integrated Review for NDA 213972 (ORLYNVAH, sulopenem etzadroxil/probenecid) signed into DARRTS on 10/24/2024. Table 45 in Section 7.6.1.5 (Treatment-Emergent Adverse Events, Trial 310) and Tables 46, 47 and 48 in Section 7.6.1.6 (Laboratory Findings, Trial 310) have been corrected to include subheadings that were missing in the original Integrated Review.

Table 45. Subjects With Adverse Events by System Organ Class and FDA Medical Query (Broad) Occurring at $\geq 0.2\%$ Frequency in the Sulopenem Arm, Safety Population, Trial 310

System Organ Class FMQ (Broad)	Sulopenem Etzadroxil/ Probenecid		Amoxicillin/ Clavulanate	
	N=1107 n (%)	N=1107 n (%)	N=1107 n (%)	N=1107 n (%)
Cardiac disorders (SOC)				
Arrhythmia	3 (0.3)		5 (0.5)	
Ear and labyrinth disorders (SOC)				
Vertigo	5 (0.5)		6 (0.5)	
Endocrine disorders (SOC)				
Hyperglycemia	1 (0.1)		0	
Gastrointestinal disorders (SOC)				
Diarrhea	92 (8.3)		46 (4.2)	
Nausea	57 (5.1)		34 (3.1)	
Vomiting	57 (5.1)		34 (3.1)	
Dyspepsia	15 (1.4)		7 (0.6)	
Constipation	3 (0.3)		1 (0.1)	
Abdominal pain	7 (0.6)		11 (1.0)	
General disorders and administration site conditions (SOC)				
Fatigue	6 (0.5)		0	
Pyrexia	2 (0.2)		1 (0.1)	
Fall	7 (0.6)		7 (0.6)	
Dizziness	5 (0.5)		6 (0.5)	
Immune system disorders (SOC)				
Hypersensitivity	4 (0.4)		1 (0.1)	

System Organ Class FMQ (Broad)	Sulopenem Etzadroxil/ Probenecid	Amoxicillin/ Clavulanate
	N=1107 n (%)	N=1107 n (%)
Infections and infestations (SOC)		
Fungal infection	33 (3.0)	13 (1.2)
Opportunistic infection	33 (3.0)	13 (1.2)
Nasopharyngitis	3 (0.3)	1 (0.1)
Viral infection	8 (0.7)	6 (0.5)
Pneumonia	2 (0.2)	1 (0.1)
Bacterial infection	3 (0.3)	4 (0.4)
Musculoskeletal and connective tissue disorders (SOC)		
Back pain	3 (0.3)	4 (0.4)
Nervous system disorders (SOC)		
Headache	25 (2.3)	17 (1.5)
Somnolence	6 (0.5)	0
Syncope	3 (0.3)	4 (0.4)
Reproductive system and breast disorders (SOC)		
Bacterial vaginosis	3 (0.3)	1 (0.1)
Skin and subcutaneous tissue disorders (SOC)		
Pruritus	2 (0.2)	1 (0.1)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any event that occurs or worsens in either intensity or frequency after the first dose of study drug in a period.

Duration is 5 days for each arm.

Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.

Abbreviations: FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; PT, preferred term; SOC, system organ class

Table 1. Subjects With One or More Chemistry Analyte Values With Elevated or Low Values Meeting Specified Levels, Safety Population, Trial 310

Laboratory Parameter	Sulopenem N=1107 n/N_w (%)	Amoxicillin/Clavulanate N=1107 n/N_w (%)
Sodium, low (mEq/L)		
Level 1 (<132)	5/1061 (0.5)	3/1059 (0.3)
Level 2 (<130)	3/1061 (0.3)	1/1059 (0.1)
Level 3 (<125)	0/1061 (0)	0/1059 (0)
Potassium, low (mEq/L)		25/1057 (2.4)
Level 1 (<3.6)	30/1055(2.8)	5/1057 (0.5)
Level 2 (<3.4)	7/1055 (0.7)	
Potassium, high (mEq/L)		
Level 1 (>5.5)	8/1055 (0.8)	3/1057 (0.3)
Level 2 (>6)	1/1055 (0.1)	0/1057 (0)
Chloride, low (mEq/L)		
Level 1 (<95)	6/1063 (0.6)	3/1060 (0.3)
Chloride, high (mEq/L)		
Level 1 (>108)	20/1063 (1.9)	29/1060 (2.7)
Bicarbonate, low (mEq/L)		
Level 1 (<20)	4/1063 (0.4)	4/1060 (0.4)
Level 2 (<18)	1/1063 (0.1)	1/1060 (0.1)
Bicarbonate, high (mEq/L)		
Level 3 (>30)	97/1063 (9.1)	95/1060 (9.0)
Glucose, low (mg/dL)		
Level 1 (<70)	20/1059 (1.9)	25/1056 (2.4)
Level 2 (<54)	4/1059 (0.4)	0/1056 (0)
Glucose, random, high (mg/dL)		
Level 2 (≥200)	43/1059 (4.1)	35/1056 (3.3)
Level 3 (>250)	16/1059 (1.5)	20/1056 (1.9)
Blood urea nitrogen, high (mg/dl)		
Level 1 (>23)	55/1062 (5.2)	56/1060 (5.3)
Level 2 (>27)	29/1062 (2.7)	20/1060 (1.9)
Level 3 (>31)	17/1062 (1.6)	11/1060 (1.0)

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](#); rows for Levels in which no values were reported were deleted from the Table.

Duration is 5 days for each arm.

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 2. Subjects With One or More Kidney Function Analyte Values Exceeding Specified Levels, Safety Population, Trial 310

Laboratory Parameter	Sulopenem N=1107 n/N _w (%)	Amoxicillin/ Clavulanate N=1107 n/N _w (%)
Creatinine, high (mg/dL)		
Level 1 (≥1.5X baseline)	15/1053 (1.4)	18/1049 (1.7)
Level 2 (≥2X baseline)	3/1053 (0.3)	2/1049 (0.2)
Level 3 (≥3X baseline)	1/1053 (0.1)	0/1049 (0)
eGFR, low (mL/min/1.73 m ²)		
Level 1 (≥25% decrease)	29/1037 (2.8)	31/1037 (3.0)
Level 2 (≥50% decrease)	3/1037 (0.3)	2/1037 (0.2)
Level 3 (≥75% decrease)	1/1037 (0.1)	0/1037 (0)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 5 days for each arm.

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 patients with data

Table 3. Subjects With One or More Hematology Analyte Values Exceeding Specified Levels, Safety Population, Trial 310

Laboratory Parameter	Sulopenem N=1107 n/N _w (%)	Amoxicillin/ Clavulanate N=1107 n/N _w (%)
Complete blood count		
WBC, low (10 ³ cells/uL)		
Level 1 (<3.5)	14/1056 (1.3)	17/1052 (1.6)
Level 2 (<3)	1/1056 (0.1)	4/1052 (0.4)
WBC, high (10 ³ cells/uL)		
Level 1 (>10.8)	45/1056 (4.3)	64/1052 (6.1)
Level 2 (>13)	8/1056 (0.8)	19/1052 (1.8)
Level 3 (>15)	2/1056 (0.2)	5/1052 (0.5)
Hemoglobin, low (g/dL)		
Level 2 (>1.5 g/dL dec. from baseline)	22/1036 (2.1)	16/1030 (1.6)
Level 3 (>2 g/dL dec. from baseline)	11/1036 (1.1)	6/1030 (0.6)
Hemoglobin, high (g/dL)		
Level 2 (>2 g/dL inc. from baseline)	7/1036 (0.7)	10/1030 (1.0)
Level 3 (>3 g/dL inc. from baseline)	2/1036 (0.2)	4/1030 (0.4)
Platelets, low (10 ³ cells/uL)		
Level 1 (<140)	12/1055 (1.1)	5/1050 (0.5)
Level 2 (<125)	8/1055 (0.8)	4/1050 (0.4)
Level 3 (<100)	3/1055 (0.3)	2/1050 (0.2)
Lymphocytes, low (10 ³ cells/uL)		
Level 1 (<1)	25/1051 (2.4)	31/1045 (3.0)
Level 2 (<0.75)	6/1051 (0.6)	10/1045 (1.0)
Level 3 (<0.5)	1/1051 (0.1)	0/1045 (0)
Lymphocytes, high (10 ³ cells/uL)		
Level 1 (>4)	11/1051 (1.0)	12/1045 (1.1)
Neutrophils, low (10 ³ cells/uL)		
Level 1 (<2)	50/1051 (4.8)	44/1045 (4.2)
Level 2 (<1)	0/1051 (0)	1/1045 (0.1)
Eosinophils, high (10 ³ cells/uL)		
Level 1 (>0.65)	9/1051 (0.9)	21/1045 (2.0)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 5 days for each arm.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

Rows for Levels in which there were no values have been deleted.

Abbreviations: dec, decrease; inc, increase; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; WBC, white blood cells

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/s/

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Integrated Review

Table 1. Application Information

Application type	NDA
Application number(s)	213972
Priority or standard	PRIORITY
Submit date(s)	4/25/2024
Received date(s)	4/25/2024
PDUFA goal date	10/25/2024
Division/office	Division of Anti-Infectives (DAI)
Review completion date	10/23/2024
Established/proper name	sulopenem etzadroxil/probenecid
(Proposed) proprietary name	ORLYNVAH
Pharmacologic class	Penem antibacterial (sulopenem etzadroxil) combined with a renal tubular transport inhibitor (probenecid)
Other product name(s)	sulopenem
Applicant	ITERUM THERAPEUTICS US LTD.
Dosage form(s)/formulation(s)	Tablet (500 mg sulopenem etzadroxil and 500 mg probenecid)
Dosing regimen	One tablet orally twice daily for 5 days
Applicant-proposed indication(s)/ population(s)	ORLYNVAH is indicated in adult women ≥18 years of age for the treatment of uncomplicated urinary tract infections caused by the following designated susceptible microorganisms: <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> , <i>Proteus mirabilis</i> ^{(b) (4)} (b) (4)
SNOMED CT code for proposed indication disease term(s)¹	68566005 Urinary tract infectious disease (disorder)
Regulatory action	Approval
Approved dosage (if applicable)	One tablet orally twice daily for 5 days
Approved indication(s)/ population(s) (if applicable)	ORLYNVAH is indicated for the treatment of uncomplicated urinary tract infections (uUTI) caused by the designated microorganisms <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> , or <i>Proteus mirabilis</i> in adult women who have limited or no alternative oral antibacterial treatment options.
SNOMED CT code for approved indication disease term(s)¹	68566005 Urinary tract infectious disease (disorder)

¹ For internal tracking purposes only.

Abbreviations: PDUFA, Prescription Drug User Fee Act; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms

Table of Contents

Table of Tables	vii
Table of Figures.....	xiii
Glossary	1
I. Executive Summary.....	3
1. Overview	3
1.1. Summary of Regulatory Action.....	3
1.2. Conclusions on Substantial Evidence of Effectiveness	5
2. Benefit-Risk Assessment.....	6
2.1. Benefit-Risk Framework	6
2.2. Conclusions Regarding Benefit-Risk	10
II. Interdisciplinary Assessment.....	11
3. Introduction	11
3.1. Review Issue List.....	12
3.1.1. Key Efficacy Review Issues	12
3.1.2. Key Safety Review Issues	12
3.2. Approach to the Clinical Review.....	12
3.3. Approach To Establishing Substantial Evidence of Effectiveness.....	13
4. Patient Experience Data	18
5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology.....	18
5.1. Nonclinical Assessment of Potential Effectiveness.....	18
5.1.1. Summary of Nonclinical Pharmacokinetic/Pharmacodynamic Information.....	19
5.2. Clinical Pharmacology/Pharmacokinetics	20
6. Efficacy (Evaluation of Benefit)	24
6.1. Assessment of Dose and Potential Effectiveness	24
6.1.1. Support for Proposed Dose of Sulopenem Etzadroxil	24
6.1.2. Support for Proposed Dose/Contribution of Probenecid	25
6.2. Clinical Studies/Trials Intended To Demonstrate Efficacy	25
6.2.1. Results of Pooled Analyses, Trials 301 and 310.....	25
6.2.2. Trial 310.....	26
6.2.2.1. Design, Trial 310.....	26
6.2.2.2. Eligibility Criteria, Trial 310.....	26

6.2.2.3. Statistical Analysis Plan, Trial 310	26
6.2.2.4. Results of Analyses, Micro-MITTS and Micro-MITTR Populations, Trial 310	28
6.2.3. Results from Other Trials.....	46
6.3. Key Efficacy Review Issues	47
7. Safety (Risk and Risk Management).....	47
7.1. Potential Risks or Safety Concerns Based on Nonclinical Data.....	47
7.1.1 Target Organs of Toxicity.....	47
7.1.2 Developmental and Reproductive Toxicity	49
7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug- Specific Factors	50
7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience	51
7.3.1. Adverse Events Identified in Postmarket Experiences	51
7.3.2. Expectations on Safety.....	51
7.3.3. Additional Safety Issues From Other Disciplines.....	51
7.4. FDA Approach to the Safety Review	52
7.5. Adequacy of the Clinical Safety Database	52
7.6. Safety Results	56
7.6.1. Safety Results, Trial 310.....	56
7.6.1.1. Overview of Treatment-Emergent Adverse Events, Trial 310.....	56
7.6.1.2. Deaths, Trial 310	57
7.6.1.3. Serious Treatment-Emergent Adverse Events, Trial 310.....	57
7.6.1.4. Adverse Events Leading to Treatment Discontinuation, Trial 310..	57
7.6.1.5. Treatment-Emergent Adverse Events, Trial 310.....	59
7.6.1.6. Laboratory Findings, Trial 310.....	63
7.6.1.7. Assessment of Drug-Induced Liver Injury, Trial 310	65
7.6.1.8. Vital-Sign Analyses, Trial 310.....	68
7.6.1.9. Subgroup Analyses, Trial 310	68
7.6.2. Summary of Safety Results, Trial 301	69
7.6.3. Summary of Safety in Phase 1 and Phase 2 Clinical Studies.....	71
7.6.4. Safety Results, Pooled Analyses, Trials 301 and 310.....	71
7.6.4.1. Overview of Treatment-Emergent Adverse Events Summary, Pooled Analyses, Trials 301 and 310	71

7.6.4.2. Deaths, Pooled Analyses, Trials 301 and 310	72
7.6.4.3. Serious Treatment-Emergent Adverse Events, Pooled Analyses, Trials 301 and 310	73
7.6.4.4. Adverse Events Leading to Treatment Discontinuation, Pooled Analyses, Trials 301 and 310	74
7.6.4.5. Treatment-Emergent Adverse Events, Pooled Analyses, Trials 301 and 310	75
7.6.4.6. Laboratory Findings, Pooled Analyses, Trials 301 and 310	77
7.6.4.7. Assessment of Drug-Induced Liver Injury, Pooled Analyses, Trials 301 and 310	80
7.6.4.8. Vital Signs, Pooled Analyses, Trials 301 and 310	84
7.6.4.9. Subgroups, Pooled Analyses, Trials 301 and 310	84
7.7. Key Safety Review Issues	86
8. Therapeutic Individualization	86
8.1. Intrinsic Factors	86
8.1.1. Hepatic Impairment.....	86
8.1.2. Renal Impairment.....	86
8.1.3. Other Intrinsic Factors	87
8.2. Extrinsic Factors	87
8.2.1. Food Effect.....	87
8.2.2. Summary of In Vitro Drug-Drug Interaction Studies	88
8.2.3. Summary of Clinical Drug-Drug Interaction Studies	89
8.2.3.1. Effect of P-gp Inhibitors on Sulopenem PK.....	89
8.2.3.2. Effect of Antacids and Proton Pump Inhibitors on Sulopenem PK.....	89
8.2.3.3. Effect of Sulopenem Etzadroxil/Probenecid on Valproic Acid PK.....	90
8.3. Plans for Pediatric Drug Development.....	90
8.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential	92
9. Product Quality	95
9.1. Device or Combination Product Considerations	95
10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review	95
11. Advisory Committee Summary.....	96
III. Additional Analyses and Information.....	98

12. Summary of Regulatory History	98
13. Pharmacology Toxicology	100
13.1. Summary Review of Studies Submitted With the Investigational New Drug Application	100
13.2. Individual Reviews of Studies Submitted With the New Drug Application	101
14. Clinical Pharmacology	101
14.1. In Vitro Studies.....	101
14.2. In Vivo Studies	101
14.3. Bioanalytical Method Validation and Performance	104
14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety...	104
14.5. Pharmacometrics Assessment.....	104
14.5.1. Review Summary	104
14.5.2. Introduction	105
14.5.3. Model Development.....	105
14.5.4. Probability of Target Attainment in Plasma and Urine.....	111
14.6. Pharmacogenetics	113
15. Study/Trial Design	114
16. Efficacy	118
16.1. Summary of Trial 301 in uUTI.....	118
16.2. Study Results, Micro-MITT Population, Trial 310	119
16.3. Study Results, ITT Population, Trial 310.....	129
16.4. Trial 302 for cUTI	129
16.5. Trial 303 for cIAI.....	133
17. Clinical Safety	134
17.1. Treatment-Emergent Adverse Events, Trial 310	134
17.2. Treatment-Emergent Adverse Events, Pooled Analysis, Trials 301 and 310	136
18. Clinical Virology	140
19. Clinical Microbiology	141
19.1. Nonclinical Microbiology.....	141
19.2. FDA Recommendations for Breakpoints or Susceptibility Test Interpretive Criteria	155
20. Mechanism of Action/Drug Resistance.....	164

20.1. Mechanism of Action	164
20.2. Drug Resistance	165
21. Other Drug Development Considerations	166
22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)	166
23. Labeling: Key Changes	168
23.1. Approved Labeling Types	174
24. Postmarketing Requirements and Commitments	175
25. Financial Disclosure	176
26. References	176
27. Review Team.....	178
27.1. Reviewer Signatures	179

Table of Tables

Table 1. Application Information	i
Table 2. Benefit-Risk Framework.....	6
Table 3. Clinical Studies/Trials Submitted in Support of Efficacy and/or Safety Determinations ¹ for Sulopenem Etzadroxil/Probenecid	14
Table 4. Patient Experience Data Submitted or Considered.....	18
Table 5. Summary of Clinical Pharmacology and Pharmacokinetics.....	20
Table 6. Sulopenem and Probenecid Plasma PK Parameters (%CV) After Single Dose Administration of the 500 mg Bilayer Tablet in Healthy Subjects.....	21
Table 7. Effect of Food on Sulopenem and Probenecid Plasma Pharmacokinetics	22
Table 8. Disposition of All Randomized Subjects (ITT Population).....	29
Table 9. Subject Disposition, Micro-MITTS Population.....	30
Table 10. Demographic Characteristics, Micro-MITTS Population	30
Table 11. Baseline Disease Characteristics, Micro-MITTS Population	31
Table 12. Treatment Exposure, Micro-MITTS Population	32
Table 13. Protocol Deviations, Micro-MITTS Population	32
Table 14. Pre-Existing Medication in $\geq 4\%$ of Subjects in Either Group, Micro- MITTS Population	33
Table 15. Concomitant Medication in $\geq 4\%$ of Subjects in Either Group, Micro- MITTS Population	33
Table 16. Concomitant Antibacterial Use in $\geq 0.5\%$ of Subjects in Either Group, Micro-MITTS Population	34
Table 17. Medical History in $\geq 4\%$ of Subjects in Any Group, Micro-MITTS Population	35
Table 18. Signs and Symptoms at Baseline, Micro-MITTS Population.....	36
Table 19. Baseline Pathogen, Micro-MITTS Population	37
Table 20. Distribution of Pathogens by ESBL Status and Amoxicillin/Clavulanate, Quinolone, Trimethoprim-Sulfamethoxazole and Nitrofurantoin Susceptibility, Micro-MITTS Population	37
Table 21. Overall Response (Primary Endpoint), Patient-Determined Clinical Response, and Microbiologic Response at TOC, Micro-MITTS Population	38
Table 22. Cross-Tabulation of Patient-Determined Clinical Response and Microbiologic Response at TOC, Micro-MITTS Population	39
Table 23. Reasons for Overall Nonresponse at TOC, Micro-MITTS Population	39
Table 24. Overall Response by Visit, Micro-MITTS Population.....	39

Table 25. Microbiological Response by Visit, Micro-MITTS Population	40
Table 26. Per Pathogen Microbiological Eradication Response at TOC, Micro-MITTS Population	41
Table 27. Investigator-Determined Clinical Response by Visit, Micro-MITTS Population	41
Table 28. Patient-Determined Clinical Response by Visit, Micro-MITTS Population	42
Table 29. Subgroup Analysis of the Primary Efficacy Endpoint, Micro-MITTS Population	42
Table 30. Sensitivity Analysis of Overall Response, Micro-MITTS Population	44
Table 31. Subject Disposition, Micro-MITTR Population	44
Table 32. Demographic Characteristics, Micro-MITTR Population	45
Table 33. Baseline Disease Characteristics, Micro-MITTR Population.....	46
Table 34. Overall Response (Primary Endpoint) at TOC, Micro-MITTR Population	46
Table 35. Exposure Multiples for Sulopenem Etzadroxil Based on Plasma Sulopenem AUC in Repeated-Dose Studies.....	48
Table 36. Exposure Multiples for Sulopenem Etzadroxil Based on Plasma Sulopenem AUC in EFD Studies.....	50
Table 37. Safety Database for Sulopenem.....	53
Table 38. Baseline Demographic and Clinical Characteristics, Safety Population, Trial 310.....	54
Table 39. Baseline Demographic and Clinical Characteristics, Integrated Safety Population, Trials 301 and 310	55
Table 40. Duration of Treatment, Safety Population, Trial 310	56
Table 41. Duration of Treatment, Integrated Safety Population, Trials 301 and 310.....	56
Table 42. Overview of Adverse Events, Safety Population, Trial 310.....	57
Table 43. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Trial 310	58
Table 44. Subjects With Adverse Events Occurring at $\geq 0.2\%$ Frequency in the Sulopenem Arm, Safety Population, Trial 310.....	60
Table 45. Subjects With Adverse Events by System Organ Class and FDA Medical Query (Broad) Occurring at $\geq 0.2\%$ Frequency in the Sulopenem Arm, Safety Population, Trial 310	61
Table 46. Subjects With One or More Chemistry Analyte Values With Elevated or Low Values Meeting Specified Levels, Safety Population, Trial 310.....	63
Table 47. Subjects With One or More Kidney Function Analyte Values Exceeding Specified Levels, Safety Population, Trial 310	64

Table 48. Subjects With One or More Hematology Analyte Values Exceeding Specified Levels, Safety Population, Trial 310	64
Table 49. Peak Post-Baseline ALT, Safety Population, Trial 310.....	65
Table 50. Peak Post-Baseline AST, Safety Population, Trial 310.....	66
Table 51. Subjects in Each Quadrant for Potential Hepatocellular DILI Screening Plot, Safety Population, Trial 310.....	67
Table 52. Overview of Adverse Events by Demographic Subgroup, Safety Population, Trial 310	68
Table 53. Overview of Adverse Events, Integrated Safety Population, Trials 301 and 310.....	72
Table 54. Deaths, Sulopenem Safety Population, Trials 301, 302, 303, and 310.....	72
Table 55. Subjects With Serious Adverse Events by System Organ Class and Preferred Term, Integrated Safety Population, Trials 301 and 310	73
Table 56. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Integrated Safety Population, Trials 301 and 310.....	75
Table 57. Subjects With Adverse Events Occurring at $\geq 0.5\%$ Frequency in the Sulopenem Arm, Integrated Safety Population, Trials 301 and 310	76
Table 58. Subjects With Adverse Events by System Organ Class and FDA Medical Query (Narrow) Occurring at $\geq 0.5\%$ Frequency in the Sulopenem Arm, Integrated Safety Population, Trials 301 and 310.....	76
Table 59. Subjects With One or More Chemistry Analyte Values With Elevated or Decreased Values Meeting Specified Levels, Integrated Safety Population, Trials 301 and 310.....	78
Table 60. Subjects With One or More Kidney Function Analyte Values Exceeding Specified Levels, Integrated Safety Population, Trials 301 and 310.....	79
Table 61. Subjects With One or More Hematology Analyte Values Exceeding Specified Levels, Integrated Safety Population, Trials 301 and 310.....	79
Table 62. Subjects With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels, Integrated Safety Population, Trials 301 and 310.....	80
Table 63. Peak Post-Baseline ALT, Integrated Safety Population, Trials 301 and 310....	81
Table 64. Peak Post-Baseline AST, Integrated Safety Population, Trials 301 and 310	81
Table 65. Subjects in Each Quadrant for Potential Hepatocellular DILI Screening Plot, Integrated Safety Population, Trials 301 and 310	82
Table 66. Percentage of Subjects With Maximum Systolic Blood Pressure by Category of Blood Pressure Post-Baseline, Integrated Safety Population, Trials 301 and 310.....	84

Table 67. Percentage of Subjects With Maximum Diastolic Blood Pressure by Category of Blood Pressure Post-Baseline, Integrated Safety Population, Trials 301 and 310.....	84
Table 68. Overview of Adverse Events by Demographic Subgroup, Integrated Safety Population, Trials 301 and 310.....	85
Table 69. Overall Response at TOC by CrCl in Micro-MITT Population.....	87
Table 70. Treatment-Emergent Clinically Significant Diarrhea by Fed/Fasted Status, Trial 301.....	88
Table 71. Nonclinical Data Supporting Labeling on Fertility, Pregnancy, and Lactation.....	92
Table 72. Reproductive Toxicity Safety Margins.....	94
Table 73. Clinical Trials Included in PopPK Analysis.....	106
Table 74. Summary of Baseline Demographic Covariates – Phase 1 Trial.....	107
Table 75. Summary of Baseline Demographic Covariates – Phase 3 Trials.....	108
Table 76. Summary of Number of Subjects and Urine Observations by Study and Covariates.....	109
Table 77. Parameter Estimates of Extended PopPK Model – Part 1.....	110
Table 78. Parameter Estimates of Extended PopPK Model – Part 2.....	111
Table 79. Covariate Distributions of the Virtual Population.....	112
Table 80. Definition of Microbiologic Response.....	117
Table 81. Composite, Clinical, and Microbiological Response at TOC in Trial 301.....	119
Table 82. Subject Disposition, Micro-MITT Population, Trial 310.....	119
Table 83. Demographic Characteristics, Micro-MITT Population, Trial 310.....	120
Table 84. Baseline Disease Characteristics, Micro-MITT Population, Trial 310.....	121
Table 85. Treatment Exposure, Micro-MITT Population, Trial 310.....	122
Table 86. Protocol Deviation, Micro-MITT Population, Trial 310.....	122
Table 87. Pre-Existing Medications in $\geq 4\%$ of Subjects in Either Group, Micro-MITT Population, Trial 310.....	123
Table 88. Concomitant Medication in $\geq 4\%$ of Subjects in Either Group, Micro-MITT Population, Trial 310.....	124
Table 89. Concomitant Antibacterial Use in $\geq 0.5\%$ of Subjects in Either Group, Micro-MITT Population, Trial 310.....	124
Table 90. Medical History in $\geq 4\%$ of Subjects in Either Group, Micro-MITT Population, Trial 310.....	125
Table 91. Signs and Symptoms at Baseline, Micro-MITT Population, Trial 310.....	126

Table 92. Baseline Pathogen, Micro-MITT Population, Trial 310.....	127
Table 93. Overall Response (Primary Endpoint), Micro-MITT Population, Trial 310...	128
Table 94. Subgroup Analysis of Overall Response at TOC, Micro-MITT Population, Trial 310.....	128
Table 95. Patient-Determined Clinical Response by Visit, ITT Population, Trial 310...	129
Table 96. Overall Response at TOC, Micro-MITT Population, Trial 302	130
Table 97. Overall Response at TOC by Stepdown Category, Sulopenem IV to PO Sulopenem Etzadroxil/Probenecid, Ertapenem IV to PO Ciprofloxacin, and Ertapenem IV to PO Amoxicillin/Clavulanate, Micro-MITT Population, Trial 302	131
Table 98. Overall Response at TOC by Stepdown Category, Sulopenem Group (IV Only), Micro-MITT Population, Trial 302	132
Table 99. Overall Response at TOC by Stepdown Category, Ertapenem Arm (IV Only), Micro-MITT Population, Trial 302	132
Table 100. Microbiologic Response and Clinical Response at Day 5, EOT, and TOC, Micro-MITT Population, Trial 302.....	132
Table 101. Applicant’s Analysis of Primary and Post Hoc Results – Clinical Response at TOC, Micro-MITT Population, Trial 303	133
Table 102. Subjects With Adverse Events by System Organ Class and Preferred Term, Safety Population, Trial 310.....	134
Table 103. Subjects With Adverse Events by System Organ Class and Preferred Term, Integrated Safety Population, Trials 301 and 310.....	137
Table 104. Microbiological Assessment of Baseline Pathogens at TOC	143
Table 105. Microbiological Definitions of Post-Baseline Pathogens.....	143
Table 106. Pathogens From Urine at Baseline – Micro-MITT Population, Trial 310.....	144
Table 107. Monomicrobial and Polymicrobial Infections at Baseline – Micro-MITT Population, Trial 310	144
Table 108. Activity of Sulopenem and Amoxicillin/Clavulanate Against Baseline Pathogens – Micro-MITT Population – Both Treatment Groups (Combined), Trial 310.....	145
Table 109. Overall Response at TOC – Micro-MITT Population, Trial 310	145
Table 110. Overall Response at TOC by Selected Baseline Pathogens – Micro-MITT Population, Trial 310	146
Table 111. Microbiologic Response Per Patient at TOC and Reasons for Overall Nonresponse at TOC – Micro-MITT Population, Trial 310.....	146
Table 112. Per-Pathogen Microbiologic Response at TOC – micro-MITT Population, Trial 310.....	149
Table 113. Pathogens From Urine at Baseline, Micro-MITTS Population, Trial 310	152

Table 114. Per-Pathogen Microbiologic Response at TOC, ME-TOC Population	152
Table 115. Correlation of Sulopenem MIC at Baseline to Overall Response in Sulopenem-Treated, Micro-MITT Population, Trial 310	152
Table 116. Clinical and Microbiological Response to Sulopenem in AmpC and Predominant ESBL-Producing Isolates at TOC, Micro-MITT Population, Trial 301	153
Table 117. Clinical and Microbiological Response to Sulopenem in AmpC and Predominant ESBL-Producing Isolates at TOC, Micro-MITT Population, Trial 310	154
Table 118. Proposed Broth Microdilution (MIC) and Disk Diffusion Susceptibility Test Criteria for Sulopenem	155
Table 119. Agency-Recommended Broth Microdilution (MIC) Interpretive Criteria (BPs) for Sulopenem	156
Table 120. Agency-Recommended Broth Microdilution (MIC) and Disk Diffusion Interpretive Criteria (BPs) for Sulopenem	159
Table 121. Acceptable Error Rates in Interpretation Between Test Methods (CLSI M23)	160
Table 122. Scatterplot Analysis of Broth Microdilution (MIC) and Disk Zone Correlation for Enterobacteriales (N=3,946)	160
Table 123. Scatterplot Analysis of Broth Microdilution (MIC) and Disk Zone Correlation for <i>E. coli</i> (N=3,026)	162
Table 124. Scatterplot Analysis of Broth Microdilution (MIC) and Disk Zone Correlation for <i>K. pneumoniae</i> (N=415)	163
Table 125. Scatterplot Analysis of Broth Microdilution (MIC) and Disk Zone Correlation for <i>P. mirabilis</i> (N=127)	164
Table 126. Key Labeling Changes and Considerations	169
Table 127. Covered Clinical Studies, Trial 310	176
Table 128. Reviewers of Integrated Assessment	178
Table 129. Additional Reviewers of Application	179
Table 27-1 Signatures of Reviewers	179

Table of Figures

Figure 1. Patients With Adverse Events by System Organ Class, Safety Population, Trial 310.....	61
Figure 2. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Trial 310	66
Figure 3. Hepatocellular Drug-Induced Liver Injury Screening Plot, Integrated Safety Population, Trials 301 and 310	82
Figure 4. Relationships Between f_{AUC}/MIC , fC_{max}/MIC , % $fT>MIC$ and Change in Bacterial Burden	102
Figure 5. Hollow Fiber Results Displaying Total and Drug-Resistant [4X Sulopenem and Meropenem] Subpopulations in No Treatment Control, Sulopenem, Meropenem, and Levofloxacin	103
Figure 6. Illustration of PopPK Model	108
Figure 7. Updated PopPK Model Equation	109
Figure 8. Prediction-Corrected Visual Predictive Check Final Model by Nominal Time After Dose, Applied Trials 101, 301, and 302	111
Figure 9. Probability of Target Attainment in Plasma.....	113
Figure 10. Probability of Target Attainment in Urine (q1h and q2h Voiding).....	113
Figure 11. Overall Response Per Pathogen for MIC to Sulopenem – Micro-MITT Population – <i>E. coli</i> (N = 439), Trial 310	147
Figure 12. Overall Response Per Pathogen for MIC to Sulopenem – Micro-MITT Population – <i>K. pneumoniae</i> (N = 60), Trial 310	147
Figure 13. Overall Response Per Pathogen for MIC to Sulopenem – Micro-MITT Population – <i>P. mirabilis</i> (N = 14), Trial 310.....	148
Figure 14. Microbiologic Response Per Pathogen for MIC to Sulopenem – Micro-MITT Population Overall – <i>E. coli</i> (N = 439), Trial 310	150
Figure 15. Microbiologic Response Per Pathogen for MIC to Sulopenem – Micro-MITT Population Overall – <i>K. pneumoniae</i> (N = 60), Trial 310.....	151
Figure 16. Microbiologic Response Per Pathogen for MIC to Sulopenem – Micro-MITT Population Overall – <i>P. mirabilis</i> (N = 14), Trial 310.....	151
Figure 17. MIC Distribution of Sulopenem for <i>E. coli</i> Isolates During Recent Surveillance and Phase 3 Clinical Trials	157
Figure 18. MIC Distribution of Sulopenem for <i>K. pneumoniae</i> Isolates During Recent Surveillance and Phase 3 Clinical Trials	157
Figure 19. MIC Distribution of Sulopenem for <i>P. mirabilis</i> Isolates During Recent Surveillance and Phase 3 Clinical Trials	158

Figure 20. Correlation Between Sulopenem Broth MIC Values and Disk Diffusion for Overall Enterobacterales (N=3,946) 160

Figure 21. Correlation Between Sulopenem Broth (MIC) Values and Disk Diffusion Zone Diameters for *E. coli* Overall (N=3,026) 161

Figure 22. Correlation Between Sulopenem Broth (MIC) Values and Disk Diffusion Zone Diameters for *K. pneumoniae* Overall (N=415) 162

Figure 23. Correlation Between Sulopenem Broth (MIC) Values and Disk Diffusion Zone Diameters for *P. mirabilis* Overall (N=127) 163

Figure 24. Autoradiograph of Competitive Binding of Unlabeled Sulopenem (CP-65,207) vs. ³H-penicillin G for *E. coli* W-7 PBPs 165

Glossary

AC	Advisory Committee
AE	adverse event
ALT	alanine aminotransferase
AMR	antimicrobial resistance
AP	alkaline phosphatase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BCRP	breast cancer resistance protein
BID	twice daily
BP	breakpoint
CFU	colony-forming units
cIAI	complicated intra-abdominal infection
CLSI	Clinical and Laboratory Standards Institute
C _{max}	maximum plasma concentration
CMC	chemistry, manufacturing, and controls
CrCl	creatinine clearance
cUTI	complicated urinary tract infection
DARRTS	Document Archiving Reporting and Regulatory Tracking System
DDI	drug-drug interactions
DPMH	Division of Pediatric and Maternal Health
ECV	epidemiological cutoff values
EOT	end of trial
ESBL	extended-spectrum β -lactamases
FDA	Food and Drug Administration
FMQ	FDA Medical Query
FV	final visit
GCP	good clinical practice
GERD	gastroesophageal reflux disease
GGT	gamma-glutamyl transferase
GI	gastrointestinal
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
IC ₅₀	half-maximal inhibitory concentration
IND	investigational new drug
IRB	institutional review board
ISP	integrated safety population
ITT	intent-to-treat
IV	intravenous
MedDRA	Medical Dictionary for Regulatory Activities
micro-MITT	microbiological modified intent-to-treat
micro-MITTS	microbiological modified intent-to-treat susceptible
micro-MITTR	microbiological modified intent-to-treat resistant
MITT	modified intent-to-treat
MIC	minimum inhibitory concentration

NDA 213972
ORLYNVAH (sulopenem etzadroxil/probenecid)

NDA	new drug application
NI	noninferiority
OPQ	Office of Pharmaceutical Quality
OSI	Office of Scientific Investigations
PBP	penicillin-binding protein
PD	pharmacodynamic
PDUFA	Prescription Drug User Fee Act
PI	Prescribing Information
PK	pharmacokinetic
PMR	postmarketing requirement
PO	oral, orally
PopPK	population pharmacokinetic
PPI	proton pump inhibitor
PT	preferred term
PTA	probability of target attainment
QIDP	Qualified Infectious Disease Product
SAE	serious adverse event
SAP	statistical analysis plan
SEE	substantial evidence of effectiveness
SOC	system organ class
SPA	special protocol assessment
STIC	Susceptibility Test Interpretive Criteria
TEAE	treatment-emergent adverse event
TOC	test of cure
ULN	upper limit of normal
UTI	urinary tract infections
uUTI	uncomplicated urinary tract infection
WBC	white blood cell

I. Executive Summary

1. Overview

1.1. Summary of Regulatory Action

On April 25, 2024, the 505(b)(2) NDA 213972 for sulopenem etzadroxil/probenecid oral tablet, a bilayer fixed-dose combination of the penem antibacterial prodrug sulopenem etzadroxil and probenecid (500 mg; 500 mg), a renal tubular transport inhibitor, was resubmitted by Iterum Therapeutics US Ltd. (Applicant) for the proposed indication of treatment of adult women ≥ 18 years of age with uncomplicated urinary tract infections (uUTI) caused by designated susceptible microorganisms. Sulopenem etzadroxil/probenecid has Qualified Infectious Disease Product (QIDP), Fast Track and Priority Review designations. The Prescription Drug User Fee Act (PDUFA) goal date is October 25, 2024. Throughout this review, the study drug product is referenced as sulopenem etzadroxil/probenecid or oral sulopenem.

NDA 213972 was originally submitted on November 25, 2020, for sulopenem etzadroxil/probenecid for the treatment of uUTI caused by designated microorganisms proven or strongly suspected to be nonsusceptible to a quinolone in adult women. The original NDA was primarily based on Trial IT001-301 (Trial 301), a phase 3, randomized, double-blind, active-controlled trial comparing oral sulopenem to oral ciprofloxacin for the treatment of uUTI in adult women. Independent statistical analyses in this trial indicated that oral sulopenem was inferior to ciprofloxacin for the primary endpoint of overall (or composite) response (including clinical and microbiological responses) in the microbiological modified intent-to-treat ciprofloxacin-susceptible (micro-MITTS) population but achieved statistical superiority in the microbiological modified intent-to-treat ciprofloxacin-resistant (micro-MITTR) population. Data from Trial 302 for the treatment of complicated urinary tract infections (cUTI) and Trial 303 for the treatment of complicated intra-abdominal infections (cIAIs) assessing the safety and efficacy of IV to oral sulopenem formulations versus active comparator regimens were also submitted in the NDA; however, both trials failed to meet their primary endpoints. The original NDA review team concluded that results from the single uUTI trial and lack of confirmatory evidence from Trials 302 and 303 were insufficient to establish substantial evidence of effectiveness (SEE); thus, the NDA received a complete response on July 23, 2021. The Division recommended that the Applicant conduct at least one additional adequate and well-controlled trial in uUTI to support this indication.

In the current NDA resubmission, data were provided from the new Trial IT001-310 (Trial 310), a phase 3, randomized, double-blind, active-controlled, noninferiority (NI) trial comparing oral sulopenem to amoxicillin/clavulanate for the treatment of uUTI caused by designated susceptible microorganisms in adult women. Oral sulopenem was NI with an NI margin of 10% and statistically superior to the comparator in the micro-MITTS (amoxicillin/clavulanate-susceptible) population. The sample size of patients with isolates that were amoxicillin/clavulanate-resistant (micro-MITTR) was too small to allow conclusions regarding efficacy.

Safety data from nearly 3000 subjects across the phase 3 sulopenem development program indicate that oral sulopenem is anticipated to be safe for its intended use. It is expected that potential safety risks can be adequately mitigated through labeling and further evaluated during routine pharmacovigilance.

Because sulopenem etzadroxil/probenecid will, if approved, be the first oral penem antibacterial drug on the U.S. market, the NDA was taken to the Antimicrobial Drugs Advisory Committee on September 9, 2024, to discuss the Applicant's desired indication and consider the information that should be conveyed to medical providers to ensure appropriate use of this drug product. While an oral penem for the treatment of resistant bacteria causing uUTI could potentially address an unmet need, its use in an ambulatory setting where treatment is most commonly empiric raises concern for inappropriate use which may contribute to antimicrobial resistance (AMR). Further, based on the failure of Trials 302 and 303 to meet their primary endpoints, there was concern for potential off-label use of sulopenem etzadroxil/probenecid as a stepdown treatment for cUTI and cIAI following initial intravenous (IV) antibacterial treatment.

Based on the totality of evidence and recommendations from the Advisory Committee (see Section [11](#)), the multidisciplinary review team recommends approval of sulopenem etzadroxil/probenecid with the following Indication: "ORLYNVAH is indicated for the treatment of uncomplicated urinary tract infections (uUTI) caused by the designated microorganisms *Escherichia coli*, *Klebsiella pneumoniae*, or *Proteus mirabilis*, in adult women who have limited or no alternative oral antibacterial treatment options." In addition, the required statement regarding Usage to Reduce Development of Drug-Resistant Bacteria will be strengthened. A Limitations of Use statement that "ORLYNVAH is not indicated for the treatment of: cUTI or cIAI or as step-down treatment after intravenous antibacterial treatment of cUTI or cIAI" will be added. Overall, as delineated in the Benefit/Risk Framework below, the review team concludes that the benefits of oral sulopenem outweigh its associated risks when used as recommended in the approved labeling.

The signatory concurs with the review team's recommendations. There is an unmet need for an oral penem to provide an oral treatment option for adult women with uUTI caused by certain resistant bacteria, such as those with infections caused by bacteria expressing extended-spectrum beta-lactamase enzymes. Trial 301 is considered as two adequate and well-controlled trials based on the statistical analysis plan (SAP), with separate analyses conducted for the micro-MITTS (ciprofloxacin-susceptible) population which failed, and the micro-MITTR (ciprofloxacin-resistant) population which was successful. The interpretable primary analysis of Trial 310 in the micro-MITTS (amoxicillin/clavulanate-susceptible) population was successful. Thus, while the signatory agrees that substantial evidence of effectiveness has been provided, there is some element of uncertainty because of the failed Trial 301 primary analysis in the micro-MITTS (ciprofloxacin-susceptible) population. Consistent with our labeling practices for antibacterial drug products that address unmet need described in our Guidance document, Antibacterial Therapies for Patients with an Unmet Medical Need for the Treatment of Serious Bacterial Diseases – Questions and Answers, (available at ([May 2022](#))) the Indication will read as described above. This Indication and other labeling will address the need to ensure appropriate use of the drug, minimize the risk of contributing to penem resistance in the U.S. population, and avoid use of the drug to treat serious infections such as cUTI or cIAI for which effectiveness has not been established.

Microbiological surveillance as a Post-Marketing Requirement (PMR) mandated by 21 CFR 505(o)(3) will evaluate the possible emergence of resistance to oral sulopenem and cross-resistance to FDA-approved IV carbapenems with the use of sulopenem etzadroxil/probenecid. In addition, FDA will conduct enhanced post-marketing pharmacovigilance to monitor for potential inappropriate use of the product.

1.2. Conclusions on Substantial Evidence of Effectiveness

SEE was established with two or more adequate and well-controlled clinical investigations.

Substantial evidence of effectiveness (SEE) for sulopenem etzadroxil/probenecid for the treatment of uUTI was established based on the results from Trials 301 and 310. For these trials, the SAP pre-specified that the composite primary efficacy endpoint of overall response (combination of clinical and microbiological responses) was analyzed independently in the micro-MITTS (comparator-susceptible) and micro-MITTR (comparator-resistant) populations.

In Trial 301, sulopenem was superior to ciprofloxacin in patients with ciprofloxacin-nonsusceptible pathogens (micro-MITTR population) using the primary efficacy endpoint of overall response. The overall response was 77/160 (48%) for sulopenem and 49/149 (33%) for ciprofloxacin with a difference of 15% (95% CI, 4.4%, 26.1%; p-value 0.0062). Among patients with uUTI caused by a ciprofloxacin-susceptible pathogen (micro-MITTS population), sulopenem was inferior to ciprofloxacin. The overall response was 218/365 (60%) for sulopenem and 296/410 (72%) for ciprofloxacin with a difference of -12.5% (95% CI, -19.1%, -5.9%). The failure of sulopenem in the micro-MITTS population in Trial 301 was driven by lower rates of microbiological success in the sulopenem arm compared to the ciprofloxacin arm.

In Trial 310, oral sulopenem was non-inferior and superior to amoxicillin/clavulanate in the micro-MITTS (i.e., amoxicillin/clavulanate-susceptible) population using the primary efficacy endpoint of overall response (clinical response and microbiological response). The overall response was 296/480 (61.7%) for sulopenem and 243/442 (55.0%) for amoxicillin/clavulanate with a difference of 6.7% (95% CI, 0.3,13.0; p-value of 0.040). While clinical response was similar between arms, the rate of microbiological response was greater in the sulopenem arm of the micro-MITTS population. The sample size of subjects with isolates that were amoxicillin/clavulanate-resistant (micro-MITTR) was too small to allow conclusions regarding efficacy in this population.

In summary, SEE for sulopenem etzadroxil/probenecid for the treatment of uUTI caused by the designated microorganisms *E. coli*, *K. pneumoniae*, or *P. mirabilis* in adult women who have limited or no alternative oral antibacterial treatment options has been provided by statistical superiority in the micro-MITTR population of Trial 301 along with NI/superiority in the micro-MITTS population of Trial 310. To note, there is some element of uncertainty because of the failed uUTI Trial 301 primary analysis in the micro-MITTS (ciprofloxacin-susceptible) population. Additionally, as discussed in this review, IV to oral sulopenem did not demonstrate efficacy for treatment of cUTI and cIAI in Trials 302 and 303, respectively.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	• Uncomplicated urinary tract infection or acute cystitis is an acute infection of the bladder in women with normal urinary tract anatomy. Signs and symptoms of uUTI include dysuria, urinary frequency, urinary urgency, and suprapubic pain (August 2019). • Urinary tract infections (UTIs) are the most common bacterial infections in the ambulatory setting in the U.S.; 50-60% of adult women will have at least one UTI during their lifetime (Medina and Castillo-Pino 2019). It is estimated that 10-12% of adult women in the United States have at least one UTI per year, with 20-30% of those having a recurrent infection (Kaye et al. 2021). • The incidence of uUTI has a double peak – first in young, sexually active women aged 15-24 years and then in postmenopausal women (Kaye et al. 2021). Risk factors include sexual intercourse, spermicide use, prior UTI, new sexual partner within the past year, and history of UTI in a first-degree female relative (Hooton 2012). • The most common causative bacterial pathogen in uUTI is <i>Escherichia coli</i> (<i>E.coli</i>) (75-95%). Additional causative pathogens include other species of Enterobacterales (e.g., <i>Proteus mirabilis</i> (<i>P.mirabilis</i>), <i>Klebsiella pneumoniae</i> (<i>K. pneumoniae</i>)) and <i>Staphylococcus saprophyticus</i> (<i>S. saprophyticus</i>) (Gupta et al. 2011). • AMR among urinary isolates is increasing across the U.S., including resistance related to production of extended-spectrum β-lactamases.	uUTI are common bacterial infections in adult women, with <i>E.coli</i> being the most common causative pathogen.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current treatment options	• Therapy for uUTI is most often empiric. Urine cultures are not typically recommended for the first incidence of uUTI (Kaye et al. 2021). • The Infectious Diseases Society of America recommends the following antibacterial drugs for the treatment of uUTI: nitrofurantoin, trimethoprim-sulfamethoxazole (TMP-SMX) (if local resistance rates of uropathogens causing uUTI do not exceed 20%), fosfomycin, or pivmecillinam. Fluoroquinolones (including ciprofloxacin) and β-lactams (including amoxicillin/clavulanate) are considered alternative antibacterials for uUTI (Gupta et al. 2011). • Some of the recommended antibacterial drugs have known adverse reactions, including pulmonary toxicity, hepatotoxicity, neuropathy, hypersensitivity reactions, tendinopathy, and QT prolongation. • In the U.S., there is increasing resistance of <i>E. coli</i> to ciprofloxacin and TMP-SMX and increased prevalence of extended-spectrum β-lactamase (ESBL) producing <i>E.coli</i> (Kaye et al. 2021). When uUTI are due to antimicrobial resistant pathogens, treatment may require IV antibacterial treatment, necessitating placement of an IV catheter and possibly hospitalization.	There are several FDA-approved antibacterial drugs for the treatment of uUTI. However, increasing antibacterial drug resistance and adverse reactions in some patients may limit treatment options. uUTI caused by organisms resistant to currently recommended first-line oral antibacterial drugs may require IV antibacterial treatment and hospitalization.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• The efficacy of sulopenem etzadroxil/probenecid for the treatment of uUTI was demonstrated in two adequate and well-controlled trials (Trials 301 and 310). • In Trial 301, sulopenem was superior to ciprofloxacin in patients with ciprofloxacin-nonsusceptible pathogens (micro-MITTR population) using the primary efficacy endpoint of overall response. The overall response was 77/160 (48%) for sulopenem and 49/149 (33%) for ciprofloxacin with a difference of 15% (95% CI, 4.4%, 26.1%; p-value 0.0062). Among patients with uUTI caused by a ciprofloxacin-susceptible pathogen (micro-MITTS population), sulopenem was inferior to ciprofloxacin. The overall response was 218/365 (60%) for sulopenem and 296/410 (72%) for ciprofloxacin with a difference of -12.5% (95% CI, -19.1%, -5.9%). The failure of sulopenem in the micro-MITTS population in Trial 301 was driven by lower rates of microbiological success in the sulopenem arm compared to the ciprofloxacin arm. • In Trial 310, oral sulopenem was non-inferior and superior to amoxicillin/clavulanate in the micro-MITTS (i.e., amoxicillin/clavulanate-susceptible) population using the primary efficacy endpoint of overall response (clinical response and microbiological response). The overall response was 296/480 (61.7%) for sulopenem and 243/442 (55.0%) for amoxicillin/clavulanate with a difference of 6.7% (95% CI, 0.3, 13.0; p-value of 0.040). While clinical response was similar between arms, the rate of microbiological response was greater in the sulopenem arm of the micro-MITTS population rather than in the amoxicillin/clavulanate arm. • In the cUTI trial (Trial 302), sulopenem (IV to oral stepdown) was inferior to the active comparator (IV ertapenem with stepdown to oral ciprofloxacin or amoxicillin/ clavulanate) based on the primary endpoint of overall response. The overall response was 265/444 (60%) for sulopenem and 296/440 (67%) for the comparator with a difference of -7.6% (95% CI, -13.9, -1.3) • In the cIAI trial (Trial 303), sulopenem (IV to oral stepdown) did not demonstrate noninferiority compared to the active comparator (IV ertapenem with stepdown to oral ciprofloxacin/metronidazole or amoxicillin/clavulanate) based on the primary endpoint of clinical response. The clinical response was 204/249 (82%) for sulopenem and 233/266 (88%) for the comparator with a difference of -6.0% (95% CI, -12.2, 0.2)	Substantial evidence of effectiveness for sulopenem etzadroxil/probenecid for the treatment of uUTI caused by the designated microorganisms <i>E. coli</i>, <i>K. pneumoniae</i>, or <i>P. mirabilis</i> in adult women who have limited or no alternative oral antibacterial treatment options has been provided by statistical superiority in the micro-MITTR population of Trial 301 and noninferiority/superiority in the micro-MITTS population of Trial 310. Sulopenem etzadroxil/probenecid provides an additional option for the treatment of uUTI in adult women. IV to oral sulopenem did not demonstrate efficacy for treatment of cUTI and cIAI in Trials 302 and 303, respectively.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and risk management	• The primary safety population consisted of 1932 subjects with uUTI from Trials 301 and 310 who received the proposed dosing regimen of sulopenem etzadroxil/probenecid. • Trial 302 in cUTI and Trial 303 in cIAI, both of which included use of both IV and oral formulations of sulopenem, provided supportive safety data. A total of 2962 subjects received sulopenem among the four phase 3 trials. • Hypersensitivity reactions, including angioedema, were observed in two subjects from a phase 1 study (IT001-101) and Trial 301 after oral sulopenem administration. • There were no deaths in Trial 310; the one death in Trial 301 was due to lung adenocarcinoma and unrelated to sulopenem. • Diarrhea was seen in 10% of subjects who received oral sulopenem, but most episodes were mild. Five (0.3%) occurrences of diarrhea required treatment discontinuation. There were no cases of <i>Clostridium difficile</i> infection (CDI) related to sulopenem. • Elevations in alanine aminotransferase more than three times the upper limit of normal were seen in 0.4% of uUTI subjects, but in general, were not treatment-limiting. • One subject in Trial 302 fulfilled laboratory criteria for Hy's Law but liver enzyme elevations resolved while still on study drug. • Other treatment-emergent adverse events related to sulopenem included headache, nausea, vomiting, and vulvovaginal mycotic infection. • Empiric use of oral sulopenem for treatment of uUTI in an ambulatory setting raises concern for the development of antimicrobial resistance in general and in particular, for cross-resistance to IV carbapenems. • Based on the failure of sulopenem to demonstrate efficacy in Trials 302 for cUTI and 303 for cIAI, potential off-label administration of oral sulopenem as stepdown treatment following IV antibacterial treatment for cUTI or cIAI raises concern for treatment failure.	The four phase 3 trials in uUTI, cUTI, and cIAI provided an adequate safety database for the proposed dosing regimen of oral sulopenem for uUTI treatment. The safety profile of sulopenem etzadroxil/probenecid appears acceptable. The identified safety risks for sulopenem etzadroxil/probenecid can be adequately mitigated through labeling and further evaluated during routine pharmacovigilance. Given that sulopenem etzadroxil/probenecid will be the first oral penem antibacterial drug on the U.S. market, effective antimicrobial stewardship and appropriate positioning of the drug in the hierarchy of uUTI treatment options by guidelines committees is critical to mitigate risk of increased carbapenem resistance associated with its use. Microbiological resistance to sulopenem will be monitored for 5 years in a required postmarketing study (PMR). Limitations of Use to prevent off-label use of oral sulopenem as step-down treatment following IV antibacterial treatment of cUTI or cIAI will be added to the prescribing information (PI).

Abbreviations: AMR, antimicrobial resistance; cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; IV, intravenous; micro-MITTR, microbiological modified intent-to-treat resistant; micro-MITTS, microbiological modified intent-to-treat susceptible; uUTI, uncomplicated urinary tract infection

2.2. Conclusions Regarding Benefit-Risk

Although multiple antibacterial drugs are FDA-approved to treat uUTI, treatment options can be limited by drug toxicities (e.g., hypersensitivity to β -lactams and QT prolongation, central nervous system effects or tendinopathies associated with quinolones) and AMR to first-line drugs including through production of ESBL ([Critchley et al. 2019](#); [Dunne et al. 2022](#)).

Carbapenem drugs are the mainstay of treatment for infections caused by ESBL-producers, but all approved members of this class require IV administration and are generally reserved for the treatment of culture-proven infections. While an oral penem for treatment of resistant bacteria causing uUTI could potentially address an unmet need, its use in an ambulatory setting where treatment is most commonly empiric raises concern for inappropriate use which may contribute to AMR.

The Applicant submitted data demonstrating safety and effectiveness of sulopenem etzadroxil/probenecid for the treatment of adult women with uUTI due to designated microorganisms.

Trial 301 demonstrated that sulopenem etzadroxil/probenecid is superior to ciprofloxacin for the treatment of subjects with uUTI caused by ciprofloxacin-resistant organisms (micro-MITTR population). The overall response at test of cure (TOC) in the sulopenem etzadroxil/probenecid arm was 48.1% compared with a rate of 32.9% in the ciprofloxacin arm with a treatment difference of 15.3% (95% CI: 4.4%, 26.1%). Of note, this treatment difference is based on analysis by the FDA statistical team utilizing the original SAP submitted by the Applicant and with inclusion of Site 202. After an unblinded interim analysis, the Applicant chose to analyze the primary efficacy endpoint utilizing an updated SAP and excluding Site 202; thus, the treatment difference the Applicant obtained was 26.6% (95% CI: 15.1%, 37.4%). Regardless, the results of both analyses were favorable to oral sulopenem.

Trial 310 demonstrated that sulopenem etzadroxil/probenecid is non-inferior and superior to amoxicillin/clavulanate for subjects with uUTI in the micro-MITTS population. The overall response at TOC in the sulopenem etzadroxil/probenecid arm was 61.7% compared to 55.0% in the amoxicillin/clavulanate arm with a treatment difference of 6.7% (95% CI: 0.3, 13.0), which met the prespecified NI margin of 10%.

The safety database for sulopenem etzadroxil/probenecid, consisting of nearly 3,000 subjects in the four phase 3 trials and more than 1,000 additional subjects in phase 1 and 2 trials, was adequate for the proposed dosing regimen and indication. Overall, sulopenem etzadroxil/probenecid appears to be safe for its intended use; potential safety risks can be adequately mitigated through labeling and further evaluated during routine pharmacovigilance.

Based on the review of all available efficacy and safety data, NDA 213972 for sulopenem etzadroxil/probenecid provides SEE and a favorable benefit-risk profile for the treatment of uUTI caused by the designated microorganisms *E. coli*, *K. pneumoniae*, or *P. mirabilis* in adult women who have limited or no alternative oral antibacterial treatment options.

II. Interdisciplinary Assessment

3. Introduction

Sulopenem etzadroxil/probenecid bilayer oral tablet is a fixed-dose combination of the penem antibacterial prodrug (sulopenem etzadroxil) and a renal tubular transport blocking drug (probenecid). Each tablet contains 500 mg sulopenem etzadroxil and 500 mg probenecid. The Applicant's proposed indication is treatment of uUTI caused by designated susceptible microorganisms in adult women ≥ 18 years of age. The proposed dose is one tablet orally (PO) administered twice daily (BID) for 5 days.

Sulopenem etzadroxil, a new molecular entity, is a β -lactam drug closely related to the carbapenems. On oral administration, sulopenem etzadroxil is rapidly hydrolyzed to sulopenem and two other products: formaldehyde and 2-ethylbutyric acid (2-EBA). Probenecid, originally approved in 1951, is co-formulated with sulopenem etzadroxil to increase the systemic exposure of sulopenem.

The Division granted sulopenem QIDP designation for the treatment of uUTIs, complicated urinary tract infections (cUTIs), and complicated intra-abdominal infections (cIAIs) on July 29, 2016, as well as fast track designation for these indications on March 15, 2019.

uUTI is the most common bacterial infection in the ambulatory care setting in the U.S. There are multiple FDA-approved drugs for uUTI treatment (see Benefit-Risk Framework), but their use is challenged by associated drug toxicities and rising antimicrobial resistance.

The Applicant previously developed an intravenous (IV) formulation of sulopenem and studied its efficacy with stepdown to oral sulopenem for cUTI and cIAI. Prior to the original submission of NDA 213972 in 2020, three phase 3 trials were completed - IT001-301 (Trial 301) for uUTI utilizing oral sulopenem, IT001-302 (Trial 302) for cUTI, and IT001-303 (Trial 303) for cIAI, each utilizing IV to oral sulopenem. On November 25, 2020, The Applicant submitted NDA 213972 as a 505(b)(2) submission for sulopenem etzadroxil/probenecid for the proposed indication of treatment of adult women with uUTI caused by designated susceptible microorganisms proven or strongly suspected to be nonsusceptible to a quinolone.

The NDA received a complete response on July 23, 2021, due to lack of substantial evidence of effectiveness (SEE) for sulopenem for the treatment of uUTI. In Trial 301, sulopenem etzadroxil/probenecid was superior to ciprofloxacin based on the primary endpoint of overall response (clinical and microbiological response) in the prespecified subgroup of participants with uUTI caused by a ciprofloxacin-resistant pathogen in the microbiological modified intent-to-treat resistant (micro-MITTR) population. However, in the prespecified subgroup of participants with uUTI caused by a ciprofloxacin-susceptible pathogens [micro-MITTS (microbiological modified intent-to-treat susceptible) population], sulopenem etzadroxil/probenecid was inferior to ciprofloxacin. Also, sulopenem failed to achieve noninferiority (NI) to the active comparator for the primary efficacy endpoints in the cUTI and cIAI studies. The safety profile for sulopenem etzadroxil was found to be acceptable.

Given the sole finding of superiority in the micro-MITTR population with inferiority in the micro-MITTS population in Trial 301 and lack of supportive evidence in the MITT populations

of the cIAI and cUTI trials, it was concluded that there was insufficient evidence to support the effectiveness of sulopenem etzadroxil/probenecid for the treatment of uUTI. The Division recommended an additional trial for uUTI with a different comparator, and that the Applicant conduct further investigations to determine the optimal sulopenem dosing regimen.

Following the complete response, the Applicant halted further development of the IV formulation. The current NDA resubmission includes results from the recommended additional uUTI trial, IT001-310 (Trial 310), in which amoxicillin/clavulanate was chosen as the comparator. Trial 310 was a phase 3, randomized, multicenter, double-blind, double-dummy controlled trial of the efficacy, tolerability, and safety of oral sulopenem etzadroxil/probenecid versus oral amoxicillin/clavulanate for the treatment of uUTI in non-pregnant adult women. Sulopenem etzadroxil/probenecid was non-inferior and statistically superior to the comparator for the primary endpoint of overall response (composite of clinical and microbiological responses) at test of cure (TOC) in the micro-MITTS population (amoxicillin/clavulanate susceptible). Based on the statistical analysis plan, NI was first tested and achieved in the microbiological modified intent-to-treat (micro-MITT) population, but a noninferiority comparison in this population is not considered appropriate due to the inclusion of patients with comparator-resistant isolates. No conclusions regarding efficacy could be drawn in the micro-MITTR population (amoxicillin/clavulanate-nonsusceptible) due to insufficient sample size. Refer to Sections [6](#) and [7](#) for detailed reviews of efficacy and safety for Trial 310.

An Advisory Committee (AC) Meeting was held on September 9, 2024, to discuss the overall benefit-risk assessment for the use of sulopenem etzadroxil/probenecid for the treatment of uUTI and to consider information that would be most important to convey to medical providers to ensure appropriate use of sulopenem etzadroxil/probenecid. Details of the Committee's deliberations are provided in Section [11](#). Based on the Committee's recommendations, the Indication statement in labeling was narrowed to indicate sulopenem etzadroxil/probenecid for the treatment of uUTI caused by the designated microorganisms *E. coli*, *K. pneumoniae*, or *P. mirabilis* in adult women who have limited or no alternative oral antibacterial treatment options.

3.1. Review Issue List

3.1.1. Key Efficacy Review Issues

None.

3.1.2. Key Safety Review Issues

None.

3.2. Approach to the Clinical Review

The primary evidence of effectiveness and safety of sulopenem etzadroxil/probenecid for the proposed indication of the treatment of uUTI in adult women was provided by two clinical trials (Trials 301 and 310). The efficacy and safety data from Trial 301 were first reviewed in the initial review cycle for NDA 213972 along with efficacy and safety data from Trials 302 and

303. In the resubmitted NDA, efficacy from the new uUTI Trial 310 was analyzed alone while safety data from Trial 310 as well as the integrated safety population (ISP) of subjects from both Trials 301 and 310 were analyzed. The submitted clinical trials (listed in [Table 3](#)) were adequate for the efficacy and safety evaluations of sulopenem etzadroxil/probenecid.

3.3. Approach To Establishing Substantial Evidence of Effectiveness

Select from the options below to indicate how SEE was established (if applicable). If multiple indications, repeat items 1–3 for each indication.

1. Verbatim indication (enter approved indication if the application was approved and the Applicant's proposed indication if the application received a complete response): For the treatment of uUTI caused by the designated microorganisms *E. coli*, *K. pneumoniae*, or *P. mirabilis* in adult women who have limited or no alternative oral antibacterial treatment options.
2. SEE was established with (*check **one** of the options for traditional or accelerated approval pathways and complete response not due to lack of demonstrating SEE*)
 - a. Adequate and well-controlled clinical investigation(s):
 - i. Two or more adequate and well-controlled clinical investigations, **OR**
 - ii. One adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations**OR**
 - b. One adequate and well-controlled clinical investigation and confirmatory evidence ([May 1998](#); [September 2019](#); [September 2023](#))
OR
 - c. Evidence that supported SEE from a prior approval (e.g., 505(b)(2) application relying only on a previous determination of effectiveness; extrapolation; over-the-counter switch) ([September 2019](#))
3. Complete response, if applicable
 - a. SEE was established
 - b. SEE was not established (*if checked, omit item 2*)

Table 3. Clinical Studies/Trials Submitted in Support of Efficacy and/or Safety Determinations¹ for Sulopenem Etzadroxil/Probenecid

Study/Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized²	Number of Centers and Countries
IT001-310 NCT05584657	Adult women with uUTI	Control type: Active concurrent noninferiority Randomization: Standard randomization, 1:1 ratio Blinding: DB, double dummy Biomarkers: None Innovative design features: None	Drug: sulopenem etzadroxil/probenecid Dosage: sulopenem etzadroxil 500 mg/probenecid 500 mg bilayer tablet BID Number treated: 1107 Duration (quantity and units): 5 d Comparator: Amoxicillin/clavulanate Dosage: 875 mg/125-mg tablet BID Number treated: 1107 Duration (quantity and units): 5 d	Primary: Overall success (clinical and microbiologic combined) at TOC (Day 12) Secondary: Key endpoints included clinical cure at TOC and microbiologic eradication at TOC	Planned: 2459 Actual: 2222	Centers: 144 ³ Countries: 1

Study/Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized²	Number of Centers and Countries
IT001-301 NCT03354598	Adult women with uUTI	Control type: Active concurrent Randomization: Standard randomization, 1:1 ratio Blinding: DB, double dummy Biomarkers: None Innovative design features: None	Drug: sulopenem etzadroxil/probenecid Dosage: sulopenem etzadroxil 500 mg/probenecid 500 mg bilayer tablet BID Number treated: 785 Duration (quantity and units): 5 d Comparator: Ciprofloxacin Dosage: Ciprofloxacin 250 mg capsules BID Number treated: 794 Duration (quantity and units): 3 d	Primary: Overall success (clinical and microbiologic combined) at TOC (Day 12) Secondary: Key endpoints included microbiologic response at TOC and clinical response at TOC	Planned: 1364 Actual: 1671	Centers: 114 Countries: 3

Study/Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized²	Number of Centers and Countries
IT001-302 NCT03357614	Adults with cUTI	Control type: Active concurrent Randomization: Standard randomization, 1:1 ratio Blinding: DB, double dummy Biomarkers: None Innovative design features: None	Drug: IV sulopenem followed by PO sulopenem etzadroxil/probenecid Dosage: IV sulopenem 1 g QD followed by sulopenem etzadroxil 500 mg/probenecid 500 mg bilayer tablet Number treated: 695 Duration (quantity and units): 7-10 (at least 5 d IV) d Comparator: IV ertapenem followed by oral ciprofloxacin or amoxicillin/clavulanate Dosage: IV ertapenem 1 g QD followed by oral ciprofloxacin 500 mg or amoxicillin/clavulanate 875 mg BID Number treated: 697 Duration (quantity and units): 7-10 (at least 5 d IV) d	Primary: Overall response at TOC (Day 21) Secondary: Key endpoints included clinical success rate at TOC and microbiologic response per patient at TOC	Planned: 1156 Actual: 1395	Centers: 131 Countries: 13

Study/Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Randomized²	Number of Centers and Countries
IT001-303 NCT03358576	Adults with cIAI	Control type: Active concurrent Randomization: Standard, 1:1 ratio Blinding: DB Biomarkers: None Innovative design features: None	Drug: IV sulopenem followed by PO sulopenem etzadroxil/probenecid Dosage: IV sulopenem 1 g QD followed by sulopenem etzadroxil 500 mg/probenecid 500-mg tablet BID Number treated: 335 Duration (quantity and units): 7-10 (at least 5 d IV) d Comparator: IV ertapenem followed by PO ciprofloxacin and metronidazole or amoxicillin/clavulanate Dosage: IV ertapenem 1 g QD followed by PO ciprofloxacin 500 mg BID and metronidazole 500 mg QID or amoxicillin/clavulanate 875 mg BID Number treated: 331 Duration (quantity and units): 7-10 (at least 5 d IV) d	Primary: Clinical response at Day 28 Secondary: Key endpoints included clinical response at end of therapy (Day 10) and Day 21	Planned: 670 Actual: 674	Centers: 91 Countries: 10

Source: Reviewer

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."

³ 144 sites out of 175 planned sites enrolled patients. Five sites enrolled only screen failures. A total of 139 sites enrolled and randomized at least one patient.

Abbreviations: BID, twice daily; DB, double-blind; IV, intravenous; N, number of subjects; NCT, national clinical trial; QD, once daily; R, randomized; TOC, test of cure

4. Patient Experience Data

Table 4. 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	See Sections 6.2 and 15 .
☐	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)		
☐	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

To support the activity of sulopenem against Enterobacterales, the Applicant conducted in vitro and in vivo pharmacokinetic/pharmacodynamic (PK/PD) index and target determination studies, along with a proof-of-concept study in an in vitro hollow-fiber infection model. For uUTI, there is no established nonclinical model to reliably determine PK/PD targets relevant to the site of infection. Additionally, significant knowledge gaps surrounding urine-specific PK/PD parameters and selection of a bacteriologic endpoint predictive of clinical efficacy limit the use of probability of target attainment (PTA) analyses to predict the efficacy of sulopenem etzadroxil/probenecid for the treatment of uUTI. Therefore, while the nonclinical data support sulopenem's activity against uropathogens, the translational utility of these nonclinical PK/PD findings is limited.

5.1.1. Summary of Nonclinical Pharmacokinetic/Pharmacodynamic Information

Dose fractionation studies were conducted in the murine thigh and in vitro 1-compartment models to determine the PK/PD index that best correlates with sulopenem's activity. Although initial findings from the murine thigh infection model suggested that sulopenem exhibits elements of both time and concentration-dependent killing, results were largely uninterpretable due to concerns with study design, data integrity and the Applicant's atypical analysis of the ensuing results (see Section 14). Subsequent in vitro studies corroborated previous findings that sulopenem does indeed display both time and concentration-dependent activity with coefficient of determination (r^2) values of 0.89 and 0.90 for free sulopenem peak concentration to minimum inhibitory concentration (MIC) free-drug maximum plasma concentration (fC_{max})/MIC and the percentage of the dosing interval that free-drug concentrations exceed the MIC ($\%fT>MIC$), respectively. Given that traditionally, $\%fT>MIC$ is the index that best correlates with the activity of beta-lactams, the Applicant's eventual use of $\%fT>MIC$ to characterize sulopenem's activity is acceptable.

Similar to the dose fractionation studies, concerns with the Applicant's initial approach for PK/PD target determination in the murine thigh infection model rendered the results unreliable (see Section 14). Subsequent PK/PD target determination studies were conducted in the in vitro 1-compartment model using a panel of 10 Enterobacterales isolates with sulopenem MICs ranging from 0.03 to 0.5 $\mu\text{g/mL}$. In this model, the magnitude of median targets for stasis, 1-log kill, and 2-log kill were 40.9, 50.2 and 62.6% $fT>MIC$, respectively.

Additionally, the Applicant evaluated the bactericidal activity of sulopenem urinary concentrations associated with the proposed 500 mg sulopenem etzadroxil/500 mg probenecid dosage for the treatment of uUTI. The simulated urinary concentrations suppressed the growth of 4 *E. coli* isolates (with sulopenem MICs ranging from 0.03 to 0.5 $\mu\text{g/mL}$) and prevented the development of resistance for the entire duration of a 5-day study in a hollow-fiber infection model.

5.2. Clinical Pharmacology/Pharmacokinetics

Table 5. Summary of Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class	Sulopenem is a penem antibacterial, and probenecid is a uricosuric and renal tubular inhibitor. A new established pharmacologic class for probenecid that reads as “renal tubular transport inhibitor” instead of “renal tubular transport blocking agent” was included in the finalized prescribing information. For additional details see FDA comments sent to the Applicant in DARRTS dated 10/11/2024.
Mechanism of action	Sulopenem inhibits bacterial cell wall synthesis by binding to essential penicillin-binding proteins (PBP). Probenecid is a uricosuric and renal tubular blocking agent that inhibits the OAT3-mediated excretion of sulopenem, thereby providing increased plasma concentrations of sulopenem
Active moieties	The drug product is a bilayer tablet comprised of the prodrug sulopenem etzadroxil and probenecid. Sulopenem etzadroxil is rapidly cleaved to release the active compound, sulopenem.
QT prolongation	At a concentration of ≥ 40 times the peak sulopenem concentrations associated with the recommended dosing regimen, clinically significant QTc interval prolongation was not observed. After a single 500-mg dose, sulopenem does not prolong the QTc interval to any clinically relevant extent. This conclusion was informed by concentration-QTc analysis performed on data from trial A7371007, a single ascending dose study of sulopenem etzadroxil. The predicted $\Delta\Delta\text{QTcF}$ (upper bounds of 90% CI) value was 0.07(4.34) ms at the geometric mean of the C_{max} (i.e., 109.7 $\mu\text{g/mL}$) associated with the highest single dose of 2800 mg IV sulopenem administered as a 1 h infusion. A thorough QTc assessment was not conducted for probenecid either under its original approval in 1951 or as part of the current application. Nonetheless, QTc prolongation is not described as an adverse reaction in the probenecid labeling.

Characteristic	Drug Information									
	General Information									
Bioanalysis	Multiple LC-MS/MS assays were developed and validated to determine concentrations of sulopenem in human plasma and urine. All bioanalytical methods met the requirements for accuracy, precision, sensitivity, and specificity.									
Healthy subjects versus patients	No clinically meaningful differences in PK were observed between healthy subjects and patients with uUTI									
Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)	Table 6. Sulopenem and Probenecid Plasma PK Parameters (%CV) After Single Dose Administration of the 500 mg Bilayer Tablet in Healthy Subjects <table border="1"> <thead> <tr> <th>PK Parameter</th> <th>Sulopenem (n=13)</th> <th>Probenecid (n=13)</th> </tr> </thead> <tbody> <tr> <td>C_{max} (µg/mL)</td> <td>1.84 (39.1)</td> <td>41.2 (38.2)</td> </tr> <tr> <td>AUC_{0-∞} (µg·h/mL)</td> <td>4.85 (25.3)</td> <td>255 (35.6)</td> </tr> </tbody> </table> Source: Summarized from Tables 7 and 23 of Applicant's Study Report IT001-105 Abbreviations: C_{max}, maximum plasma concentration; CV, coefficient of variation; PK, pharmacokinetic; AUC_{0-∞}, area under the concentration-time curve estimated to infinity; n, number of subjects evaluated	PK Parameter	Sulopenem (n=13)	Probenecid (n=13)	C _{max} (µg/mL)	1.84 (39.1)	41.2 (38.2)	AUC _{0-∞} (µg·h/mL)	4.85 (25.3)	255 (35.6)
PK Parameter	Sulopenem (n=13)	Probenecid (n=13)								
C _{max} (µg/mL)	1.84 (39.1)	41.2 (38.2)								
AUC _{0-∞} (µg·h/mL)	4.85 (25.3)	255 (35.6)								
Range of effective dose(s) or exposure	No dose-ranging studies were conducted. The effective dose is 500 mg sulopenem etzadroxil and 500 mg probenecid									
Maximally tolerated dose or exposure	The maximum tolerated oral doses of sulopenem etzadroxil were 4000 mg in the single-ascending dose trial and 1200 mg BID for 10 days in the multiple-ascending dose trial.									
Dose proportionality	The AUC of sulopenem increased in an approximately dose proportional manner for single oral doses of 400 mg to 2000 mg. C _{max} increased less than dose proportionally with increasing doses.									
Accumulation	No significant accumulation of sulopenem was observed with repeat dosing of sulopenem following the proposed twice daily oral dosage in adults with creatinine clearance (CrCl) >90 mL/min									
Time to achieve steady-state	Steady state is achieved on Day 1 for sulopenem									
Bridge between to-be-marketed and clinical trial/study formulations	The bilayer tablet used in the phase 3 uUTI trials is the same as the to-be-marketed tablet formulation.									

Characteristic	Drug Information														
Bioavailability	Absorption The absolute bioavailability of sulopenem following administration of a single dose of 500 mg sulopenem etzadroxil and 500 mg probenecid as the oral bilayer tablet under fasted conditions was 40%.														
T _{max} Food effect (fed/fasted) Geometric least square mean and 90% CI	1 h for sulopenem and 3 h for probenecid.														
Table 7. Effect of Food on Sulopenem and Probenecid Plasma Pharmacokinetics															
	<table border="1"> <thead> <tr> <th>Component</th> <th>Meal Type</th> <th>AUC_{0-∞} (µg·h/mL)</th> <th>C_{max} (µg/mL)</th> <th>T_{max} (h) Median (Range)</th> </tr> </thead> <tbody> <tr> <td>Sulopenem</td> <td rowspan="2">High-fat meal (800-1000 calories, 50% from fat) vs. fasted</td> <td>1.48 (1.38, 1.60)</td> <td>1.45 (1.20, 1.75)</td> <td>2.0 (1.0-3.0)</td> </tr> <tr> <td>Probenecid</td> <td>0.92 (0.8, 1.1)</td> <td>0.73 (0.5, 0.86)</td> <td>2.0 (1.5-6.0)</td> </tr> </tbody> </table>	Component	Meal Type	AUC _{0-∞} (µg·h/mL)	C _{max} (µg/mL)	T _{max} (h) Median (Range)	Sulopenem	High-fat meal (800-1000 calories, 50% from fat) vs. fasted	1.48 (1.38, 1.60)	1.45 (1.20, 1.75)	2.0 (1.0-3.0)	Probenecid	0.92 (0.8, 1.1)	0.73 (0.5, 0.86)	2.0 (1.5-6.0)
Component	Meal Type	AUC _{0-∞} (µg·h/mL)	C _{max} (µg/mL)	T _{max} (h) Median (Range)											
Sulopenem	High-fat meal (800-1000 calories, 50% from fat) vs. fasted	1.48 (1.38, 1.60)	1.45 (1.20, 1.75)	2.0 (1.0-3.0)											
Probenecid		0.92 (0.8, 1.1)	0.73 (0.5, 0.86)	2.0 (1.5-6.0)											
Source: Summarized from Tables 7 and 23 of Applicant's Study Report IT001-105. Based on administration of the to-be-marketed 500 mg sulopenem etzadroxil/probenecid bilayer tablet															
Abbreviations: AUC _{0-∞} , area under the concentration-time curve estimated to infinity; C _{max} , maximum plasma concentration; PK, pharmacokinetic; T _{max} , time to maximum concentration; vs, versus															
Volume of distribution Plasma protein binding Drug as substrate of transporters	Distribution The mean apparent volumes of distribution for sulopenem and probenecid are 134 L and 8.81 L, respectively. Sulopenem is 10.7% bound to plasma proteins. Sulopenem is a substrate of OAT3 and sulopenem etzadroxil is a substrate of P-gp. Probenecid is a substrate of BCRP. In a clinical DDI study with a P-gp inhibitor (itraconazole), the effect on the AUC and C _{max} of sulopenem was not clinically significant.														
Mass balance results	Elimination Following oral administration of a 2000-mg dose of [14C] sulopenem etzadroxil, 85.1% of the radiolabeled dose was recovered in urine (44.3%) and feces (40.8%) as unchanged sulopenem and metabolites. Sulopenem accounted for 26.9% and 3.1% of the administered dose in urine and feces, respectively.														
Clearance	Mean apparent oral clearance values are 77.6 and 2.06 L/h for sulopenem and probenecid, respectively.														
Half-life	Mean plasma half-lives are 1.2 and 2.9 h for sulopenem and probenecid, respectively.														
Metabolic pathway(s)	Sulopenem etzadroxil is rapidly hydrolyzed after oral administration to sulopenem in the intestines and in systemic circulation. Sulopenem and two inactive metabolites formed by β-lactam cyclic amide bond hydrolysis (M1a and M1b) are the major circulating entities. Sulopenem, M1a and M1b accounted for 32%, 21.8% and 43.6%, respectively, of circulating radioactivity in the mass balance study. No metabolism of sulopenem was observed in vitro with recombinant CYP or UGT enzymes.														
Primary excretion pathways (% dose)	Primarily excreted in urine, i.e., 44.3% of oral radiolabeled dose in mass balance studies. 26.9% of total urinary recovery was in the form of unchanged sulopenem.														

Characteristic	Drug Information
	Intrinsic Factors and Specific Populations
Body weight	No clinically significant differences in PK of sulopenem were observed based on body weight ranging from 38.8 to 140 kg in the subjects enrolled in phase 1 trials and phase 3 Trials 301, 302 and 303. No PK assessments were conducted in Trial 310.
Age	No clinically significant differences in the PK of sulopenem were observed based on age ranging from 18-91 years.
Renal impairment	No dosage adjustment is needed in patients with CrCl $\geq$ 15 mL/min. Use is not recommended in patients with CrCl $<$ 15 mL/min or those on hemodialysis.
Hepatic impairment	No dosage adjustment is needed in patients with hepatic impairment.
	Drug Interaction Liability (Drug as Perpetrator)
Inhibition/induction of metabolism	In vitro, sulopenem etzadroxil is an inhibitor of CYP3A4/5. However, because it is rapidly hydrolyzed to sulopenem, clinically relevant DDIs are not expected with CYP3A4/5 substrates.
Inhibition/induction of transporter systems	Probenecid is a known inhibitor of OAT1 and OAT3 and was observed to inhibit BCRP in vitro. Sulopenem etzadroxil is an inhibitor of BCRP and P-gp. However, because it is rapidly hydrolyzed to sulopenem, clinically significant DDIs are not expected with BCRP or P-gp substrates.

Source: Summary of Clinical Pharmacology and Study reports

Abbreviations: AUC, area under the concentration-time curve; BCRP, breast cancer resistance protein; BID, twice daily; C_{max} , maximum plasma concentration; CYP, cytochrome P450 enzyme; CYP3A4, cytochrome P450, family 3, subfamily A, polypeptide 4; CYP3A5, cytochrome P450, family 3, subfamily A, polypeptide 5; DDI, drug-drug interaction; IV, intravenous; LC-MS/MS, liquid chromatography with tandem mass spectrometry; OAT1, organic anion transporter-1; OAT3, organic anion transporter-3; P-gp, P-glycoprotein; PK, pharmacokinetic; QTc, corrected QT interval; $\Delta\Delta QTcF$, QTcF placebo-corrected change from the baseline; UGT, uridine diphosphate glucuronosyltransferase; uUTI, uncomplicated urinary tract infection

6. Efficacy (Evaluation of Benefit)

6.1. Assessment of Dose and Potential Effectiveness

The Applicant's proposed dosage of 500 mg sulopenem etzadroxil/500 mg probenecid BID orally was evaluated in two phase 3 uUTI trials (Trials 301 and 310). In Trial 301, the proposed dosing regimen, 500 mg sulopenem etzadroxil/500 mg probenecid BID demonstrated superiority to ciprofloxacin 500 mg BID for the treatment of uUTI in patients who presented with a ciprofloxacin-resistant pathogen at baseline but failed to demonstrate noninferiority to ciprofloxacin in patients with a ciprofloxacin-susceptible pathogen at baseline. In Trial 310, 500 mg sulopenem etzadroxil/500 mg probenecid BID was non-inferior to 875 mg amoxicillin/125 mg clavulanate BID for the treatment of uUTI in the amoxicillin/clavulanate susceptible population. Despite the limitations of nonclinical PK/PD data (see Section 5.1), the results of PTA analyses and a 5-day in vitro hollow-fiber infection model study are supportive of the effectiveness of 500 mg sulopenem etzadroxil/500 mg probenecid BID in the treatment of uUTI. The underlying causes of the mixed clinical trial efficacy outcomes are likely multifactorial, and PTA analyses are unable to predict the performance of 500 mg sulopenem etzadroxil/500 mg probenecid BID against different comparators in an efficacy trial.

6.1.1. Support for Proposed Dose of Sulopenem Etzadroxil

Probability of Target Attainment Analyses

Urinary drug concentrations are considered important to the successful treatment of uUTIs, while the relative importance of plasma drug concentrations to efficacy is unclear. The Applicant conducted PTA analyses for both plasma and urinary drug concentrations using %fT>MIC targets derived from a murine thigh infection model and an in vitro 1-compartment infection model to support the proposed dosage of 500 mg sulopenem etzadroxil/500 mg probenecid BID and to support a cutoff value of 0.5 µg/mL for Enterobacterales susceptibility. Due to deficiencies in the murine thigh infection model study design and limited interpretability of the findings, the resulting targets (i.e., 16.6 and 20.3% fT>MIC for stasis and 1-log kill, respectively) were deemed unreliable. Because the in vitro 1-compartment model does not account for bladder tissue architecture or the complexities of urodynamics, it is unclear whether the derived targets are reasonable surrogates for the relevant infection site. Nonetheless, PTA based on the median in vitro targets of 40.9, 50.2 and 62.6% fT>MIC for stasis, 1-log kill, and 2-log kill, respectively, which numerically offered a more conservative appraisal of efficacy than those determined in the murine thigh infection model, were prioritized to support the proposed dosage. PTA results showed that the free plasma concentrations associated with the Applicant's proposed dose regimen resulted in achievement of the in vitro targets in ≥90% of simulated subjects at MICs ranging from 0.031 to 0.25 µg/mL. The Applicant also evaluated the probability of achieving PK/PD targets in urine by simulating 1 h and 2 h bladder voiding patterns. Based on the urine concentrations associated with the Applicant's proposed dose regimen, urine PTA analyses

showed achievement of the in vitro targets in $\geq 90\%$ of simulated subjects at MICs ranging from 2 to 8 $\mu\text{g/mL}$ (see Section 14).

Findings From In Vitro Hollow-Fiber Study

To further support the proposed dosage of 500 mg sulopenem etzadroxil/500 mg probenecid BID for the treatment of uUTI, the Applicant evaluated the bactericidal activity of urinary concentrations associated with the proposed dosage. The simulated urinary concentrations were demonstrated to suppress the growth of four *E. coli* isolates (with sulopenem MIC values in the clinically relevant range of 0.03 to 0.5 $\mu\text{g/mL}$) and prevented the development of resistance for the entire duration of a 5-day study in a hollow-fiber infection model (see Section 14).

6.1.2. Support for Proposed Dose/Contribution of Probenecid

Probenecid lacks antimicrobial activity; instead, it inhibits OAT3-mediated renal clearance of β -lactams such as sulopenem, thus resulting in increased plasma drug concentrations. Multiple-dose administration of 500 mg probenecid increased sulopenem plasma area under the concentration-time curve (AUC) by 1.8-fold with a corresponding 1.9-fold reduction in renal clearance. This dose

(b) (4)

in the setting of uUTI (where there are uncertainties surrounding the relative importance of urinary versus plasma concentrations), the available data are inconclusive on the contribution of probenecid to efficacy. There are no clinical studies evaluating the efficacy of sulopenem etzadroxil for the treatment of uUTI in the presence and absence of probenecid. Additionally, interpretation of the observed changes in sulopenem urinary PK in the presence of probenecid is limited by the general uncertainties surrounding urine-specific PK/PD parameters and the complexities of sulopenem's PK/PD behavior. Nonetheless, the totality of available clinical and nonclinical data do support the efficacy of the combined sulopenem etzadroxil/probenecid dosage in the treatment of uUTIs.

6.2. Clinical Studies/Trials Intended To Demonstrate Efficacy

6.2.1. Results of Pooled Analyses, Trials 301 and 310

Trial IT001-301 comparing sulopenem to ciprofloxacin for treatment of uUTI in adult women was reviewed for the initial NDA submission and is not included in this review. Please refer to the previous NDA 213972 Multidisciplinary Review and Evaluation dated July 22, 2021, for a full discussion of the design, analysis, and results from this trial and Section 16.1 for a summary of this trial. The current NDA resubmission is based on the most recent phase 3 trial (Trial IT001-310 or Trial 310 for short) which had a different comparator than was used in the previously reviewed Trial IT001-301 and is reviewed in this section. No pooled analyses are presented. Because the Division of Anti-Infectives recommends that Limitations of Use in

labeling be included for cUTI and cIAI, the results of Trials 302 (cUTI) and 303 (cIAI) are discussed briefly in Section [16](#).

6.2.2. Trial 310

6.2.2.1. Design, Trial 310

Trial 310 was a phase 3, multicenter, double-blinded, double-dummy, randomized, controlled study to compare oral sulopenem to oral amoxicillin/clavulanate for the treatment of uUTI in adult women. Eligible adult women were randomized 1:1 to receive either oral sulopenem etzadroxil/probenecid 500 mg/500 mg BID for 5 days or oral amoxicillin/clavulanate 875 mg/125 mg BID for 5 days. Subjects were followed-up at Day 12 TOC visit and Day 28 (final visit).

6.2.2.2. Eligibility Criteria, Trial 310

Subjects had to meet the following criteria to be eligible for the study:

1. Female subjects ≥ 18 years of age with ≥ 24 hours and ≤ 96 hours of urinary symptoms attributable to a UTI
2. Two of the following signs and symptoms of uUTI: urinary frequency, urinary urgency, pain or burning on micturition, suprapubic pain
3. A mid-stream urine specimen with:
 - a. a machine-read dipstick positive for nitrite AND any positive leukocyte esterase OR
 - b. evidence of pyuria alone.

Subjects who met any of the following specified criteria were excluded from the study, for example, presence of signs and symptoms suggestive of acute pyelonephritis defined as: fever (temperature $>38^{\circ}$ Celsius), chills, costovertebral angle tenderness, flank pain, nausea, and/or vomiting.

See Section [15](#) for full inclusion and exclusion criteria.

6.2.2.3. Statistical Analysis Plan, Trial 310

The primary efficacy endpoint was overall success (combined clinical and microbiologic success) on Day 12 (± 1 days)/TOC in micro-MITT, micro-MITT comparator-susceptible (micro-MITTS) and micro-MITT comparator-resistant or nonsusceptible (micro-MITTR) populations. The micro-MITT population included all randomized patients who received at least one single dose of study medication and had a positive study entry urine culture defined as $\geq 10^5$ colony-forming units (CFU)/mL of a uropathogen (Enterobacterales or *Staphylococcus saprophyticus* (*S. saprophyticus*) only) and no more than 2 species of microorganisms identified in the study entry urine culture, regardless of colony count. Comparator susceptibility was based on MIC [susceptible: MIC $\leq 8/4$ mg/L; nonsusceptible: intermediate (MIC 16/8 mg/L) or resistant (MIC $\geq 32/16$ mg/L)] to the components of the comparator study drug, amoxicillin and clavulanate, respectively.

For the definitions of overall success, clinical success, and microbiological success endpoints, please see Section [15](#).

Analysis of the Primary Efficacy Endpoint

To control for inflation of the overall type I error rate, the hierarchical testing procedure of Westfall and Krishen ([Westfall and Krishen 2001](#)) was proposed by the Applicant and used to test the hypotheses of the primary efficacy endpoint in these populations in the sequential order described below.

- NI in the micro-MITT population.
- NI in the micro-MITTS population or superiority in the micro-MITTR population.
- Superiority test of overall success in the micro-MITT population.

Testing was to proceed to the next comparison only if the null hypothesis in the comparison was rejected. For pre-specified sequential hypothesis testing, no adjustment to the alpha level was required. However, in the second step of the hierarchy, the trial did not adjust for multiplicity in testing in the micro-MITTS and micro-MITTR populations because at the time of study design the analyses in these populations were considered to address separate questions as if they were separate studies under a single protocol for logistical reasons.

Two-sided 95% CIs for the treatment difference in success proportions (sulopenem-active control) would be determined using the method of Miettinen and Nurminen. NI was established if the lower bound of the CI was greater than -10% and superiority was established if the lower bound of the CI was greater than 0.

The FDA had communicated the following comment regarding the planned analysis: “We strongly recommend testing NI in the micro-MITTS population as the primary endpoint. An alternative is hierarchical testing for (i) NI in the micro-MITTS population followed by (ii) superiority in the micro-MITT population. It would be an important review issue if the trial is unable to demonstrate noninferiority in the micro-MITTS population, which is not currently assessed in the first level of the planned hierarchical testing. We note that the trial is adequately powered for the analysis of noninferiority in the micro-MITTS population.”

Because the hierarchical testing rejected the null hypothesis in the first level of testing for noninferiority in the micro-MITT (as will be subsequently discussed), the analysis of the primary endpoint in the micro-MITTS in the second level of the hierarchy was considered to have the statistical interpretability of a prespecified primary analysis.

In addition, the FDA finds the NI testing in a population that included patients with isolates that were not susceptible to the comparator (Step 1), uninterpretable for regulatory purposes.

Secondary Efficacy Endpoints

Clinical response and microbiologic response were analyzed. Overall success, clinical success, and microbiologic success by baseline pathogen and monomicrobial/polymicrobial infection were analyzed.

Overall response by baseline uropathogen resistance class(es) were presented.

Interim Analysis

A blinded interim analysis for sample size re-estimation was to be performed when clinical and microbiologic response data at Day 12 (± 1 day)/TOC were available for approximately 50% of the subjects (approximately 983 subjects). The sample size of the study would be computed to ensure that there was sufficient power for the primary efficacy endpoint in the micro-MITTS population. It was anticipated that this would ensure the study was sufficiently powered to test the primary endpoint in the micro-MITT and micro-MITTR populations as well.

Following the blinded interim analysis, the Data Monitoring Committee recommended that in order to maintain 80%-90% power, the trial should continue to enroll to achieve a minimum of 1966 subjects (original sample size in protocol) up to a maximum of 2428 subjects (to achieve 90% power). On October 23, 2023, enrollment was completed with 2222 randomized patients as the Applicant considered that adequate statistical power had been achieved.

6.2.2.4. Results of Analyses, Micro-MITTS and Micro-MITTR Populations, Trial 310

The study was conducted in the U.S. between October 18, 2022 and November 21, 2023. The clinicaltrials.gov identifier for the study was NCT05584657. In the following subsections, the intent-to-treat (ITT) population will be discussed briefly, followed by results in the micro-MITTS population and micro-MITTR population. As noted above, because the hierarchical testing rejected the null hypothesis in the first level of testing, the analysis of the primary endpoint in the micro-MITTS in the second level of the hierarchy was considered to have the statistical interpretability of a prespecified primary analysis.

Disposition, Baseline Demographics and Baseline Characteristics

Disposition

The following [Table 8](#) summarizes the disposition of subjects. A total of 2222 subjects were randomized and included in the ITT population of all randomized subjects. Four subjects in each arm were excluded from a modified intent-to-treat (MITT) population for not receiving study drug. A total of 44.6% of ITT subjects were included in the micro-MITT population (with a nominally significantly higher proportion in the sulopenem than in the control group). A total of 922 and 67 of subjects were included in the micro-MITTS population and micro-MITTR population, respectively.

Overall, approximately 95% of the ITT subjects completed study drug treatment, while 4% discontinued treatment prematurely. The primary reasons for discontinuation of treatment were noncompliance with study drug and withdrawal by subject. Approximately 95% of the ITT subjects completed the study. The primary reasons for study discontinuation were loss to follow-up (1.8%) and withdrawal by subject (3.0%). The two treatment groups were comparable with respect to the reasons for treatment discontinuation or study discontinuation.

Table 8. Disposition of All Randomized Subjects (ITT Population)

Study Population/Disposition Parameter	Sulopenem N=1111 n (%)	Amoxicillin/Clavulanate N=1111 n (%)	Total N=2222 n (%)
ITT	1111 (100.0)	1111 (100.0)	2222 (100.0)
MITT			
Yes	1107 (99.6)	1107 (99.6)	2214 (99.6)
No	4 (<1)	4 (<1)	8 (<1)
Micro-MITT			
Yes	522 (47.0)	468 (42.1)	990 (44.6)
No	589 (53.0)	643 (57.9)	1232 (55.4)
Reasons for excluding from micro-MITT			
Study entry uropathogen demonstrated <10 ⁵ CFU/mL	111 (10.0)	127 (11.4)	238 (10.7)
No study entry pathogen	245 (22.1)	276 (24.8)	521 (23.4)
No culture or no growth or contaminated	229 (20.6)	236 (21.2)	465 (20.9)
Not in the MITT population	4 (<1)	4 (<1)	8 (<1)
Micro-MITTR	42 (3.8)	25 (2.3)	67 (3.0)
Micro-MITTS	480 (43.2)	442 (39.8)	922 (41.5)
Completed study drug	1057 (95.1)	1063 (95.7)	2120 (95.4)
Reason for discontinuation of treatment			
Adverse event	8 (<1)	4 (<1)	12 (<1)
Loss to follow-up	6 (<1)	11 (1.0)	17 (<1)
Non-compliance with study drug	16 (1.4)	12 (1.1)	28 (1.3)
Other	8 (<1)	7 (<1)	15 (<1)
Physician decision	1 (<1)	0	1 (<1)
Withdrawal by subject	15 (1.4)	14 (1.3)	29 (1.3)
Completed study	1056 (95.0)	1050 (94.5)	2106 (94.8)
Reason for discontinuation from study			
Adverse event	4 (<1)	1 (<1)	5 (<1)
Loss to follow-up	17 (1.5)	23 (2.1)	40 (1.8)
Other	1 (<1)	2 (<1)	3 (<1)
Physician decision	1 (<1)	0	1 (<1)
Withdrawal by subject	32 (2.9)	35 (3.2)	67 (3.0)

Source: Tables 15 and 21 of the Study Report and Statistical Reviewer's analysis
Abbreviations: ITT, intent-to-treat; MITT, modified intent-to-treat; micro-MITT, microbiological modified intent-to-treat; micro-MITTR, resistant micro-MITT population; micro-MITTS, susceptible micro-MITT population

Data presented in the following sections are discussed separately for the micro-MITTS population, the micro-MITTR population, with a focus in the micro-MITTS population.

Study Results, Trial 310/Micro-MITTS Population

Overall, approximately 96% of the micro-MITTS subjects completed study drug treatment, while 4% discontinued treatment prematurely. The primary reasons for discontinuation of treatment were noncompliance with study drug and withdrawal by subject. Approximately 95% of the micro-MITTS subjects completed the study. The primary reasons for study discontinuation were loss to follow-up (2.1%) and withdrawal by subject (2.3%).

Table 9. Subject Disposition, Micro-MITTS Population

Disposition Parameter	Sulopenem N=480	Amoxicillin/Clavulanate N=442	Total N=922
End of treatment status, n (%)			
Completed	461 (96.0)	422 (95.5)	883 (95.8)
Discontinued	19 (4.0)	20 (4.5)	39 (4.2)
Reason for discontinuation of treatment, n (%)			
Adverse event	2 (<1)	4 (<1)	6 (<1)
Lost to follow-up	4 (<1)	4 (<1)	8 (<1)
Non-compliance with study drug	6 (1.3)	5 (1.1)	11 (1.2)
Other	1 (<1)	2 (<1)	3 (<1)
Physician decision	1 (<1)	0	1 (<1)
Withdrawal by subject	5 (1.0)	5 (1.1)	10 (1.1)
End of study status, n (%)			
Completed	455 (94.8)	425 (96.2)	880 (95.4)
Discontinued	25 (5.2)	17 (3.8)	42 (4.6)
Reason for discontinuation from study, n (%)			
Adverse event	1 (<1)	1 (<1)	2 (<1)
Loss to follow-up	10 (2.1)	9 (2.0)	19 (2.1)
Withdrawal by subject	14 (2.9)	7 (1.6)	21 (2.3)

Source: Table 14.1.3.4 of the Study Report and Statistical Reviewer's analysis
Abbreviations: micro-MITTS, susceptible micro-MITT population; N, number of patients in treatment group; n, number of patients with given characteristic

Baseline Demographics and Clinical Characteristics

Demographic characteristics in the micro-MITTS population are summarized in the following [Table 10](#). The mean age was 49.3 years and mean BMI was 29.1 kg/m². Ethnicity was primarily Hispanic or Latino (63.1%), and race was predominantly White (79.5%). The two treatment groups were generally balanced in these demographic characteristics.

Table 10. Demographic Characteristics, Micro-MITTS Population

Demographic Characteristics	Sulopenem N=480	Amoxicillin/Clavulanate N=442	Total N=922
Age, years			
Mean (SD)	50.1 (17.54)	48.5 (17.32)	49.3 (17.45)
Median	51.0	49.0	50.0
Min, max	18.0, 91.0	18.0, 93.0	18.0, 93.0
Age group (years), n (%)			
<65	367 (76.5)	350 (79.2)	717 (77.8)
≥65	113 (23.5)	92 (20.8)	205 (22.2)
Sex, n (%)			
Female	480 (100.0)	442 (100.0)	922 (100.0)
Race, n (%)			
American Indian or Alaska Native	1 (<1)	1 (<1)	2 (<1)
Asian	10 (2.1)	8 (1.8)	18 (2.0)
Black or African American	78 (16.3)	78 (17.6)	156 (16.9)
Native Hawaiian or other Pacific Islander	0	1 (<1)	1 (<1)
Other	8 (1.7)	4 (<1)	12 (1.3)
White	383 (79.8)	350 (79.2)	733 (79.5)
Ethnicity, n (%)			
Hispanic or Latino	304 (63.3)	278 (62.9)	582 (63.1)
Not Hispanic or Latino	176 (36.7)	163 (36.9)	339 (36.8)
Not reported	0	1 (<1)	1 (<1)

Demographic Characteristics	Sulopenem N=480	Amoxicillin/Clavulanate N=442	Total N=922
Height (cm)			
Mean (SD)	161.7 (7.27)	162.0 (7.00)	161.8 (7.14)
Median	162.0	162.0	162.0
Min, max	125.0, 180.0	142.0, 185.0	125.0, 185.0
Weight (kg)			
Mean (SD)	75.8 (16.97)	76.4 (18.14)	76.0 (17.53)
Median	73.0	74.0	73.4
Min, max	39.0, 192.7	40.8, 163.6	39.0, 192.7
Body mass index (kg/m ²)			
Mean (SD)	29.0 (6.32)	29.1 (6.71)	29.1 (6.51)
Median	28.0	27.9	28.0
Min, max	15.5, 67.5	17.6, 59.8	15.5, 67.5
Body mass index (kg/m ²), n (%)			
<25	124 (25.8)	137 (31.0)	261 (28.3)
25-30	178 (37.1)	144 (32.6)	322 (34.9)
>30	178 (37.1)	161 (36.4)	339 (36.8)

Source: Table 31 of the Study Report and Statistical Reviewer's analysis
Abbreviations: Max, maximum; Min, minimum; micro-MITTS, susceptible micro-MITT population; N, number of patients in treatment group; n, number of patients with given characteristic; SD, standard deviation

Baseline disease characteristics of diabetes and creatinine clearance (CrCl) were comparable between the two treatment groups. About 16% of the subjects were diabetic and 20% of the subjects had a CrCl <60 mL/min.

Table 11. Baseline Disease Characteristics, Micro-MITTS Population

Disease Characteristics	Sulopenem N=480 n (%)	Amoxicillin/Clavulanate N=442 n (%)	Total N=922 n (%)
Diabetes, n (%)			
Yes	80 (16.7)	66 (14.9)	146 (15.8)
No	400 (83.3)	376 (85.1)	776 (84.2)
Creatinine clearance (mL/min)			
N	477	435	912
Mean (SD)	83.8 (27.76)	85.1 (29.35)	84.4 (28.52)
Median	82.3	83.8	83.4
Min, max	8.2, 155.8	16.4, 182.0	8.2, 182.0
Creatinine clearance (mL/min), n (%)			
<60	104 (21.7)	83 (18.8)	187 (20.3)
≥60	373 (77.7)	352 (79.6)	725 (78.6)
Missing	3 (<1)	7 (1.6)	10 (1.1)

Source: Table 31 of the Study Report and Statistical Reviewer's analysis
Abbreviations: max, maximum; micro-MITTS, microbiological modified intent-to-treat susceptible; min, minimum; N, number of patients in treatment group; n, number of patients with given characteristic; SD, standard deviation

Treatment exposure is shown in the following [Table 12](#). The mean capsule compliance and tablet compliance rates were 98.3% and the mean duration of exposure was 5.2 days.

Table 12. Treatment Exposure, Micro-MITTS Population

	Sulopenem N=480 n (%)	Amoxicillin/Clavulanate N=442 n (%)	Total N=922 n (%)
Compliance			
Capsule compliance (%)			
N	478	436	914
Mean (SD)	98.2 (11.12)	98.4 (9.89)	98.3 (10.55)
Median	100.0	100.0	100.0
Min, max	10.0, 100.0	10.0, 100.0	10.0, 100.0
Tablet compliance (%)			
N	478	436	914
Mean (SD)	98.1 (11.39)	98.5 (9.81)	98.3 (10.66)
Median	100.0	100.0	100.0
Min, max	10.0, 100.0	10.0, 100.0	10.0, 100.0
Duration (days)			
Mean (SD)	5.2 (0.76)	5.2 (0.80)	5.2 (0.78)
Median	5.0	5.0	5.0
Min, max	1.0, 8.0	1.0, 7.0	1.0, 8.0

Source: Table 131 of Study Report and Statistical Reviewer's analysis

Abbreviations: Max, maximum; micro-MITTS, microbiological modified intent-to-treat susceptible; Min, minimum; N, number of patients in treatment group; n, number of patients with given characteristic; SD, standard deviation

In the micro-MITTS population, approximately 54% of the subjects reported a protocol deviation. Major deviations were reported for 7 subjects (0.9%) and minor deviations for 492 subjects (53.4%) (Table 13). The most common minor deviation was in study procedures (a protocol-required visit outside the visit window). The two groups were generally balanced in protocol deviations.

Table 13. Protocol Deviations, Micro-MITTS Population

	Sulopenem N=480 n (%)	Amoxicillin/ Clavulanate N=442 n (%)	Total N=922 n (%)
Protocol Deviation			
Subjects with any deviations	264 (55.0)	229 (51.8)	493 (53.5)
Major deviations			
Exclusion criteria met but randomized	2 (0.4)	5 (1.1)	7 (0.8)
Investigational product/study drug that was affected by a temperature excursion was dispensed prior to approval to use	0	1 (0.2)	1 (0.1)
SAE not reported to (b) (4) /Sponsor within 24 hours of knowledge of occurrence.	0	1 (0.2)	1 (0.1)
Minor deviations			
Exclusion (all remaining)	263 (54.8)	229 (51.8)	492 (53.4)
Inclusion criteria not met	6 (1.3)	2 (0.5)	8 (0.9)
Informed consent	6 (1.3)	9 (2.0)	15 (1.6)
Restricted concomitant medication	17 (3.5)	21 (4.8)	38 (4.1)
Study procedures	9 (1.9)	5 (1.1)	14 (1.5)
	250 (52.1)	221 (50.0)	471 (51.1)

Source: Statistical Reviewer's analysis

Abbreviations: micro-MITTS, microbiological modified intent-to-treat susceptible; N, number of patients in treatment group; n, number of subjects with given characteristic; SAE, serious adverse event

In the micro-MITTS population, the most common classes of pre-existing medications were 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (15.3%), angiotensin-

converting enzyme inhibitors (plain) (10.7%), and biguanides (11.3%). The two groups were generally balanced in types of pre-existing medication use.

Table 14. Pre-Existing Medication in ≥4% of Subjects in Either Group, Micro-MITTS Population

ATC Class (Level 3) Medication	Sulopenem N=480 n (%)	Amoxicillin/ Clavulanate N=442 n (%)	Total N=922 n (%)
Number of subjects with at least one prior medication	308 (64.2)	276 (62.4)	584 (63.3)
ACE inhibitors, plain	47 (9.8)	52 (11.8)	99 (10.7)
Lisinopril	37 (7.7)	47 (10.6)	84 (9.1)
Angiotensin II receptor blockers (arbs), plain	50 (10.4)	38 (8.6)	88 (9.5)
Losartan	38 (7.9)	22 (5.0)	60 (6.5)
Beta blocking agents, selective	27 (5.6)	19 (4.3)	46 (5.0)
Biguanides	57 (11.9)	47 (10.6)	104 (11.3)
Metformin	55 (11.5)	40 (9.0)	95 (10.3)
Dihydropyridine derivatives	22 (4.6)	24 (5.4)	46 (5.0)
Amlodipine	20 (4.2)	19 (4.3)	39 (4.2)
HMG-CoA reductase inhibitors	78 (16.3)	63 (14.3)	141 (15.3)
Atorvastatin	33 (6.9)	32 (7.2)	65 (7.0)
Other Antidepressants	20 (4.2)	24 (5.4)	44 (4.8)
Platelet aggregation inhibitors excl. heparin	20 (4.2)	17 (3.8)	37 (4.0)
Progestogens and estrogens, fixed combinations	34 (7.1)	46 (10.4)	80 (8.7)
Proton pump inhibitors	51 (10.6)	26 (5.9)	77 (8.4)
Omeprazole	29 (6.0)	18 (4.1)	47 (5.1)
Selective beta-2-adrenoreceptor agonists	25 (5.2)	24 (5.4)	49 (5.3)
Selective serotonin reuptake inhibitors	23 (4.8)	24 (5.4)	47 (5.1)
Thiazides, plain	22 (4.6)	22 (5.0)	44 (4.8)
Hydrochlorothiazide	22 (4.6)	22 (5.0)	44 (4.8)
Thyroid hormones	33 (6.9)	34 (7.7)	67 (7.3)
Levothyroxine	25 (5.2)	29 (6.6)	54 (5.9)
Vitamin D and analogues	30 (6.3)	23 (5.2)	53 (5.7)

Source: Statistical Reviewer's analysis

Abbreviations: ACE, angiotensin-converting enzyme; ATC, anatomical therapeutic chemical; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme; micro-MITTS, microbiological modified intent-to-treat susceptible; N, number of patients in treatment group; n, number of subjects with given characteristic

In the micro-MITTS population, concomitant medication use reflected pre-existing medication use (most numbers were identical). The most common classes were still HMG-CoA reductase inhibitors (15.3%), angiotensin-converting enzyme (ACE) inhibitors (plain) (10.7%), and biguanides (11.3%). The two groups were generally balanced in concomitant medication use.

Table 15. Concomitant Medication in ≥4% of Subjects in Either Group, Micro-MITTS Population

Concomitant Medication	Sulopenem N=480 n (%)	Amoxicillin/ Clavulanate N=442 n (%)	Total N=922 n (%)
Number of subjects with at least one medication use	321 (66.9)	282 (63.8)	603 (65.4)
ACE inhibitors, plain	47 (9.8)	52 (11.8)	99 (10.7)
Lisinopril	37 (7.7)	47 (10.6)	84 (9.1)
Angiotensin II receptor blockers (arbs), plain	50 (10.4)	38 (8.6)	88 (9.5)
Losartan	38 (7.9)	22 (5.0)	60 (6.5)

Concomitant Medication	Sulopenem N=480 n (%)	Amoxicillin/ Clavulanate N=442 n (%)	Total N=922 n (%)
Beta blocking agents, selective	27 (5.6)	19 (4.3)	46 (5.0)
Biguanides	57 (11.9)	47 (10.6)	104 (11.3)
Metformin	55 (11.5)	40 (9.0)	95 (10.3)
Dihydropyridine derivatives	23 (4.8)	25 (5.7)	48 (5.2)
Amlodipine	21 (4.4)	20 (4.5)	41 (4.4)
HMG-CoA reductase inhibitors	78 (16.3)	63 (14.3)	141 (15.3)
Atorvastatin	33 (6.9)	32 (7.2)	65 (7.0)
Antidepressants	20 (4.2)	24 (5.4)	44 (4.8)
Progestogens and estrogens, fixed combinations	34 (7.1)	46 (10.4)	80 (8.7)
Proton pump inhibitors	51 (10.6)	27 (6.1)	78 (8.5)
Omeprazole	29 (6.0)	18 (4.1)	47 (5.1)
Selective beta-2-adrenoreceptor agonists	26 (5.4)	25 (5.7)	51 (5.5)
Selective serotonin reuptake inhibitors	23 (4.8)	24 (5.4)	47 (5.1)
Thiazides, plain	22 (4.6)	22 (5.0)	44 (4.8)
Hydrochlorothiazide	22 (4.6)	22 (5.0)	44 (4.8)
Thyroid hormones	33 (6.9)	34 (7.7)	67 (7.3)
Levothyroxine	25 (5.2)	29 (6.6)	54 (5.9)
Vitamin D and analogues	30 (6.3)	24 (5.4)	54 (5.9)

Source: Statistical Reviewer's analysis

Abbreviations: ACE, angiotensin-converting enzyme; ATC, anatomical therapeutic chemical; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme; micro-MITTS, microbiological modified intent-to-treat susceptible; N, number of patients in treatment group; n, number of subjects with given characteristic

In the micro-MITTS population, a total of 6.2% of the subjects (comparable in the two treatment groups) reported concomitant antibacterial drug use (Table 16). The most common class was nitrofurantoin derivatives (2.3%). These subjects were included in the primary efficacy analysis and most subjects were coded as failures for reasons of uUTI symptoms and/or microbiological failures, rather than for receiving non-study antibacterial therapy for uUTI. Only 5 subjects in the sulopenem group and 2 subjects in the control group were considered as overall successes. A sensitivity analysis with these successes considered as failures will be provided in Table 30.

Table 16. Concomitant Antibacterial Use in ≥0.5% of Subjects in Either Group, Micro-MITTS Population

Concomitant Antibacterial Use	Sulopenem N=480 n (%)	Amoxicillin/ Clavulanate N=442 n (%)	Total N=922 n (%)
Number of subjects with at least one medication use	28 (5.8)	29 (6.6)	57 (6.2)
Combinations of sulfonamides and trimethoprim, incl. derivatives	7 (1.5)	6 (1.4)	13 (1.4)
Sulfamethoxazole; trimethoprim	7 (1.5)	6 (1.4)	13 (1.4)
First-generation cephalosporins	3 (0.6)	4 (0.9)	7 (0.8)
Cefalexin	3 (0.6)	3 (0.7)	6 (0.7)
Fluoroquinolones	4 (0.8)	7 (1.6)	11 (1.2)
Ciprofloxacin	4 (0.8)	7 (1.6)	11 (1.2)
Nitrofurantoin derivatives	9 (1.9)	12 (2.7)	21 (2.3)
Nitrofurantoin	9 (1.9)	11 (2.5)	20 (2.2)

Source: Statistical Reviewer's analysis

Abbreviations: incl, including; micro-MITTS, microbiological modified intent-to-treat susceptible; N, number of subjects in treatment group; n, number of subjects with given characteristic

In the micro-MITTS population, about 78% of the subjects reported prior medical history. The most common system organ classes represented were Surgical and Medical procedures (41.3%), Social Circumstances (39.4%, including post-menopause), and Vascular Disorders (32.4%, including hypertension). The two treatment groups were generally balanced in terms of occurrence of various conditions in the prior medical history.

Table 17. Medical History in ≥4% of Subjects in Any Group, Micro-MITTS Population

System Organ Class Preferred Term	Sulopenem N=480 n (%)	Amoxicillin/ Clavulanate N=442 n (%)	Total N=922 n (%)
Number of subjects with any medical history	394 (82.1)	327 (74.0)	721 (78.2)
Blood and lymphatic system disorders	26 (5.4)	20 (4.5)	46 (5.0)
Anemia	25 (5.2)	19 (4.3)	44 (4.8)
Endocrine disorders	44 (9.2)	44 (10.0)	88 (9.5)
Hypothyroidism	35 (7.3)	39 (8.8)	74 (8.0)
Eye disorders	20 (4.2)	14 (3.2)	34 (3.7)
Gastrointestinal disorders	75 (15.6)	56 (12.7)	131 (14.2)
Gastroesophageal reflux disease	51 (10.6)	28 (6.3)	79 (8.6)
Hepatobiliary disorders	24 (5.0)	13 (2.9)	37 (4.0)
Immune system disorders	37 (7.7)	24 (5.4)	61 (6.6)
Seasonal allergy	20 (4.2)	14 (3.2)	34 (3.7)
Infections and infestations	57 (11.9)	38 (8.6)	95 (10.3)
Investigations	27 (5.6)	9 (2.0)	36 (3.9)
Metabolism and nutrition disorders	170 (35.4)	125 (28.3)	295 (32.0)
Hypercholesterolemia	30 (6.3)	23 (5.2)	53 (5.7)
Hyperlipidemia	48 (10.0)	42 (9.5)	90 (9.8)
Obesity	31 (6.5)	27 (6.1)	58 (6.3)
Type 2 diabetes mellitus	77 (16.0)	62 (14.0)	139 (15.1)
Vitamin D deficiency	26 (5.4)	20 (4.5)	46 (5.0)
Musculoskeletal and connective tissue disorders	77 (16.0)	54 (12.2)	131 (14.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	37 (7.7)	21 (4.8)	58 (6.3)
Nervous system disorders	58 (12.1)	41 (9.3)	99 (10.7)
Migraine	24 (5.0)	10 (2.3)	34 (3.7)
Psychiatric disorders	97 (20.2)	88 (19.9)	185 (20.1)
Anxiety	46 (9.6)	35 (7.9)	81 (8.8)
Depression	49 (10.2)	46 (10.4)	95 (10.3)
Insomnia	31 (6.5)	28 (6.3)	59 (6.4)
Renal and urinary disorders	19 (4.0)	26 (5.9)	45 (4.9)
Reproductive system and breast disorders	35 (7.3)	12 (2.7)	47 (5.1)
Respiratory, thoracic and mediastinal disorders	58 (12.1)	54 (12.2)	112 (12.1)
Asthma	32 (6.7)	34 (7.7)	66 (7.2)
Social circumstances	201 (41.9)	162 (36.7)	363 (39.4)
Menopause	39 (8.1)	26 (5.9)	65 (7.0)
Post-menopause	162 (33.8)	134 (30.3)	296 (32.1)
Surgical and medical procedures	213 (44.4)	168 (38.0)	381 (41.3)
Caesarean section	35 (7.3)	32 (7.2)	67 (7.3)
Cholecystectomy	31 (6.5)	16 (3.6)	47 (5.1)
Female sterilization	45 (9.4)	21 (4.8)	66 (7.2)
Hysterectomy	68 (14.2)	64 (14.5)	132 (14.3)
Intra-uterine contraceptive device insertion	22 (4.6)	19 (4.3)	41 (4.4)

System Organ Class Preferred Term	Sulopenem N=480 n (%)	Amoxicillin/ Clavulanate N=442 n (%)	Total N=922 n (%)
Vascular disorders	156 (32.5)	143 (32.4)	299 (32.4)
Hypertension	148 (30.8)	133 (30.1)	281 (30.5)

Source: Statistical Reviewer's analysis

Abbreviations: incl, including; micro-MITTS, microbiological modified intent-to-treat susceptible; N, number of subjects in treatment group; n, number of subjects with given characteristic

As shown in the following [Table 18](#), almost all subjects in the micro-MITTS population reported uUTI signs and/or symptoms at baseline. The signs and symptoms were comparable between the two treatment groups.

Table 18. Signs and Symptoms at Baseline, Micro-MITTS Population

Signs and Symptoms	Sulopenem N=480 n (%)	Amoxicillin/ Clavulanate N=442 n (%)	Total N=922 n (%)
Number of subjects with any signs or symptoms	480 (100.0)	441 (99.8)	921 (99.9)
Burning (dysuria) when passing urine			
Mild	92 (19.2)	78 (17.6)	170 (18.4)
Moderate	205 (42.7)	198 (44.8)	403 (43.7)
No symptom	79 (16.5)	66 (14.9)	145 (15.7)
Severe	104 (21.7)	99 (22.4)	203 (22.0)
Frequency of urination or going to the toilet very often			
Mild	72 (15.0)	80 (18.1)	152 (16.5)
Moderate	236 (49.2)	219 (49.5)	455 (49.3)
No symptom	24 (5.0)	16 (3.6)	40 (4.3)
Severe	148 (30.8)	126 (28.5)	274 (29.7)
Pain or uncomfortable pressure in the lower abdomen/pelvic area			
Mild	110 (22.9)	121 (27.4)	231 (25.1)
Moderate	199 (41.5)	161 (36.4)	360 (39.0)
No symptom	107 (22.3)	98 (22.2)	205 (22.2)
Severe	64 (13.3)	61 (13.8)	125 (13.6)
Urgency of urination or a strong and uncontrollable urge to pass urine			
Mild	84 (17.5)	70 (15.8)	154 (16.7)
Moderate	173 (36.0)	166 (37.6)	339 (36.8)
No symptom	66 (13.8)	71 (16.1)	137 (14.9)
Severe	157 (32.7)	134 (30.3)	291 (31.6)

Source: Table 32 of the Study Report and Statistical Reviewer's analysis

Abbreviations: micro-MITTS, microbiological modified intent-to-treat susceptible; N, number of subjects in treatment group; n, number of subjects with given characteristic

As shown in the following [Table 19](#), in the micro-MITTS population, the most common pathogens at baseline were *E. coli* (83.9%), *k. pneumoniae* (11.6%), and *P. mirabilis* (2.8%). The two treatment groups were generally balanced in terms of baseline pathogens. Only 6 subjects had polymicrobial infections at baseline.

Table 19. Baseline Pathogen, Micro-MITTS Population

Pathogen	Sulopenem N=480 n (%)	Amoxicillin/Clavulanate N=442 n (%)	Total N=922 n (%)
<i>Citrobacter freundii</i>	1 (0.2)	0	1 (0.1)
<i>Citrobacter koseri</i>	3 (0.6)	2 (0.5)	5 (0.5)
<i>Enterobacter hormaechei</i>	1 (0.2)	0	1 (0.1)
<i>Escherichia coli</i>	400 (83.3)	374 (84.6)	774 (83.9)
<i>Escherichia sp</i>	1 (0.2)	0	1 (0.1)
<i>Klebsiella oxytoca</i>	0	2 (0.5)	2 (0.2)
<i>Klebsiella pneumoniae</i>	57 (11.9)	50 (11.3)	107 (11.6)
<i>Klebsiella sp</i>	1 (0.2)	1 (0.2)	2 (0.2)
<i>Klebsiella variicola</i>	5 (1.0)	1 (0.2)	6 (0.7)
<i>Pantoea sp</i>	1 (0.2)	0	1 (0.1)
<i>Proteus mirabilis</i>	13 (2.7)	13 (2.9)	26 (2.8)
<i>Providencia stuartii</i>	1 (0.2)	1 (0.2)	2 (0.2)
Subjects with one pathogen	476 (99.2)	440 (99.5)	916 (99.3)
Subjects with two pathogens	4 (0.8)	2 (0.5)	6 (0.7)

Source: Table 33 of the Study Report, Table 14.1.10.3 from submission (SN75), and Statistical Reviewer's analysis
Abbreviations: micro-MITTS, microbiological modified intent-to-treat susceptible; N, number of subjects in treatment group; n, number of patients with given characteristic

Distribution of Baseline Study Uropathogens by Antibiotic Resistance

Distribution of baseline study uropathogens by antibiotic resistance is shown in [Table 20](#). A total of 8.9% of micro-MITTS subjects had at least 1 baseline Enterobacterales pathogen that was extended-spectrum β -lactamase-positive, as determined by having a ceftriaxone MIC of >1 $\mu\text{g/mL}$. A total of 13%, 30.7%, 26.9% of subjects' isolates were non-susceptible to nitrofurantoin, trimethoprim-sulfamethoxazole and quinolones, respectively. Susceptibility was comparable (not nominally statistically significant) between the two treatment groups.

Table 20. Distribution of Pathogens by ESBL Status and Amoxicillin/Clavulanate, Quinolone, Trimethoprim-Sulfamethoxazole and Nitrofurantoin Susceptibility, Micro-MITTS Population

Parameter	Sulopenem N=480 n (%)	Amoxicillin/ Clavulanate N=442 n (%)	Total N=922 n (%)
ESBL status			
Negative	443 (92.3)	397 (89.8)	840 (91.1)
Positive	37 (7.7)	45 (10.2)	82 (8.9)
Amoxicillin/clavulanate			
Susceptible	480 (100.0)	442 (100.0)	922 (100.0)
Nitrofurantoin			
Susceptible	416 (86.7)	386 (87.3)	802 (87.0)
Non-susceptible	64 (13.3)	56 (12.7)	120 (13.0)
Trimethoprim-sulfamethoxazole			
Susceptible	331 (69.0)	308 (69.7)	639 (69.3)
Non-susceptible	149 (31.0)	134 (30.3)	283 (30.7)
Quinolone			
Susceptible	360 (75.0)	314 (71.0)	674 (73.1)
Non-susceptible	120 (25.0)	128 (29.0)	248 (26.9)
ESBL positive and quinolone non-susceptible	33 (6.9)	40 (9.0)	73 (7.9)
ESBL positive, quinolone non-susceptible, and trimethoprim-sulfamethoxazole non-susceptible	24 (5.0)	29 (6.6)	53 (5.7)

Parameter	Sulopenem N=480 n (%)	Amoxicillin/ Clavulanate N=442 n (%)	Total N=922 n (%)
ESBL positive, quinolone non-susceptible, trimethoprim-sulfamethoxazole non-susceptible, and nitrofurantoin non-susceptible	4 (0.8)	1 (0.2)	5 (0.5)
B-lactam non-susceptible, quinolone non-susceptible, trimethoprim-sulfamethoxazole non-susceptible, and nitrofurantoin non-susceptible	6 (1.3)	4 (0.9)	10 (1.1)

Source: Table 34 of the Study Report and Statistical Reviewer's analysis

Abbreviations: ESBL, extended spectrum β -lactamase; micro-MITTS, microbiological modified intent-to-treat susceptible; N, number of subjects in treatment group; n, number of patients with given characteristic

Primary and Key Secondary Efficacy Results

Primary Efficacy Analysis Results

In the micro-MITTS population, the overall success proportions were 61.7% and 55.0% in the sulopenem and amoxicillin/clavulanate treatment groups, respectively, with a difference of 6.7% [95% CI: 0.3%, 13.0%] and a two-sided p-value of 0.040 for superiority. The results demonstrated NI using a -10% NI margin and superiority of sulopenem to the active control. The treatment effect for overall success was driven by microbiological success, as the clinical success proportions were similar between the two treatment groups.

Table 21. Overall Response (Primary Endpoint), Patient-Determined Clinical Response, and Microbiologic Response at TOC, Micro-MITTS Population

Outcome	Sulopenem N=480 n (%)	Amoxicillin/ Clavulanate N=442 n (%)	Difference (%) (95% CI) Two-Sided p-Value for Superiority
Overall response	296 (61.7)	243 (55.0)	6.7 (0.3, 13.0) 0.040
Overall nonresponse	160 (33.3)	177 (40.0)	
Indeterminate	24 (5.0)	22 (5.0)	
Patient-determined clinical success	371 (77.3)	339 (76.7)	0.6 (-4.8, 6.1)
Investigator-determined clinical success	421 (87.7)	386 (87.3)	0.4 (-3.9, 4.7)
Microbiologic success	361 (75.2)	295 (66.7)	8.5 (2.6, 14.3)

Source: Table 86 of the Study Report and Statistical Reviewer's analysis

Abbreviations: micro-MITTS, microbiological modified intent-to-treat susceptible; N, number of subjects in treatment group; n, number of subjects with given characteristic; TOC, test of cure

[Table 22](#) shows the cross-tabulation of patient-determined clinical response and microbiological response at TOC in the micro-MITTS population. There were discordant responses. Among subjects with clinical success, only 80% (296/371) and 72% (243/339) had microbiological eradication in the sulopenem group and active control group, respectively.

Table 22. Cross-Tabulation of Patient-Determined Clinical Response and Microbiologic Response at TOC, Micro-MITTS Population

Response	Sulopenem n (%) N=480			Amoxicillin/Clavulanate n (%) N=442		
	Eradication	Indeterminate	Persistence	Eradication	Indeterminate	Persistence
Clinical success	296 (79.8)	6 (1.6)	69 (18.6)	243 (71.7)	5 (1.5)	91 (26.8)
Clinical failure	63 (69.2)	1 (1.1)	27 (29.7)	48 (55.8)	3 (3.5)	35 (40.7)
Indeterminate	2 (11.1)	16 (88.9)	0 (0.0)	4 (23.5)	13 (76.5)	0 (0.0)

Source: Statistical Reviewer's analysis. Percentage was by clinical response in each arm
Abbreviations: micro-MITTS, microbiological modified intent-to-treat susceptible; N, number of subjects in treatment group; n, number of subjects with given characteristic; TOC, test of cure

The following [Table 23](#) shows the reasons for non-response. The majority of subjects with non-response experienced clinical failure and/or microbiologic failure. Only a few subjects had non-response due to antibacterial therapy alone or receipt of non-study antibacterial therapy for uUTI.

Table 23. Reasons for Overall Nonresponse at TOC, Micro-MITTS Population

Number of Non-Responders/ Reasons for Overall Non-Response at TOC	Sulopenem N=480 n (%)	Amoxicillin/ Clavulanate N=442 n (%)
Number of non-responders	160 (33.3)	177 (40.0)
Failure for uUTI symptoms or baseline culture demonstrates $\geq 10^3$ CFU/mL	159 (33.1)	173 (39.1)
Urine culture at the TOC visit demonstrates $\geq 10^3$ CFU/mL of the baseline uropathogen (microbiologic failure only)	70 (14.6)	91 (20.6)
No resolution or worsening of symptoms of uUTI present at trial entry and/or new uUTI symptoms (clinical failure only)	63 (13.1)	47 (10.6)
Urine culture $\geq 10^3$ and at least one symptom not resolved (both clinical and microbiologic failure)	26 (5.4)	35 (7.9)
Antibacterial therapy alone	1 (0.2)	4 (0.9)
Receipt of non-study antibacterial therapy for uUTI	8 (1.7)	4 (0.9)

Source: Table 87 of the Study Report and Statistical Reviewer's analysis
A subject may be classified into multiple categories.
Abbreviations: CFU, colony-forming units; micro-MITTS, microbiological modified intent-to-treat susceptible; N, number of subjects in treatment group; n, number of subjects with given characteristic; TOC, test of cure; uUTI, uncomplicated urinary tract infection

The overall success proportions at Day 5 were 52.5% and 51.1% in the sulopenem and control groups, respectively, increased slightly to 61.7% and 55.0%, respectively, at Day 12, and stabilized at 61.5% and 55.9%, respectively, at Day 28.

Table 24. Overall Response by Visit, Micro-MITTS Population

Overall Response by Visit	Sulopenem (N=480) n (%)	Amoxicillin/ Clavulanate (N=442) n (%)	Difference (%) (95% CI)
End of treatment (Day 5)			
Overall responder	252 (52.5)	226 (51.1)	1.4 (-5.1, 7.8)
Overall non-responder	214 (44.6)	200 (45.2)	
Indeterminate	14 (2.9)	16 (3.6)	

	Sulopenem (N=480) n (%)	Amoxicillin/ Clavulanate (N=442) n (%)	Difference (%) (95% CI)
Overall Response by Visit			
TOC (Day 12)			
Overall responder	296 (61.7)	243 (55.0)	6.7 (0.3, 13.0)
Overall non-responder	160 (33.3)	177 (40.0)	
Indeterminate	24 (5.0)	22 (5.0)	
Final visit (Day 28)			
Overall responder	295 (61.5)	247 (55.9)	5.6 (-0.8, 11.9)
Overall non-responder	143 (29.8)	157 (35.5)	
Indeterminate	42 (8.8)	38 (8.6)	

Source: Table 100 of the Study Report and Statistical Reviewer's analysis

Abbreviations: micro-MITTS, microbiological modified intent-to-treat susceptible; N, number of subjects in treatment group; n, number of subjects with given characteristic; TOC, test of cure

Key Secondary Efficacy Endpoints

In the sulopenem group, the microbiological eradication proportion was highest (85.8%) at Day 5, then decreased to 75.2% at Day 12 and 71.5% at Day 28. In the active control group, it was highest (79.2%) at Day 5, then decreased to 66.7% at Day 12, and remained essentially unchanged at 66.5% at Day 28.

Table 25. Microbiological Response by Visit, Micro-MITTS Population

Timepoint/Response	Sulopenem (N=480) n (%)	Amoxicillin/ Clavulanate (N=442) n (%)	Difference (%) (95% CI)
End of treatment (Day 5)			
Eradication	412 (85.8)	350 (79.2)	6.6 (1.8, 11.6)
Indeterminate	18 (3.8)	17 (3.8)	
Persistence	50 (10.4)	74 (16.7)	
Test of cure (Day 12)			
Eradication	361 (75.2)	295 (66.7)	8.5 (2.6, 14.3)
Indeterminate	23 (4.8)	21 (4.8)	
Persistence	96 (20)	126 (28.5)	
Final visit (Day 28)			
Eradication	343 (71.5)	294 (66.5)	4.9 (-1.0, 10.9)
Indeterminate	36 (7.5)	29 (6.6)	
Persistence	101 (21)	118 (26.7)	
Persistence with increasing MIC	0	1 (0.2)	

Source: Table 100 of Study and Statistical Reviewer's analysis

Abbreviations: MIC, minimum inhibitory concentration; micro-MITTS, microbiological modified intent-to-treat susceptible; N, number of subjects in treatment group; n, number of subjects with given characteristic; TOC, test of cure

Microbiological response by baseline pathogen is shown in the following [Table 26](#). For the two most common pathogens (*E. coli*, and *K. pneumoniae*), the success (eradication) proportion was higher in the sulopenem group than in the active control group.

Table 26. Per Pathogen Microbiological Eradication Response at TOC, Micro-MITTS Population

Pathogen	Sulopenem (N=480)	Amoxicillin/Clavulanate (N=442)
All <i>Escherichia</i> species	305/401 (76.1)	254/374 (67.9)
<i>Escherichia coli</i>	304/400 (76.0)	254/374 (67.9)
<i>Escherichia sp</i>	1/1 (100.0)	0
All <i>Klebsiella</i> species	48/63 (76.2)	31/ 54 (57.4)
<i>K. oxytoca</i>	0	2/2 (100.0)
<i>K. pneumoniae</i>	42/57 (73.7)	27/50 (54.0)
<i>Klebsiella spp</i>	1/1 (100.0)	1/1 (100.0)
<i>K. variicola</i>	5/5 (100.0)	1/1 (100.0)
<i>Proteus mirabilis</i>	5/13 (38.5)	9/13 (69.2)
<i>Staphylococcus saprophyticus</i> *	9/9 (100.0)	1/3 (33.3)
All <i>Citrobacter</i> species	4/4 (100.0)	2/2 (100.0)
<i>C. freundii</i>	1/1 (100.0)	0
<i>C. koseri</i>	3/3 (100.0)	2/2 (100.0)
All <i>Enterobacter</i> species	1/1 (100.0)	0/0 (0.0)
<i>E. hormaechei</i>	1/1 (100.0)	0/0 (0.0)
<i>Providencia stuartii</i>	1/1 (100.0)	1/1 (100.0)
<i>Pantoea spp</i>	1/1 (100.0)	0/0 (0.0)

Source: Table 118 of the Study Report and Statistical Reviewer's analysis. *Not included in the micro-MITT population
Abbreviations: micro-MITTS, microbiological modified intent-to-treat susceptible; N, number of subjects in treatment group; TOC, test of cure

Investigator-determined and patient-determined clinical responses are summarized in the following two tables, [Table 27](#) and [Table 28](#). There were no notable differences in each response between the two treatment groups at each visit.

Table 27. Investigator-Determined Clinical Response by Visit, Micro-MITTS Population

Timepoint/Response	Sulopenem N=480 n (%)	Amoxicillin/ Clavulanate N=442 n (%)	Difference (%) (95% CI)
End of treatment (Day 5)			
Clinical success	404 (84.2)	365 (82.6)	1.6 (-3.2, 6.5)
Clinical failure	62 (12.9)	60 (13.6)	
Indeterminate	14 (2.9)	17 (3.8)	
TOC (Day 12)			
Clinical success	421 (87.7)	386 (87.3)	3.8 (-3.9, 4.7)
Clinical failure	43 (9.0)	42 (9.5)	
Indeterminate	16 (3.3)	14 (3.2)	
Final visit (Day 28)			
Clinical success	411 (85.6)	377 (85.3)	0.3 (-4.2, 4.9)
Clinical failure	43 (9.0)	47 (10.6)	
Indeterminate	26 (5.4)	18 (4.1)	

Source: Statistical Reviewer's analysis
Abbreviations: micro-MITTS, microbiological modified intent-to-treat susceptible; N, number of subjects in treatment group; n, number of subjects with given characteristic; TOC, test of cure

Patient-determined clinical response improved over time from Day 5 to Day 28 in both groups. The two treatment groups had similar proportions of subjects with clinical success. In both treatment groups, proportions of patient-determined clinical success were lower than proportions of investigator-determined clinical success at all timepoints, suggesting that a patient's

perception of clinical success encompasses characteristics that were either not well-captured or that lag behind investigators' assessments of response.

Table 28. Patient-Determined Clinical Response by Visit, Micro-MITTS Population

Timepoint/Response	Sulopenem n (%) N=480	Amoxicillin/ Clavulanate n (%) N=442	Difference (%) (95% CI)
End of treatment (Day 5)			
Clinical success	282 (58.8)	271 (61.3)	-2.6 (-8.9, 3.8)
Clinical failure	187 (39.0)	156 (35.3)	
Indeterminate	11 (2.3)	15 (3.4)	
TOC (Day 12)			
Clinical success	371 (77.3)	339 (76.7)	0.6 (-4.8, 6.1)
Clinical failure	91 (19.0)	86 (19.5)	
Indeterminate	18 (3.8)	17 (3.8)	
Final visit (Day 28)			
Clinical success	380 (79.2)	357 (80.8)	-1.6 (-6.8, 3.6)
Clinical failure	68 (14.2)	55 (12.4)	
Indeterminate	32 (6.7)	30 (6.8)	

Source: Table 115 of the Study Report and Statistical Reviewer's analysis

Abbreviations: micro-MITTS, microbiological modified intent-to-treat susceptible; N, number of subjects in treatment group; n, number of subjects with given characteristic; TOC, test of cure

Subgroup Analyses of the Primary Efficacy Endpoint, Micro-MITTS Population

Subgroup analyses were performed to assess the treatment effects among different subgroups based on age, race, ethnicity, body mass index and diabetes. Breslow-Day tests did not suggest any heterogeneity of odds ratios in the primary efficacy endpoint. When the sample size was greater than 90 in each group, the lower limits of the 95% CIs were larger than -10%. In a few subgroups (age >65 years, Hispanic or Latino ethnicity, and non-diabetes), nominally statistically significant differences were seen. However, caution is needed to interpret these results because multiple comparisons were conducted.

Table 29. Subgroup Analysis of the Primary Efficacy Endpoint, Micro-MITTS Population

Variable	Sulopenem n (%) N=480	Amoxicillin/ Clavulanate n (%) N=442	Difference (%) (95%CI)
Age, years			
<65	231/367 (62.9)	205/350 (58.6)	4.4 (-2.8, 11.5)
≥65	65/113 (57.5)	38/92 (41.3)	16.2 (2.4, 29.4)
Race			
American Indian or Alaska Native	1/1 (100)	0/1 (0)	
Asian	8/10 (80.0)	7/8 (87.5)	-7.5 (-43.2, 32.9)
Black or African American	45/78 (57.7)	39/78 (50.0)	7.7 (-7.9, 23.3)
Native Hawaiian or other Pacific Islander	0	0/1 (0)	
White	235/383 (61.6)	196/350 (56.0)	5.6 (-1.5, 12.7)
Other	6/8 (75.0)	1/4 (25.0)	50.0 (-10.9, 83.3)

Variable	Sulopenem n (%) N=480	Amoxicillin/ Clavulanate n (%) N=442	Difference (%) (95%CI)
Ethnicity			
Hispanic or Latino	201/304 (66.1)	160/278 (57.6)	8.6 (0.7, 16.4)
Not Hispanic or Latino	95/176 (54.0)	83/163 (50.9)	3.1 (-7.6, 13.6)
Not reported		0/1	
Body mass index (kg/m²)			
<25	81/124 (65.3)	82/137 (59.9)	5.5 (-6.3, 17.1)
25-30	118/178 (66.3)	85/144 (59.0)	7.3 (-3.3, 17.8)
>30	97/178 (54.5)	76/161 (47.2)	7.3 (-3.4, 17.8)
Diabetes			
Yes	37/80 (46.3)	28/66 (42.4)	3.8 (-12.4, 19.7)
No	259/400 (64.8)	215/376 (57.2)	7.7 (0.3, 15.0)
Creatinine clearance			
<60	63/104 (60.6)	37/83 (44.6)	16.0 (1.6, 29.8)
≥60	231/373 (61.9)	204/352 (58.0)	4.0 (-3.2, 11.1)
Missing	2/3 (66.7)	2/7 (28.6)	
Quinolone susceptibility			
Susceptibility	234/360 (65.0)	180/314 (57.3)	7.7 (0.3, 15.0)
Resistant/non-susceptible	62/120 (51.7)	63/128 (49.2)	2.4 (-10.0, 14.8)
Extended spectrum β-lactamase			
Positive	22/37 (59.5)	20/45 (44.4)	15.0 (-6.8, 35.4)
Negative	274/443 (61.9)	223/397 (56.2)	5.7 (-1.0, 12.3)

Source: Tables 93, 96, and 99 of the Study Report and Statistical Reviewer's analysis
Abbreviations: micro-MITTS, microbiological modified intent-to-treat susceptible; N, number of subjects in treatment group; n, number of subjects with given characteristic

Sensitivity Analyses of Primary Efficacy Endpoint

Contaminated Urine Sample Treated as Failure

At TOC in the micro-MITTS population, there were 23 and 24 subjects in the sulopenem and active control groups, respectively, that were coded by the Applicant as “Eradication” with ≥3 organisms present (indicating contamination at collection). Thirteen and 18 of these subjects were coded as success for the overall response. If these successes were changed to failures, then the treatment effect was slightly higher, as shown in [Table 30](#).

Complete Eradication (<100 CFU/mL)

The overall response at TOC when using complete eradication (<100 CFU/mL) as the definition of microbiologic success was lower in both groups, but the treatment effect was similar to that observed in the primary analysis (6.5% versus 6.7%) ([Table 30](#)).

Concomitant Use of Antibacterial Drugs

Five and two subjects in the sulopenem and the control group, respectively, who received concomitant antibacterial drugs were considered as successes in the primary efficacy analysis. If those 7 subjects were considered as failures, the difference between the two groups reduced from 6.7% in the primary analysis to 6.1%, only demonstrating NI.

Table 30. Sensitivity Analysis of Overall Response, Micro-MITTS Population

Analysis	Sulopenem	Amoxicillin/ Clavulanate	Difference (%)
	(N=480) n (%)	(N=442) n (%)	(95% CI) Two-Sided p-Value
Primary analysis (contamination as success)	296 (61.7)	243 (55.0)	6.7 (0.3, 13.0) 0.040
Contamination as failure	283 (59.0)	225 (50.9)	8.1 (1.6, 14.4) 0.014
Complete eradication (<100 CFU/mL)	280 (58.3)	229 (51.8)	6.5 (0.1, 12.9) 0.047
Concomitant use of antibacterials as failure	291 (60.6)	241 (54.5)	6.1 (-0.3, 12.4) 0.06

Source: Table 103 of the Study Report and Statistical Reviewer's analysis

Abbreviations: CFU, colony-forming units; micro-MITTS, microbiological modified intent-to-treat susceptible; N, number of subjects in treatment group; n, number of subjects with given characteristic

Study Results, Trial 310/Micro-MITTR Population

Disposition

The study included 67 subjects in total for the micro-MITTR population and failed to enroll the planned sample size (134 per group). Overall, 95.5% of the micro-MITTR subjects completed study drug treatment and completed the study, while 4.5% discontinued treatment prematurely and discontinued the study prematurely. The primary reasons for discontinuation of treatment and discontinuation from the study were loss to follow-up (1.5%) and withdrawal by subjects (3.0%).

Table 31. Subject Disposition, Micro-MITTR Population

Disposition Parameter	Sulopenem	Amoxicillin/ Clavulanate	Total
	N=42 n (%)	N=25 n (%)	N=67 n (%)
End of treatment status, n (%)			
Completed	40 (95.2)	24 (96.0)	64 (95.5)
Discontinued	2 (4.8)	1 (4.0)	3 (4.5)
Reason for discontinuation of treatment, n (%)			
Loss to follow-up	0	1 (4.0)	1 (1.5)
Withdrawal by subject	2 (4.8)	0	2 (3.0)
End of study status, n (%)			
Completed	40 (95.2)	24 (96.0)	64 (95.5)
Discontinued	2 (4.8)	1 (4.0)	3 (4.5)
Reason for discontinuation from study, n (%)			
Loss to follow-up	0	1 (4.0)	1 (1.5)
Withdrawal by subject	2 (4.8)	0	2 (3.0)

Source: Table 14.1.3.5 of the Study Report and Statistical Reviewer's analysis

Abbreviations: micro-MITTR, microbiological modified intent-to-treat resistant; N, number of subjects in treatment group; n, number of subjects with given characteristic

Baseline Demographics and Clinical Characteristics

The mean age was 51.8 years and mean BMI was 29.9 kg/m². Ethnicity was primarily Hispanic or Latino (68.7%), and race was predominantly White. The two groups were generally balanced in these demographic characteristics.

Table 32. Demographic Characteristics, Micro-MITTR Population

Demographic Characteristics	Sulopenem N=42 n (%)	Amoxicillin/ Clavulanate N=25 n (%)	Total N=67 n (%)
Age, years			
Mean (SD)	52.2 (14.43)	51.1 (14.56)	51.8 (14.38)
Median	53.0	53.0	53.0
Min, max	25.0, 79.0	24.0, 77.0	24.0, 79.0
Age group (years), n (%)			
<65	33 (78.6)	21 (84.0)	54 (80.6)
≥65	9 (21.4)	4 (16.0)	13 (19.4)
Sex, n (%)			
Female	42 (100.0)	25 (100.0)	67 (100.0)
Race, n (%)			
Black or African American	6 (14.3)	6 (24.0)	12 (17.9)
White	36 (85.7)	19 (76.0)	55 (82.1)
Ethnicity, n (%)			
Hispanic or Latino	29 (69.0)	17 (68.0)	46 (68.7)
Not Hispanic or Latino	13 (31.0)	8 (32.0)	21 (31.3)
Height (cm)			
Mean (SD)	162.2 (6.99)	162.7 (7.70)	162.4 (7.21)
Median	161.5	165.0	163.0
Min, max	147.0, 175.0	144.0, 173.0	144.0, 175.0
Weight (kg)			
Mean (SD)	79.8 (16.96)	77.6 (14.15)	79.0 (15.89)
Median	78.2	73.0	75.0
Min, max	53.1, 117.8	59.6, 119.0	53.1, 119.0
Body mass index (kg/m ²)			
Mean (SD)	30.2 (5.72)	29.4 (5.06)	29.9 (5.46)
Median	30.2	27.9	29.3
Min, max	21.5, 43.6	21.1, 41.2	21.1, 43.6
Body mass index group (kg/m ²), n (%)			
<25	8 (19.0)	3 (12.0)	11 (16.4)
25-30	12 (28.6)	12 (48.0)	24 (35.8)
>30	22 (52.4)	10 (40.0)	32 (47.8)

Source: Table 39 of the Study Report and Statistical Reviewer's analysis

Abbreviations: max, maximum; micro-MITTR, microbiological modified intent-to-treat resistant; min, minimum; N, number of subjects in treatment group; n, number of subjects with given characteristic; SD, standard deviation

A small proportion of subjects (12%) were diabetic and 16.4% had impaired renal function (creatinine clearance <60 mL/min). There were no statistically significant imbalances in these characteristics.

Table 33. Baseline Disease Characteristics, Micro-MITTR Population

Disease Characteristics	Sulopenem	Amoxicillin/ Clavulanate	Total
	N=42 n (%)	N=25 n (%)	N=67 n (%)
Diabetes, n (%)			
No	36 (85.7)	23 (92.0)	59 (88.1)
Yes	6 (14.3)	2 (8.0)	8 (11.9)
Creatinine clearance (mL/min)			
N	42	25	67
Mean (SD)	84.3 (30.11)	85.4 (28.64)	84.7 (29.35)
Median	85.3	76.7	84.6
Min, max	19.4, 178.1	39.0, 165.8	19.4, 178.1
Creatinine clearance (mL/min), n (%)			
<60	9 (21.4)	2 (8.0)	11 (16.4)
≥60	33 (78.6)	23 (92.0)	56 (83.6)

Source: Table 39 of the Study Report and Statistical Reviewer's analysis

Abbreviation: micro-MITTR, microbiological modified intent-to-treat resistant; N, number of subjects in treatment group; n, number of subjects with given characteristic; SD, standard deviation

Primary and Secondary Efficacy Endpoints

The analyses of the primary efficacy endpoint (overall response), clinical response, and microbiologic response in the micro-MITTR population are summarized in the following [Table 34](#). Due to the small sample size, results were inconclusive due to statistical uncertainty regarding treatment effects.

Table 34. Overall Response (Primary Endpoint) at TOC, Micro-MITTR Population

Outcome	Sulopenem	Amoxicillin/Clavulanate	Difference (95% CI)
	N=42 n (%)	N=25 n (%)	
Overall response	22 (52.4)	17 (68.0)	-15.6 (-37.5, 9.1)
Overall nonresponse	17 (40.5)	7 (28.0)	
Indeterminate	3 (7.1)	1 (4.0)	
Clinical success	26 (61.9)	18 (72.0)	-10.1 (-31.5, 14.0)
Microbiologic success	29 (69.0)	20 (80.0)	-11.0 (-30.7, 12.0)

Source: Tables 120, 127, 129 of the Study Report and Statistical Reviewer's analysis

Abbreviation: micro-MITTR, microbiological modified intent-to-treat resistant; N, number of subjects in treatment group; n, number of subjects with given characteristic TOC, test of cure

Study Results, Trial 310, Micro-MITT and ITT Populations

Please see Sections [16.2](#) and [16.3](#) for a discussion of results from the Micro-MITT and ITT Populations of Trial 310.

6.2.3. Results from Other Trials

Study Results, Trial 302 for cUTI

In view of the failure of sulopenem to meet the primary endpoint in Trial 302 for cUTI, there is concern for possible off-label use of oral sulopenem as stepdown therapy following initial IV antibacterial treatment of cUTI. Please see Section [16.4](#) for a discussion of results from Trial 302.

Study Results, Trial 303 for cIAI

In view of the failure of sulopenem to meet the primary endpoint in Trial 303 for cIAI, there is concern for possible off-label use of oral sulopenem as stepdown therapy following initial IV antibacterial treatment of cIAI. Please see Section [16.5](#) for a discussion of results from Trial 303.

6.3. Key Efficacy Review Issues

None.

7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

Nonclinical studies submitted to support the safety evaluation for this NDA include the following studies with sulopenem etzadroxil: safety pharmacology studies (neurofunctional, in vitro and in vivo cardiovascular, and pulmonary function assessments), pharmacokinetic and toxicokinetic assessments (absorption, distribution, metabolism, and excretion), general toxicology studies (1-month studies in rats and monkeys), in vitro and in vivo genetic toxicology studies, and developmental and reproductive toxicology studies (male and female fertility study in rats, embryo-fetal development studies in mice, rats, and rabbits, a pre-postnatal development study in rats and a juvenile toxicology study in rats). Also, a 14-day combination toxicology study with orally administered sulopenem etzadroxil and probenecid was conducted in rats. Additional nonclinical safety studies with sulopenem, the active metabolite of sulopenem etzadroxil, that were evaluated in support of the NDA include an in vitro hERG assessment, in vitro plasma-protein binding, CYP450 inhibition, mass balance, and metabolite profiling studies, and a full battery of genetic toxicology studies. Additional information regarding genetic toxicity findings for probenecid was obtained from historical probenecid product labels previously approved by the FDA.

7.1.1 Target Organs of Toxicity

Kidney

Adult rats were administered sulopenem etzadroxil in oral doses of 100, 400, and 2000 mg/kg/day in the 1-month toxicology study in rats. Renal effects included minimal vacuolation of the tubular epithelium, tubular hypertrophy, and a potentially adverse effect, i.e., a low incidence of tubular degeneration. These effects occurred primarily in high-dose males and females in the 2000 mg/kg/day group and to a lesser extent in mid-dose males receiving 400 mg/kg/day.

In a definitive juvenile toxicity study, oral administration of sulopenem etzadroxil in doses of 25, 75, and 225 mg/kg/day to juvenile rats for 85 days beginning on postnatal Day 5 and continuing to postnatal Day 90, was associated with more varied and severe renal histopathology findings

compared to the findings in adult rats in the 1-month toxicology study. Renal histopathology in juvenile male and/or female rats included slight degeneration of tubular epithelium, renal infarcts, and intratubular concretions. The findings in juvenile rats occurred at lower sulopenem etzadroxil doses and exposures than the doses associated with renal findings in adult rats in the 1-month study, and the findings were poorly reversible or, in the case of tubular concretions, irreversible after a 2-week recovery period (see Sections 5.4 and 5.5.6 in the NDA 213972 Multidisciplinary Review dated July 22, 2021, for more information). The results are consistent with a potential for more severe renal toxicity in juvenile rats compared to adults and suggest increased monitoring for renal toxicity may be warranted for clinical administration of sulopenem etzadroxil to pediatric patients.

Gastrointestinal Tract

Sulopenem etzadroxil-related findings in gastrointestinal (GI) tissues were observed in the 14-day combination-toxicology study with sulopenem etzadroxil plus probenecid in rats (mixed cell infiltrates, hyperplasia of glandular epithelium and edema in the large intestine) and the 1-month study in monkeys (minimal mucosal hyperplasia). The sulopenem etzadroxil doses at which GI effects were observed in the 14-day combination toxicology study in rats (800 mg/kg/day) and the 1-month study in monkeys (400 mg/kg/day) are approximately 7- and 6-times, respectively, the clinical sulopenem exposure for the maximum recommended human dose of sulopenem etzadroxil based on plasma AUC comparison (see Sections 5.4, 5.5.1 and 5.5.2 in the NDA 213972 Multidisciplinary Review dated July 22, 2021).

Immune/Hematopoietic Systems

In the 1-month toxicology study, monkeys also exhibited positive Coombs test results that tended to increase with the sulopenem etzadroxil dose and likely contributed to antibody mediation of minimal erythrocyte loss and compensatory erythropoiesis in monkeys. The lowest sulopenem etzadroxil dose (400 mg/kg/day) at which these effects were observed is approximately 6-times the clinical sulopenem exposure for the maximum recommended human dose of sulopenem etzadroxil based on plasma AUC comparison (see Sections 5.4 and 5.5.1 in the NDA 213972 Multidisciplinary Review dated July 22, 2021).

Exposure Multiples for Repeated-Dose Studies

Table 35. Exposure Multiples for Sulopenem Etzadroxil Based on Plasma Sulopenem AUC in Repeated-Dose Studies.

Study Type (Species)/ Study No.	LOAEL NOAEL (mg/kg/day)	Sulopenem Nonclinical AUC (ng•hr/ml) (Exposure Multiple)^a	Adverse Effects (Doses Found [mg/kg/day])
Sulopenem Etzadroxil			
1-month toxicity study (rat)/ Study No.: 06 ^(b) ₍₄₎ 278	LOAEL = 400 NOAEL = 100	65200 (4.4) ^b 7240 (0.5) ^b	Tubular regeneration (400 and 2000 for males and 2000 for females)
Juvenile toxicity study (rat)/ Study No.: 181T001-8383182-02	LOAEL = 25 NOAEL <25	4700 (0.3) ^c ----	Slight degeneration of tubular epithelium, renal infarcts, and intratubular concretions (25, 75 and 225)
14-day combination toxicology study (rat)/	LOAEL = 800	100000 (6.7) ^d	Mixed cell infiltrates, hyperplasia of glandular epithelium and

Study Type (Species)/ Study No.	LOAEL NOAEL (mg/kg/day)	Sulopenem Nonclinical AUC (ng•hr/ml) (Exposure Multiple) ^a	Adverse Effects (Doses Found [mg/kg/day])
Study No.: 18IT001- (b) (4) -417503-02	NOAEL = 100	9740 (0.7) ^d	edema in the large intestine (800)
1-month toxicology study (monkey)/ Study No.: 06GR263	LOAEL = 400 NOAEL = 50	94600 (6.4) ^e 11100 (0.8) ^e	Positive Coombs' test and decreased RBC parameters (400 and 1000) Minimal mucosal hyperplasia in the jejunum and ileum (1000)

Source: Reviewer table from nonclinical study data provided by the Applicant

Nonclinical AUC is an average of male and female AUC in the nonclinical study unless otherwise indicated.

^a The mean plasma AUC_{0-∞} for sulopenem after administration of a single administration of a ORLYNVAH is 7410 ng•hr/ml. For the MRHD of two ORLYNVAH tablets per day the AUC_{0-24hr} is expected to be 14820 ng•hr/ml.

^b Plasma AUC_{0-24hr} for sulopenem from the 1-month toxicology study in rats (Study No.: 06GR278)

^c Plasma AUC_{0-24hr} for sulopenem from the juvenile toxicology study in rats (Study No.: 18IT001-8383182-02)

^d Plasma AUC_{0-24hr} for sulopenem from the 14-day combination-toxicology study in rats (Study No.: 18IT001-WIL-417503-02). Plasma AUC values were the average of male and female values in the groups receiving the LOAEL and NOAEL doses.

^e Plasma AUC_{0-24hr} for sulopenem from the 1-month toxicology study in monkeys (Study No.: 06GR263)

Abbreviations: AUC, area under the concentration-time curve; AUC_{0-∞}, area under the concentration-time curve estimated to infinity; AUC_{0-24hr}, area under the concentration-time curve from time 0 to 24 h; LOAEL, lowest observed adverse effect level; MRHD, maximum recommended human dose; NOAEL, no observed adverse effect level; RBC, red blood cell

7.1.2 Developmental and Reproductive Toxicity

Oral administration of sulopenem etzadroxil to pregnant females was associated with maternal and fetal toxicity in embryo-fetal development studies in mice, rats, and rabbits.

In mice, sulopenem etzadroxil administered to pregnant females in oral doses of 100, 400, and 2000 mg/kg/day during the period of organogenesis was associated with maternal toxicity (clinical signs and reduced maternal body weights) and fetal toxicity including reduced fetal weights and a fetal malformation. Maternal clinical signs including respiratory distress, abdominal distension, decreased motor activity and reduced maternal body weight gain occurred in the 2000 mg/kg/day group. In the same group, reduced fetal weights were observed, and a fetal malformation, cleft palate, occurred with an increased fetal and litter incidence relative to control values.

Sulopenem etzadroxil administered in oral doses of 100, 400, and 2000 mg/kg/day to pregnant females during the period of organogenesis in a rat embryo-fetal development study was associated with maternal weight loss and reduced maternal weight gain and reduced fetal body weights. Maternal toxicity occurred in the mid- and high-dose groups receiving 400 and 2000 mg/kg/day, respectively. Fetal weight loss occurred in the 2000 mg/kg/day group.

In rabbits, oral doses of sulopenem etzadroxil (5, 15, and 50 mg/kg/day) administered to pregnant females during the period of organogenesis were associated with reduced maternal weight gain occurring in a dose-dependent manner in all the treatment groups. In addition, post-implantation loss was increased and reductions in the number of viable fetuses, gravid uterine weights, and fetal body weights occurred in the mid- and high-dose groups receiving 15 and 50 mg/kg/day, respectively.

Table 36. Exposure Multiples for Sulopenem Etzadroxil Based on Plasma Sulopenem AUC in EFD Studies.

Study Type (Species)/ Study No.	NOAEL (mg/kg/day)	Sulopenem Nonclinical AUC (ng•hr/ml) (Exposure Multiple) ^a	Adverse Effects (Doses Found [mg/kg/day])
Sulopenem Etzadroxil			
EFD Study (mice)/ Study No.: 09GR119	Maternal toxicity = 400	38700 ^b (2.6)	Clinical signs (signs of respiratory distress, cold to touch (2000) Reduced maternal weight gains (2000)
	Fetal toxicity = 400	38700 ^b (2.6)	Reduced fetal weights (2000) cleft palate (2000)
EFD Study (rat)/ Study No.: 08GR040	Maternal toxicity = 100	29300 ^c (2.0)	Reduced maternal body weights and body weight gain (400 and 2000)
	Fetal toxicity = 400	6170 ^c (0.4)	Reduced fetal weights (2000)
EFD Study (rabbit)/ Study No.: 08GR037	Maternal toxicity: none	----	Reduced maternal body weight gain (5, 15, and 50)
	Fetal toxicity = 5	1870 ^d (0.1)	Increased post-implantation loss, and reduced number of viable fetuses, gravid uterine weights, fetal weights (15 and 50)

Source: Reviewer table from nonclinical study data provided by the Applicant

Nonclinical AUC is an average of male and female AUC in the nonclinical study unless otherwise indicated.

^a The mean plasma AUC_{0-∞} for sulopenem after administration of a single administration of a ORLYNVAH is 7410 ng•hr/ml. For the MRHD of two ORLYNVAH tablets per day the AUC_{0-24hr} is expected to be 14820 ng•hr/ml.

^b Plasma AUC_{0-24hr} for sulopenem from the EFD study in mice (Study No.: 09GR119)

^c Plasma AUC_{0-24hr} for sulopenem from the EFD study in rats (Study No.: 08GR040)

^d Plasma AUC_{0-24hr} for sulopenem from the EFD study in rabbits (Study No.: 08GR037)

Abbreviations: AUC, area under the concentration-time curve; AUC_{0-∞}, area under the concentration-time curve estimated to infinity; AUC_{0-24hr}, area under the concentration-time curve from time 0 to 24 h; EFD, Embryofetal development; MRHD, maximum recommended human dose; NOAEL, no observed adverse effect level

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

Oral sulopenem etzadroxil is the pro-drug of the penem antibacterial drug, sulopenem and is hydrolyzed rapidly to sulopenem upon oral ingestion. Penem antibacterials are a class of beta-lactams structurally similar to carbapenems. If approved, sulopenem would be the first oral penem on the U.S. market so there are no in-class comparators. In general, carbapenems have a favorable safety profile and are well-tolerated. Common adverse reactions associated with their use include headache, nausea, diarrhea, vomiting, rash, and injection site reactions. Labeled Warnings and Precautions for carbapenems (imipenem-cilastatin, ertapenem, meropenem) include hypersensitivity reactions, seizures and other adverse central nervous system experiences, *Clostridioides difficile*-associated disease, severe cutaneous adverse reactions, thrombocytopenia in patients with renal dysfunction, development of drug-resistant bacteria and drug-drug interactions (DDIs) with valproic acid resulting in reduction of its plasma concentrations and increased seizure potential.

Reported postmarketing adverse events (AEs) for carbapenems include anaphylaxis, hepatitis and hepatic failure, hematologic adverse reactions including pancytopenia and hemolytic anemia, central nervous system disturbances, muscular weakness, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms, erythema multiforme, acute generalized exanthematous pustulosis, drug fever, and acute renal failure.

Probenecid has been in use since the 1950s and is generally well-tolerated with a favorable safety profile. Labeled Warnings and Precautions for probenecid include exacerbation of gout, increased plasma concentration of methotrexate, severe allergic reactions including anaphylaxis, hematuria, renal colic, costovertebral pain, formation of uric acid stones, and antagonism of the uricosuric action of probenecid with concomitant use of salicylates. Adverse reactions observed with probenecid include headache, dizziness, precipitation of acute gouty arthritis, hepatic necrosis, nausea, vomiting, anorexia, sore gums, genitourinary AEs including uric acid stones and nephrotic syndrome, hypersensitivity reactions, aplastic anemia, leukopenia, hemolytic anemia, anemia, dermatitis, alopecia, and flushing.

The risks and safety concerns for oral sulopenem are anticipated to be similar to carbapenems as summarized above except that because sulopenem etzadroxil/probenecid is an oral tablet, injection site reactions would not be expected. Adverse events of special interest monitored by the Applicant during the uUTI development program included diarrhea and renal disorders; infusion-related events were monitored in Trials 302 and 303 utilizing sulopenem IV but will not be discussed further in this review.

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

Not applicable. Sulopenem etzadroxil/probenecid is not approved in the U.S. or in any foreign market; therefore, no postmarketing experience is available for sulopenem etzadroxil/probenecid.

7.3.1. Adverse Events Identified in Postmarket Experiences

Not applicable.

7.3.2. Expectations on Safety

Not applicable.

7.3.3. Additional Safety Issues From Other Disciplines

Not applicable.

7.4. FDA Approach to the Safety Review

The primary safety analysis for the resubmitted NDA was conducted on data derived from the phase 3 uUTI Trial 310. Additional analyses were conducted on the combined phase 3 uUTI study populations from Trials 301 and 310. During the first review cycle, safety data from Trials 301, 302 and 303 were analyzed, along with phase 1 studies (conducted by the Applicant and Pfizer) and phase 2 studies (conducted by Pfizer). While specific safety findings from these three trials (301, 302 and 303) are presented in this review when relevant, please refer to the NDA Multi-Disciplinary Review and Evaluation {NDA 213972} dated July 22, 2021 for complete details. Identified safety issues during the previous review cycle included hypersensitivity reactions (angioedema), elevated alanine aminotransferase (ALT), and gastrointestinal adverse reactions.

No major data quality or integrity issues were identified for Trial 310. Coding of verbatim terms to the Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (PTs) was generally acceptable. A treatment-emergent adverse event (TEAE) was defined by the Applicant as an AE that newly appeared or worsened in severity following study drug initiation. A TEAE was considered drug-related if the AE was possibly or probably related to study drug. Safety evaluations included recording of AEs, vital signs, and collection of laboratory results. While the TOC visit was Day 12 (+/-1 day), AEs were collected through the final study visit (Day 28 ± 2 days). MedDRA version 26.1 was used for Trial 310 (MedDRA version 21.0 was used for Trials 301, 302, and 303; MedDRA version 22.0 was used for the phase 1 studies). AEs were classified by investigators as mild (does not interfere with the patient's usual function), moderate (interferes to some extent with the patient's usual function), or severe (interferes significantly with the patient's usual function). An AE was defined as a serious adverse event (SAE) if the event:

- Resulted in death,
- Was life-threatening,
- Required hospitalization or prolongation of hospitalization,
- Resulted in persistent or significant disability/incapacity,
- Resulted in congenital anomaly/birth defect,
- Was assessed as being a medically important event based on medical and scientific judgement. Such medically important events may not be immediately life-threatening or result in death or hospitalization but may require medical or surgical intervention to prevent one of the above outcomes.

The clinical data scientist performed standard safety analyses including FDA medical queries (FMQs) to identify safety signals. In this review, the terms AE and TEAE are used interchangeably and sulopenem etzadroxil/probenecid is also referenced as oral sulopenem.

7.5. Adequacy of the Clinical Safety Database

The safety database is adequate. Trial 301 in the original NDA submission included 825 subjects who received sulopenem etzadroxil/probenecid for the treatment of uUTI. Thirteen subjects (8

from the sulopenem arm, 5 from the ciprofloxacin arm) in Trial 301 were from site 218 and excluded from the FDA's safety database (b) (7)(A). Trial 310 added an additional 1107 subjects resulting in a total clinical safety database of 1932 subjects who received oral sulopenem etzadroxil/probenecid for the treatment of uUTI (Table 37).

Additional safety data were available from 1030 subjects who received IV sulopenem and oral sulopenem etzadroxil/probenecid in the phase 3 cUTI and cIAI trials as well as 2006 subjects from twenty-four phase 1 and phase 2 studies who received IV and oral formulations of sulopenem.

The numbers of subjects, dosing, and duration of exposure in Trial 310 (in addition to the previously reviewed studies) are sufficient to conduct a safety review.

Table 37. Safety Database for Sulopenem

Clinical Trial Groups N=8003	Sulopenem Etzadroxil +	
	Probenecid/Sulopenem (n=4968)	Active Control (n=3035)
Controlled trials conducted for this indication *		
Trial 301 (uUTI)	825	822
Trial 310 (uUTI)	1107	1107*
Controlled trials conducted for other indications		
Trial 302 (cUTI)	695	697**
Trial 303 (cIAI)	335	333**
Five Applicant-conducted phase 1 studies (IV/oral)	276	-
Fourteen Pfizer-conducted phase 1 studies (IV/oral)	298	-
Five Pfizer-conducted, phase 2 studies (IV)	1432	76

Source: Reviewer Table

* Active comparator was oral ciprofloxacin in Trial 301 and oral amoxicillin/clavulanate in Trial 310.

**Active comparator was IV ertapenem followed by oral ciprofloxacin or amoxicillin/clavulanate in Trial 302. Active comparator was IV ertapenem followed by oral ciprofloxacin and metronidazole or amoxicillin/clavulanate in Trial 303.

Abbreviations: cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; IV, intravenous; N, number of subjects in trial groups; n, number of subjects in treatment or control groups; uUTI, uncomplicated urinary tract infection

Baseline Demographic and Clinical Characteristics

In Trial 310, baseline demographic and clinical characteristics were similar between treatment arms (Table 38). All subjects were female and from the United States. The median age in the sulopenem arm was 50 years and 48 years in the comparator arm. In both arms, most subjects (around 80%) were less than 65 years old. There were slightly more subjects (7.2%) in the sulopenem arm who were aged 75 years or older compared to the amoxicillin/clavulanate arm (5.8%). In both arms, the majority of subjects were white and Hispanic or Latino. A greater number of subjects (39.3%) in the sulopenem arm had a BMI >30 kg/m² than in the amoxicillin/clavulanate arm (36.5%). The number of subjects with CrCl >60 mL/min was comparable between arms, but there were more subjects (1.7%) in the amoxicillin/clavulanate arm with a CrCl <30 mL/min compared to sulopenem subjects (0.8%). There was a higher percentage of subjects with a CrCl of 30-60 mL/min in the sulopenem arm (18.0%) compared to subjects in the amoxicillin/clavulanate arm (15.4%).

Table 38. Baseline Demographic and Clinical Characteristics, Safety Population, Trial 310

Characteristic	Sulopenem Etzadroxil/ Probenecid N=1107	Amoxicillin/ Clavulanate N=1107
Sex, n (%)		
F	1107 (100)	1107 (100)
Age, years		
Mean (SD)	49.1 (17)	47.9 (17)
Median (min, max)	50 (18, 91)	48 (18, 93)
Age group, years, n (%)		
<65	883 (79.8)	895 (80.8)
≥65	224 (20.2)	212 (19.2)
Age group ≥75, years, n (%)		
>=75	80 (7.2)	64 (5.8)
Race, n (%)		
American Indian or Alaska Native	2 (0.2)	4 (0.4)
Asian	19 (1.7)	15 (1.4)
Black or African American	194 (17.5)	217 (19.6)
Native Hawaiian or Other Pacific Islander	1 (0.1)	2 (0.2)
Other	16 (1.4)	14 (1.3)
White	875 (79.0)	855 (77.2)
Ethnicity, n (%)		
Hispanic or Latino	741 (66.9)	760 (68.7)
Not Hispanic or Latino	366 (33.1)	346 (31.3)
Not Reported	0	1 (0.1)
Country of participation, n (%)		
USA	1107 (100)	1107 (100)
Body mass index by category (kg/m ²), n (%)		
<25	272 (24.6)	322 (29.1)
25-30	400 (36.1)	381 (34.4)
>30	435 (39.3)	404 (36.5)
Creatinine clearance by category (mL/min), n (%)		
<30	9 (0.8)	19 (1.7)
30-60	199 (18.0)	170 (15.4)
>60	890 (80.4)	906 (81.8)
Missing	9 (0.8)	12 (1.1)

Source: adsl.xpt; Software: R

Note: CSR reported 740 Hispanic or Latino in sulopenem etzadroxil/probenecid arm and 761 in amoxicillin/clavulanate arm

Abbreviations: CSR, Clinical Study Report; max, maximum; min, minimum; N, number of subjects in treatment group; n, number of subjects with given characteristic; SD, standard deviation

[Table 39](#) shows the baseline demographic and clinical characteristics of the integrated safety population (Trials 301 and 310). As in Trial 310, the median age in the sulopenem subjects was 50 years with the majority of patients under age 65 years. Most subjects in both treatment arms were white. Trial 301 included ex-U.S. sites in Russia and Ukraine; in the integrated safety population, 10.1% of sulopenem subjects were from Russia and 7.5% of sulopenem subjects were from Ukraine. BMI was similar for the sulopenem and amoxicillin/clavulanate arms, but more subjects in the ciprofloxacin arm (42.0%) had a BMI <25 kg/m² than subjects in the sulopenem (30.6%) or amoxicillin/clavulanate (29.1%) arms. The distribution of CrCl was similar between the sulopenem and ciprofloxacin arms. The percentage of subjects with a CrCl of 30-60 mL/min was lower in the amoxicillin/clavulanate arm (15.4%) compared to subjects in the sulopenem arm (21.0%) and ciprofloxacin arm (25.1%).

Table 39. Baseline Demographic and Clinical Characteristics, Integrated Safety Population, Trials 301 and 310

Characteristic	Sulopenem N=1932	Amoxicillin/ Clavulanate N=1107	Ciprofloxacin N=822
Sex, n (%)			
Female	1932 (100)	1107 (100)	822 (100)
Age, years			
Mean (SD)	49.4 (17.7)	47.9 (17)	50.2 (19)
Median (min, max)	50 (18, 91)	48 (18, 93)	51 (18, 96)
Age group, years, n (%)			
<65	1490 (77.1)	895 (80.8)	589 (71.7)
≥65	442 (22.9)	212 (19.2)	233 (28.3)
Age group ≥75, years, n (%)			
≥75	166 (8.6)	64 (5.8)	97 (11.8)
Race, n (%)			
American Indian or Alaska Native	12 (0.6)	4 (0.4)	3 (0.4)
Asian	30 (1.6)	15 (1.4)	7 (0.9)
Black or African American	268 (13.9)	217 (19.6)	66 (8.0)
Native Hawaiian or other Pacific Islander	1 (0.1)	2 (0.2)	1 (0.1)
Other	20 (1.0)	14 (1.3)	3 (0.4)
White	1601 (82.9)	855 (77.2)	742 (90.3)
Ethnicity, n (%)			
Hispanic or Latino	1032 (53.4)	760 (68.7)	255 (31.0)
Not Hispanic or Latino	895 (46.3)	346 (31.3)	566 (68.9)
Not reported	4 (0.2)	1 (0.1)	1 (0.1)
Unknown	1 (0.1)	0	0
Country of participation, n (%)			
United States	1593 (82.5)	1107 (100)	461 (56.1)
Russia	195 (10.1)	0	224 (27.3)
Ukraine	144 (7.5)	0	137 (16.7)
Is in United States, n (%)			
United States	1593 (82.5)	1107 (100)	461 (56.1)
Non-United States	339 (17.5)	0	361 (43.9)
Body mass index by category (kg/m ²), n (%)			
<25	591 (30.6)	322 (29.1)	345 (42.0)
25-30	648 (33.5)	381 (34.4)	224 (27.3)
>30	690 (35.7)	404 (36.5)	241 (29.3)
Missing	3 (0.2)	0	12 (1.5)
Creatinine clearance by category (mL/min), n (%)			
<30	24 (1.2)	19 (1.7)	10 (1.2)
30-60	405 (21.0)	170 (15.4)	206 (25.1)
>60	1494 (77.3)	906 (81.8)	605 (73.6)
Missing	9 (0.5)	12 (1.1)	1 (0.1)

Source: adsl.xpt; Software: R

Abbreviations: max, maximum; min, minimum; N, number of subjects in treatment group; n, number of subjects with given characteristic; SD, standard deviation

As shown in [Table 40](#), the mean duration of treatment in the sulopenem arm in Trial 310 was 5.2 days with most subjects (97.0%) treated for ≥4 to <7 days.

Table 40. Duration of Treatment, Safety Population, Trial 310

Parameter	Sulopenem N=1107	Amoxicillin/ Clavulanate N=1107
Duration of treatment, days		
Mean (SD)	5.2 (0.8)	5.2 (0.8)
Median (Q1, Q3)	5 (5, 6)	5 (5, 6)
Min, max	1, 8	1, 10
Total exposure (person years)	16	16
Patients treated, by duration, n (%)		
<1 day	0	0
≥1 to <4 days	28 (2.5)	27 (2.4)
≥4 to <7 days	1074 (97.0)	1075 (97.1)
≥7 days	5 (0.5)	5 (0.5)

Source: adex.xpt and adsl.xpt; Software: R

Duration is 5 days for each arm.

Abbreviations: max, maximum; min, minimum; N, number of subjects in treatment arm; n, number of subjects with given treatment duration; Q1 first quartile; Q3, third quartile; SD, standard deviation

As shown in [Table 41](#), the mean duration of treatment in the sulopenem arm in the ISP was also 5.2 days with most subjects (97.2%) treated for ≥4 to <7 days.,

Table 41. Duration of Treatment, Integrated Safety Population, Trials 301 and 310

Parameter	Sulopenem N=1932	Amoxicillin/ Clavulanate N=1107	Ciprofloxacin N=822
Duration of treatment, days			
Mean (SD)	5.2 (0.8)	5.2 (0.8)	3.2 (0.5)
Median (Q1, Q3)	5 (5, 6)	5 (5, 6)	3 (3, 4)
Min, max	1, 8	1, 10	1, 6
Total exposure (person years)	27	16	7
Patients treated, by duration, n (%)			
<1 days	0	0	0
≥1 to <4 days	48 (2.5)	27 (2.4)	606 (73.7)
≥4 to <7 days	1877 (97.2)	1075 (97.1)	216 (26.3)
≥7 days	7 (0.4)	5 (0.5)	0

Source: adsl.xpt; Software: R

Duration is 5 days for Sulopenem or Amoxicillin/clavulanate, 3 days for Ciprofloxacin.

Abbreviations: max, maximum; min, minimum; N, number of subjects in treatment arm; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation

7.6. Safety Results

7.6.1. Safety Results, Trial 310

7.6.1.1. Overview of Treatment-Emergent Adverse Events, Trial 310

As shown in [Table 42](#), the overall incidence of TEAEs was higher in the sulopenem arm (18.9%) compared to the amoxicillin/clavulanate arm (12.3%). Most TEAEs in both arms were of mild or moderate severity, but 5 subjects (0.5%) in the sulopenem arm experienced a severe AE

compared to 3 subjects (0.3%) in the comparator arm. Eight subjects (0.7%) in the sulopenem arm and 4 subjects (0.4%) in the amoxicillin/clavulanate arm had AEs leading to permanent discontinuation (Section 7.6.1.4) of drug. There were no SAEs in the sulopenem arm.

Table 42. Overview of Adverse Events, Safety Population, Trial 310

Event Category	Sulopenem	Amoxicillin/ Clavulanate
	N=1107 n (%)	N=1107 n (%)
SAE	0	5 (0.5)
SAEs with fatal outcome	0	0
Life-threatening SAEs	0	0
AE leading to permanent discontinuation of study drug	8 (0.7)	4 (0.4)
AE leading to dose modification of study drug	0	0
AE leading to interruption of study drug	0	0
AE leading to reduction of study drug	0	0
AE leading to dose delay of study drug	0	0
Any AE	209 (18.9)	136 (12.3)
Severe and worse	5 (0.5)	3 (0.3)
Moderate	54 (4.9)	37 (3.3)
Mild	149 (13.5)	96 (8.7)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any event that occurs or worsens in either intensity or frequency after the first dose of study drug in a period.

Duration is 5 days for each arm.

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

7.6.1.2. Deaths, Trial 310

There were no deaths in Trial 310.

7.6.1.3. Serious Treatment-Emergent Adverse Events, Trial 310

There were no SAEs in the sulopenem arm, and 5 SAEs in the amoxicillin/clavulanate arm. The SAEs in the comparator arm will not be discussed further.

7.6.1.4. Adverse Events Leading to Treatment Discontinuation, Trial 310

The proportion of subjects with TEAEs leading to treatment discontinuation was comparable in both treatment arms (0.7% in the sulopenem arm and 0.4% in the amoxicillin/clavulanate arm). In the sulopenem arm, these included the following PTs, most of which (except chills, headache and syncope) were related to the Gastrointestinal Disorders system organ class (SOC): nausea (n = 4), gastroesophageal reflux disease ([GERD] n = 3), diarrhea (n = 3), constipation (n = 1), flatulence (n = 1), abdominal pain (n = 1), chills (n = 1), headache (n = 1), and syncope (n = 1).

Table 43. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Trial 310

System Organ Class Preferred Term	Sulopenem N=1107 n (%)	Amoxicillin/ Clavulanate N=1107 n (%)
Any AE leading to discontinuation	8 (0.7)	4 (0.4)
Gastrointestinal disorders (SOC)	7 (0.6)	3 (0.3)
Nausea	4 (0.4)	0
Gastroesophageal reflux disease	3 (0.3)	0
Diarrhea	3 (0.3)	1 (0.1)
Constipation	1 (0.1)	0
Flatulence	1 (0.1)	0
Abdominal pain	1 (0.1)	1 (0.1)
Diverticulum	0	1 (0.1)
General disorders and administration site conditions (SOC)	1 (0.1)	0
Chills	1 (0.1)	0
Nervous system disorders (SOC)	2 (0.2)	0
Headache	1 (0.1)	0
Syncope	1 (0.1)	0
Renal and urinary disorders (SOC)	0	1 (0.1)
Nephrolithiasis	0	1 (0.1)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any event that occurs or worsens in either intensity or frequency after the first dose of study drug in a period.

Duration is 5 days for each arm.

Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with adverse event; SOC, system organ class

The proportion of subjects who terminated the study early was approximately 5% in both treatment arms with the majority of discontinuations being lost to follow-up or withdrawal by subject. However, there were three subjects in the sulopenem arm who discontinued the study due to an AE. Sulopenem subjects with AEs leading to treatment or study discontinuation are briefly described below:

- Subject (b) (6) had an AE of mild worsened acid reflux. The subject took a single dose of sulopenem etzadroxil/probenecid on study Day 1 and experienced worsened acid reflux. Sulopenem was discontinued and she was prescribed Tums. The AE recovered/resolved on the same day. The investigator assessed the event as probably related to study drug. The FDA reviewer agrees with the investigator's assessment.
- Subject (b) (6) had AEs of moderate diarrhea, worsened acid reflux, and nausea that began on Day 2. Nexium and Zantac were prescribed, and sulopenem was discontinued on Day 3. All three AEs recovered/resolved on Day 4. The investigator considered nausea possibly related to study drug and diarrhea and worsened acid reflux as probably related. The FDA reviewer agrees that the three AEs were probably related to sulopenem.
- Subject (b) (6) had AEs of mild constipation, nausea, and headache. The subject took a single dose of sulopenem on Day 1 and developed these three AEs on the same day. No therapy was prescribed. Sulopenem was discontinued on Day 1 with resolution of the AEs on Day 3. The AEs resulted in study discontinuation. The investigator considered the AEs as possibly related to sulopenem. The FDA reviewer agrees that nausea and headache were

possibly related to sulopenem but notes that constipation is unlikely to be related to sulopenem.

- Subject (b) (6) had an AE of severe vasovagal syncope on Day 1 after a single dose of sulopenem. The AE resolved the same day and resulted in treatment and study discontinuation. The AE was considered possibly related to sulopenem by the investigator, and the FDA reviewer agrees.
- Subject (b) (6) had AEs of moderate diarrhea, mild nausea, and mild chills starting on Day 2. Sulopenem was discontinued on Day 4, after six total doses. Nausea resolved on Day 4 and chills and diarrhea resolved on Day 6. The investigator considered nausea and diarrhea to be possibly related to study drug and chills unlikely related to study drug. The FDA reviewer agrees with this assessment.
- Subject (b) (6) had AEs of mild diarrhea and nausea that began on Day 1. Sulopenem was discontinued on Day 2 after 3 total doses. Diarrhea and nausea resolved on Day 4 but led to study discontinuation. The investigator assessed the two AEs as possibly related to sulopenem. The FDA reviewer agrees with this assessment.
- Subject (b) (6) had an AE of mild abdominal pain that occurred on Study Day 1. Sulopenem was discontinued the same day after two total doses. No therapy was prescribed for abdominal pain, and the AE resolved on Day 3. The investigator considered the AE unlikely related to study drug. Although the narrative is limited, the FDA reviewer disagrees and notes that abdominal pain could potentially be related to sulopenem.
- Subject (b) (6) had AEs of mild flatulence and acid reflux that occurred on Day 5. Sulopenem was discontinued on Day 5 after eight total doses. The AEs resolved without therapy. The two AEs were assessed as possibly related to sulopenem, and the FDA reviewer agrees.

The most common adverse reactions leading to discontinuation (nausea, diarrhea, and gastroesophageal reflux) will be included in Section 6 of the Prescribing Information.

7.6.1.5. Treatment-Emergent Adverse Events, Trial 310

TEAEs occurred in 18.9% of the subjects in the sulopenem arm and 12.3% of subjects in the amoxicillin/clavulanate arm. As shown in [Table 44](#), this difference in TEAEs was largely driven by diarrhea (8.1% in the sulopenem arm versus 4.1% in the amoxicillin/clavulanate arm). The following TEAEs (listed in decreasing order of frequency) occurred more commonly in the sulopenem etzadroxil/probenecid arm and were seen in $\geq 1\%$ of subjects: diarrhea (8.1%), nausea (4.3%), vulvovaginal mycotic infection (3.0%), headache (2.2%), vomiting (1.4%), and gastroesophageal reflux disease (1.0%). Fatigue (0.5%) and urine odor abnormal (0.4%) occurred in the sulopenem etzadroxil/probenecid arm, but not in the amoxicillin/clavulanate arm. Abdominal pain occurred in 0.6% of subjects in the sulopenem arm and in 1.0% of subjects in the amoxicillin/clavulanate arm.

Table 44. Subjects With Adverse Events Occurring at $\geq 0.2\%$ Frequency in the Sulopenem Arm, Safety Population, Trial 310

Preferred Term	Sulopenem N=1107 n (%)	Amoxicillin/ Clavulanate N=1107 n (%)
Any AE	209 (18.9)	136 (12.3)
Diarrhea	90 (8.1)	45 (4.1)
Vulvovaginal mycotic infection	33 (3.0)	13 (1.2)
Nausea	48 (4.3)	32 (2.9)
Vomiting	16 (1.4)	4 (0.4)
Gastroesophageal reflux disease	11 (1.0)	1 (0.1)
Headache	24 (2.2)	17 (1.5)
Fatigue	5 (0.5)	0
Urine odor abnormal	4 (0.4)	0
COVID-19	5 (0.5)	2 (0.2)
Chills	2 (0.2)	0
Constipation	3 (0.3)	1 (0.1)
Gastroenteritis	2 (0.2)	0
Flatulence	2 (0.2)	1 (0.1)
Vaginal discharge	2 (0.2)	1 (0.1)
Vertigo	3 (0.3)	2 (0.2)
Back pain	3 (0.3)	4 (0.4)
Dizziness	2 (0.2)	4 (0.4)
Dyspepsia	3 (0.3)	5 (0.5)
Abdominal pain	7 (0.6)	11 (1.0)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any event that occurs or worsens in either intensity or frequency after the first dose of study drug in a period.

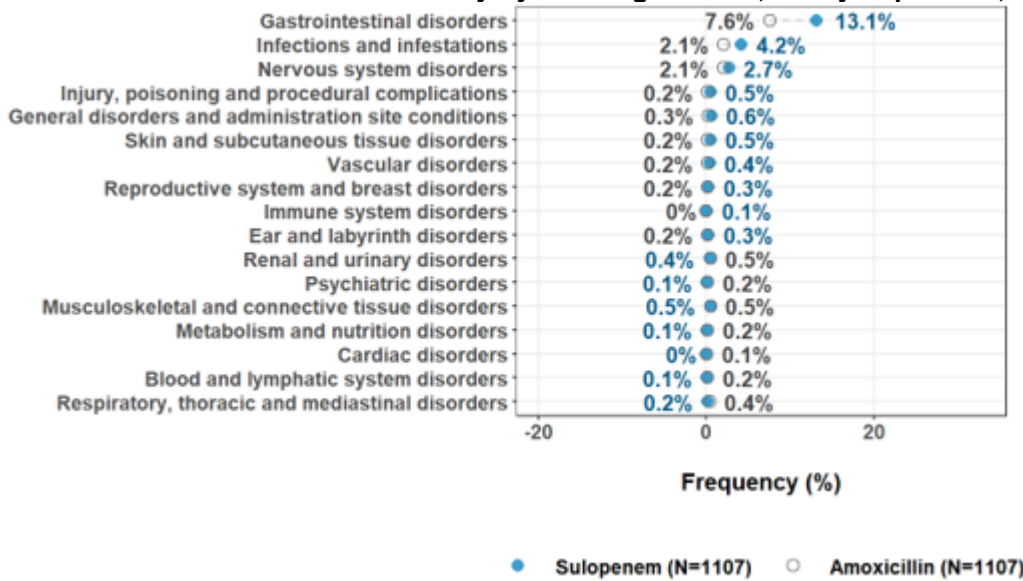
Duration is 5 days for each arm.

Coded as MedDRA preferred terms.

Abbreviations: AE, adverse event; COVID-19, coronavirus disease of 2019; N, number of subjects in treatment arm; n, number of subjects with adverse event

As shown in [Figure 1](#), AEs in the sulopenem arm occurred most commonly in the Gastrointestinal disorders, Infections and infestations, and Nervous system disorders SOCs. More subjects in the sulopenem than comparator arms had TEAEs by FMQs in the following SOCs: Gastrointestinal disorders, Infections and infestations, General disorders and administrative site conditions, and Nervous system disorders. In the GI SOC, there were higher frequencies of diarrhea (8.1%), nausea (4.3%), and vomiting (1.4%) in the sulopenem arm compared to the amoxicillin/clavulanate arm. The fungal infection FMQ accounted for more TEAEs in the Infections and infestations SOC in the sulopenem etzadroxil/probenecid arm (3.0%) compared to the amoxicillin/clavulanate arm (1.2%). Fatigue (General disorders and administrative site conditions SOC) and somnolence (Nervous system disorders SOC) occurred only in the sulopenem etzadroxil/probenecid arm (both 0.5%). Headache also occurred more frequently in the oral sulopenem arm (2.3%) compared to the amoxicillin/clavulanate arm (1.5%).

Figure 1. Patients With Adverse Events by System Organ Class, Safety Population, Trial 310



Source: adae.xpt; Software: R
 Treatment-emergent adverse events defined as any event that occurs or worsens in either intensity or frequency after the first dose of study drug in a period.
 Abbreviations: N, number of subjects in treatment arm

Table 45. Subjects With Adverse Events by System Organ Class and FDA Medical Query (Broad) Occurring at ≥0.2% Frequency in the Sulopenem Arm, Safety Population, Trial 310

System Organ Class Preferred Term	Sulopenem N=1107 n (%)	Amoxicillin/ Clavulanate N=1107 n (%)
Arrhythmia	3 (0.3)	5 (0.5)
Vertigo	5 (0.5)	6 (0.5)
Diarrhea	92 (8.3)	46 (4.2)
Nausea	57 (5.1)	34 (3.1)
Vomiting	57 (5.1)	34 (3.1)
Dyspepsia	15 (1.4)	7 (0.6)
Constipation	3 (0.3)	1 (0.1)
Abdominal pain	7 (0.6)	11 (1.0)
Fatigue	6 (0.5)	0
Pyrexia	2 (0.2)	1 (0.1)
Fall	7 (0.6)	7 (0.6)
Dizziness	5 (0.5)	6 (0.5)
Hypersensitivity	4 (0.4)	1 (0.1)
Fungal infection	33 (3.0)	13 (1.2)
Opportunistic infection	33 (3.0)	13 (1.2)
Nasopharyngitis	3 (0.3)	1 (0.1)
Viral infection	8 (0.7)	6 (0.5)
Pneumonia	2 (0.2)	1 (0.1)
Bacterial infection	3 (0.3)	4 (0.4)
Back pain	3 (0.3)	4 (0.4)
Headache	25 (2.3)	17 (1.5)
Somnolence	6 (0.5)	0
Syncope	3 (0.3)	4 (0.4)

System Organ Class Preferred Term	Sulopenem N=1107 n (%)	Amoxicillin/ Clavulanate N=1107 n (%)
Bacterial vaginosis	3 (0.3)	1 (0.1)
Pruritus	2 (0.2)	1 (0.1)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any event that occurs or worsens in either intensity or frequency after the first dose of study drug in a period.

Duration is 5 days for each arm.

Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.

Abbreviations: FMQ, FDA medical query; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; SOC, system organ class

Diarrhea

Diarrhea was the most common TEAE in the sulopenem etzadroxil/probenecid arm and had a higher incidence (8.1% versus 4.1%) than in the amoxicillin/clavulanate arm. In most patients (7.5%), diarrhea was considered to be related to study drug. The mean duration of diarrhea in the sulopenem group was 2.9 days, and the mean duration from end of sulopenem treatment to resolution of diarrhea was 4.1 days. There were no cases of *Clostridioides difficile* infection in the sulopenem etzadroxil/probenecid arm. There was one subject with *Clostridioides difficile* infection in the amoxicillin/clavulanate arm.

Most cases of diarrhea in the oral sulopenem arm were mild or moderate, but there were three cases (0.3%) of severe diarrhea. The subjects with severe diarrhea were not administered therapy for diarrhea and did not discontinue study drug. One of the subjects had diarrhea for one day and the other two subjects had diarrhea for three days. As discussed above in Section [7.6.1.4](#), three patients discontinued sulopenem due to mild or moderate diarrhea.

Vomiting

Vomiting was more common in the sulopenem etzadroxil/probenecid arm, occurring in 1.4% of subjects compared to 0.4% in the comparator arm. Most cases of vomiting were considered mild, and none were severe. No patients discontinued sulopenem etzadroxil/probenecid due to vomiting. The mean duration of vomiting in the sulopenem arm was 1.7 days.

Gastroesophageal Reflux Disease

The incidence of GERD was higher in the sulopenem etzadroxil/probenecid arm, occurring in 1% of subjects compared to 0.1% in the comparator arm. Most cases of GERD were mild. There were no severe cases of GERD; however, as described above in Section [7.6.1.4](#), GERD led to discontinuation of sulopenem in three subjects. The mean duration of GERD was 3.1 days in the sulopenem arm.

Fungal Infection

The number of subjects having an AE of fungal infection was higher in the sulopenem etzadroxil/probenecid arm (3.0%) than in the amoxicillin/clavulanate arm (1.2%). All cases were under the PT vulvovaginal mycotic infection. AEs were either mild or moderate and did not lead to treatment discontinuation.

Fatigue

Five subjects (0.5%) experienced fatigue in the sulopenem etzadroxil/probenecid arm whereas no subjects experienced fatigue in the comparator arm. Four of the five subjects experienced mild fatigue and one experienced moderate fatigue. The mean duration of fatigue was 2.7 days. No subjects discontinued study drug due to fatigue.

Urine Odor Abnormal

The AE of urine odor abnormal only occurred in the sulopenem arm. Four subjects (0.4%) experienced this AE. All cases were considered mild, and none resulted in treatment discontinuation. This AE was also seen in Trial 301 and phase 1 studies of sulopenem. Per the NDA Multi-disciplinary Review and Evaluation {NDA 213972} dated July 22, 2021, the Applicant reported that sulfur-containing sulopenem metabolites are the likely cause of the abnormal urine odor.

7.6.1.6. Laboratory Findings, Trial 310

In Trial 310, there were no significant differences between treatment arms in baseline average chemistry and hematology values or significant interval changes in mean values between baseline and TOC.

As shown in [Table 46](#), the frequency of patients with one or more chemistry analyte values with specified elevated or low values was comparable between the two arms.

Table 46. Subjects With One or More Chemistry Analyte Values With Elevated or Low Values Meeting Specified Levels, Safety Population, Trial 310

Laboratory Parameter	Sulopenem N=1107 n/N_w (%)	Amoxicillin/ Clavulanate N=1107 n/N_w (%)
Level 1 (<132)	5/1061 (0.5)	3/1059 (0.3)
Level 2 (<130)	3/1061 (0.3)	1/1059 (0.1)
Level 3 (<125)	0/1061 (0)	0/1059 (0)
Level 1 (<3.6)	30/1055 (2.8)	25/1057 (2.4)
Level 2 (<3.4)	7/1055 (0.7)	5/1057 (0.5)
Level 1 (>5.5)	8/1055 (0.8)	3/1057 (0.3)
Level 2 (>6)	1/1055 (0.1)	0/1057 (0)
Level 1 (<95)	6/1063 (0.6)	3/1060 (0.3)
Level 1 (>108)	20/1063 (1.9)	29/1060 (2.7)
Level 1 (<20)	4/1063 (0.4)	4/1060 (0.4)
Level 2 (<18)	1/1063 (0.1)	1/1060 (0.1)
Level 3 (>30)	97/1063 (9.1)	95/1060 (9.0)
Level 1 (<70)	20/1059 (1.9)	25/1056 (2.4)
Level 2 (<54)	4/1059 (0.4)	0/1056 (0)
Level 2 (≥200)	43/1059 (4.1)	35/1056 (3.3)
Level 3 (>250)	16/1059 (1.5)	20/1056 (1.9)

Laboratory Parameter	Sulopenem N=1107 n/N _w (%)	Amoxicillin/ Clavulanate N=1107 n/N _w (%)
Level 1 (>23)	55/1062 (5.2)	56/1060 (5.3)
Level 2 (>27)	29/1062 (2.7)	20/1060 (1.9)
Level 3 (>31)	17/1062 (1.6)	11/1060 (1.0)

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](#); rows for Levels in which no values were reported were deleted from the Table.

Duration is 5 days for each arm.

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

Similarly, as shown in [Table 47](#), the number of patients with elevated creatinine or Levels 1 or 2 decrease in GFR was comparable between the sulopenem and amoxicillin/clavulanate arms.

Table 47. Subjects With One or More Kidney Function Analyte Values Exceeding Specified Levels, Safety Population, Trial 310

Laboratory Parameter	Sulopenem N=1107 n/N _w (%)	Amoxicillin/ Clavulanate N=1107 n/N _w (%)
Level 1 (≥1.5X baseline)	15/1053 (1.4)	18/1049 (1.7)
Level 2 (≥2X baseline)	3/1053 (0.3)	2/1049 (0.2)
Level 3 (≥3X baseline)	1/1053 (0.1)	0/1049 (0)
Level 1 (≥25% decrease)	29/1037 (2.8)	31/1037 (3.0)
Level 2 (≥50% decrease)	3/1037 (0.3)	2/1037 (0.2)
Level 3 (≥75% decrease)	1/1037 (0.1)	0/1037 (0)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 5 days for each arm.

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 patients with data

[Table 48](#) shows patients with one or more hematology analyte values exceeding specified levels. Overall, the two arms were similar but there were more subjects in the amoxicillin/clavulanate arm compared to the sulopenem arm with elevated WBC count (>13) and elevated eosinophils (>0.65).

Table 48. Subjects With One or More Hematology Analyte Values Exceeding Specified Levels, Safety Population, Trial 310

Laboratory Parameter	Sulopenem N=1107 n/N _w (%)	Amoxicillin/ Clavulanate N=1107 n/N _w (%)
Level 1 (<3.5)	14/1056 (1.3)	17/1052 (1.6)
Level 2 (<3)	1/1056 (0.1)	4/1052 (0.4)
Level 1 (>10.8)	45/1056 (4.3)	64/1052 (6.1)
Level 2 (>13)	8/1056 (0.8)	19/1052 (1.8)
Level 3 (>15)	2/1056 (0.2)	5/1052 (0.5)

Laboratory Parameter	Sulopenem N=1107 n/N_w (%)	Amoxicillin/ Clavulanate N=1107 n/N_w (%)
Level 2 (>1.5 g/dL dec. from baseline)	22/1036 (2.1)	16/1030 (1.6)
Level 3 (>2 g/dL dec. from baseline)	11/1036 (1.1)	6/1030 (0.6)
Level 2 (>2 g/dL inc. from baseline)	7/1036 (0.7)	10/1030 (1.0)
Level 3 (>3 g/dL inc. from baseline)	2/1036 (0.2)	4/1030 (0.4)
Level 1 (<140)	12/1055 (1.1)	5/1050 (0.5)
Level 2 (<125)	8/1055 (0.8)	4/1050 (0.4)
Level 3 (<100)	3/1055 (0.3)	2/1050 (0.2)
Level 1 (<1)	25/1051 (2.4)	31/1045 (3.0)
Level 2 (<0.75)	6/1051 (0.6)	10/1045 (1.0)
Level 3 (<0.5)	1/1051 (0.1)	0/1045 (0)
Level 1 (>4)	11/1051 (1.0)	12/1045 (1.1)
Level 1 (<2)	50/1051 (4.8)	44/1045 (4.2)
Level 2 (<1)	0/1051 (0)	1/1045 (0.1)
Level 1 (>0.65)	9/1051 (0.9)	21/1045 (2.0)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 5 days for each arm.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

Rows for Levels in which there were no values have been deleted.

Abbreviations: dec, decrease; inc, increase; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; WBC, white blood cells

7.6.1.7. Assessment of Drug-Induced Liver Injury, Trial 310

There were no significant differences between the two treatment arms in the proportions of patients with abnormal liver chemistry values (ALT, aspartate aminotransferase [AST], alkaline phosphatase [AP], total bilirubin). No subjects in the sulopenem arm had elevations in AP >1.5X upper limit of normal (ULN) compared to two (0.2%) subjects in the amoxicillin/clavulanate arm. One (0.1%) subject in the sulopenem arm had an elevated bilirubin level >2X ULN compared to 3 (0.3%) subjects in the amoxicillin/clavulanate arm.

Peak post-baseline elevations of ALT and AST among subjects in Trial 310 are shown in [Table 49](#) and [Table 50](#), respectively. In general, the number of subjects with an elevated ALT or AST were comparable between the two arms. No patients in the sulopenem arm had an ALT ≥5x ULN. A single patient in the sulopenem arm had an AST ≥5x ULN. No subject in either arm had an ALT or AST value >10X ULN.

Table 49. Peak Post-Baseline ALT, Safety Population, Trial 310

ALT Post-Baseline	Sulopenem N=1107 n/N_w (%)	Amoxicillin/ Clavulanate N=1107 n/N_w (%)
≤ULN	1033/1061 (97.4)	1032/1060 (97.4)
>ULN to <2x ULN	22/1061 (2.1)	22/1060 (2.1)
≥2x ULN to <3x ULN	4/1061 (0.4)	2/1060 (0.2)

	Sulopenem N=1107 n/N_w (%)	Amoxicillin/ Clavulanate N=1107 n/N_w (%)
ALT Post-Baseline		
≥3x ULN to <5x ULN	2/1061 (0.2)	1/1060 (0.1)
≥5x ULN to <10x ULN	0/1061 (0)	3/1060 (0.3)

Source: adlb.xpt; Software: R

Duration is 5 days for each arm.

Abbreviations: ALT, alanine aminotransferase; 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 50. Peak Post-Baseline AST, Safety Population, Trial 310

	Sulopenem N=1107 n/N_w (%)	Amoxicillin/ Clavulanate N=1107 n/N_w (%)
AST Post-Baseline		
≤ULN	1037/1060 (97.8)	1040/1060 (98.1)
>ULN to <2x ULN	17/1060 (1.6)	15/1060 (1.4)
≥2x ULN to <3x ULN	4/1060 (0.4)	3/1060 (0.3)
≥3x ULN to <5x ULN	1/1060 (0.1)	2/1060 (0.2)
≥5x ULN to <10x ULN	1/1060 (0.1)	0/1060 (0)

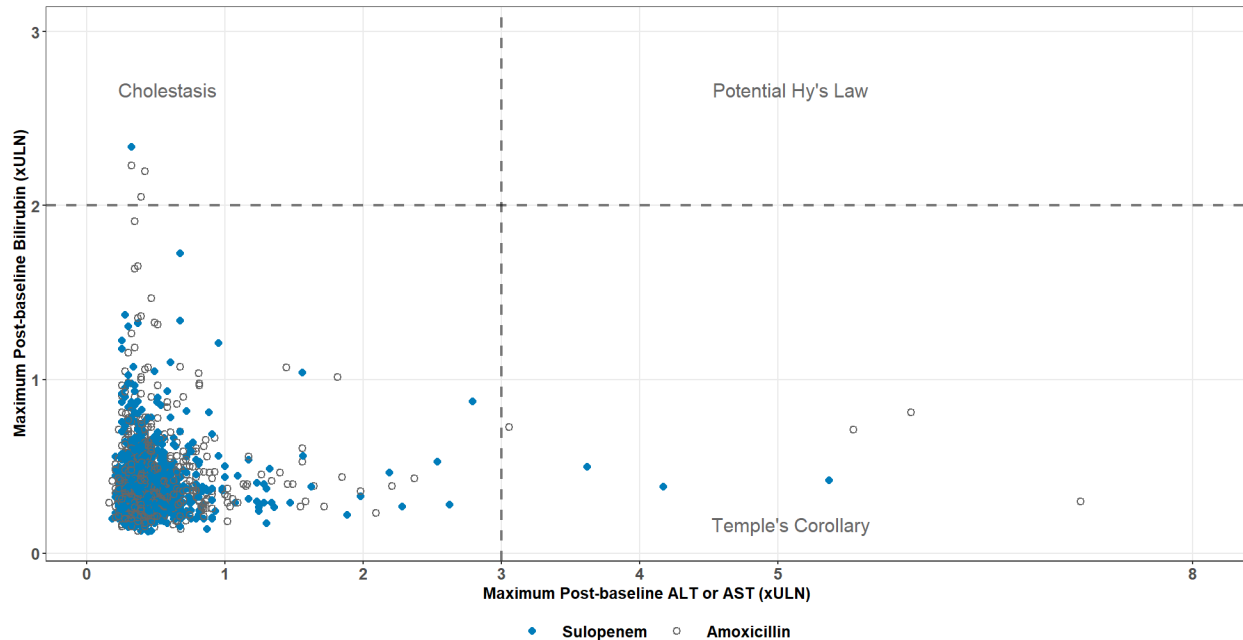
Source: adlb.xpt; Software: R

Duration is 5 days for each arm.

Abbreviations: AST, aspartate aminotransferase; 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

[Figure 2](#) shows an eDISH plot for potential cases of serious drug-induced liver injury. There were no Hy's Law cases in Trial 310 in either arm.

Figure 2. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Trial 310



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 postbaseline period.

A potential Hy's Law case was defined as having any postbaseline total bilirubin equal to or exceeding 2X ULN after a postbaseline ALT or AST equal to or exceeding 3X ULN. Those subjects who meet total bilirubin equal to or exceeding 2X ULN criteria within 30 days of the ALT or AST equal to or exceeding 3X ULN criteria are circled in red.

The within 30 days analysis window rule does not apply to cholestasis and temple's corollary cases.

All subjects with at least one postbaseline ALT or AST, bilirubin and ULN are plotted.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

For number of subjects in each quadrant, see the table "Subjects in Each Quadrant for Potential Hepatocellular Drug-Induced Liver Injury Screening Plot ..." and the listing "Listing of Subjects in Hepatocellular Drug-Induced Liver Injury Screening...."

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal

Table 51. Subjects in Each Quadrant for Potential Hepatocellular DILI Screening Plot, Safety Population, Trial 310

Quadrant	Sulopenem N=1107 n/N _w (%)	Amoxicillin/ Clavulanate N=1107 n/N _w (%)
Potential Hy's Law (right upper)	0/1061 (0)	0/1060 (0)
Cholestasis (left upper)	1/1061 (0.1)	3/1060 (0.3)
Temple's corollary (right lower)	3/1061 (0.3)	4/1060 (0.4)
Total	4/1061 (0.4)	7/1060 (0.7)

Source: adlb.xpt; Software: R

A potential Hy's Law case was defined as having any postbaseline total bilirubin equal to or exceeding 2X ULN after a postbaseline ALT or AST equal to or exceeding 3X ULN.

The within 30 days analysis window rule does not apply to cholestasis 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 liver injury; 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

Subjects With Elevated Liver Enzymes Postbaseline

Narratives for subjects in the sulopenem arm with ALT or AST values >3x ULN or Bilirubin >2x ULN are discussed below. The first three subjects had normal liver function tests at baseline,

while the last subject had abnormal liver function tests at baseline. Please also refer to Section [7.6.4.7](#).

- Subject (b) (6) was a 74-year-old woman who received five days of sulopenem etzadroxil/probenecid. On Day 12, ALT had increased to 192 U/L, AST had increased to 87 U/L, and gamma-glutamyl transferase (GGT) had increased to 248 U/L. AP and bilirubin were normal. At Day 28, AST and ALT had normalized and GGT trended down to 119 U/L (normal range 7-38 U/L). The subject was asymptomatic but had underlying non-alcoholic steatohepatitis and was taking Crestor and metformin. Sulopenem may have contributed to the increase in GGT, AST, and ALT, but attribution of causality is confounded by the subject's comorbidities and concomitant medications.
- Subject (b) (6) was a 23-year-old woman with ALT and AST elevated at 92 U/L and 231 U/L, respectively, at the Day 12 visit. Additionally, lactate dehydrogenase was elevated at 510 U/L. GGT, AP, and bilirubin levels were normal. On Day 15, ALT and AST were trending down and lactate dehydrogenase had normalized. Liver enzymes were normal on Day 22. The subject was asymptomatic and her only other medication was Lo Loestrin Fe. Investigations included negative viral hepatitis serologies, negative urine toxicology screen, normal % carbohydrate-deficient transferrin, and normal CK-18 M30 Apoptosense. Given the time course and lack of an alternative cause, sulopenem was potentially the cause of the elevation in liver enzymes.
- Subject (b) (6) was a 27-year-old woman who received 5 days of sulopenem etzadroxil/probenecid. On Day 12, total bilirubin and direct bilirubin were elevated at 2.83 mg/dL and 0.49 mg/dL, respectively. ALT, AST, GGT, and AP were normal. Labs were repeated on Day 37 and the bilirubin had normalized. The subject was asymptomatic and her only concomitant medication was an oral contraceptive (Yasmine). Urine toxicology screen and hepatitis serologies were negative. Testing for % carbohydrate-deficient-transferrin was normal. The etiology of the asymptomatic hyperbilirubinemia is unclear, but Gilbert syndrome is a consideration.
- Subject (b) (6) was a 38-year-old woman who received 5 days of sulopenem etzadroxil/probenecid. At baseline, ALT (236 U/L), AST (180 U/L), and GGT (123 U/L) were elevated. At Day 5, these lab values remained abnormal with decreases in ALT and AST values and slight increase in GGT. At Day 12, ALT, AST and GGT remained elevated. She had a past history of elevated liver function tests with no clear etiology. As these laboratory abnormalities were present at baseline, sulopenem was likely not the cause.

7.6.1.8. Vital-Sign Analyses, Trial 310

Review of mean values and mean changes in vital signs from baseline to Day 12 did not reveal significant differences between the two arms.

7.6.1.9. Subgroup Analyses, Trial 310

All subjects in Trial 310 were female. In the sulopenem arm, the frequency of AEs was overall balanced across age groups. AEs occurred with a similar frequency between white and Black subjects within both arms. The small number of subjects of other races preclude further

conclusions about race-based AE imbalances. In the sulopenem arm, AEs were less frequent (14.4%) in Hispanic or Latino subjects than in non-Hispanic/Latino subjects (27.9%). The reason for this finding is unclear and differs from Trial 301 where AEs were more frequent in Hispanic or Latino subjects (28.9%) than in non-Hispanic/Latino subjects (22.7%). The frequency of AEs was similar in sulopenem subjects with CrCl 30-60 mL/min and sulopenem subjects with CrCl >60 mL/min. The number of subjects with CrCl <30 mL/min was too low to draw conclusions. Sulopenem-treated subjects with a BMI of <25 had the highest frequency of AEs compared with subjects with higher BMIs; this may be a chance finding as a biologically plausible cause is not apparent.

Table 52. Overview of Adverse Events by Demographic Subgroup, Safety Population, Trial 310

Characteristic	Sulopenem N=1107 n/N_s (%)	Amoxicillin/ Clavulanate N=1107 n/N_s (%)
Sex, n (%)		
Female	209/1107 (18.9)	136/1107(12.3)
Age group, years, n (%)		
18-29	35/177 (19.8)	16/190 (8.4)
30-60	122/615 (19.8)	80/620 (12.9)
>=60	52/315 (16.5)	40/297 (13.5)
>=65	37/224 (16.5)	35/212 (16.5)
>=75	12/80 (15.0)	15/64 (23.4)
Race, n (%)		
American Indian or Alaska Native	1/2 (50.0)	0/4 (0)
Asian	6/19 (31.6)	5/15 (33.3)
Black or African American	36/194 (18.6)	26/217 (12.0)
Native Hawaiian or Other Pacific Islander	0/1 (0)	0/2 (0)
Other	5/16 (31.2)	4/14 (28.6)
White	161/875 (18.4)	101/855 (11.8)
Ethnicity, n (%)		
Hispanic or Latino	107/741 (14.4)	84/760 (11.1)
Not Hispanic or Latino	102/366 (27.9)	52/346 (15.0)
Not Reported	0/0 (NA)	0/1 (0)
Body mass index by category (Kg/m²)		
<25	65/272 (23.9)	38/322 (11.8)
25-30	65/400 (16.2)	44/381 (11.5)
>30	79/435 (18.2)	54/404 (13.4)
Creatinine clearance by category (mL/min), n (%)		
<30	1/9 (11.1)	5/19 (26.3)
30-60	33/199 (16.6)	20/170 (11.8)
>60	173/890 (19.4)	107/906 (11.8)
Missing	2/9 (22.2)	4/12 (33.3)

Source: adae.xpt; Software: R

Abbreviations: NA, not applicable; N, number of subjects in treatment arm; n, number of subjects with adverse event; N_s, total number of patients for each specific subgroup and were assigned to that specific arm

7.6.2. Summary of Safety Results, Trial 301

The safety data from Trial 301 were reviewed in the initial review cycle for NDA 213972. The Agency's safety database excluded 13 subjects (8 in the sulopenem arm and 5 in the ciprofloxacin arm) from Site 218

(b) (7)(A)

(b) (7)(A) The Applicant included these subjects in their safety database. For completeness, a summary of safety findings from Trial 301 is provided below. For detailed analysis, please refer to the NDA Multi-disciplinary Review and Evaluation {NDA 213972} dated July 22, 2021. Identified safety issues during the previous review cycle included hypersensitivity reactions, elevated ALT, and GI adverse reactions.

A total of 825 subjects in the sulopenem arm were included in the safety database of Trial 301. More subjects in the sulopenem arm (25.1%) experienced a TEAE than subjects in the ciprofloxacin arm (14.0%), largely driven by TEAEs in the Gastrointestinal disorders SOC (17% in the sulopenem arm, 7.9% in the ciprofloxacin arm) and to a lesser extent by TEAEs under the SOCs of Infections and infestations (4.6% in the sulopenem arm, 2.6% in the ciprofloxacin arm), Nervous system disorders (3.8% in the sulopenem arm, 2.8% in the ciprofloxacin arm), and Renal and urinary disorders (1.5% in the sulopenem arm, 0.1% in the ciprofloxacin arm). The following TEAEs occurred in 1% or more of subjects in the sulopenem arm and were more frequent in the sulopenem arm compared to the ciprofloxacin arm (listed in descending order): diarrhea (12.5%), nausea (3.9%), headache (2.2%), abdominal pain (2.2%), vomiting (1.6%), vulvovaginal mycotic infection (1.3%), dizziness (1.1%), and urine odor abnormal (1.0%). A total of 13 (1.6%) subjects in the sulopenem arm had a TEAE leading to study drug discontinuation compared to 8 (1.0%) subjects in the ciprofloxacin arm. The following TEAEs led to sulopenem discontinuation: vomiting (n=3), abdominal pain (n=2), diarrhea (n=2), dizziness (n=2), nausea (n=1), angioedema (n=1), dyspnea (n=1), and hypertension (n=1).

Given that there was a notable imbalance in diarrhea between arms, further analysis was conducted. Diarrhea occurred in 103 (12.5%) subjects in the sulopenem arm and 21 (2.6%) in the ciprofloxacin arm. In the sulopenem arm, all diarrhea was either mild (10.2%) or moderate (2.3%). The FDA reviewer noted that the average duration of diarrhea was longer by about one day in subjects in the sulopenem arm compared to subjects in the ciprofloxacin arm, and subjects who took sulopenem with food had a shorter duration of diarrhea (a difference of 2 days on average) compared to subjects who did not take all their sulopenem doses with food.

There was one death in Trial 301 and this subject is described in Section [7.6.4.2](#) Six subjects (0.7%) in the sulopenem arm (described in Section [7.6.4.3](#) and two subjects (0.2%) in the ciprofloxacin arm experienced SAEs.

On review of mean chemistry and hematology laboratory values at baseline and Day 12 (TOC), the proportions of sulopenem subjects with postbaseline abnormalities, including liver enzyme elevations, were low and no significant differences were noted between treatment arms. There were no cases meeting Hy's Law criteria in the sulopenem arm, and no imbalances were noted in peak AST elevations between arms. The FDA reviewer, Dr. Mukil Natarajan, noted that several of the subjects with ALT elevations had baseline abnormal ALT values that were likely due to underlying conditions such as fatty liver disease. Dr. Natarajan concluded that sulopenem may cause elevation of ALT.

No significant differences in vital signs were seen between the two arms. Electrocardiograms were not collected in the phase 3 trials as there was adequate data on sulopenem and cardiac conduction from the phase 1 Study A7371007, which was reviewed by the QT Interdisciplinary Review Team in 2017.

Subgroup analyses revealed that subjects with Hispanic/Latino ethnicity, BMI>30, and those in the United States were more likely to have a TEAE compared to the overall population. Among these groups, the difference in the incidence of TEAEs between the arms was largely accounted for by diarrhea. Most subjects of Hispanic/Latino ethnicity and BMI>30 were enrolled in the United States. The FDA reviewer suspected the higher incidence of diarrhea could be due to different physiological responses based on ethnicity or obesity or could be due to differences in AE reporting by country/site. The FDA reviewer noted that the rate of TEAEs in Ukraine was notably lower than in the United States or Russia with no TEAEs of diarrhea reported from subjects in Ukraine.

The integrated assessment of safety included data from Trials 301, 302, and 303 as well as phase 1 and 2 studies. The following safety issues were identified:

- Angioedema: As discussed in Section [7.6.4.1](#), one sulopenem subject in Trial 301 experienced angioedema. In addition, a subject in a phase 1 study experienced angioedema after a dose of sulopenem etzadroxil/probenecid. Hypersensitivity will be included as a warning in the labeling.
- Gastrointestinal AEs: GI AEs, including diarrhea, nausea, and abdominal pain, were common among subjects taking sulopenem. Diarrhea was the most common AE among sulopenem subjects, and in general was mild and not treatment-limiting. Taking sulopenem etzadroxil/probenecid with food appeared to shorten the duration of diarrhea. GI AEs are to be included in Section 6 of labeling.
- Elevations in ALT: As noted in Section [7.6.4.7](#), elevations in ALT were more common among sulopenem subjects compared to ciprofloxacin subjects in Trial 301 and in the integrated phase 3 population (Trials 301, 302, and 303). Please refer to Section [7.6.4.7](#). Elevated transaminases will be noted in Section 6 of labeling.

The safety findings from Trial 310 were consistent with the safety findings from Trial 301. No new safety signals were identified in Trial 310.

7.6.3. Summary of Safety in Phase 1 and Phase 2 Clinical Studies

The phase 1 and 2 studies were reviewed during the initial review cycle (see the NDA Multi-disciplinary Review and Evaluation {NDA 213972} dated July 22, 2021). Safety signals identified in phase 1 studies were diarrhea, nausea, abdominal pain, headache, dizziness, rash, and abnormal urine odor. Additionally, as noted above, one subject who received oral sulopenem etzadroxil/probenecid experienced angioedema of the face and lips and discontinued study drug. The safety signals in the phase 3 trials were consistent with the observed AEs in the phase 1 studies.

In the Pfizer-conducted phase 2 studies, there were three deaths in subjects who received sulopenem. Dr. Natarajan reviewed the narratives. Two deaths were due to underlying malignancy and not related to sulopenem. The third death was related to myocardial infarction and pneumonia which were unlikely to be related to sulopenem.

7.6.4. Safety Results, Pooled Analyses, Trials 301 and 310

7.6.4.1. Overview of Treatment-Emergent Adverse Events Summary, Pooled Analyses, Trials 301 and 310

An overview of TEAEs, SAEs and drug discontinuations in the ISP (Trials 301 and 310) is provided in [Table 53](#). Six (0.3%) subjects in the sulopenem arm had a SAE. All six subjects were enrolled in Trial 301. One SAE, angioedema, was judged as related to sulopenem etzadroxil/probenecid and led to treatment discontinuation; the remaining SAEs are described in [Section 7.6.4.3](#). The single death was due to underlying lung adenocarcinoma and was not related to study drug (see [Section 7.6.4.2](#)). TEAEs resulting in treatment discontinuation were reported in 21 (1.1%) subjects in the sulopenem group with the majority of the TEAEs being gastrointestinal AEs, including diarrhea, nausea, vomiting, abdominal pain, and gastroesophageal reflux disease (see [Section 7.6.4.4](#)). The overall incidence of TEAEs was higher (21.5%) in the sulopenem group than in the comparator groups (amoxicillin/clavulanate, 12.3%; ciprofloxacin, 14.0%). In all three groups, the majority of TEAEs were mild or moderate with severe AEs being uncommon.

Table 53. Overview of Adverse Events, Integrated Safety Population, Trials 301 and 310

Event Category	Sulopenem	Amoxicillin/ Clavulanate	Ciprofloxacin
	N=1932 n (%)	N=1107 n (%)	N=822 n (%)
SAE	6 (0.3)	5 (0.5)	2 (0.2)
SAEs with fatal outcome	1 (0.1)	0	0
Life-threatening SAEs	0	0	0
SAEs requiring hospitalization	4 (0.2)	0	2 (0.2)
AE leading to permanent discontinuation of study drug	21 (1.1)	4 (0.4)	8 (1.0)
AE leading to dose modification of study drug	0	0	0
AE leading to interruption of study drug	0	0	0
AE leading to reduction of study drug	0	0	0
AE leading to dose delay of study drug	0	0	0
Any AE	416 (21.5)	136 (12.3)	115 (14.0)
Severe and worse	12 (0.6)	3 (0.3)	1 (0.1)
Moderate	110 (5.7)	37 (3.3)	27 (3.3)
Mild	293 (15.2)	96 (8.7)	87 (10.6)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any event that occurs or worsens in either intensity or frequency after the first dose of study drug in a period.

Duration is 5 days for Sulopenem or Amoxicillin/clavulanate, 3 days for Ciprofloxacin.

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, Pooled Analyses, Trials 301 and 310

There was one death in Trial 301, and no deaths in Trial 310. In Trial 301, Subject (b) (6) was a 71-year-old Hispanic/Latina woman in the United States who received sulopenem etzadroxil/probenecid from (b) (6), was diagnosed with lung adenocarcinoma on (b) (6) and died on (b) (6). This death was judged to be

related to complications of the underlying cancer and not to study drug as it occurred months after sulopenem exposure, and it is biologically implausible for cancer to develop after a brief sulopenem exposure.

[Table 54](#) summarizes the deaths in the sulopenem arms of the phase 3 trials (Trials 301, 302, 303 and 310). Six deaths occurred in the sulopenem arms of Trials 302 and 303. None of the deaths were attributable to sulopenem. For further details, please refer to the NDA Multi-disciplinary Review and Evaluation {NDA 213972} dated July 22, 2021.

Table 54. Deaths, Sulopenem Safety Population, Trials 301, 302, 303, and 310

Trial	Age (Years)/Sex	AE Associated With Death	Study Day	
			Start of AE	Study Day of Death
301	71/F	Lung adenocarcinoma	15	171
302	60/M	Renal cell carcinoma	5	25
302	73/F	Salivary gland neoplasm	6	6
303	76/F	Cardiac arrest	11	11
303	88/F	Multiple organ dysfunction syndrome	5	5
303	77/F	Cerebrovascular accident	4	4
303	74/F	Sudden death	28	28

Source: Reviewer table

Abbreviations: AE, adverse event; F, female; M, male

7.6.4.3. Serious Treatment-Emergent Adverse Events, Pooled Analyses, Trials 301 and 310

In the uUTI ISP, six subjects (0.3%) who received sulopenem etzadroxil/probenecid experienced SAEs compared to five (0.5%) and 2 (0.2%) in the amoxicillin/clavulanate and ciprofloxacin arms, respectively. All six sulopenem subjects were enrolled in Trial 301. In the sulopenem arm, the SAEs included angioedema, lung adenocarcinoma, presyncope, small intestinal obstruction, abdominal pain upper, chest pain, pyelonephritis acute, and urosepsis. Only the SAE of angioedema was attributed to sulopenem etzadroxil/probenecid. As presyncope, small intestinal obstruction, abdominal pain and chest pain occurred on Day 21 or later, the clinical reviewer judged these events as less likely to be related to sulopenem. The SAE of lung adenocarcinoma was not related to sulopenem etzadroxil/probenecid as discussed above. Pyelonephritis and urosepsis were attributed to an obstructing kidney stone rather than to study drug. For further details, please refer to the NDA Multi-disciplinary Review and Evaluation {NDA 213972} dated July 22, 2021.

Table 55. Subjects With Serious Adverse Events by System Organ Class and Preferred Term, Integrated Safety Population, Trials 301 and 310

System Organ Class Preferred Term	Sulopenem	Amoxicillin/ Clavulanate	Ciprofloxacin
	N=1932 n (%)	N=1107 n (%)	N=822 n (%)
Any SAE	6 (0.3)	5 (0.5)	2 (0.2)
Gastrointestinal disorders (SOC)	2 (0.1)	1 (0.1)	1 (0.1)
Abdominal pain	1 (0.1)	0	0
Small intestinal obstruction	1 (0.1)	0	0
Diarrhea	0	0	1 (0.1)
Diverticulum	0	1 (0.1)	0
General disorders and administration site conditions (SOC)	1 (0.1)	1 (0.1)	0
Chest pain	1 (0.1)	1 (0.1)	0
Hepatobiliary disorders (SOC)	0	0	1 (0.1)
Bile duct stone	0	0	1 (0.1)
Infections and infestations (SOC)	1 (0.1)	1 (0.1)	1 (0.1)
Pyelonephritis acute	1 (0.1)	0	0
Urosepsis	1 (0.1)	0	0
Genital herpes	0	1 (0.1)	0
Pneumonia	0	0	1 (0.1)
Metabolism and nutrition disorders (SOC)	0	1 (0.1)	0
Dehydration	0	1 (0.1)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	1 (0.1)	0	0
Lung adenocarcinoma	1 (0.1)	0	0
Nervous system disorders (SOC)	1 (0.1)	0	0
Presyncope	1 (0.1)	0	0
Renal and urinary disorders (SOC)	0	1 (0.1)	0
Nephrolithiasis	0	1 (0.1)	0
Skin and subcutaneous tissue disorders (SOC)	1 (0.1)	0	0
Angioedema	1 (0.1)	0	0

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any event that occurs or worsens in either intensity or frequency after the first dose of study drug in a period.

Serious adverse events defined as any untoward medical occurrence that at any dose 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 is 5 days for sulopenem or amoxicillin, 3 days for ciprofloxacin.

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

In the integrated phase 3 safety population (Trials 301, 302, 303) of the original NDA submission, 45 (2.4%) subjects in the sulopenem arm experienced an SAE compared to 20 (1.1%) in the comparator arm. Please refer to Tables 95 and 96 in the NDA Multi-disciplinary Review and Evaluation {NDA 213972} dated July 22, 2021. The clinical reviewer noted that most of the imbalance between treatment arms was accounted for by SAEs within the SOC of Infections and infestations; the PTs of abdominal abscess and urinary tract infections were common. The reviewer concluded that the events were not directly attributable to sulopenem, but likely reflected treatment failure or complications of the primary infection.

7.6.4.4. Adverse Events Leading to Treatment Discontinuation, Pooled Analyses, Trials 301 and 310

TEAEs resulting in treatment discontinuation were reported in 21 (1.1%) subjects in the pooled sulopenem group of the ISP with the majority of these TEAEs falling under the Gastrointestinal disorders SOC, including nausea (0.3%), diarrhea (0.3%), abdominal pain (0.2%), gastroesophageal reflux disease (0.2%), vomiting (0.2%), constipation (0.1%), dyspepsia (0.1%), eructation (0.1%), and flatulence (0.1%). Three (0.2%) subjects experienced dizziness leading to treatment discontinuation. Non-gastrointestinal AEs leading to treatment discontinuation in 0.1% of subjects treated with sulopenem were angioedema, syncope, chills, fatigue, dysgeusia, headache, dyspnea, pruritus, and hypertension.

Table 56. Subjects With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Integrated Safety Population, Trials 301 and 310

System Organ Class Preferred Term	Amoxicillin/ Sulopenem Clavulanate Ciprofloxacin		
	N=1932 n (%)	N=1107 n (%)	N=822 n (%)
Any AE leading to discontinuation	21 (1.1)	4 (0.4)	8 (1.0)
Gastrointestinal disorders (SOC)	15 (0.8)	3 (0.3)	8 (1.0)
Nausea	6 (0.3)	0	5 (0.6)
Diarrhea	5 (0.3)	1 (0.1)	2 (0.2)
Abdominal pain	3 (0.2)	1 (0.1)	2 (0.2)
Gastroesophageal reflux disease	3 (0.2)	0	0
Vomiting	3 (0.2)	0	3 (0.4)
Constipation	1 (0.1)	0	0
Dyspepsia	1 (0.1)	0	0
Eructation	1 (0.1)	0	0
Flatulence	1 (0.1)	0	0
Diverticulum	0	1 (0.1)	0
General disorders and administration site conditions (SOC)	3 (0.2)	0	0
Chills	2 (0.1)	0	0
Fatigue	1 (0.1)	0	0
Nervous system disorders (SOC)	6 (0.3)	0	3 (0.4)
Dizziness	3 (0.2)	0	1 (0.1)
Dysgeusia	1 (0.1)	0	0
Headache	1 (0.1)	0	2 (0.2)
Syncope	1 (0.1)	0	0
Renal and urinary disorders (SOC)	0	1 (0.1)	0
Nephrolithiasis	0	1 (0.1)	0
Respiratory, thoracic and mediastinal disorders (SOC)	1 (0.1)	0	0
Dyspnea	1 (0.1)	0	0
Skin and subcutaneous tissue disorders (SOC)	2 (0.1)	0	0
Angioedema	1 (0.1)	0	0
Pruritus	1 (0.1)	0	0
Vascular disorders (SOC)	1 (0.1)	0	0
Hypertension	1 (0.1)	0	0

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any event that occurs or worsens in either intensity or frequency after the first dose of study drug in a period.

Duration is 5 days for sulopenem or amoxicillin, 3 days for ciprofloxacin.

Abbreviations: AE, adverse event; N, number of subjects in treatment arm; n, number of subjects with adverse event; SOC, system organ class

On review of Trials 302 and 303 during the initial NDA review, the clinical reviewer identified 5 subjects who discontinued sulopenem due to nonserious AEs. The following AEs were possibly or likely related to study drug: pruritus, hepatitis toxic (See Section 7.6.4.7), diarrhea, and rash. One AE was coded as cerebrovascular accident, but it was not clear if an actual stroke occurred. For details, please refer to Table 98 in the NDA Multi-disciplinary Review and Evaluation {NDA 213972} dated July 22, 2021.

7.6.4.5. Treatment-Emergent Adverse Events, Pooled Analyses, Trials 301 and 310

In the ISP (Trials 301 and 310), the most common AE in subjects treated with sulopenem etzadroxil/probenecid was diarrhea, which occurred in 194 (10%) subjects, compared to 4.1% and 2.6% of subjects treated with amoxicillin/clavulanate and ciprofloxacin, respectively. The second most common AE in subjects treated with sulopenem etzadroxil/probenecid was nausea, which occurred in 80 (4.1%) of subjects. In addition to diarrhea and nausea, the following AEs occurred in >1% of subjects treated with oral sulopenem: vulvovaginal mycotic infection (2.4%), headache (2.2%), vomiting (1.5%), and abdominal pain (1.1%). Gastroesophageal reflux disease (0.7%) and urine odor abnormal (0.6%) occurred infrequently in subjects treated with sulopenem but in more sulopenem subjects than in the comparator groups.

Table 57. Subjects With Adverse Events Occurring at $\geq 0.5\%$ Frequency in the Sulopenem Arm, Integrated Safety Population, Trials 301 and 310

Preferred Term	Sulopenem	Amoxicillin/ Clavulanate	Ciprofloxacin
	N=1932 n (%)	N=1107 n (%)	N=822 n (%)
Any AE	416 (21.5)	136 (12.3)	115 (14.0)
Diarrhea	194 (10.0)	45 (4.1)	21 (2.6)
Nausea	80 (4.1)	32 (2.9)	30 (3.6)
Vulvovaginal mycotic infection	46 (2.4)	13 (1.2)	7 (0.9)
Headache	42 (2.2)	17 (1.5)	18 (2.2)
Vomiting	29 (1.5)	4 (0.4)	11 (1.3)
Abdominal pain	22 (1.1)	11 (1.0)	9 (1.1)
Gastroesophageal reflux disease	13 (0.7)	1 (0.1)	0
Urine odor abnormal	12 (0.6)	0	1 (0.1)
Dizziness	11 (0.6)	4 (0.4)	5 (0.6)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any event that occurs or worsens in either intensity or frequency after the first dose of study drug in a period.

Duration is 5 days for sulopenem or amoxicillin/clavulanate, 3 days for ciprofloxacin.

Coded as MedDRA preferred terms.

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event

In the ISP, AEs by FMQ occurring in $\geq 0.5\%$ of sulopenem subjects were in the following SOCs: Gastrointestinal disorders, Infections and infestations, Nervous system disorders, and General disorders and administration site conditions.

Table 58. Subjects With Adverse Events by System Organ Class and FDA Medical Query (Narrow) Occurring at $\geq 0.5\%$ Frequency in the Sulopenem Arm, Integrated Safety Population, Trials 301 and 310

System Organ Class FMQ (Narrow)	Sulopenem	Amoxicillin/ Clavulanate	Ciprofloxacin
	N=1932 n (%)	N=1107 n (%)	N=822 n (%)
Gastrointestinal disorders (SOC)			
Diarrhea	90 (4.7)	45 (4.1)	21 (2.6)
Nausea	80 (4.1)	32 (2.9)	30 (3.6)
Vomiting	29 (1.5)	4 (0.4)	11 (1.3)
Abdominal pain	22 (1.1)	11 (1.0)	9 (1.1)
General disorders and administration site conditions (SOC)			
Dizziness	15 (0.8)	6 (0.5)	6 (0.7)
Fatigue	9 (0.5)	0	3 (0.4)
Infections and infestations (SOC)			
Fungal infection	49 (2.5)	13 (1.2)	8 (1.0)
Nasopharyngitis	12 (0.6)	1 (0.1)	6 (0.7)
Viral infection	11 (0.6)	5 (0.5)	0
Nervous system disorders (SOC)			
Headache	43 (2.2)	17 (1.5)	18 (2.2)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any event that occurs or worsens in either intensity or frequency after the first dose of study drug in a period.

Duration is 5 days for sulopenem or amoxicillin/clavulanate, 3 days for ciprofloxacin.

Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.

Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.

Abbreviations: FMQ, FDA medical query; incl, including; N, number of subjects in treatment arm; n, number of subjects with adverse event; SOC, system organ class

In the integrated phase 3 population from the initial NDA review consisting of the combined safety population of Trials 301, 302, and 303, 397 (21.4%) out of 1855 subjects in the sulopenem arm experienced at least one TEAE compared to 305 (16.5%) out of 1852 subjects in the comparator arm. The following TEAEs occurred in $\geq 0.5\%$ of subjects in the sulopenem arm: diarrhea (7.4%), nausea (2.9%), headache (2.2%), abdominal pain (1.5%), vomiting (1.2%), dizziness (0.8%), vulvovaginal mycotic infection (0.8%), and hypertension (0.7%). The clinical reviewer noted that much of the imbalance in TEAEs between sulopenem and the comparator was accounted for by PTs in the gastrointestinal SOC, mainly diarrhea and abdominal pain. For further details, please refer to the NDA Multi-disciplinary Review and Evaluation {NDA 213972} dated July 22, 2021.

7.6.4.6. Laboratory Findings, Pooled Analyses, Trials 301 and 310

No major laboratory abnormalities were noted in the sulopenem arm of the ISP. Distribution of abnormal chemistry laboratory findings as shown in [Table 59](#), are similar between the sulopenem and comparator arms. There was a slightly higher percentage of subjects with level 2 (≥ 200 mg/dL) glucose elevation in the sulopenem arm (4%) compared with the amoxicillin/clavulanate (3.3%) or ciprofloxacin (2.7%) arms. However, the percentage of subjects with level 3 (≥ 250 mg/dL) glucose elevations were balanced among the three arms. While elevations in potassium were balanced between the sulopenem arm and ciprofloxacin arms, a higher percentage of sulopenem subjects had Level 1 (>5.5 mEq/L) and Level 2 (>6

mEq/L) elevations in potassium compared to amoxicillin/clavulanate arm subjects. Overall, there do not appear to be major differences between sulopenem and the comparators with respect to chemistry laboratory findings. The imbalances noted in potassium and glucose values are not likely to be significant in the context of uUTI treatment.

Table 59. Subjects With One or More Chemistry Analyte Values With Elevated or Decreased Values Meeting Specified Levels, Integrated Safety Population, Trials 301 and 310

Laboratory Parameter	Sulopenem	Amoxicillin/ Clavulanate	Ciprofloxacin
	N=1932 n/N _w (%)	N=1107 n/N _w (%)	N=822 n/N _w (%)
Sodium, low (mEq/L)			
Level 1 (<132)	9/1867 (0.5)	3/1059 (0.3)	6/797 (0.8)
Level 2 (<130)	5/1867 (0.3)	1/1059 (0.1)	1/797 (0.1)
Potassium, low (mEq/L)			
Level 1 (<3.6)	46/1842 (2.5)	25/1057 (2.4)	10/769 (1.3)
Level 2 (<3.4)	10/1842 (0.5)	5/1057 (0.5)	3/769 (0.4)
Potassium, high (mEq/L)			
Level 1 (>5.5)	22/1842 (1.2)	3/1057 (0.3)	9/769 (1.2)
Level 2 (>6)	9/1842 (0.5)	0/1057 (0)	5/769 (0.7)
Level 3 (>6.5)	3/1842 (0.2)	0/1057 (0)	3/769 (0.4)
Chloride, high (mEq/L)			
Level 1 (>108)	63/1869 (3.4)	29/1060 (2.7)	26/797 (3.3)
Level 2 (>112)	2/1869 (0.1)	0/1060 (0)	1/797 (0.1)
Level 3 (>115)	1/1869 (0.1)	0/1060 (0)	0/797 (0)
Glucose, low (mg/dL)			
Level 1 (<70)	45/1856 (2.4)	25/1056 (2.4)	18/784 (2.3)
Level 2 (<54)	6/1856 (0.3)	0/1056 (0)	2/784 (0.3)
Level 3 (<40)	1/1856 (0.1)	0/1056 (0)	0/784 (0)
Glucose, random, high (mg/dL)			
Level 2 (≥200)	74/1856 (4.0)	35/1056 (3.3)	21/784 (2.7)
Level 3 (>250)	29/1856 (1.6)	20/1056 (1.9)	8/784 (1.0)
Blood urea nitrogen, high (mg/dL)			
Level 1 (>23)	101/1868 (5.4)	56/1060 (5.3)	46/797 (5.8)
Level 2 (>27)	54/1868 (2.9)	20/1060 (1.9)	20/797 (2.5)
Level 3 (>31)	31/1868 (1.7)	11/1060 (1.0)	9/797 (1.1)

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 5 days for sulopenem or amoxicillin/clavulanate, 3 days for ciprofloxacin.

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

As shown in [Table 60](#), there was a higher percentage (1.7%) of subjects with Level 1 (≥1.5X baseline) elevations in creatinine in the amoxicillin/clavulanate arm compared to the percentage (0.9%) in the sulopenem arm; however, the percentages for Level 2 (≥2X baseline) and Level 3 (≥3X baseline) elevations were comparable. The percentage (2.4%) of subjects with Level 1 (≥25%) decrease in GFR in the sulopenem arm was slightly lower than the amoxicillin/clavulanate arm (3.0%) but slightly higher than the ciprofloxacin arm (1.7%). As discussed above in [Section 7.5](#), the distribution of CrCl was similar between the sulopenem and ciprofloxacin arms. The percentage of subjects with a CrCl of 30-60 mL/min was lower in the

amoxicillin/clavulanate arm (15.4%) compared to subjects in the sulopenem arm (21.0%) and ciprofloxacin arm (25.1%). However, the percentage of subjects with a CrCl <30 mL/min was comparable among the three arms (1.2% for sulopenem and ciprofloxacin, 1.7% for amoxicillin/clavulanate).

Table 60. Subjects With One or More Kidney Function Analyte Values Exceeding Specified Levels, Integrated Safety Population, Trials 301 and 310

Laboratory Parameter	Sulopenem	Amoxicillin/ Clavulanate	Ciprofloxacin
	N=1932 n/N _w (%)	N=1107 n/N _w (%)	N=822 n/N _w (%)
Creatinine, high (mg/dL)			
Level 1 (≥1.5X baseline)	16/1836 (0.9)	18/1049 (1.7)	3/768 (0.4)
Level 2 (≥2X baseline)	3/1836 (0.2)	2/1049 (0.2)	1/768 (0.1)
Level 3 (≥3X baseline)	1/1836 (0.1)	0/1049 (0)	0/768 (0)
eGFR, low (mL/min/1.73 m ²)			
Level 1 (≥25% decrease)	43/1816 (2.4)	31/1037 (3.0)	13/765 (1.7)
Level 2 (≥50% decrease)	3/1816 (0.2)	2/1037 (0.2)	1/765 (0.1)
Level 3 (≥75% decrease)	1/1816 (0.1)	0/1037 (0)	0/765 (0)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 5 days for sulopenem or Amoxicillin/clavulanate, 3 days for ciprofloxacin.

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

Variations in hematology values were similar in the three treatment arms in the ISP. The percentage of subjects with Level 1 (>10.8 x 10³ cells/μL) elevations in the white blood cell (WBC) count in the sulopenem arm (3.9%) was lower than in the amoxicillin/clavulanate arm (6.1%), but higher than the ciprofloxacin arm (2.5%). The amoxicillin/clavulanate arm also had a higher percentage (1.8%) of subjects with Level 2 (>13 x 10³ cells/μL) elevations in WBC count compared to the sulopenem arm (0.9%) and ciprofloxacin arm (0.8%). Overall, these differences are not likely to be clinically significant; most patients had a normal WBC count as would be expected with uUTI.

Table 61. Subjects With One or More Hematology Analyte Values Exceeding Specified Levels, Integrated Safety Population, Trials 301 and 310

Laboratory Parameter	Sulopenem	Amoxicillin/ Clavulanate	Ciprofloxacin
	N=1932 n/N _w (%)	N=1107 n/N _w (%)	N=822 n/N _w (%)
Complete blood count			
WBC, low (10 ³ cells/μL)			
Level 1 (<3.5)	26/1849 (1.4)	17/1052 (1.6)	13/787 (1.7)
Level 2 (<3)	5/1849 (0.3)	4/1052 (0.4)	3/787 (0.4)
WBC, high (10 ³ cells/μL)			
Level 1 (>10.8)	73/1849 (3.9)	64/1052 (6.1)	20/787 (2.5)
Level 2 (>13)	17/1849 (0.9)	19/1052 (1.8)	6/787 (0.8)
Level 3 (>15)	7/1849 (0.4)	5/1052 (0.5)	1/787 (0.1)
Hemoglobin, low (g/dL)			
Level 2 (>1.5 g/dL dec. from baseline)	39/1822 (2.1)	16/1030 (1.6)	17/779 (2.2)
Level 3 (>2 g/dL dec. from baseline)	18/1822 (1.0)	6/1030 (0.6)	4/779 (0.5)

Laboratory Parameter	Sulopenem N=1932 n/N_w (%)	Amoxicillin/ Clavulanate N=1107 n/N_w (%)	Ciprofloxacin N=822 n/N_w (%)
Hemoglobin, high (g/dL)			
Level 2 (>2 g/dL inc. from baseline)	14/1822 (0.8)	10/1030 (1.0)	3/779 (0.4)
Level 3 (>3 g/dL inc. from baseline)	5/1822 (0.3)	4/1030 (0.4)	0/779 (0)
Platelets, low (10 ³ cells/μL)			
Level 1 (<140)	14/1845 (0.8)	5/1050 (0.5)	7/778 (0.9)
Level 2 (<125)	9/1845 (0.5)	4/1050 (0.4)	4/778 (0.5)
Level 3 (<100)	3/1845 (0.2)	2/1050 (0.2)	1/778 (0.1)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 5 days for sulopenem or amoxicillin/clavulanate, 3 days for ciprofloxacin.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

Abbreviations: dec, decrease; inc, increase; N, number of subjects in treatment arm; n, number of subjects meeting criteria; NA, not applicable; N_w, number of subjects with data; WBC, white blood cell

7.6.4.7. Assessment of Drug-Induced Liver Injury, Pooled Analyses, Trials 301 and 310

As shown in [Table 62](#), the numbers of subjects with elevations in liver biochemistry analyte values were generally balanced among the 3 treatment arms. No subjects in any arm had elevations of AST or ALT >10X ULN.

There were more subjects (0.4%) in the sulopenem arm with elevations of ALT >3X ULN arm compared to subjects (0.1%) in the ciprofloxacin arm. The percentage of subjects (0.4%) in the sulopenem and amoxicillin/clavulanate arms with ALT level >3X ULN was equivalent.

Table 62. Subjects With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels, Integrated Safety Population, Trials 301 and 310

Laboratory Parameter	Sulopenem N=1932 n/N_w (%)	Amoxicillin/ Clavulanate N=1107 n/N_w (%)	Ciprofloxacin N=822 n/N_w (%)
Alkaline phosphatase, high (U/L)			
Level 1 (>1.5X ULN)	4/1867 (0.2)	2/1060 (0.2)	2/797 (0.3)
Level 2 (>2X ULN)	0/1867 (0)	0/1060 (0)	2/797 (0.3)
Level 3 (>3X ULN)	0/1867 (0)	0/1060 (0)	1/797 (0.1)
Alanine aminotransferase, high (U/L)			
Level 1 (>3X ULN)	7/1867 (0.4)	4/1060 (0.4)	1/797 (0.1)
Level 2 (>5X ULN)	1/1867 (0.1)	3/1060 (0.3)	0/797 (0)
Level 3 (>10X ULN)	0/1867 (0)	0/1060 (0)	0/797 (0)
Aspartate aminotransferase, high (U/L)			
Level 1 (>3X ULN)	4/1865 (0.2)	2/1060 (0.2)	2/796 (0.3)
Level 2 (>5X ULN)	2/1865 (0.1)	0/1060 (0)	1/796 (0.1)
Level 3 (>10X ULN)	0/1865 (0)	0/1060 (0)	0/796 (0)

Laboratory Parameter	Sulopenem	Amoxicillin/ Clavulanate	Ciprofloxacin
	N=1932 n/N _w (%)	N=1107 n/N _w (%)	N=822 n/N _w (%)
Bilirubin, total, high (mg/dL)			
Level 1 (>1.5X ULN)	4/1868 (0.2)	6/1060 (0.6)	4/797 (0.5)
Level 2 (>2X ULN)	1/1868 (0.1)	3/1060 (0.3)	2/797 (0.3)
Level 3 (>3X ULN)	0/1868 (0)	0/1060 (0)	1/797 (0.1)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 5 days for sulopenem or amoxicillin/clavulanate, 3 days for ciprofloxacin.

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 "Patients in Each Quadrant for Potential Hepatocellular DILI Screening Plot." and "Patients 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: 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; ULN, upper limit of normal; U/L, units per liter

Peak post-baseline elevations of ALT and AST among subjects in the integrated phase 3 uUTI (Trials 301 and 310) population are shown in [Table 63](#) and [Table 64](#), respectively. ALT elevations between 2x ULN and <5X ULN were slightly more common in the subjects treated with sulopenem than in the comparators. Peak post-baseline AST elevations were similar between the sulopenem arm and the comparators.

Table 63. Peak Post-Baseline ALT, Integrated Safety Population, Trials 301 and 310

ALT Post-Baseline	Sulopenem	Amoxicillin/ Clavulanate	Ciprofloxacin
	N=1932 n/N _w (%)	N=1107 n/N _w (%)	N=822 n/N _w (%)
≤ULN	1799/1867 (96.4)	1032/1060 (97.4)	769/797 (96.5)
>ULN to <2x ULN	52/1867 (2.8)	22/1060 (2.1)	27/797 (3.4)
≥2x ULN to <3x ULN	9/1867 (0.5)	2/1060 (0.2)	0/797 (0)
≥3x ULN to <5x ULN	6/1867 (0.3)	1/1060 (0.1)	1/797 (0.1)
≥5x ULN to <10x ULN	1/1867 (0.1)	3/1060 (0.3)	0/797 (0)

Source: adlb.xpt; Software: R

Duration is 5 days for sulopenem or amoxicillin/clavulanate, 3 days for ciprofloxacin.

Abbreviations: ALT, alanine aminotransferase; 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 64. Peak Post-Baseline AST, Integrated Safety Population, Trials 301 and 310

AST Post-Baseline	Sulopenem	Amoxicillin/ Clavulanate	Ciprofloxacin
	N=1932 n/N _w (%)	N=1107 n/N _w (%)	N=822 n/N _w (%)
≤ULN	1809/1865 (97.0)	1040/1060 (98.1)	771/796 (96.9)
>ULN to <2x ULN	46/1865 (2.5)	15/1060 (1.4)	22/796 (2.8)
≥2x ULN to <3x ULN	6/1865 (0.3)	3/1060 (0.3)	1/796 (0.1)
≥3x ULN to <5x ULN	2/1865 (0.1)	2/1060 (0.2)	1/796 (0.1)
≥5x ULN to <10x ULN	2/1865 (0.1)	0/1060 (0)	1/796 (0.1)

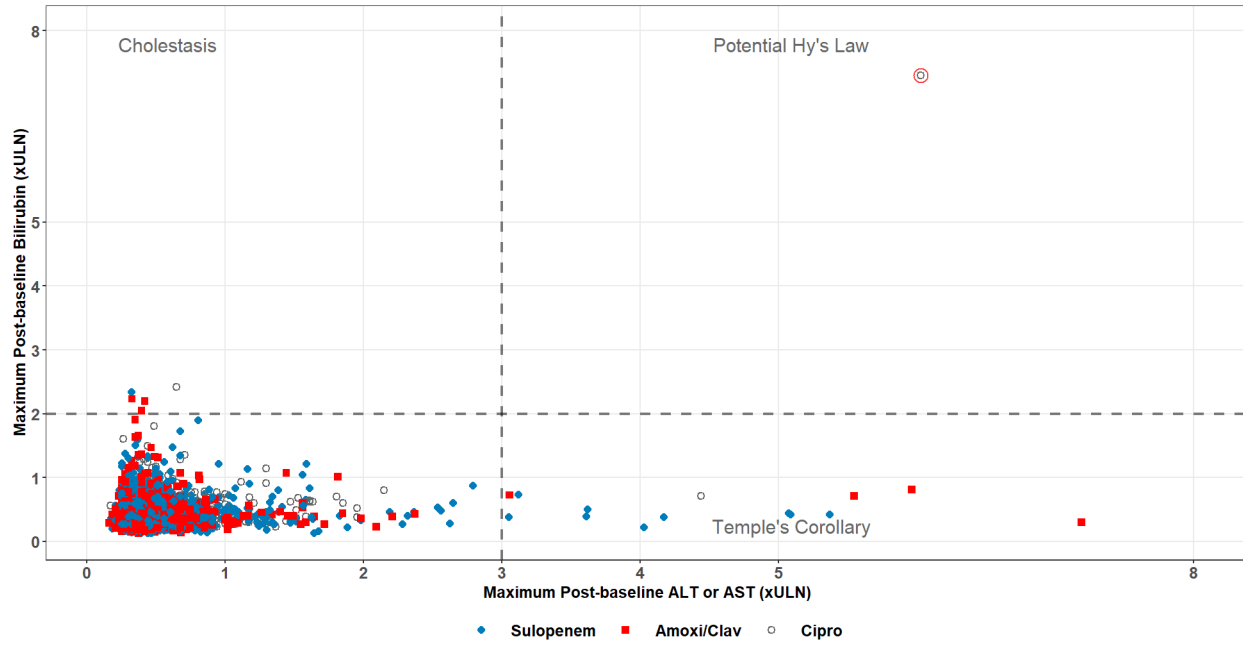
Source: adlb.xpt; Software: R

Duration is 5 days for sulopenem or amoxicillin/clavulanate, 3 days for ciprofloxacin.

Abbreviations: AST, aspartate aminotransferase; 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

Figure 3 shows a screening assessment for potential cases of serious drug-induced liver injury in the integrated uUTI safety population; no potential Hy's law cases were noted in the sulopenem arm.

Figure 3. Hepatocellular Drug-Induced Liver Injury Screening Plot, Integrated Safety Population, Trials 301 and 310



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 postbaseline period.

A potential Hy's Law case was defined as having any postbaseline total bilirubin equal to or exceeding 2X ULN after a postbaseline ALT or AST equal to or exceeding 3X ULN. Those subjects who meet total bilirubin equal to or exceeding 2X ULN criteria within 30 days of the ALT or AST equal to or exceeding 3X ULN criteria are circled in red.

The within 30 days analysis window rule does not apply to cholestasis and temple's corollary cases.

All subjects with at least one postbaseline ALT or AST, bilirubin and ULN are plotted.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

For number of subjects in each quadrant, see the table "Subjects in Each Quadrant for Potential Hepatocellular Drug-Induced Liver Injury Screening Plot ..." and the listing "Listing of Subjects in Hepatocellular Drug-Induced Liver Injury Screening..."

Abbreviations: ALT, alanine aminotransferase; Amoxi, amoxicillin; AST, aspartate aminotransferase; Cipro, ciprofloxacin; Clav, clavulanate; ULN, upper limit of normal

Table 65. Subjects in Each Quadrant for Potential Hepatocellular DILI Screening Plot, Integrated Safety Population, Trials 301 and 310

Quadrant	Sulopenem	Amoxicillin/ Clavulanate	Ciprofloxacin
	N=1932 n/N _w (%)	N=1107 n/N _w (%)	N=822 n/N _w (%)
Potential Hy's Law (right upper)	0/1867 (0)	0/1060 (0)	1/797 (0.1)
Cholestasis (left upper)	1/1867 (0.1)	3/1060 (0.3)	1/797 (0.1)
Temple's corollary (right lower)	9/1867 (0.5)	4/1060 (0.4)	1/797 (0.1)
Total	10/1867 (0.5)	7/1060 (0.7)	3/797 (0.4)

Source: adlb.xpt; Software: R

A potential Hy's Law case was defined as having any postbaseline total bilirubin equal to or exceeding 2X ULN after a postbaseline ALT or AST equal to or exceeding 3X ULN.

The within 30 days analysis window rule does not apply to cholestasis 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 liver injury; 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

Subject (b) (6) in the sulopenem arm from Trial 310 had cholestasis and is discussed in further detail in Section 7.6.1.7. There were 9 (0.5%) subjects in the sulopenem arm (6 from Trial 301 and 3 from Trial 310) that had ALT and/or AST $\geq 3\times$ the upper limit of normal. The 3 subjects from Trial 310 (subjects (b) (6)) are discussed in further detail in Section 7.6.1.7. The six subjects from 301 (subjects (b) (6)) were reviewed during the initial NDA submission (See NDA Multi-disciplinary Review and Evaluation {NDA 213972} dated July 22, 2021).

Six of the 9 subjects listed above in the oral sulopenem arm of the phase 3 uUTI population had postbaseline ALT elevations of $\geq 3\times$ to $<5\times$ ULN (subjects (b) (6) from Trial 301 and subjects (b) (6) from Trial 310). Of these six subjects, four had abnormal ALT values at baseline, including one patient with underlying fatty liver disease and one patient with a history of abnormal liver function tests. In three of the four subjects, the ALT remained elevated at TOC (no further information was available on these patients) while one subject achieved a normal ALT at TOC. Two subjects had normal ALT values at baseline; one had underlying nonalcoholic steatohepatitis and was also on a statin and metformin. Elevated ALT was noted at TOC but normalized at Day 28. The other subject had no underlying medical conditions or concomitant medications and remained asymptomatic but was noted to have elevated ALT at TOC; follow-up laboratory tests were not obtained. Attribution of causality to sulopenem etzadroxil/probenecid in most of these patients cannot be ruled out but is confounded by baseline elevations in ALT or underlying conditions.

One subject in the sulopenem etzadroxil/probenecid arm of Trial 301 (subject (b) (6)), a 28-year-old woman with a medical history significant for obesity and use of an oral contraceptive pill, had postbaseline ALT elevation $>5\times$ ULN. Liver function tests were normal at baseline except for a mild elevation of AP at 125 U/L. At the TOC visit, the AP had increased further (223 U/L), and ALT was elevated to 208 U/L (normal range 6 to 41 U/L). The subject was asymptomatic. Laboratory testing was repeated 5 days later with a decrease in ALT to 46 U/L and a downward trend in the AP to 169 U/L. The cause of the ALT elevation was not known, but potentially could have been related to sulopenem etzadroxil/probenecid.

In the sulopenem arm of the four phase 3 trials, 9 (0.3%) subjects and 1 (<0.1) subject had ALT elevations of $>5\times$ ULN and $>10\times$ ULN, respectively. Of these subjects, one was in Trial 301 as described above and eight subjects were in Trials 302 and 303. On review of the narratives of these eight subjects, attribution of causality to sulopenem appeared confounded by the subjects' underlying medical conditions and/or concomitant medications.

One subject from Trial 302 (Subject (b) (6)) discontinued IV sulopenem due to the AE of toxic hepatitis. The subject was a 47-year-old woman with pyelonephritis who had normal ALT, AP and bilirubin at baseline and mild elevation of AST. On Study Day 5, while on IV sulopenem, ALT and AST were $>3\times$ ULN. On Day 7, the subject was diagnosed with probable toxic hepatitis, and sulopenem was discontinued. AST and ALT trended down at Day 10 with normalization of values at TOC. Sulopenem may have contributed to the elevations in liver enzymes, but attribution of causality is confounded by the concomitant medications of paracetamol and methimazole.

One subject in Trial 302 ((b) (6)) with schizoaffective disorder on valproic acid had normal AST, ALT and bilirubin values at baseline but met laboratory criteria for Hy's Law with an ALT of 269 U/L, AST of 313 U/L and total bilirubin of 2.8 mg/dL after completing 5 days of IV

sulopenem. However, study drug was continued, and the subject was switched to oral sulopenem etzadroxil/probenecid on Days 6 and 7 with near normalization in liver enzymes by Day 10. Penem antibacterial drugs are known to be associated with decreased valproic acid levels (which were noted in this subject). While IV sulopenem may have caused elevated liver enzymes in this patient, the abnormalities resolved while on oral sulopenem which may suggest hepatic adaptation.

7.6.4.8. Vital Signs, Pooled Analyses, Trials 301 and 310

Review of post-baseline blood pressure readings did not reveal major differences between the sulopenem and the comparator arms. Given the expected clinical stability of subjects with uUTI, this finding was not surprising.

Table 66. Percentage of Subjects With Maximum Systolic Blood Pressure by Category of Blood Pressure Post-Baseline, Integrated Safety Population, Trials 301 and 310

Systolic Blood Pressure (mmHg)	Sulopenem	Amoxicillin/ Clavulanate	Ciprofloxacin
	N=1932 n/N _w (%)	N=1107 n/N _w (%)	N=822 n/N _w (%)
<90	0/1903 (0)	0/1084 (0)	1/809 (0.1)
≥90	1903/1903 (100)	1084/1084 (100)	808/809 (99.9)
≥120	1474/1903 (77.5)	825/1084 (76.1)	627/809 (77.5)
≥140	216/1903 (11.4)	114/1084 (10.5)	75/809 (9.3)
≥160	18/1903 (0.9)	16/1084 (1.5)	11/809 (1.4)
≥180	4/1903 (0.2)	4/1084 (0.4)	2/809 (0.2)

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

Table 67. Percentage of Subjects With Maximum Diastolic Blood Pressure by Category of Blood Pressure Post-Baseline, Integrated Safety Population, Trials 301 and 310

Diastolic Blood Pressure (mmHg)	Sulopenem	Amoxicillin/ Clavulanate	Ciprofloxacin
	N=1932 n/N _w (%)	N=1107 n/N _w (%)	N=822 n/N _w (%)
<60	9/1903 (0.5)	3/1084 (0.3)	3/809 (0.4)
≥60	1894/1903 (99.5)	1081/1084 (99.7)	806/809 (99.6)
≥90	145/1903 (7.6)	68/1084 (6.3)	70/809 (8.7)
≥110	4/1903 (0.2)	3/1084 (0.3)	2/809 (0.2)
≥120	1/1903 (0.1)	0/1084 (0)	1/809 (0.1)

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

7.6.4.9. Subgroups, Pooled Analyses, Trials 301 and 310

All subjects in Trials 301 and 310 were female. Within the sulopenem arm, TEAEs were evenly distributed across age groups, but occurred more frequently than in comparator arms. In contrast, AEs occurred more frequently in subjects ≥75 years of age compared to other age groups in the amoxicillin/clavulanate arm. AEs occurred with similar frequency in white and Black subjects among treatment arms. The small number of subjects of other races preclude further conclusions based on race. The frequency of AEs in subjects from Ukraine compared to the frequency of AEs in subjects from the United States or Russia was markedly lower in both the sulopenem and

ciprofloxacin arms. The reason for this difference is unclear but may be related to differences in reporting among the different populations. In the sulopenem arm, there were no major differences in occurrences of AEs by BMI category. The frequency of AEs was similar in sulopenem subjects with CrCl 30-60 mL/min and sulopenem subjects with CrCl >60 mL/min. The number of subjects with CrCl <30 mL/min was too low to draw conclusions.

Table 68. Overview of Adverse Events by Demographic Subgroup, Integrated Safety Population, Trials 301 and 310

Characteristic	Sulopenem N=1932 n/N_s (%)	Amoxicillin/ Clavulanate N=1107 n/N_s (%)	Ciprofloxacin N=822 n/N_s (%)
Sex, n (%)			
Female	416/1932 (21.5)	136/1107 (12.3)	115/822 (14.0)
Age group, years, n (%)			
18-29	74/336 (22.0)	16/190 (8.4)	21/165 (12.7)
30-60	229/1002 (22.9)	80/620 (12.9)	47/352 (13.4)
≥60	113/594 (19.0)	40/297 (13.5)	47/305 (15.4)
≥65	90/442 (20.4)	35/212 (16.5)	37/233 (15.9)
≥75	38/166 (22.9)	15/64 (23.4)	16/97 (16.5)
Race, n (%)			
American Indian or Alaska Native	5/12 (41.7)	0/4 (0)	1/3 (33.3)
Asian	9/30 (30.0)	5/15 (33.3)	1/7 (14.3)
Black or African American	56/268 (20.9)	26/217 (12.0)	8/66 (12.1)
Native Hawaiian or Other Pacific Islander	0/1 (0)	0/2 (0)	1/1 (100)
Other	7/20 (35.0)	4/14 (28.6)	0/3 (0)
White	339/1601 (21.2)	101/855 (11.8)	104/742 (14.0)
Ethnicity, n (%)			
Hispanic or Latino	191/1032 (18.5)	84/760 (11.1)	44/255 (17.3)
Not Hispanic or Latino	222/895 (24.8)	52/346 (15.0)	71/566 (12.5)
Not Reported	2/4 (50.0)	0/1 (0)	0/1 (0)
Unknown	1/1 (100)	0/0 (NA)	0/0 (NA)
Country of participation, n (%)			
Russia	42/195 (21.5)	0/0 (NA)	37/224 (16.5)
Ukraine	7/144 (4.9)	0/0 (NA)	2/137 (1.5)
USA	367/1593 (23.0)	136/1107 (12.3)	76/461 (16.5)
Is in USA, n (%)			
USA	367/1593 (23.0)	136/1107 (12.3)	76/461 (16.5)
Non-USA	49/339 (14.5)	0/0 (NA)	39/361 (10.8)
Body mass index by category (kg/m ²), n (%)			
<25	131/591 (22.2)	38/322 (11.8)	46/345 (13.3)
25-30	128/648 (19.8)	44/381 (11.5)	26/224 (11.6)
>30	157/690 (22.8)	54/404 (13.4)	42/241 (17.4)
Missing	0/3 (0)	0/0 (NA)	1/12 (8.3)
Creatinine clearance by category (mL/min), n(%)			
<30	2/24 (8.3)	5/19 (26.3)	2/10 (20.0)
30-60	89/405 (22.0)	20/170 (11.8)	32/206 (15.5)
>60	323/1494 (21.6)	107/906 (11.8)	81/605 (13.4)
Missing	2/9 (22.2)	4/12 (33.3)	0/1 (0)

Source: ADSL.xpt; Software: R

Abbreviations: N, number of subjects in treatment arm; n, number of subjects with adverse event; N_s, total number of patients for each specific subgroup and were assigned to that specific arm

7.7. Key Safety Review Issues

None.

8. Therapeutic Individualization

8.1. Intrinsic Factors

8.1.1. Hepatic Impairment

The effect of hepatic impairment has not been evaluated for either IV or oral sulopenem. Sixty-five patients across all 4 phase 3 trials (301, 302, 303, and 310) had a history of hepatic disease, including hepatic steatosis and nonspecific liver disorder. However, none of these patients had a Child-Pugh categorization of the severity of their hepatic impairment and the safety of sulopenem etzadroxil/probenecid in these patients was comparable to the rest of the phase 3 trial population. In vitro, sulopenem is not metabolized by recombinant CYP or UGT enzymes. Additionally, the mass balance study (Study A8811006) indicated that biliary excretion does not play a role in sulopenem elimination. Therefore, hepatic impairment is not expected to have a clinically significant effect on sulopenem exposures, and no dosage adjustment is recommended based on hepatic impairment.

8.1.2. Renal Impairment

The Applicant did not propose any alternative dosage recommendations for the use of sulopenem etzadroxil/probenecid in patients with renal impairment. In the mass balance study, approximately 26.9% of total radioactivity was recovered in urine as unchanged sulopenem following oral administration of a 2000 mg dose of [¹⁴C] sulopenem etzadroxil. In the dedicated renal impairment study (A8811009), when compared to subjects with normal renal function, sulopenem plasma AUC_{0-∞} increased 2.0-, 3.0- and 7.4-fold in subjects with mild (CrCl 60 to <90 mL/min), moderate (CrCl 30 to <60 mL/min) and severe (CrCl 15 to <30 mL/min) renal impairment, respectively, following administration of a 1000 mg dose of sulopenem etzadroxil. Because sulopenem exhibits dose proportionality within the dose range of 400 to 2000 mg, similar fold increases in AUC are anticipated for the Applicant's proposed 500 mg dose of sulopenem etzadroxil. Although assessment of the effect of renal impairment on sulopenem PK was conducted in the absence of probenecid, the observed exposure changes with sulopenem etzadroxil are expected to approximate the fold changes in exposure with administration of the bilayer tablet due to the decline in probenecid's effectiveness as an OAT3 inhibitor as renal function declines.

From an efficacy perspective, there is theoretical concern for a reduction in efficacy with declining renal function given that renal impairment is associated with decreases in renal clearance and ultimately, urinary concentrations of sulopenem. In Trial 301, overall response at the TOC visit was lower in subjects with CrCl <60 mL/min compared to those with CrCl ≥60 mL/min. However, in Trial 310, overall response was comparable for subjects with CrCl above and below this threshold ([Table 69](#)). Of note, CrCl <60 mL/min was not a pre-specified

criterion for treatment group randomization, and thus, other confounders may have contributed to the observed outcomes in Trial 301. Therefore, the totality of information is inconclusive on the effect of renal impairment on sulopenem's efficacy in the treatment of uUTI and the need for an alternative dosage strategy.

Table 69. Overall Response at TOC by CrCl in Micro-MITT Population

Variable	Trial 301	Trial 310
	N (%)	N (%)
CrCL ≥60 mL/min	369	406
Overall success	235 (63.7)	250 (61.6)
CrCL <60 mL/min	169	113
Overall success	70 (41.4)	66 (58.4)

Source: Table 60 of the Applicant's Individual Study Report IT001-310 and Statistical Reviewer's analysis

Abbreviations: CrCl, creatinine clearance; micro-MITT, microbiological modified intent-to-treat; N, number of subjects; TOC, test of cure

From a safety perspective, data from trial A8811009 and phase 3 Trials 301 and 310 did not associate mild, moderate or severe renal impairment with a higher incidence of TEAEs as compared with subjects with normal renal function. Given these observations, sulopenem's short plasma half-life of 1.2 h and the proposed 5-day duration of therapy, 500 mg sulopenem etzadroxil/500 mg probenecid BID is expected to be safe in patients with CrCl ≥15 mL/min. However, there are no PK or safety data in patients with CrCl <15 mL/min or those on hemodialysis to inform dosage recommendations in these subpopulations. Moreover, uUTI in patients on hemodialysis may not be considered uncomplicated. Therefore, use of 500 mg sulopenem etzadroxil/500 mg probenecid bilayer tablet is not recommended in patients with CrCl <15 mL/min and those on hemodialysis.

8.1.3. Other Intrinsic Factors

Population PK analysis involving PK data from phase 1 trials and phase 3 Trials 301, 302 and 303 indicated that sex, body weight (38.8 to 140 kg) and age (18 to 91 years) did not have a clinically significant effect on the PK of sulopenem.

8.2. Extrinsic Factors

8.2.1. Food Effect

Following administration of the to-be-marketed sulopenem etzadroxil/probenecid bilayer tablet formulation to healthy adult volunteers, area under the concentration-time curve estimated to infinity ($AUC_{0-\infty}$) and maximum plasma concentration (C_{max}) increased 48% and 45%, respectively, with a high fat meal (800-1000 calories; 50% fat) compared to fasted conditions. The Applicant proposes that the bilayer tablet should be taken with food (b) (4) because food increases the oral bioavailability and tolerability of sulopenem. This recommendation is consistent with the instructions provided to Trial 301 and 310 participants. Because neither trial recorded the type of food consumed, caloric content or timing of food intake, fed status was poorly defined. Study 310 only provided a comparison of efficacy outcomes based on fed status. Nonetheless, Trial 301 did provide a comparison of safety and efficacy outcomes under fed and fasted conditions. In this trial, while the incidence of clinically

significant treatment-emergent diarrhea was comparable under fed (7.1%) and fasted conditions (7.4%) (Table 70), food appeared to decrease the mean duration of treatment-emergent diarrhea from 5.6 days to 3.7 days. The lack of a notable difference in the incidence of diarrhea is consistent with the safety findings from the dedicated food effect Study 105, where the incidence of GI-related TEAEs following administration of the bilayer tablet were identical (7.1%) in the fed and fasted states. In both Trial 301 and 310, food did not appear to significantly impact efficacy as administration of the bilayer tablet in the fed or fasted states resulted in comparable overall response rates of 63.5% and 62.8%, respectively, at the TOC visit for the entire microbiologically-evaluable population. Additionally, in PTA analyses, simulated sulopenem exposures under fed conditions yielded target attainment at MIC values that were either comparable or a single-fold dilution higher than under fasted conditions. Based on the findings that food increases bioavailability and may improve tolerability by shortening the duration of clinically significant treatment-emergent diarrhea, the clinical pharmacology review team recommends administering the sulopenem etzadroxil/probenecid bilayer tablet with food.

Table 70. Treatment-Emergent Clinically Significant Diarrhea by Fed/Fasted Status, Trial 301

Parameter	Sulopenem	
	Fasted	Fed
Total number of patients with treatment-emergent clinically significant diarrhea	32/430 (7.4)	28/396 (7.1)
Intensity ^[1]		
Mild	26/430 (6.0)	20/396 (5.1)
Moderate	6/430 (1.4)	8/396 (2.0)
Severe	0	0
Drug relationship ^[2]		
Related	30/430 (7.0)	24/396 (6.1)
Not related	2/430 (0.5)	4/396 (1.0)
Total number of episodes of diarrhea	511	306
Duration of treatment-emergent diarrhea (days)		
N ^[3]	32	28
Mean (SD)	5.6 (4.00)	3.7 (2.61)
Median	5.0	3.0
Min, max	1, 22	1, 11
Duration of study drug related treatment-emergent diarrhea (days)		
N*	30	24
Mean (SD)	5.4 (4.10)	4.0 (2.67)
Median	5.0	3.0
Min, max	1, 22	1, 11

Source: Table 14.3.3.1.17 of Applicant's Study IT001-301

¹ Worst Intensity Per Patient

² Drug-Related If at Least One AE of Diarrhea is Drug Related

Abbreviations: AE, adverse event; max, maximum; min, minimum; N, number of subjects in the safety population; uUTI, uncomplicated urinary tract infection; SD, standard deviation

8.2.2. Summary of In Vitro Drug-Drug Interaction Studies

In vitro studies indicated that sulopenem is a substrate of OAT3, and the prodrug sulopenem etzadroxil is a substrate of P-gp and inhibitor of CYP3A4/5, P-gp, breast cancer resistance protein (BCRP), OAT1 and OAT3. No clinical studies of sulopenem etzadroxil as an OAT1/3,

CYP3A4/5, BCRP and P-gp inhibitor were conducted by the Applicant. Given that sulopenem etzadroxil is rapidly hydrolyzed upon oral administration and was undetected in plasma in the human mass balance study (A8811006), the potential for clinically relevant DDIs with OAT1/3 is considered to be low. Because sulopenem etzadroxil is administered orally, it has the potential to inhibit CYP3A4/5, BCRP and P-gp in the gut. The sulopenem etzadroxil half-maximal inhibitory concentration (IC_{50}) for inhibition of CYP3A4/5 could not be calculated within the concentration range studied in vitro and was estimated to be $>150 \mu\text{M}$. Although the IC_{50} values for BCRP ($IC_{50} = 20.4 \mu\text{M}$) and P-gp ($IC_{50} = 1.91 \mu\text{M}$) are likely to be exceeded by more than 10-fold in the GI tract following administration of a single 500 mg dose of sulopenem etzadroxil, the Applicant's in vitro stability and release studies indicated that sulopenem etzadroxil is rapidly degraded in simulated intestinal fluid. Therefore, sulopenem etzadroxil's inhibition of BCRP and P-gp is expected to be transient. Similarly, regardless of the magnitude of the in vitro IC_{50} for CYP3A4/5 inhibition, sulopenem etzadroxil's effect as a CYP3A4/5 inhibitor is also expected to be transient and not to result in clinically significant DDIs with CYP3A4/5 substrates.

Probenecid is a known OAT1/3 inhibitor and was found to be a substrate and inhibitor of BCRP in vitro. No clinical evaluations of probenecid as a BCRP substrate and inhibitor were performed. The in vitro IC_{50} of probenecid as a BCRP inhibitor was $814 \mu\text{M}$, resulting in an I_{gut} to IC_{50} ratio of 10, which is the threshold for characterizing an orally administered drug as a BCRP inhibitor in the 2020 FDA Guidance for Industry, *In Vitro Drug Interaction Studies- Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* ([January 2020](#)). However, because of probenecid's low aqueous solubility (0.06 mg/mL), the probability of clinically significant BCRP-mediated DDIs with probenecid is low.

8.2.3. Summary of Clinical Drug-Drug Interaction Studies

8.2.3.1. Effect of P-gp Inhibitors on Sulopenem PK

Because sulopenem etzadroxil was identified as a P-gp substrate in vitro, the Applicant conducted a clinical DDI study to evaluate the effect of P-gp inhibitors on sulopenem exposure using oral itraconazole. In Study IT001-103, administration of a clinical dose of 200 mg itraconazole (2 x 100 mg capsules) daily for 3 days in the fasted state, followed by concomitant administration of sulopenem etzadroxil/probenecid on Day 4 in the fed state resulted in a non-clinically significant increase in sulopenem exposure. Therefore, no dosage adjustment is required for coadministration of sulopenem etzadroxil/probenecid with P-gp inhibitors.

8.2.3.2. Effect of Antacids and Proton Pump Inhibitors on Sulopenem PK

Results of in vitro solubility studies indicated that sulopenem etzadroxil is a Biopharmaceutical Classification System Class IV drug (i.e., low permeability and low solubility) that does not exhibit pH-dependent solubility within a pH range of 1.2 to 6.8. Based on this information, coadministration of gastric pH modifiers would not be expected to impact sulopenem's exposure. However, per the Applicant, in vitro stability studies indicated that sulopenem etzadroxil was

unstable in simulated gastric fluid (containing pepsin) but stable in simulated enzyme-free intestinal fluid. Therefore, gastric pH modifiers were predicted to decrease sulopenem etzadroxil's vulnerability to acid degradation and thus increase the bioavailability of sulopenem. Given that the stability of sulopenem etzadroxil was evaluated in gastric fluid in the presence of pepsin, it is unclear that its degradation was precipitated exclusively by low gastric pH. The Applicant conducted a clinical DDI study (A8811018) using pantoprazole, a proton pump inhibitor (PPI), and aluminum hydroxide, an antacid. Administration of 40 mg pantoprazole for 3 days, followed by coadministration with sulopenem etzadroxil on Day 4 under fasted conditions did not significantly impact sulopenem exposure. Therefore, no dosage adjustment is necessary for coadministration with a PPI. Administration of a single dose of 600 mg aluminum hydroxide with sulopenem etzadroxil under fasted conditions decreased AUC_{0-last} and C_{max} by less than 20%. According to the FDA guidance on conducting DDI studies with gastric-acid reducing agents, PPIs present the worst-case scenario for pH-dependent DDIs due to their long-lasting effects on gastric pH. Thus, the negative finding from Study A8811018 indicates an overall lack of pH-dependent DDI. Therefore, no dosage adjustment is required for coadministration with antacids.

8.2.3.3. Effect of Sulopenem Etzadroxil/Probenecid on Valproic Acid PK

Concomitant administration of carbapenem antibacterial drugs and valproic acid has been associated with clinically significant reductions in serum valproic acid concentrations, resulting in a loss of seizure control. Because sulopenem (a penem) is structurally similar to carbapenems, the Applicant conducted a DDI study (Study 104) with valproic acid using the sulopenem etzadroxil/probenecid bilayer tablet, a standalone sulopenem immediate release tablet, and IV sulopenem. In this study, multiple dose administration of 500 mg sulopenem etzadroxil with valproic acid decreased valproic acid AUC and C_{max} by approximately 25% and 19%, respectively. Similarly, coadministration of 1000 mg IV sulopenem with valproic acid also resulted in reductions of valproic acid plasma AUC and C_{max} of 33% and 28%, respectively. However, when administered concomitantly with sulopenem etzadroxil and probenecid, less than 10% reduction in valproic acid plasma exposures were observed. These results indicate that probenecid negates the reduction in valproic acid plasma concentrations caused by sulopenem. These findings were corroborated in the Applicant's phase 3 cUTI trial in one patient in the sulopenem arm who received concomitant valproic acid treatment. Following the IV sulopenem treatment phase of the study (i.e., Days 1-5), valproic acid plasma/serum levels decreased to 21000 ng/mL (in serum) from a baseline of 54800 ng/mL (in plasma). However, following the switch to oral step-down therapy with sulopenem etzadroxil/probenecid, valproic acid levels recovered to 50100 ng/mL (in plasma) and 50600 ng/mL (in serum) at the end of treatment visit.

8.3. Plans for Pediatric Drug Development

There are currently no clinical data available on the safety and efficacy of sulopenem in pediatric patients <18 years old. An Agreed initial Pediatric Study Plan (iPSP) was finalized on February 21, 2018. (b) (4)

the decision to focus

development on oral sulopenem etzadroxil/probenecid for uUTI only, following the complete response of the initial NDA in July 2021, (b) (4) The Applicant submitted an amended iPSP on February 15, 2023, with plans for single-dose PK studies as well as a phase 3 uUTI pediatric study: (b) (4)

(b) (4) As FDA-approved labeling for probenecid indicates that it is contraindicated for pediatric patients under the age of 2 years, the Applicant planned to request a partial waiver from conducting a phase 3 study in pediatric patients <2 years of age with uUTI. Additionally, given that UTIs in pediatric patients <2 years of age are generally considered complicated, the Pediatric Review Committee (PeRC) and the Division had previously agreed (November 8, 2017) that it would be reasonable for the Applicant to request a waiver for uUTI studies for sulopenem etzadroxil/probenecid in pediatric subjects <2 years of age. The Applicant also planned to request deferral of phase 1 and phase 3 pediatric studies for patients aged 2 to <18 years until 3Q2024 as efficacy had not yet been established in adults. Additionally, the iPSP was updated with results from juvenile rat toxicology studies.

Of note, to assess the appropriateness of the partial waiver request for pediatric patients under the age of 2 years based on the labeled contraindication to probenecid, the clinical review team reviewed the literature, available copies of hand-written records from the original probenecid NDA (07898) review in 1951, and a consult response from the Division of Pediatric and Maternal Health (DPMH) dated April 30, 2021. In their review, DPMH concluded that studying probenecid in pediatric patients <2 years of age could be considered as no apparent scientific basis for this contraindication was found. However, given that PeRC and the Division had previously determined that UTIs in pediatric patients <2 years of age are generally considered complicated, the Applicant's request to waive uUTI studies for sulopenem etzadroxil/probenecid in pediatric subjects <2 years of age was deemed acceptable.

Consequently, in their revised proposed amended iPSP dated September 10, 2023, the Applicant requested a partial waiver from conducting studies in pediatric patients <2 years of age due to the difficulties in diagnosing and studying uUTI in this age group. The Applicant also stated their intent to utilize the adult commercial tablet formulation for pediatric patients aged 6 years to <17 years and (b) (4) in pediatric patients aged 2 years to <6 years. To this end, the Applicant plans to (b) (4)

The Applicant's pediatric study plan includes the following:

- IT001-109: A sulopenem etzadroxil/probenecid single oral dose PK study in patients 12 years to <17 years hospitalized with bacterial infection and receiving background antibacterial therapy.
- IT001-110: A sulopenem etzadroxil/probenecid single oral dose PK study in patients 2 years to <12 years hospitalized with bacterial infection and receiving background antibacterial therapy.
- IT001-311: A phase 3 (b) (4) study in pediatric subjects aged 2 years to <17 years with uUTI to evaluate safety (b) (4) of sulopenem etzadroxil/probenecid (b) (4)

Per the Amended Agreed iPSP, phase 1 studies will start 1Q2025 with expected clinical study report submissions 4Q2026 and 4Q2029. The Applicant anticipates the phase 3 pediatric study will begin 1Q2030 with topline data available 2Q2032 and final clinical study report submission 4Q2032.

8.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential

Nonclinical Pregnancy, Lactation, and Fertility Data

See [Table 71](#) and [Table 72](#) for the nonclinical information supporting product labeling in Sections [8.1](#), [8.2](#), and [13.1](#). Additional details are available in the NDA 213972 Multidisciplinary Review dated July 22, 2021.

Table 71. Nonclinical Data Supporting Labeling on Fertility, Pregnancy, and Lactation

Labeling Section	Nonclinical Data
8.1 Pregnancy	Sulopenem Etzadroxil Sulopenem etzadroxil was orally administered during organogenesis in embryo-fetal studies in mice, rats, and rabbits. In pregnant mice, an increased litter incidence of a fetal malformation, cleft palate, was observed with an oral dose of sulopenem etzadroxil associated with a sulopenem exposure approximately 23 times the clinical sulopenem exposure for the MRHD of 1000 mg/day sulopenem etzadroxil. No maternal toxicity or fetal malformations occurred in mice with doses ≤ 400 mg/kg/day (approximately 3 times the clinical sulopenem exposure for the MRHD of sulopenem etzadroxil based on plasma AUC comparison). In pregnant rats and rabbits, orally administered sulopenem etzadroxil was not associated with fetal malformations at any dose, but in rats, maternal toxicity and reduced fetal body weights occurred at sulopenem etzadroxil doses associated with sulopenem plasma exposures approximately 2 and 6 times, respectively, the clinical sulopenem exposure for the MRHD of sulopenem etzadroxil. The doses at which no maternal toxicity or fetal toxicity occurred in rats were, respectively, 100 mg/kg/day and 400 mg/kg/day (less than or equal to and approximately 2 times, respectively, the clinical sulopenem exposure for the MRHD of sulopenem etzadroxil based on plasma AUC comparison). In rabbits, maternal toxicity, reduced numbers of viable fetuses, and reduced fetal body weights occurred at sulopenem etzadroxil doses associated with sulopenem plasma exposures approximately 0.1 and 0.2 times, respectively, the clinical sulopenem exposure for the MRHD of sulopenem etzadroxil. Maternal body weight gain and food consumption were decreased in all the sulopenem etzadroxil dose groups. The dose at which no fetal toxicity occurred was 5 mg/kg/day (approximately 0.1-times the clinical sulopenem exposure for the MRHD of sulopenem etzadroxil based on plasma AUC comparison). In a pre-postnatal study in rats, sulopenem etzadroxil was administered by oral gavage to pregnant females from gestation day 6 through the lactation period to LD 20 in maternal doses of 100, 300, and 1000 mg/kg/day. No adverse effects on the survival, growth, behavior, or reproduction of first-generation offspring occurred with any of the sulopenem etzadroxil doses up to the high dose of 1000 mg/kg/day (approximately 10-times

Labeling Section	Nonclinical Data
	the MRHD of sulopenem etzadroxil based on body surface area comparison). Probenecid Available published data over several decades of probenecid use in pregnant woman have not identified a drug-associated risk of miscarriage, major birth defects, or adverse maternal or fetal outcomes. No embryo-fetal development studies with probenecid have been conducted in animals. Probenecid crosses the placental barrier and appears in cord blood.
8.2 Lactation	<u>Human Data</u> Sulopenem Etzadroxil There are no data on the presence of sulopenem etzadroxil or its metabolite in human milk, the effects on the breastfed infant, or the effects on milk production. Probenecid Probenecid is present in human milk based on a case report. There are no reports of adverse effects in infants associated with probenecid exposure through breastmilk. There is no information on the effects of probenecid on milk production. <u>Animal Data</u> Sulopenem Etzadroxil The active metabolite of sulopenem etzadroxil, sulopenem, was present in rat milk after oral dosing of sulopenem etzadroxil to lactating female rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk.
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	<u>Impairment of Fertility</u> Sulopenem Etzadroxil Male and female fertility and early embryonic development were examined in rats (20/sex/group) orally administered sulopenem etzadroxil in daily doses of 100, 400, or 2000 mg/kg beginning 28 days prior to mating and throughout the mating period in males and for 14 days before mating, throughout the mating period, and until GD 7 in females. There were no treatment-related effects on estrous cycle length, mating and fertility rates, implantation, conceptus viability, sperm concentration and motility, or accessory male sex gland weights. No adverse effects on male and female fertility or early embryonic development in female rats were observed at doses up to 2000 mg/kg/day (approximately 10- and 12-times in male and female rats, respectively, the clinical sulopenem exposure for the MRHD of sulopenem etzadroxil based on plasma AUC comparison).

Source: Reviewer-generated table based on data and information from the study reports provided by the Applicant for sulopenem etzadroxil and FDA-approved labeling for probenecid
Abbreviations: AUC, area under the concentration-time curve; GD, gestation day; LD, lactation day; MRHD, maximum recommended human dose

Table 72. Reproductive Toxicity Safety Margins

Study Type (Species)/ Study No.	Sulopenem Etzadroxil NOAEL (mg/kg/day)	Plasma AUC Exposure for Sulopenem (ng•hr/ml)	Safety Margin (Multiples) ^a
Sulopenem Etzadroxil			
Fertility (rat)/ Study No.: 08GR017	Male: 2000 Female: 2000	144000 ^b 180000 ^b	9.7 12.1
EFD (mice)/ Study No.: 09GR119	Maternal toxicity: 400 Fetal toxicity: 400	38700 ^c 38700 ^c	2.6 2.6
EFD (rat)/ Study No.: 08GR040	Maternal toxicity: 100 Fetal toxicity: 400	6170 ^d 29300 ^d	0.4 2.0
EFD (rabbit)/ Study No.: 08GR037	Maternal toxicity: none Fetal toxicity: 5	---- 1870 ^e	---- 0.1
Sulopenem Etzadroxil			
Study Type (Species)/ Study No.	Sulopenem Etzadroxil NOAEL (mg/kg/day)	HED (mg/kg/day) ^f	Safety Margin (Multiples) ^g
PPND (rat)/ Study No.: 18IT001-8383180-02	Maternal toxicity: 1000 F1 toxicity: 1000	161.3 161.3	9.7 9.7

Source: Reviewer-generated table based on data and information from the study reports provided by the Applicant for sulopenem etzadroxil and FDA-approved labeling for probenecid

^a The mean plasma AUC_{0-inf} for sulopenem after administration of a single administration of a ORLYNVAH is 7410 ng•hr/ml. For the MRHD of two ORLYNVAH tablets per day the AUC_{0-24hr} is expected to be 14820 ng•hr/ml.

^b Plasma AUC_{0-24hr} for sulopenem from the 1-month toxicokinetic study in rats (Study No.: 07KL014)

^c Plasma AUC_{0-24hr} for sulopenem from the EFD study in mice (Study No.: 09GR119)

^d Plasma AUC_{0-24hr} for sulopenem from the EFD study in rats (Study No.: 08GR040)

^e Plasma AUC_{0-24hr} for sulopenem from the EFD study in rabbits (Study No.: 08GR037)

^f The sulopenem etzadroxil HED from the PPND study in rats (Study No.: 18IT001-8383180-02) based on body surface area comparison between rats and humans. The sulopenem etzadroxil HED in rats is the NOAEL for sulopenem etzadroxil divided by 6.2.

^g The dose of sulopenem etzadroxil in the maximum recommended daily dose of ORLYNVAH (two tablets per day) is 1000 mg/day or 16.67 mg/kg/day for a typical human subject weighing 60 kg.

Abbreviations: AUC, area under the concentration-time curve; EFD, embryo-fetal development; HED, human equivalent dose; MRHD, maximum recommended human dose; NOAEL, no observed adverse effect level; PPND, pre-postnatal development

Human Pregnancy Data

Pregnant women were excluded from all clinical studies of sulopenem. However, one pregnancy occurred in the sulopenem arm of Trial 310. A 22-year-old woman (Subject (b) (6)) received 5 days of sulopenem etzadroxil/probenecid. The baseline urine pregnancy test was negative as was a urine pregnancy test on Day 28. On Day 41, a serum pregnancy test was positive. Possible conception dates were determined to be 12-22 days after the sulopenem course was completed; therefore, it was unlikely the subject was pregnant while receiving sulopenem. The subject gave birth to a full term healthy female baby.

There was also one pregnancy in the sulopenem arm of Trial 301. A 26-year-old woman had a negative screening urine pregnancy test at the trial site but three days later, the central laboratory reported the pregnancy test as positive. Study drug was stopped. The subject had an uneventful pregnancy and gave birth to a healthy male baby 8 months later.

During the initial review of NDA 213972, DPMH was consulted to assist with the Pregnancy and Lactation subsections of labeling. In their consult response dated May 4, 2021, DPMH noted that as a penem antibacterial drug, sulopenem is very similar to carbapenems, and teratogenic risks and adverse maternal and fetal outcomes have not been identified with carbapenem use during

pregnancy. Additionally, based on decades of experience with carbapenems, sulopenem is not expected to cause harmful effects in breastfed infants. DPMH also observed that available published studies over several decades of probenecid use in pregnancy have not identified a drug-related risk of miscarriage, congenital malformations, or adverse maternal or fetal outcomes. Therefore, DPMH did not recommend a postmarketing pregnancy study or postmarketing lactation study for sulopenem etzadroxil/probenecid.

9. Product Quality

Approval

This NDA was recommended for approval from the Product Quality perspective in the first review cycle (refer to the Office of Pharmaceutical Quality (OPQ) Integrated Quality Assessment # 1, dated June 1, 2021, in the Document Archiving Reporting and Regulatory Tracking System. The drug product is a pink, oval-shaped, film coated, immediate release, bilayer tablet, containing 500 mg sulopenem etzadroxil and 500 mg probenecid, and conventional excipients of compendial grade. With the current NDA resubmission (SDN# 71, dated April 25, 2024), several changes and updates have been proposed in Module 3, such as removal of blister packaging originally proposed for the drug product. The OPQ review team has assessed the NDA 213972 resubmission with respect to chemistry, manufacturing, and controls and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. The currently proposed commercial packaging configurations for the drug product include high density polyethylene bottles only (10-count and 30-count) with child-resistant caps. Based on the overall stability data package submitted in the original NDA and the resubmission, the proposed expiration dating of 60 months is granted for the drug product to be stored at room temperature (20-25°C). All proposed commercial manufacturing and testing facilities have been found acceptable and an overall “Approve” recommendation was entered into Panorama by the Office of Pharmaceutical Manufacturing Assessment on September 6, 2024. As such, OPQ recommends approval of this NDA from a quality perspective (refer to the OPQ Integrated Quality Assessment # 2, dated September 25, 2024, in DARRTS).

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 Trial 310 was conducted in compliance with good clinical practice (GCP) guidelines and all local regulatory requirements were followed. The trial protocol and amendments and informed consent documentation were reviewed by institutional

review boards. The Applicant certified that none of the investigators for Trial 310 had any financial interests or arrangements with the Applicant.

In the original NDA submission, the Applicant provided attestation that Trial 301 was conducted in compliance with good clinical practice guidelines and all local regulatory requirements were followed. The trial protocol and amendments were reviewed by institutional review boards. The Applicant certified that none of the investigators for Trial 301 had any financial interests or arrangements with the Applicant.

A review of clinical sites for Trial 310 was conducted by the Office of Scientific Investigations (OSI) to ensure data quality. Three sites (Site 115 in California, Site 129 in Arkansas, and Site 251 in Florida) were inspected based on high enrollment and high treatment response. Per the Clinical Inspection Summary by Dr. John Lee, the data from the inspected sites appear to be acceptable in support of the proposed indication for sulopenem etzadroxil/probenecid. The primary and key secondary efficacy endpoint data were verifiable, and no significant underreporting of AEs was observed. The trial appeared to have been conducted in compliance with good clinical practice principles and regulations at Sites 115 and 129. A GCP deficiency (lack of consistent documentation of adequate contraception history and negative pregnancy testing) was noted at Site 251 but was unlikely to be important to efficacy analysis of study data. For additional details, please refer to Section 22 and the clinical inspection summary written by Dr. John Lee from OSI, dated October 7, 2024, in DARRTS.

For Trial 301, routine PDUFA surveillance inspections were conducted for four clinical investigators. In addition, combined PDUFA/for-cause inspections of two clinical sites (Sites 202 and 218) were conducted to address specific data reliability concerns raised by the Applicant. The Applicant listed several reasons for their exclusion of Site 202: (1) pulse-field gel electrophoresis (PFGE) analysis of some urinary isolates identified from the baseline urine bacterial cultures were either genetically indistinguishable or closely related; (2) a high contamination rate of urine samples; and (3) artificial intelligence software that suggested intentional patient nonadherent behavior. The FDA inspection could not confirm that a single urine sample was used to enrolled multiple subjects at Site 202. In addition, it was concluded that the medication adherence software results may have been misinterpreted as many subjects with “red flag” events were well-documented to have taken the dose. Finally, the decision to exclude Site 202 was made after unblinding of the interim analysis. FDA concluded that there did not appear to be sufficient cause to exclude data from Site 202. (b) (7)(A)

For these reasons, FDA agreed with the Applicant that data from Site 218 should be excluded. For details on clinical site inspections for Trial 301, please refer to the NDA Multi-Disciplinary Review and Evaluation {NDA 213972} dated July 22, 2021, and the clinical inspection summary written by Dr. Cheryl Grandinetti from OSI, dated June 18, 2021, in DARRTS.

11. Advisory Committee Summary

Because oral sulopenem etzadroxil/probenecid, if approved, would be the first oral penem on the U.S. market, the Division took NDA 213972 to an Antimicrobial Advisory Committee meeting

on September 9, 2024 to discuss concerns for possible inappropriate use of this drug in an ambulatory setting which may lead to increasing antimicrobial resistance as well as considerations that should be communicated to prescribers in order to ensure appropriate use of sulopenem etzadroxil/probenecid.

The following discussion questions were posed to the AC:

- The Applicant is seeking an indication for sulopenem etzadroxil/probenecid in adult women ≥ 18 years of age for the treatment of uUTI caused by designated susceptible microorganisms. Discuss the overall benefits and risks for the use of sulopenem etzadroxil/probenecid for this indication.
- Considering the totality of the evidence in this application, discuss considerations that would be important for medical providers to know to ensure appropriate use of sulopenem etzadroxil/probenecid.

Although there were no voting questions, the AC members discussed concerns for potential downstream risks to both individual patients and to society from antimicrobial cross-resistance to carbapenems arising from unrestricted empiric use of oral sulopenem for uUTI in an ambulatory setting. The potential lack of mechanisms for effective antimicrobial stewardship in an ambulatory setting in general was discussed. Given the totality of evidence presented in the FDA Briefing Document and the concerns outlined above, the AC members recommended restricting the indication and providing limitations of use statements.

III. Additional Analyses and Information

12. Summary of Regulatory History

On March 1, 2016, Iterum Therapeutics US Ltd. (Sponsor) submitted IND 129849, for sulopenem etzadroxil (PF-03709270 sulopenem oral prodrug) tablets.

A type C Guidance meeting was held on February 27, 2017, to discuss the development program for PF-03709270. The Sponsor stated that following completion of the ongoing phase 1 clinical program the Sponsor would select the prodrug to move forward into clinical development.

An End of Phase 2 meeting was held on July 21, 2017, to discuss the design of Trial 301 for the treatment of uncomplicated urinary tract infection (uUTI). During this meeting, the Division emphasized that the clinical response component of the overall response endpoint (combined clinical and microbiological responses) should be defined as the resolution of all urinary tract infection (UTI) symptoms present at trial entry. Discussion also included considerations of evaluation of sulopenem versus ciprofloxacin based on assessment of non-inferiority (NI) in the micro-MITTS (ciprofloxacin-susceptible) population and assessment of superiority in the micro-MITTR population (ciprofloxacin-resistant population). The Division noted that the primary analysis population in an NI analysis should only include patients with pathogens susceptible to the proposed comparator.

A type B, chemistry, manufacturing and controls (CMC) meeting was held on August 28, 2017. During this meeting the data needed to demonstrate comparability between the sources of the drug substance, frequency of microbial testing, impurity testing, dissolution methods, suitability of batch manufacture and the overall CMC-development program to support NDA submission was discussed.

On September 19, 2017, the Sponsor submitted their initial pediatric study plan (iPSP) to IND 129849 and an Agreed iPSP letter was issued on February 26, 2018.

On October 27, 2017, PF-03709270/probenecid (sulopenem etzadroxil/probenecid) bilayer tablet was granted Qualified Infectious Disease Product (QIDP) designation for uUTI, complicated urinary tract infection (cUTI), and complicated intra-abdominal infection (cIAI) and Fast Track designation for these same indications on March 15, 2019.

On December 8, 2017, in follow-up to a meeting request to discuss the statistical analysis plan for study IT001-301, the Division provided the Sponsor with comments on the proposed framework for hypothesis testing and interim analysis. The Division commented that discordant results in the two primary analyses (assessment of NI in the microbiological modified intent-to-treat ciprofloxacin-susceptible (micro-MITTS) population and assessment of superiority in the microbiological modified intent-to-treat ciprofloxacin-resistant (micro-MITTR) population) could be problematic and that there would need to be an understanding of the reasons for discrepant findings. Further, such results may also have labeling implications.

On December 27, 2017, the Sponsor submitted a Special Protocol Assessment (SPA) for Protocol IT001-301, entitled: "A prospective, Phase 3, randomized, multi-center, double-blind

study of the efficacy, tolerability, and safety of oral sulopenem etzadroxil/probenecid versus oral ciprofloxacin for treatment of uncomplicated urinary tract infections in adult women.” The Division issued a Special Protocol-Agreement letter for Protocol IT001-301 on February 6, 2018.

A SPA modification request was submitted on June 18, 2018. The modification included a request to increase the sample size, update inclusion criteria, add urine pharmacokinetic (PK) assessments to be consistent with FDA Guidance for uUTI, and to include a recommendation to dose sulopenem etzadroxil/probenecid with food. A Special Protocol Modification Agreement letter was issued on July 10, 2018.

On August 6, 2018, the Sponsor notified FDA of the change in designation of the Sponsor to an affiliated entity, and noted the change from Iterum Therapeutics, US, Ltd. to Iterum Therapeutics International, Ltd.

On February 13, 2020, a type-B Pre-NDA, CMC meeting was held to discuss the content and structure of Section 2.3 (Overall Quality Summary) and Module 3, Quality section of the forthcoming NDA.

On September 28, 2020, a type B meeting was held to discuss the Pre-NDA submission. The Division stated that a determination of substantial evidence of effectiveness and adequate safety to support a labeled indication for the treatment of adult women with uUTI due to quinolone-resistant pathogens would be a review issue. The Sponsor enquired about a limited patient population uUTI indication and proposed submission of the NDA under the LPAD pathway. There were no agreements for late submission(s), therefore the NDA application was expected to be complete at the time of submission.

On November 25, 2020, Iterum Therapeutics US Ltd. (Applicant) submitted NDA 213972 for oral sulopenem etzadroxil/probenecid for the proposed indication of treatment of uUTI caused by designated susceptible microorganisms proven or strongly suspected to be nonsusceptible to a quinolone. NDA 213972 was filed on January 21, 2021, and the NDA received a Priority Review designation. The basis for the NDA submission was the single uUTI Trial 301. Data from Trials 302 (for cUTI) and 303 (for cIAI) were submitted as supportive data only, as both trials failed to meet their primary endpoints.

On February 25, 2021, the Division provided an update on the NDA review during the Mid-Cycle Communication teleconference; on May 26, 2021, the Late-Cycle Meeting was held with the Applicant to discuss substantive review issues. No Advisory Committee meeting was held during the first cycle review.

The NDA received a complete response action on July 23, 2021, due to lack of substantial evidence of effectiveness (SEE). While sulopenem etzadroxil/probenecid demonstrated superiority to ciprofloxacin for the overall (clinical and microbiological) response rate in the micro-MITTR population, the product was inferior in the micro-MITTS population. Additionally, the cUTI Trial 302 and cIAI Trial 303, conducted with IV sulopenem followed by oral sulopenem etzadroxil/probenecid stepdown therapy, failed to meet their primary endpoints and thus, were not considered to provide supportive evidence of effectiveness. FDA recommended that the Applicant conduct an additional trial for uUTI using a different comparator.

On September 23, 2021, a type-A, Post Action meeting was held to discuss and clarify the deficiencies outlined in the complete response letter and on December 21, 2021, a type B,

Guidance meeting was held wherein the Division and the Applicant discussed the design of a new study protocol for the indication of uUTI.

A type B guidance meeting was held on March 10, 2022, to discuss clinical development plans to support approval of sulopenem etzadroxil/probenecid tablets for the treatment of uUTI under the LPAD pathway. The Applicant proposed a NI study using amoxicillin/clavulanate as the comparator. The Division commented that a first-line treatment, such as nitrofurantoin, may be a better choice for the comparator to assess the efficacy of sulopenem etzadroxil/probenecid.

On March 16, 2022, in follow-up to a type B guidance meeting request, the Division issued Written Response Only comments to the Applicant to address questions on the developmental plans for PK/pharmacodynamic (PD) studies.

On June 1, 2022, the Applicant submitted a SPA request for Protocol IT001-310 titled, “A prospective, Phase 3, randomized, multi-center, double-blind study of the efficacy, tolerability, and safety of oral sulopenem etzadroxil/probenecid versus oral amoxicillin/clavulanate for treatment of uncomplicated urinary tract infections (uUTI) in adult women.” A Special Protocol-Agreement letter was issued for Protocol IT001-310 on July 7, 2022.

During development the Applicant submitted multiple requests to amend the Agreed iPSP. On September 25, 2023, the Division issued the final Amended Agreed iPSP Agreement letter. The Applicant submitted the Agreed Amended iPSP in the NDA to address the requirements of the Pediatric Equity Research Act (PREA). The Applicant requested a deferral in children ages 2 to <18 years and a partial waiver in children ages <2 years.

NDA 213972 was resubmitted on April 25, 2024, for the proposed indication of use in adult women ≥ 18 years of age for the treatment of uncomplicated urinary tract infections caused by the following designated susceptible microorganisms: *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis* [REDACTED] ^{(b) (4)}. On April 26, 2024, a proprietary name review request was received for the name ORLYNVAH. The name was found conditionally acceptable on July 17, 2024.

On September 9, 2024, the NDA was discussed at the Antimicrobial Drugs Advisory Committee. The PDUFA goal date for the NDA is October 25, 2024.

13. Pharmacology Toxicology

13.1. Summary Review of Studies Submitted With the Investigational New Drug Application

Please see the NDA 213972 Multidisciplinary Review dated July 22, 2021. No new pharmacology/toxicology studies were submitted to the IND as part of the NDA resubmission.

13.2. Individual Reviews of Studies Submitted With the New Drug Application

Please see the NDA 213972 Multidisciplinary Review dated July 22, 2021, for a full review of all the pivotal pharmacology/toxicology studies included with the original NDA submission. No new pharmacology/toxicology studies appropriate for review in Subsection 13.2 were submitted in the NDA resubmission.

14. Clinical Pharmacology

14.1. In Vitro Studies

No new in vitro metabolism or transporter profiling, distribution or protein binding studies were conducted for the NDA resubmission; these were detailed under the original NDA submission. For a review of these studies, see NDA 213972 Multi-disciplinary Review and Evaluation dated July 22, 2021.

14.2. In Vivo Studies

No new clinical pharmacology trials were conducted for the NDA 213972 resubmission. Refer to the NDA Multi-disciplinary Review and Evaluation dated July 22, 2021, for a detailed review of all phase 1 single and multiple-ascending dose, mass balance, bioavailability, renal impairment and drug-drug interaction study reports.

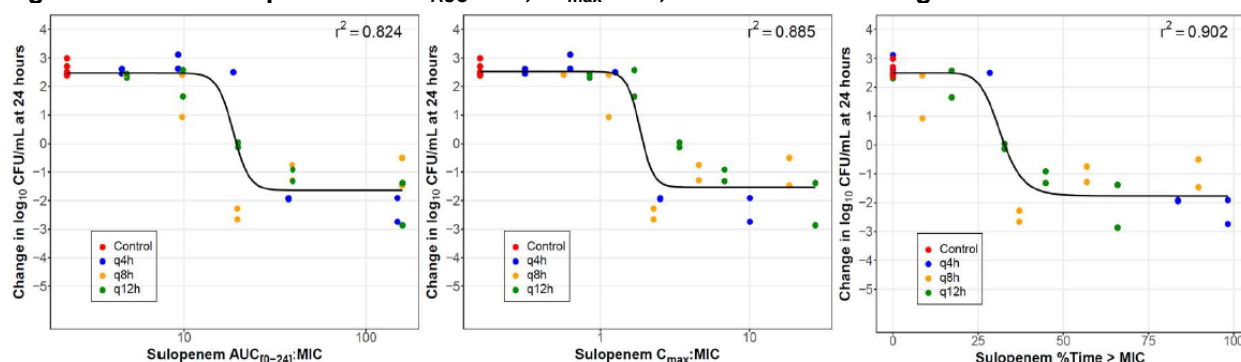
Nonclinical PK/PD Studies

Identification of PK/PD Index for Sulopenem

PK/PD index and target determination for sulopenem were previously conducted using neutropenic and immune-competent murine thigh infection models. As with other beta-lactams, the percent of time that free drug concentrations remain above the minimum inhibitory concentration (%fT_{>MIC}) was expected to be the PK/PD driver of sulopenem's efficacy. However, the Applicant's dose fractionation studies failed to illustrate definitively the index most relevant to efficacy, instead suggesting that the relevant index is pathogen-specific. Because the relevant PK/PD index for antibacterial drugs is typically pathogen independent, the discordance between pathogens was partly illustrative of the complexities of sulopenem's PK/PD properties. However, ambiguities within the study methodology and inconsistencies with data analysis raised concerns about the reliability and interpretability of study findings. Refer to NDA 213972 Multi-disciplinary Review and Evaluation dated July 22, 2021, for further details. As a result of these observations, the Applicant was asked to conduct additional dose fractionation studies to better understand sulopenem's PK/PD behavior. Because sulopenem has a short murine half-life of ~5 min, completion of PK/PD studies in the murine model of infection is technically challenging. Therefore, the review team agreed that the Applicant may conduct subsequent PK/PD studies in an in vitro model of infection.

Using a wild-type strain of *E. coli* (NCTC 13441), a series of duplicate dose-fractionation studies were conducted in a 1-compartment in vitro infection model using 5 different total sulopenem daily doses of 62.5, 125, 250, 500 and 2000 mg divided equally according to q4h, q8h or q12h dosing regimens. To approximate oral absorption, sulopenem was infused into the in vitro system over 2 h. A Hill-type model was fit to the resulting PK and PD (i.e., changes in bacterial burden) to determine which of the 3 traditional PK/PD indices best correlates with sulopenem's activity. %fT>MIC held the strongest correlation with sulopenem's activity based on r^2 values (Figure 4), followed closely by free-drug maximum plasma concentration/MIC. These findings suggest that sulopenem exhibits both time and concentration-dependent bacterial killing.

Figure 4. Relationships Between f_{AUC}/MIC , fC_{max}/MIC , %fT>MIC and Change in Bacterial Burden



Source: Figure 5 of Applicant's ICPD Report on In Vitro Pharmacokinetics and Pharmacodynamics of Sulopenem
Abbreviations: AUC_{0-24h}, area under the concentration-time curve from time 0 to 24 h; CFU, colony-forming units; C_{max}, maximum plasma concentration; f_{AUC} , free-drug area under the concentration-time curve; fC_{max} , free-drug maximum plasma concentration; ICPD, Institute for Clinical Pharmacodynamics; MIC, minimum inhibitory concentration; q4h, every 4 hours; q8h, every 8 hours; q12h, every 12 hours

Reviewer's comment: %fTime>MIC was selected as the PK/PD index for sulopenem as it is the index typically attributed to the beta-lactam drug class. However, the fact that free-drug maximum plasma concentration/MIC is also highly correlated with bacterial killing suggests sulopenem's dosing could be also optimized by maximizing maximum plasma concentration.

Determination of PK/PD Targets for Sulopenem

Instead of a separate set of dose-ranging studies dedicated to target determination, the Applicant relied upon the results of the dose fractionation studies against a set of Gram-positive and Gram-negative pathogens to determine the magnitude of %fT>MIC (the assumed PK/PD index for sulopenem) required for stasis and 1-log kill. The atypical approach to target determination and concerns with reliability of data precluded use of this data to inform probability of target attainment (PTA) analyses.

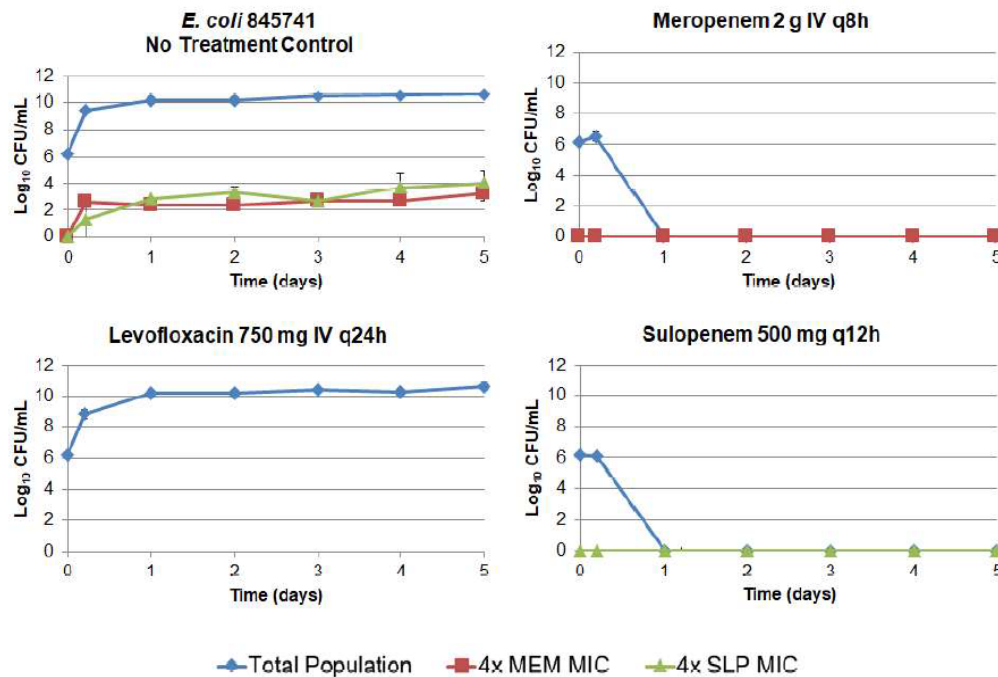
Dose-ranging studies were conducted in duplicate in the 1-compartment in vitro infection model against a panel of 10 Enterobacteriales (i.e., 6 *E. coli* and 4 *K. pneumoniae*) with sulopenem MICs of 0.03 to 0.5 $\mu\text{g}/\text{mL}$. Free sulopenem exposures associated with doses ranging from 7.81 to 2000 mg q12h were simulated in the model to determine the magnitude of sulopenem %fT>MIC required to achieve stasis, 1-log and 2-log kill. Similar to the dose fractionation studies, sulopenem was infused into the in vitro system over 2 h to simulate oral absorption, and a Hill-type model was fitted to the resulting data to determine individual as well as pooled targets for each of the bacteriologic endpoints of interest. 1-log kill was achieved in all but 1 isolate,

while 2-log kill was achieved in only 4 of the 10 isolates. The median %fT>MIC targets were 40.9, 50.2 and 62.6% for stasis, 1-log and 2-log kill, respectively.

Proof-of-Concept Study in a Hollow Fiber Infection Model

In a series of studies conducted in a hollow fiber infection model, sulopenem urinary exposures associated with 500 mg q12h regimen were simulated against 4 extended-spectrum β -lactamase (ESBL)-positive *E. coli* isolates with sulopenem MICs 0.03 to 0.06 μ g/mL. The selected isolates were resistant to levofloxacin and susceptible to meropenem to allow for the use of levofloxacin 750 mg q24h and meropenem 2 g q8h as negative and positive controls, respectively. For all 4 isolates, sulopenem exposures associated with 500 mg q12h produced a sustained reduction in bacterial burden from baseline and suppressed the development of resistance. Representative results for 1 of the isolates, *E. coli* 845741, are shown in [Figure 5](#).

Figure 5. Hollow Fiber Results Displaying Total and Drug-Resistant [4X Sulopenem and Meropenem] Subpopulations in No Treatment Control, Sulopenem, Meropenem, and Levofloxacin



Source: Figure 22 of Applicant's ICPD Report on In Vitro Pharmacokinetics and Pharmacodynamics of Sulopenem
Abbreviations: CFU, colony-forming units; ICPD, Institute for Clinical Pharmacodynamics; IV, intravenous; MIC, minimum inhibitory concentration; MEM, meropenem; q4h, every 4 hours; q8h, every 8 hours; q12h, every 12 hours; SLP, sulopenem

Reviewer's comment: For levofloxacin and meropenem, the Applicant's hollow fiber studies simulated plasma drug exposures instead of urinary exposures. Per the Applicant, use of these exposures was intended to establish the sensitivity of the model in discerning positive and negative results, and not intended to facilitate a head-to-head comparison of urinary drug activity across the 3 drugs.

14.3. Bioanalytical Method Validation and Performance

A complete review of the validation and performance of the bioanalytical methods was conducted under the original NDA submission to confirm the reliability of the sulopenem and probenecid clinical PK data. Refer to the NDA 213972 Multi-disciplinary Review and Evaluation dated July 22, 2021, for details.

14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety

Not applicable.

14.5. Pharmacometrics Assessment

14.5.1. Review Summary

The Applicant previously developed a population PK (PopPK) model using plasma PK data from nine phase 1 and three phase 3 trials, in which sulopenem etzadroxil was administered either as a monolayer tablet, the to-be-marketed bilayer tablet and a powder-in-bottle (PIB) formulation with or without probenecid. Briefly, the PopPK model was previously reviewed in detail and found to reasonably describe the concentration-time profiles of sulopenem in healthy subjects and subjects with uUTI. Additionally, the PopPK model was considered acceptable in generating exposure parameters (i.e., area under the concentration-time curve during the dosing interval and maximum plasma concentration) to support labeling statements. However, potential correlations between intrinsic and extrinsic factors (i.e., renal function, food effects, and formulations) (with or without probenecid) may confound the evaluation and interpretation of covariate effects on sulopenem PK, and as such, careful consideration should be exercised when interpreting simulations (e.g., PTA) based on the correlated covariates. Refer to the NDA 213972 Multi-disciplinary Review and Evaluation dated July 22, 2021, for details on the PopPK model evaluation and utility.

In the current submission, the PopPK model was extended to describe the disposition of sulopenem in urine (i.e., fraction of elimination from the central compartment to urine compartment) based on urinary exposure data obtained from a subset of the studied PK population (i.e., healthy subjects). Additionally, urine PTA was conducted to predict the proportion of subjects achieving specified target exposures in the urine. Although the updated PopPK model is generally acceptable for characterizing sulopenem urine PK in phase 1 Trial 101 and phase 3 Trial 302, the model did not reasonably describe the phase 3 Trial 301 urine data. It is unclear whether this is due to a difference in sulopenem urine PK between healthy subjects and those with uUTI. Further, there are uncertainties regarding the assumed bladder voiding frequencies that limit the interpretability of the urine PTA results. Nonetheless, the plasma-based PTA results support a susceptible breakpoint of up to 0.5 mcg/mL.

14.5.2. Introduction

The objectives of the PopPK analysis were to:

- Develop a PopPK model to describe the disposition of sulopenem in plasma and urine
- Evaluate the impact of clinically relevant covariates on the PK of sulopenem
- Predict the probability of PK/PD target attainment in plasma and urine

14.5.3. Model Development

The clinical Pharmacology Review Team previously reviewed the model development, evaluation of model performance and covariate analysis; refer to NDA 213972 Multi-disciplinary Review and Evaluation dated July 22, 2021. Briefly, the PopPK model is based on data from 12 studies as summarized in ([Table 73](#)); there are no PK data available from Trial 310. A summary of the number of observations from each trial and demographic information are provided in [Table 74](#), [Table 75](#) and [Table 76](#). Phase 1 studies included rich PK sampling while sparse samples were obtained in the phase 3 trial participants. A graphical illustration of the initial model, which was a 3-compartment model with non-linear elimination developed using only plasma PK data, is shown in [Figure 6](#).

For urine observations, urine concentration and volume data were collected for 243 subjects in Trials 101, 301, and 302 ([Table 76](#)). The final and updated PopPK model was based on urine measurements results from Day 1 of Trial 101, where the urine collection process was well-controlled and yielded reliable urine concentration and volume data (i.e., with sampling at 2 h intervals through 12 h post dosing in 32 subjects) in healthy subjects. In total, 32 unique subjects contributed 159 urine concentration and urine volume observations. Because urine PK data were available for only a subset of subjects in the PK population, the Applicant limited their analyses to estimation of urine-specific parameters (i.e., urine fraction, inter-individual variability in urine fraction, and a residual error of the urine concentration data) by fixing the plasma PopPK model parameters to individual's empirical Bayes estimates.

Table 73. Clinical Trials Included in PopPK Analysis

Study number	Study Design	Number of subjects with PK samples	Formulation	Dose	Probenecid
A1091001	Phase 1 Multiple Dose	40	IV	800 mg, 1200 mg, 1600 mg, 2000 mg	No
A7371007	Phase 1 Single Dose	24	IV	400 mg, 800 mg, 1600 mg, 2400 mg, 2800 mg	No
A8811001	Phase 1 Single Dose	9	PIB	400 mg, 600 mg, 1000 mg, 2000 mg	No
A8811008	Phase 1 Single Dose	24	Tablet*	1200 mg	Yes
A8811009	Phase 1 Renal Impairment	29	IV and Tablet	IV: 200mg, 800 mg, Tablet: 1000 mg	No
A8811015	Phase 1 Multiple Dose	48	Tablet	500 mg, 1000 mg, 1500 mg BID for 7 days	Yes
IT001-101	Phase 1 Multiple Dose	64	PIB	500 mg BID	Yes
IT001-102	Phase 1 Single Dose Four-Way Crossover	13	PIB	500 mg	Yes
IT001-105	Phase 1 Single Dose Three Period	46	IV/Bilayer Tablet/PIB	IV: 366 mg and 1000 mg, Bilayer Tablet, PIB: 500 mg	Yes
IT001-301	Phase 3 uUTI PK Substudy	125	Bilayer Tablet	500 mg BID	Yes
IT001-302	Phase 3 uUTI PK Substudy	125	IV/Bilayer Tablet	IV: 1000 mg Oral: 500 mg BID	Yes
IT001-303	Phase 3 cIAI PK Substudy	125	IV/Bilayer Tablet	IV: 1000 mg Oral: 500 mg BID	Yes

Source: Table 1 of Applicant's Population PK (PopPK) and PTA Analysis Report

*Only standard release formulation to be included.

Study A8811008, A8811015, IT001-101 and IT001-105

Abbreviations: BID, twice daily; cIAI, complicated intra-abdominal infections; IV, intravenous; PIB, powder-in-bottle; PK, pharmacokinetic; PTA, probability of target attainment; Tablet, monolayer tablet; uUTI, uncomplicated urinary tract infection

Table 74. Summary of Baseline Demographic Covariates – Phase 1 Trial

Study	IT001-105	A1091001	A7371007	A8811009
	(N = 46)	(N = 40)	(N = 24)	(N = 29)
Age (yr)				
Mean (SD)	35.8 (9.0)	35.4 (10)	36.2 (12)	62.5 (9.9)
Median (range)	37.0 (21.0 - 54.0)	35.0 (20.0 - 55.0)	37.5 (20.0 - 54.0)	61.0 (38.0 - 78.0)
Weight (kg)				
Mean (SD)	79.2 (11)	77.8 (8.9)	82.7 (10)	80.5 (9.8)
Median (range)	77.9 (58.9 - 104)	78.0 (57.0 - 97.0)	82.0 (65.0 - 100)	80.0 (57.7 - 96.8)
Gender				
Female	6 (13.0%)	0 (0.0%)	1 (4.2%)	12 (41.4%)
Male	40 (87.0%)	40 (100.0%)	23 (95.8%)	17 (58.6%)
Race				
Asian	2 (4.3%)	0 (0.0%)	1 (4.2%)	0 (0.0%)
Black	31 (67.4%)	3 (7.5%)	12 (50.0%)	3 (10.3%)
Other	2 (4.3%)	2 (5.0%)	0 (0.0%)	1 (3.4%)
White	11 (23.9%)	35 (87.5%)	11 (45.8%)	25 (86.2%)
Creatinine clearance (ml/min)				
Mean (SD)	115 (19)	131 (16)	120 (22)	62.0 (32)
Median (range)	113 (81.5 - 160)	132 (90.0 - 159)	118 (82.9 - 171)	52.6 (21.4 - 123)

Study	IT001-101	A8811008	IT001-102	A8811015	A8811001
	(N = 56)	(N = 12)	(N = 23)	(N = 48)	(N = 9)
Age (yr)					
Mean (SD)	37.7 (11)	37.1 (10)	38.7 (12)	33.5 (11)	32.4 (10)
Median (range)	35.5 (18.0 - 59.0)	32.5 (24.0 - 54.0)	38.0 (20.0 - 59.0)	28.5 (18.0 - 55.0)	34.0 (21.0 - 52.0)
Weight (kg)					
Mean (SD)	82.1 (12)	85.8 (9.8)	81.3 (11)	81.6 (12)	75.0 (8.0)
Median (range)	82.6 (55.4 - 118)	85.0 (69.0 - 104)	80.3 (61.3 - 105)	82.5 (61.0 - 111)	77.0 (64.0 - 89.0)
Gender					
Female	3 (5.4%)	0 (0.0%)	4 (17.4%)	2 (4.2%)	0 (0.0%)
Male	53 (94.6%)	12 (100.0%)	19 (82.6%)	46 (95.8%)	9 (100.0%)
Race					
Asian	0 (0.0%)	1 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Black	40 (71.4%)	4 (33.3%)	17 (73.9%)	23 (47.9%)	4 (44.4%)
Other	0 (0.0%)	3 (25.0%)	0 (0.0%)	8 (16.7%)	0 (0.0%)
White	16 (28.6%)	4 (33.3%)	6 (26.1%)	17 (35.4%)	5 (55.6%)
Creatinine clearance (ml/min)					
Mean (SD)	120 (24)	108 (21)	124 (23)	114 (21)	115 (15)
Median (range)	118 (83.1 - 183)	110 (68.7 - 135)	122 (93.1 - 163)	111 (79.1 - 160)	116 (93.3 - 144)

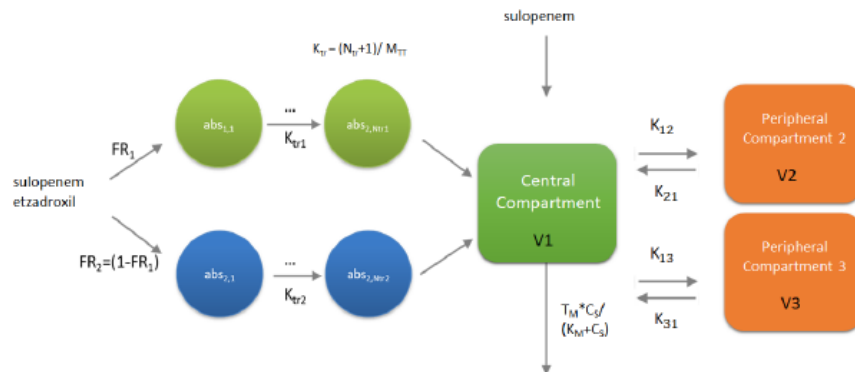
Source: Tables 2 and 3 of Applicant's Population PK and PTA Analysis Report
 Abbreviations: N, number of subjects; PK, pharmacokinetic; PTA, probability of target attainment; SD, standard deviation

Table 75. Summary of Baseline Demographic Covariates – Phase 3 Trials

Study	IT001-301	IT001-302	IT001-303	All
	(N = 118)	(N = 122)	(N = 125)	(N = 365)
Age (yr)				
Mean (SD)	48.6 (17)	59.6 (17)	56.3 (17)	54.9 (18)
Median (range)	49.0 (18.0 - 84.0)	63.0 (18.0 - 91.0)	56.0 (18.0 - 90.0)	56.0 (18.0 - 91.0)
Weight (kg)				
Mean (SD)	75.4 (19)	77.3 (17)	83.3 (20)	78.8 (19)
Median (range)	72.6 (44.5 - 133)	76.0 (38.8 - 129)	80.0 (50.0 - 140)	76.3 (38.8 - 140)
Gender				
Female	118 (100.0%)	58 (47.5%)	55 (44.0%)	231 (63.3%)
Male	0 (0.0%)	64 (52.5%)	70 (56.0%)	134 (36.7%)
Race				
Asian	1 (0.8%)	1 (0.8%)	0 (0.0%)	2 (0.5%)
Black	13 (11.0%)	0 (0.0%)	0 (0.0%)	13 (3.6%)
Other	4 (3.4%)	0 (0.0%)	0 (0.0%)	4 (1.1%)
White	100 (84.7%)	121 (99.2%)	125 (100.0%)	346 (94.8%)
Creatinine clearance (ml/min) IV dose				
Mean (SD)	na	89.3 (37)	104 (40)	96.5 (39)
Median (range)	na	86.1 (16.9 - 243)	98.1 (21.2 - 219)	92.1 (16.9 - 243)
Creatinine clearance (ml/min) IV dose				
Mean (SD)	117 (47)	92.2 (37)	123 (42)	111 (44)
Median (range)	109 (25.5 - 292)	92.3 (19.1 - 243)	117 (35.0 - 251)	103 (19.1 - 292)
Food status, oral				
Fasted	8 (6.8%)	18 (16.4%)	5 (4.8%)	31 (9.3%)
Food, meal	55 (46.6%)	79 (71.8%)	81 (77.1%)	215 (64.6%)
Food, snack	15 (12.7%)	10 (9.1%)	12 (11.4%)	37 (11.1%)
Missing	5 (4.2%)	0 (0.0%)	0 (0.0%)	5 (1.5%)
Planned meal	22 (18.6%)	3 (2.7%)	6 (5.7%)	31 (9.3%)
Planned Snack	13 (11.0%)	0 (0.0%)	1 (1.0%)	14 (4.2%)

Source: Table 4 of Applicant's Population PK and PTA Analysis Report
 Abbreviations: IV, intravenous; N, number of subjects; PK, pharmacokinetic; PTA, probability of target attainment; SD, standard deviation

Figure 6. Illustration of PopPK Model



Source: Figure 7 of Applicant's Population PK and PTA Analysis Report
 The model structure reflects the previously reviewed PopPK model based on plasma PK data
 Abbreviations: PK, pharmacokinetic; PopPK, population PK; PTA, probability of target attainment

Table 76. Summary of Number of Subjects and Urine Observations by Study and Covariates

Study	IT001-101	IT001-301	IT001-302	All
	(N = 32)	(N = 101)	(N = 110)	(N = 243)
	n (%)	n (%)	n (%)	n (%)
Co-medication				
Without probenecid	16 (50.0%)			16 (6.6%)
With 500 mg probenecid	16 (50.0%)	101 (100.0%)	110 (100.0%)	227 (93.4%)
Prandial Status				
Fasted	16 (50.0%)	6 (5.9%)	18 (16.4%)	40 (16.5%)
Fed	16 (50.0%)	90 (89.1%)	92 (83.6%)	198 (81.5%)
No restrictions		5 (5.0%)		5 (2.1%)
Population Type				
cUTI			110 (100.0%)	110 (45.3%)
Healthy Volunteer	32 (100.0%)			32 (13.2%)
uUTI		101 (100.0%)		101 (41.6%)
Renal Impairment				
<30 mL/min		1 (1.0%)	4 (3.6%)	5 (2.1%)
30-60 mL/min		5 (5.0%)	19 (17.3%)	24 (9.9%)
60-90 mL/min	4 (12.5%)	29 (28.7%)	36 (32.7%)	69 (28.4%)
>90 mL/min	28 (87.5%)	66 (65.3%)	51 (46.4%)	145 (59.7%)

Source: Table A.12.1 of Applicant's Population PK and PTA Analysis Report
Abbreviations: cUTI, complicated urinary tract infection; N, number of subjects; PK, pharmacokinetic; PTA, probability of target attainment; uUTI, uncomplicated urinary tract infection

The previously reviewed plasma PopPK model was modified to specify a urine compartment, resulting in a 3-compartment model with nonlinear elimination (at concentrations exceeding those associated with the proposed dosage) mathematically described by:

Figure 7. Updated PopPK Model Equation

$$\begin{aligned} \frac{dA_{\text{central}}}{dt} &= \frac{k_{tr1} + k_{tr2}}{2} - k_{12} \cdot A_{\text{central}} + k_{21} \cdot A_{\text{peripheral2}} - k_{13} \cdot A_{\text{central}} + k_{31} \cdot A_{\text{peripheral3}} - k_e \\ \frac{dA_{\text{peripheral2}}}{dt} &= k_{12} \cdot A_{\text{central}} - k_{21} \cdot A_{\text{peripheral2}} \\ \frac{dA_{\text{peripheral3}}}{dt} &= k_{13} \cdot A_{\text{central}} - k_{31} \cdot A_{\text{peripheral3}} \\ \frac{dA_{\text{urine}}}{dt} &= k_e \cdot \text{UrineFraction} \end{aligned}$$

where the micro-constants of the mass transfer are defined as

$$k_{tr1} = \frac{N_{tr1} + 1}{MTT_1}; \quad k_e = \frac{T_M \cdot C_S}{K_M + C_S}; \quad k_{12} = \frac{Q}{V_1}; \quad k_{21} = \frac{Q}{V_2}; \quad k_{13} = \frac{Q_2}{V_1}; \quad k_{31} = \frac{Q_2}{V_3}.$$

and urine concentrations defined as

$$\text{Conc}_{\text{urine}} = \frac{A_{\text{urine}}}{V_{\text{urine}}}$$

Source: Section A.12.3 of Applicant's Population PK and PTA Analysis Report
Abbreviations: PK, pharmacokinetic; PTA, probability of target attainment

To update the previous PopPK model, implementation of the urine observations assumed complete voiding of the bladder (i.e., urine compartment) with the observed urine volume reflecting the total amount produced within the collection interval (i.e., between two observations). The final model PK parameters and inter-subject variabilities (IIVs) are shown in

[Table 77](#) and [Table 78](#), respectively. Parameters were generally estimated with precision (relative standard errors <50%). The estimated urine fraction was 48% (95% CI, 40% to 56%; based on logit-transformed point estimate, $e^{\text{THETA31}/(1+e^{\text{THETA31}})}$) of the plasma clearance rate with an IIV variance estimate of 0.219 (i.e., 49.5% coefficient of variation with 20.3% shrinkage) and proportional residual error variance estimate of 0.29 (residual standard error 19%; shrinkage, 2.8%).

Using the final model parameter estimates and assuming no difference between healthy volunteers and patients, urine PK was simulated for Trials 101, 301 and 302 population. Prediction-corrected visual predictive check plots for the sulopenem urinary concentrations in the presence or absence of food and probenecid indicate that although the updated model tends to reasonably capture the central tendency for data in Trials 101 and 302, there are underpredictions for the respective 95th percentiles of the observed urine data in these two studies. Furthermore, the relatively wide 95% CI of the predicted 5th percentiles for the observed urine data in Trials 101 and 302 are likely due to small sample size and high variability ([Figure 8](#)). For Trial 301, the updated PopPK model underpredicts the urine exposures, and it is unclear which factor(s) (i.e., potential difference in urine PK between subjects in Trial 101 and Trial 301, shorter urine PK collection period in Trial 301, or relatively higher variabilities of the nominal urine concentration compared to those of Trials 101 and 302) may account for the underpredictions. Because of these limitations, the urine PTA findings based on the updated PopPK model should be interpreted with caution.

Table 77. Parameter Estimates of Extended PopPK Model – Part 1

Parameter	Alias	Estimate	Relative SE (%)	Transformed Estimate	95% CI	Transformation
θ_1	T_M ($\mu\text{g}/\text{h}$)	7.74		2.30e+03	(2.07e+03 - 2.56e+03)	log
θ_2	K_M ($\mu\text{g}/\text{mL}$)	4.22		68.0	(61.2 - 75.7)	log
θ_3	V_1 (L)	2.59		13.3	(12.6 - 14.1)	log
θ_4	V_2 (L)	2.06		7.85	(7.06 - 8.73)	log
θ_5	Q_1 (L/h)	2.49		12.1	(10.6 - 13.7)	log
θ_6	MTT1 (h)*	0.271		1.31	NC	log
θ_7	NTR1*	0.219		1.24	NC	log
θ_8	Bioavailability oral %*	-1.32		0.211	NC	logit
θ_9	MTT2 (h)*	0.411		1.51	NC	log
θ_{10}	NTR2*	2.70		14.9	NC	log
θ_{11}	Q_2 (L/h)	0.685		1.98	(1.61 - 2.44)	log
θ_{12}	V_3 (L)	1.56		4.76	(4.28 - 5.30)	log
θ_{13}	Fraction of dose to first absorption chain	1.83		0.862	NC	logit
θ_{14}	Proportional error Phase 1 oral	0.323	0.8		(0.318 - 0.328)	none
θ_{15}	Proportional error Phase 1 IV	0.193	0.7		(0.190 - 0.196)	none
θ_{16}	Probenecid on T_M *	-0.315			NC	none
θ_{17}	High dose probenecid on T_M *	-0.511			NC	none
θ_{18}	Creatinine clearance on T_M	0.00735	2.3		(0.00702 - 0.00768)	none
θ_{19}	Food on bioavailability, bi-layer*	-0.429			NC	none
θ_{20}	Food on MTT1, monolayer tablet and PIB*	0.718			NC	none
θ_{21}	Time dependency on bioavailability*	0.270			NC	none
θ_{22}	PIB on MTT1*	-0.242			NC	none
θ_{23}	Probenecid on V_1 , V_2 and V_3 *	-0.0993			NC	none
θ_{24}	Food on bioavailability, PIB and monolayer*	-0.303			NC	none
θ_{25}	Proportional error Phase 3 oral	0.455	3.3		(0.426 - 0.484)	none
θ_{26}	Proportional error Phase 3 IV	0.683	2.8		(0.646 - 0.720)	none
θ_{27}	Study 301 and 302 on MTT1	0.369	11.9		(0.283 - 0.455)	none
θ_{28}	Sex (female) on T_M	-0.145	14.6		(-0.187 - -0.103)	none
θ_{29}	Body weight on V_1 , V_2 and V_3	1.00			NC	none
θ_{30}	Study 303 on MTT1	0.674	9		(0.555 - 0.793)	none
θ_{31}	Fraction of plasma clearance to urine	-0.0809		0.480	(0.401 - 0.560)	logit

Source: Table A.12.3 of Applicant's Population PK and PTA Analysis Report

Parameter values for the Phase 3 PopPK model. Estimates are shown as normal and transformed, according to the transformation type. Relative SE (%) are given for the normal parameters. Transformed 95% CI are given for the transformed parameters.

Fixed parameters based on Phase 1 model.

Abbreviations: Km, concentration for half maximum rate of elimination; MTT1, mean transit time for first transit chain; NC, not calculated; NTR1, number of transit compartments for first transit chain; PTA, probability of target attainment; PopPK, population PK Q1, first intercompartment clearance; Q2, second intercompartment clearance; SE, standard error; Tm, maximum rate of elimination; V1, central volume of distribution; V2, peripheral compartment 2 volume of distribution; V3, peripheral compartment 3 volume of distribution; w2/x, variance of the IIV of parameter X, IIV is derived from variance according to $\sqrt{w2/x}$ 100

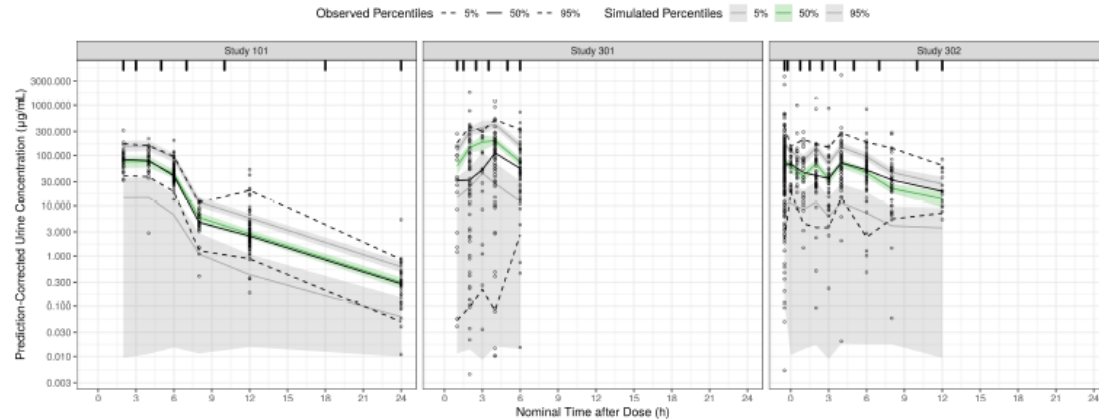
Table 78. Parameter Estimates of Extended PopPK Model – Part 2

Parameter	Alias	Estimate	Relative SE (%)	Transformed Estimate	95% CI	Transformation
$\omega_{1.1}$	ω_{TM}^2	0.0670	9.9		(0.0540 - 0.0800)	none
$\omega_{2.1}$	$\omega_{V1, TM}^2$	0.0190	43.9		(0.00269 - 0.0353)	none
$\omega_{2.2}$	ω_{V1}^2	0.0321	19.4		(0.0199 - 0.0443)	none
$\omega_{3.1}$	$\omega_{V2, TM}^2$	0.0280	33.9		(0.00940 - 0.0466)	none
$\omega_{3.2}$	$\omega_{V2, V1}^2$	0.0346	20.8		(0.0205 - 0.0487)	none
$\omega_{3.3}$	ω_{V2}^2	0.0617	23		(0.0339 - 0.0895)	none
$\omega_{4.1}$	$\omega_{V3, TM}^2$	0.0276	32.3		(0.0101 - 0.0451)	none
$\omega_{4.2}$	$\omega_{V3, V1}^2$	0.0203	30.1		(0.00832 - 0.0323)	none
$\omega_{4.3}$	$\omega_{V3, V2}^2$	0.0471	20.4		(0.0282 - 0.0660)	none
$\omega_{4.4}$	ω_{V3}^2	0.0533	21.4		(0.0310 - 0.0756)	none
$\omega_{6.6}$	ω_{MTT1}^2 *	0.0335			NC	none
$\omega_{7.7}$	ω_{NTR1}^2 *	0.652			NC	none
$\omega_{8.8}$	ω_F^2	0.129	7.7		(0.109 - 0.149)	none
$\omega_{11.11}$	ω_{FRAC}^2 *	1.47			NC	none
$\omega_{13.13}$	$\omega_{IOV, MTT1}^2$ *	0.107			NC	none
$\omega_{1.1}$	$\omega_{FRAC, Urine}^2$	0.219	52.7		(-0.00640 - 0.444)	none
$\sigma_{2.2}$	$\sigma_{Prop, RUV, Urine}^2$	0.290	19		(0.182 - 0.398)	none

Source: Table A.12.4 of Applicant's Population PK and PTA Analysis Report
 Parameter values for the Phase 3 PopPK model. Estimates are shown as normal and transformed, according to the transformation type. Relative SE (%) are given for the normal parameters. Transformed 95% CI are given for the transformed parameters. Fixed parameters based on Phase 1 model.

Abbreviations: F, bioavailability; FRAC, fraction of dose going into the slow transit chain; IOV, inter occasion variability; MTT1, mean transit time for first transit chain; NC, not calculated; NTR1, number of transit compartments for first transit chain; PopPK, population PK; SE, standard error; Tm, maximum rate of elimination; V1, central volume of distribution; V2, peripheral compartment 2 volume of distribution; V3, peripheral compartment 3 volume of distribution

Figure 8. Prediction-Corrected Visual Predictive Check Final Model by Nominal Time After Dose, Applied Trials 101, 301, and 302



Source: Figure A.12.2 of Applicant's Population PK and PTA Analysis Report
 Study IT001-301 sites 149 and 202 were excluded from this VPC given implausible urine volumes. All observations and predictions are adjusted using prediction correction.

Circles: Observations, Solid Black Line: Median of the observed sulopenem concentrations, Dashed Lines: 5th and 95th percentile of the observed sulopenem concentrations, Shaded Area, with corresponding solid lines: The shaded areas indicate the 95% CI around the median (green area), and 5th and 95th percentiles of the simulated concentrations (grey areas). Black Tick Marks: Marks the binning intervals for the VPC.

Abbreviations: PK, pharmacokinetic; PTA, probability of target attainment; VPC, visual predictive check

14.5.4. Probability of Target Attainment in Plasma and Urine

The final PopPK model was subsequently used to simulate and estimate PTAs for both plasma and urine using Monte Carlo simulations. Patient covariates incorporated in the PopPK model (i.e., body weight, sex, and creatinine clearance [CrCl]) were obtained by re-sampling

individuals, with replacement, from the analysis dataset (from Trials 101, 301, and 302), resulting in the covariate distributions summarized in [Table 79](#). Although in the current regulatory setting, uUTI is generally considered to occur in women with normal genitourinary anatomy inclusion of data from male trial participants (who are expected to exhibit lower sulopenem exposures than females based on model predictions) was reasonable to allow a more conservative estimation of PTA (Section [2.1](#)). To account for the impact of bladder emptying, two voiding frequencies (i.e., 1 h and 2 h) were evaluated. However, it is unclear whether these voiding patterns are readily generalizable in clinical settings. The urine production rate (L/h) used in the simulations was based on literature reports indicating normal urine production rates of 0.5-1.5 mL/kg/h. A value of 1 mL/kg/h appeared to best align with observed urine production rates in 101, 301, and 302 (calculated as measured urine volume (L) divided by time in between observations).

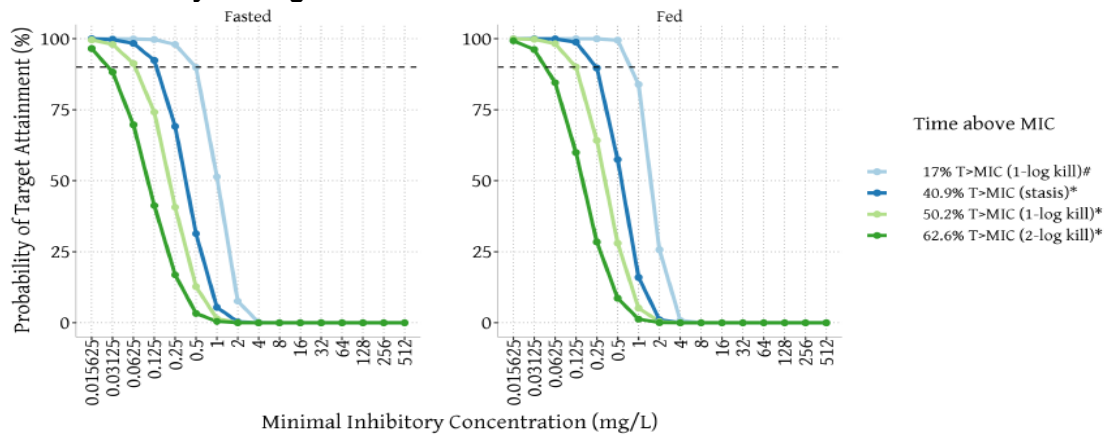
Table 79. Covariate Distributions of the Virtual Population

Study	Statistic	IT001-101	IT001-301*	IT001-302	Simulations
Formulation	Powder in a Bottle	32 (100%)			
	Bilayer Tablet		83 (100%)	110 (100%)	10000 (100%)
Administration Route	PO	32 (100%)	83 (100%)	110 (100%)	10000 (100%)
Prandial State	Fasted	16 (50%)	4 (4.82%)	18 (16.4%)	5000 (50%)
	Fed	16 (50%)	74 (89.2%)	92 (83.6%)	5000 (50%)
	No restrictions		5 (6.02%)		
	- probenecid	16 (50%)			
Co-medication	+ probenecid	16 (50%)	83 (100%)	110 (100%)	10000 (100%)
	No probenecid	16 (50%)			
Probenecid Dose (mg)	500 mg probenecid	16 (50%)	83 (100%)	110 (100%)	10000 (100%)
Gender	Male	30 (93.8%)		59 (53.6%)	3610 (36.1%)
	Female	2 (6.25%)	83 (100%)	51 (46.4%)	6390 (63.9%)
Body weight (kg)	Mean (SD)	84.1 (12.4)	74.1 (18.6)	77.3 (16.9)	79 (18.8)
	Median (range)	83.7 (62.8, 118)	70.4 (44.5, 133)	76.2 (38.8, 129)	76.4 (38.8, 140)
Creatinine Clearance (mL/min)	Mean (SD)	120 (25)	114 (47.4)	87.9 (36.3)	96.7 (31.4)
	Median (range)	118 (83.9, 183)	107 (25.5, 247)	82.2 (17, 243)	96.5 (17, 140)
Urine production rate (L/h)	Mean (SD)	0.098 (0.043)	0.0699 (0.0502)	0.087 (0.0517)	0.079 (0.0188)
	Median (range)	0.0857 (0.0368, 0.187)	0.061 (0.000889, 0.244)	0.0731 (0.00187, 0.35)	0.0764 (0.0388, 0.14)

Source: Table A.12.2 of Applicant's Population PK and PTA Analysis Report
Abbreviations: PK, pharmacokinetic; PTA, probability of target attainment; PO, orally; MIC, minimum inhibitory concentration; N, total number of subjects; SD, standard deviation

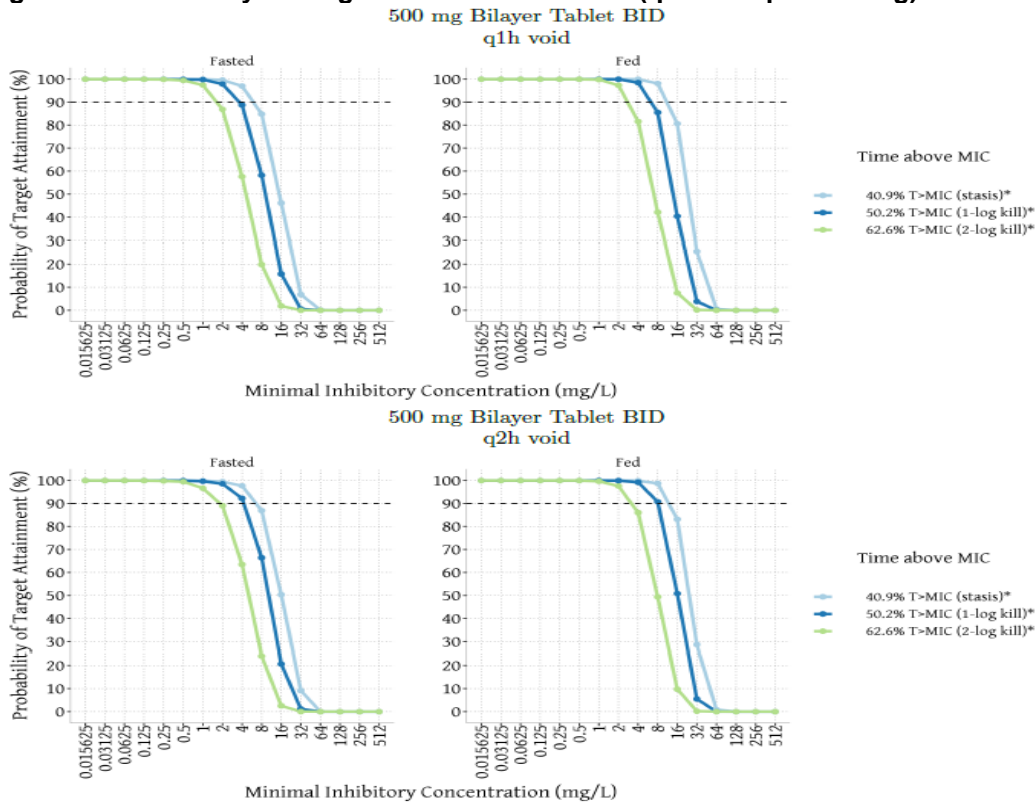
A total of 5000 subjects were simulated where each subject had one MIC value drawn from the distribution for Trial 301. Probability of achieving the %fT>MIC targets derived from nonclinical PK/PD studies was then assessed for a 500 mg sulopenem etzadroxil/500 mg probenecid dose. Typically, PTA analyses rely upon the epidemiological MIC distribution, but this alternative was acceptable given that the MIC distribution from Trial 301 mirrors the epidemiological values (see Section [19.1](#)). Given the review team's finding that the murine thigh infection model-informed PK/PD targets are unreliable (see Section [5.1](#)), PTA results in plasma and urine are only presented for the in vitro PK/PD targets.

Figure 9. Probability of Target Attainment in Plasma



Source: Figure 32 of Applicant's Population PK and PTA Analysis Report
 Dashed Line: 90% of simulated subjects (N=5000) reaching the respective %T>MIC targets.
 Abbreviations: MIC, minimum inhibitory concentration; N, total number of subjects

Figure 10. Probability of Target Attainment in Urine (q1h and q2h Voiding)



Source: Figure 34 of Applicant's Population PK and PTA Analysis Report
 Dashed Line: 90% of simulated subjects (N=5000) reaching the respective %T>MIC target.
 Abbreviations: BID, twice daily; PK, pharmacokinetic; PTA, probability of target attainment; MIC, minimum inhibitory concentration; N, total number of subjects; q1h, every hour; q2h, every 2 hours

14.6. Pharmacogenetics

Not applicable.

15. Study/Trial Design

Inclusion criteria, exclusion criteria, analysis populations, and efficacy endpoints of Trial 310 are described below.

Inclusion Criteria

Patients had to meet the following criteria to be eligible for the study:

- Female patients ≥ 18 years of age with ≥ 24 hours and ≤ 96 hours attributable to a UTI
- Two of the following signs and symptoms of uUTI: urinary frequency, urinary urgency, pain or burning on micturition, suprapubic pain
- A mid-stream urine specimen with:
 - a machine-read dipstick positive for nitrite AND any positive leukocyte esteraseOR
 - evidence of pyuria alone as defined by either:
 - a machine-read dipstick positive for large leukocyte esteraseOR
 - at least 10 white blood cells per cubic millimeter on microscopic analysis of unspun urineOR
 - white blood cell count ≥ 10 cells/HPF in the sediment of a spun urine
- Has given written informed consent to participate in the study

Exclusion Criteria

Patients who met any of the following criteria were excluded from the study:

- Presence of signs and symptoms suggestive of acute pyelonephritis defined as: fever (temperature $>38^{\circ}$ Celsius), chills, costovertebral angle tenderness, flank pain, nausea, and/or vomiting
- Receipt of antibacterial drug therapy potentially effective as treatment of uUTI within the prior 7 days
- Concurrent use of non-study treatments that would have a potential effect on outcome evaluations in patients with uUTI, including analgesics (e.g., non-steroidal anti-inflammatory drugs, aspirin, paracetamol etc.), phenazopyridine, and cranberry products. Note: Patients could be included if these medications were previously taken and had ceased at the time of Screening onward.
- Any anatomical abnormality of the urinary tract, including surgically modified urinary tract anatomy, and obstructive uropathy due to nephrolithiasis, stricture, tumor, or fibrosis
- Ongoing urinary retention

- Neurogenic bladder
- Current resident of a long-term care facility
- Instrumentation of urinary tract in the previous 30 days
- An indwelling urinary catheter, ureteral stent or other foreign material in the urinary tract
- Any history of trauma to the pelvis or urinary tract
- Current urine culture, if available while evaluating eligibility, that was positive for more than 2 microorganisms regardless of colony count (contaminated), or confirmed a fungal UTI
- Receiving hemodialysis, hemofiltration, peritoneal dialysis, or had a renal transplant
- Immunocompromised as evidenced by any of the following:
 - Known HIV positive, with either a recent (in the past 6 months) AIDS-defining condition or a CD4 + T lymphocyte count $<200/\text{mm}^3$
 - Known neutropenia (defined as absolute neutrophil count $<1000 \text{ cells}/\text{mm}^3$)
 - Systemic or hematological malignancy requiring chemotherapeutic or radiation/immunologic interventions within 6 weeks prior to randomization or anticipated to begin prior to completion of study
 - Immunosuppressive therapy, including maintenance corticosteroid therapy ($>40 \text{ mg}/\text{day}$ equivalent prednisolone for 5 days or more in the 30 days prior to randomization)
- Known liver function abnormalities as defined by the following laboratory criteria:
 - Alanine aminotransferase or aspartate aminotransferase $>3\text{x}$ upper limit of normal, and/or
 - Total bilirubin $>2\text{x}$ upper limit of normal
- Females of child-bearing potential who were unable to take adequate contraceptive precautions, had a positive pregnancy test result within 24 hours of study entry, were otherwise known to be pregnant, or were currently breastfeeding
- Poorly controlled diabetes mellitus, including the presence of ketoacidosis and hyperosmolar hyperglycemia
- History of seizures
- History of blood dyscrasias
- History of uric acid kidney stones
- Acute (current) gouty arthritis
- Concomitant administration of valproic acid
- History of allergy or hypersensitivity to carbapenems, β -lactams or probenecid, as formulated with their excipients
- Unlikely to survive the 4-week study period or had a rapidly progressive or terminal illness, including septic shock, associated with a high risk of mortality
- The use of any other investigational drug in the 30 days prior to the first dose of study drug, or prior participation in any sulopenem clinical trial

Urine samples, including results from urine tests, collected as part of routine standard of care, prior to obtaining informed consent, may have been used to assess eligibility for enrollment into study and/or for baseline urine culture.

Analysis Populations

Intent-to-Treat (ITT): all randomized patients regardless of whether or not the patient received study drug.

Modified ITT (MITT): randomized patients who received at least a single dose of study medication.

Micro-MITT: all MITT patients with a positive study entry urine culture defined as $\geq 10^5$ colony-forming units (CFU)/mL of a uropathogen (*Enterobacterales* or *S. saprophyticus* only) and no more than 2 species of microorganisms identified in the study entry urine culture, regardless of colony count.

The primary comparisons for regulatory approval were in two mutually exclusive subpopulations of the microbiological modified intent-to-treat (micro-MITT) population defined by a baseline characteristic, the micro-MITTS and micro-MITTR populations:

- **Micro-MITTS population:** the subset of patients whose baseline pathogens were determined to be susceptible (MIC $\leq 8/4$ mg/L) to the comparator study drug, amoxicillin/clavulanate.
- **Micro-MITTR population:** the subset of patients whose baseline pathogen was determined to be non-susceptible [intermediate (MIC 16/8 mg/L) or resistant (MIC $\geq 32/16$ mg/L)] to the comparator study drug, amoxicillin/clavulanate.

Efficacy Endpoints

Primary Efficacy Endpoint

The primary efficacy endpoint was overall success (combined clinical and microbiologic success) on Day 12 (± 1 days)/test of cure (TOC) in the micro-MITT, micro-MITTS and micro-MITTR populations.

A patient was defined as an overall success if the following criteria were met:

- The patient was alive
- The patient received no rescue therapy for uUTI
 - If an antibiotic active against the urinary tract pathogen was given for other reasons, then the patient would be considered indeterminate
- The patient had resolution of the symptoms of uUTI present at trial entry and no new uUTI symptoms (based on the Patient Symptom Assessment Questionnaire)
- Urine culture taken on Day 12 (± 1 day)/TOC demonstrated $< 10^3$ CFU/mL of the baseline uropathogen based on results of quantitative cultures performed on collected urine specimens.

All other patients would be considered as failures unless data were unavailable to determine whether the patient was a success or a failure. In this case, the patient would be considered as having an indeterminate response. Patients with an indeterminate response were included in the denominator for determination of the overall success rate.

For overall response, if the urine culture was contaminated, baseline pathogen(s) was/were considered eradicated. For microbiologic response, contaminated results were considered a negative culture and therefore an eradication. We will conduct additional analysis to address the effect of contamination coded as eradication for the primary efficacy endpoint.

Secondary Efficacy Endpoints Included

Microbiologic Response

In the protocol, microbiological response was assessed using the following definitions:

Table 80. Definition of Microbiologic Response

Response	Definition
Success	The urine culture demonstrates $<10^3$ CFU/mL of the baseline uropathogen (also referred to as eradication) at the time-point of analysis
Persistence	A uropathogen present at baseline grew at $\geq 10^3$ CFU/mL at the time-point of analysis
Persistence with increasing MIC	A urine culture taken after at least 2 full days of treatment grew $\geq 10^3$ CFU/mL of the baseline uropathogen and displayed ≥ 4 -dilutions higher MIC, as compared to baseline, to study drug received at the time-point of analysis
Indeterminate	Patient was lost to follow-up, or an assessment was not undertaken such that no urine culture was obtained (or culture results could not be interpreted for any reason) at the time-point of analysis

Source: Page 47 of the Study Protocol
Abbreviations: CFU, colony-forming units; MIC, minimum inhibitory concentration

Patient-Determined Clinical Response

A patient was defined as a clinical success if the following criteria were met:

- The patient was alive
- The patient received no rescue therapy for uUTI
 - If an antibiotic active against the urinary tract pathogen was given for other reasons, the patient was considered indeterminate.
- The patient had resolution of the symptoms of uUTI present at trial entry and no new uUTI symptoms based on the Patient Symptom Assessment Questionnaire
 - Baseline symptoms associated with another known condition (e.g., overactive bladder) do not need to be resolved

All other patients were considered as failures unless data were unavailable to determine if the patient was a success or a failure. In this case, the patient was be considered as having an indeterminate response. Patients with an indeterminate response were included in the denominator for determination of the response rate.

Investigator-Determined Clinical Response

The following clinical response definitions were used by the investigators:

- **Clinical success:** all pre-therapy signs and symptoms of the index infection had resolved such that no additional antibiotics were required.
- **Clinical failure:** patients who met any one of the following criteria:
 - Death related to uUTI prior to end of trial (EOT), TOC, and final visit (FV), respectively
 - Persistence or progression of any pre-therapy uUTI signs and symptoms or use of additional antibiotics for the current infection
 - Patient previously met criteria for failure and received rescue antibiotics
- **Indeterminate:** Data not available for evaluation of efficacy for any reason, including but not limited to:
 - Patient lost to follow-up or assessment not undertaken such that a determination of clinical response could not be made at either the EOT, TOC or FV, respectively
 - Death prior to EOT, TOC, or FV, respectively, where uUTI was clearly non-contributory

16. Efficacy

The results from Trial 301, the micro-MITT and ITT populations of Trial 310, Trial 302 for cUTI, and Trial 303 for cIAI are included in this section. Trials 301, 302 and 303 were included in the initial NDA submission; therefore, only a brief summary of these three trials is included in this review.

16.1. Summary of Trial 301 in uUTI

A total of 1660 adult women with uUTI were randomized and received trial medications in this multinational, randomized, double-blind clinical trial comparing oral sulopenem etzadroxil 500 mg and probenecid 500 mg twice daily (BID) for 5 days to oral ciprofloxacin 250 mg BID for 3 days. The micro-MITT population, which included all patients who had at least one uropathogen isolated at baseline ($\geq 10^5$ CFU/mL), consisted of 1105 patients; the median age was 53 years; median weight in the randomized population was 70.4 kg. Patients were enrolled from the United States (55%) and Eastern Europe (45%). Patients were Caucasian (90%), African American (9%) or of other races (1%).

Composite response (combined microbiological response and clinical cure) was determined by comparing the response rate of sulopenem to ciprofloxacin at the TOC visit (12 days after randomization) in two primary populations: Micro-MITTS (micro-MITT population with baseline pathogens susceptible to ciprofloxacin, MIC ≤ 1 μ g/mL) and Micro-MITTR (micro-MITT population with baseline pathogens non-susceptible to ciprofloxacin, MIC ≥ 2 μ g/mL).

Clinical cure was defined as the resolution of patient-reported uUTI symptoms and no new uUTI symptoms. Microbiological response was defined as a reduction of all baseline uropathogens to less than 10³ CFU/mL in the urine.

Sulopenem demonstrated efficacy in the micro-MITTR population but did not demonstrate efficacy in the micro-MITTS population.

Table 81. Composite, Clinical, and Microbiological Response at TOC in Trial 301

Study Population/Response	Sulopenem n/N (%)	Ciprofloxacin n/N (%)	Difference (95% CI)	P value
Micro-MITTR population				
Composite response	78/162 (48.1)	49/149 (32.9)	15.3 (4.3, 25.8)	0.006
Clinical cure	136/162 (84.0)	69/149 (46.3)	19.5 (10.0, 29.0)	
Microbiological response	92/162 (56.8)	66/149 (44.3)	12.5 (1.4, 23.3)	
Micro-MITTS population				
Composite response	227/376 (60.4)	300/418 (71.8)	-11.4 (-17.9, -4.8)	
Clinical cure	205/376 (81.1)	351/418 (84.0)	-2.9 (-8.2, 2.4)	
Microbiological response	262/376 (69.7)	336/418 (80.4)	-10.7 (-16.7, -4.7)	

Source: Tables 93, 96, and 99 of the updated Study Report and Statistical Reviewer's analysis
The 95% CI was calculated using the unstratified Miettinen and Nurminen method; The P value was calculated using Cochran-Mantel-Haenszel test.
Abbreviations: micro-MITTR, microbiological modified intent-to-treat resistant; micro-MITTS, microbiological modified intent-to-treat susceptible; N, total number of subjects in study population; n, number of subjects with specified response; TOC, test of cure

16.2. Study Results, Micro-MITT Population, Trial 310

The Applicant listed the micro-MITT population as Step 1 in the hierarchical testing procedure and reported the results. Therefore, we include the results from this population in the review. As the micro-MITT population was mainly composed of micro-MITTS subjects, the results were very similar to those in the micro-MITTS population.

Disposition

Overall, approximately 96% of the 990 micro-MITT subjects completed study drug treatment, while 4% discontinued treatment prematurely. The primary reasons for discontinuation of treatment were non-compliance with study drug (1.1%) and withdrawal by subject (1.2%). The primary reasons for discontinuation of study were loss to follow-up (2.0%) and withdrawal by subject (2.3%).

Table 82. Subject Disposition, Micro-MITT Population, Trial 310

Disposition	Sulopenem	Amoxicillin/ Clavulanate	Total
	N=522 n (%)	N=468 n (%)	N=990 n (%)
End of treatment status			
Completed	501 (96.0)	447 (95.5)	948 (95.8)
Discontinued	21 (4.0)	21 (4.5)	42 (4.2)

	Sulopene m N=522 n (%)	Amoxicillin/ Clavulanate N=468 n (%)	Total N=990 n (%)
Disposition			
Reason for discontinuation of treatment			
Adverse event	2 (<1)	4 (<1)	6 (<1)
Loss to follow-up	4 (<1)	5 (1.1)	9 (<1)
Non-compliance with study drug	6 (1.1)	5 (1.1)	11 (1.1)
Other	1 (<1)	2 (<1)	3 (<1)
Physician decision	1 (<1)	0	1 (<1)
Withdrawal by subject	7 (1.3)	5 (1.1)	12 (1.2)
End of study status			
Completed	495 (94.8)	450 (96.2)	945 (95.5)
Discontinued	27 (5.2)	18 (3.8)	45 (4.5)
Reason for discontinuation from study			
Adverse event	1 (<1)	1 (<1)	2 (<1)
Loss to follow-up	10 (1.9)	10 (2.1)	20 (2.0)
Withdrawal by subject	16 (3.1)	7 (1.5)	23 (2.3)

Source: Table 14.1.3.3 of the Study Report and Statistical Reviewer's analysis
Abbreviations: micro-MITT, microbiological -modified Intent-to-treat population; N, total number of subjects in micro-MITT population; n, number of subjects with specified disposition

Baseline Demographics and Clinical Characteristics

Demographic characteristics in the micro-MITT population are reported in the following [Table 83](#). The mean age was 49.5 years old. White subjects were 80% of the population.

Table 83. Demographic Characteristics, Micro-MITT Population, Trial 310

Demographic Characteristics	Sulopenem N=522	Amoxicillin/ Clavulanate N=468	Total N=990
Age, years			
Mean (SD)	50.3 (17.31)	48.6 (17.18)	49.5 (17.26)
Median	52.0	50.0	51.0
Min, max	18.0, 91.0	18.0, 93.0	18.0, 93.0
Age Group (years), n (%)			
<65	400 (76.6)	372 (79.5)	772 (78.0)
≥65	122 (23.4)	96 (20.5)	218 (22.0)
Sex, n (%)			
Female	522 (100.0)	468 (100.0)	990 (100.0)
Race, n (%)			
American Indian or Alaska Native	1 (<1)	1 (<1)	2 (<1)
Asian	10 (1.9)	8 (1.7)	18 (1.8)
Black or African American	84 (16.1)	84 (17.9)	168 (17.0)
Native Hawaiian or other Pacific Islander	0	1 (<1)	1 (<1)
Other	8 (1.5)	4 (<1)	12 (1.2)
White	419 (80.3)	370 (79.1)	789 (79.7)
Ethnicity, n (%)			
Hispanic or Latino	333 (63.8)	296 (63.2)	629 (63.5)
Not Hispanic or Latino	189 (36.2)	171 (36.5)	360 (36.4)
Not reported	0	1 (<1)	1 (<1)

Demographic Characteristics	Sulopenem N=522	Amoxicillin/ Clavulanate N=468	Total N=990
Height (cm)			
Mean (SD)	161.7 (7.25)	162.0 (7.05)	161.8 (7.15)
Median	162.0	162.0	162.0
Min, max	125.0, 180.0	142.0, 185.0	125.0, 185.0
Weight (kg)			
Mean (SD)	76.1 (16.99)	76.4 (17.92)	76.2 (17.43)
Median	73.4	74.0	73.5
Min, max	39.0, 192.7	40.8, 163.6	39.0, 192.7
Body mass index (kg/m²)			
Mean (SD)	29.1 (6.28)	29.1 (6.62)	29.1 (6.44)
Median	28.1	27.9	28.0
Min, max	15.5, 67.5	17.6, 59.8	15.5, 67.5
Body mass index group (kg/m²), n (%)			
<25	132 (25.3)	140 (29.9)	272 (27.5)
25-30	190 (36.4)	157 (33.5)	347 (35.1)
>30	200 (38.3)	171 (36.5)	371 (37.5)

Source: Table 22 of the Clinical Study Report and Statistical Reviewer's analysis

Abbreviations: max, maximum; micro-MITT, microbiological-Modified Intent-to-treat population; min, minimum; N, total number of subjects in micro-MITT population; n, number of subjects with specified characteristics; SD, standard deviation

Baseline disease characteristics are summarized in the following [Table 84](#). Approximately 16% of subjects had diabetes. The mean creatinine clearance was 84 mL/min and 20% of the subjects had creatinine clearance of <60 mL/min. The two treatment groups were comparable.

Table 84. Baseline Disease Characteristics, Micro-MITT Population, Trial 310

Disease Characteristics	Sulopenem N=522	Amoxicillin/ Clavulanate N=468	Total N=990
Diabetes, n (%)			
Yes	86 (16.5)	68 (14.5)	154 (15.6)
No	436 (83.5)	400 (85.5)	836 (84.4)
Creatinine clearance (mL/min)			
N	519	461	980
Mean (SD)	83.9 (27.92)	85.0 (29.29)	84.4 (28.56)
Median	83.1	83.7	83.4
Min, max	8.2, 178.1	16.4, 182.0	8.2, 182.0
Creatinine clearance (mL/min), n (%)			
<60	113 (21.6)	86 (18.4)	199 (20.1)
≥60	406 (77.8)	375 (80.1)	781 (78.9)
Missing	3 (<1)	7 (1.5)	10 (1.0)

Source: Table 22 of the Clinical Study Report and Statistical Reviewer's analysis

Abbreviations: max, maximum; min, minimum; micro-MITT, microbiological-modified intent-to-treat population; N, total number of subjects in micro-MITT population; n, number of subjects with specified characteristics; SD, standard deviation

Treatment exposure is summarized in the following [Table 85](#). The two treatment groups were comparable in capsule compliance and tablet compliance.

Table 85. Treatment Exposure, Micro-MITT Population, Trial 310

	Sulopenem N=522 n (%)	Amoxicillin/ Clavulanate N=468 n (%)	Total N=990 n (%)
Compliance			
Capsule compliance (%)			
N	518	462	980
Mean (SD)	98.4 (10.69)	98.3 (10.46)	98.3 (10.58)
Median	100.0	100.0	100.0
Min, max	10.0, 100.0	10.0, 100.0	10.0, 100.0
Tablet compliance rate (%)			
N	518	462	980
Mean (SD)	98.3 (10.95)	98.4 (10.39)	98.3 (10.69)
Median	100.0	100.0	100.0
Min, max	10.0, 100.0	10.0, 100.0	10.0, 100.0
Duration (days)			
Mean (SD)	5.2 (0.76)	5.2 (0.81)	5.2 (0.79)
Median	5.0	5.0	5.0
Min, max	1.0, 8.0	1.0, 7.0	1.0, 8.0

Source: Statistical Reviewer's analysis

Abbreviations: max, maximum; micro-MITT, microbiological-modified intent-to-treat population; min, minimum; N, total number of subjects in micro-MITT population; n, number of subjects with specified parameter; SD, standard deviation

As indicated in [Table 86](#), the deviations were classified as reportable (major) or non-reportable (minor). In the micro-MITT population, major deviations were reported for 9 subjects (0.9%) and minor deviations for 515 subjects (52%) in the micro-MITT population. The most common minor deviation was a protocol required visit outside the visit window. The two groups were generally balanced in protocol deviations.

Table 86. Protocol Deviation, Micro-MITT Population, Trial 310

	Sulopenem N=522 n (%)	Amoxicillin/ Clavulanate N=468 n (%)	Total N=990 n (%)
Protocol Deviation			
Subjects with any deviations	278 (53.3)	238 (50.9)	516 (52.1)
Major deviations	3 (0.6)	6 (1.3)	9 (0.9)
Exclusion criteria met but randomized	3 (0.6)	4 (0.9)	7 (0.7)
Investigational product/study drug that was affected by a temperature excursion was dispensed prior to approval to use	0	1 (0.2)	1 (0.1)
SAE not reported to (b) (4) /Sponsor within 24 hours of knowledge of occurrence	0	1 (0.2)	1 (0.1)
Minor deviations	277 (53.1)	238 (50.9)	515 (52.0)
Exclusion (all remaining)	6 (1.1)	2 (0.4)	8 (0.8)
Inclusion criteria not met	8 (1.5)	9 (1.9)	17 (1.7)
Informed consent	18 (3.4)	22 (4.7)	40 (4.0)
Restricted concomitant medication	10 (1.9)	6 (1.3)	16 (1.6)
Study procedures	263 (50.4)	229 (48.9)	492 (49.7)

Source: Statistical Reviewer's analysis

Abbreviations: micro-MITT, microbiological-modified intent-to-treat population; N, total number of patients in micro-MITT population; n, number of subjects with specified deviations; SAE, serious adverse event

As indicated in [Table 87](#), in the micro-MITT population, the most common classes of pre-existing medications were 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors

(15.5%), angiotensin-converting enzyme inhibitors (plain) (10.9%), and biguanides (10.9%). The two groups were generally balanced in pre-existing medication use.

Table 87. Pre-Existing Medications in ≥4% of Subjects in Either Group, Micro-MITT Population, Trial 310

ATC Class (Level 3) Medication	Sulopenem (N=522) n (%)	Amoxicillin/ Clavulanate (N=468) n (%)	Total (N=990) n (%)
Number of subjects with at least one prior medication	334 (64.0)	291 (62.2)	625 (63.1)
ACE inhibitors, plain	52 (10.0)	56 (12.0)	108 (10.9)
Lisinopril	40 (7.7)	50 (10.7)	90 (9.1)
Angiotensin II receptor blockers (ARBs), plain	55 (10.5)	41 (8.8)	96 (9.7)
Losartan	40 (7.7)	25 (5.3)	65 (6.6)
Benzodiazepine derivatives	21 (4.0)	16 (3.4)	37 (3.7)
Beta blocking agents, selective	28 (5.4)	20 (4.3)	48 (4.8)
Biguanides	59 (11.3)	49 (10.5)	108 (10.9)
Metformin	57 (10.9)	42 (9.0)	99 (10.0)
Dihydropyridine derivatives	28 (5.4)	25 (5.3)	53 (5.4)
Amlodipine	25 (4.8)	20 (4.3)	45 (4.5)
HMG-CoA reductase inhibitors	87 (16.7)	66 (14.1)	153 (15.5)
Atorvastatin	35 (6.7)	34 (7.3)	69 (7.0)
Other antidepressants	24 (4.6)	25 (5.3)	49 (4.9)
Platelet aggregation inhibitors excl. heparin	22 (4.2)	17 (3.6)	39 (3.9)
Progestogens and estrogens, fixed combinations	37 (7.1)	46 (9.8)	83 (8.4)
Proton pump inhibitors	55 (10.5)	26 (5.6)	81 (8.2)
Omeprazole	31 (5.9)	18 (3.8)	49 (4.9)
Selective beta-2-adrenoreceptor agonists	28 (5.4)	27 (5.8)	55 (5.6)
Selective serotonin reuptake inhibitors	24 (4.6)	26 (5.6)	50 (5.1)
Thiazides, plain	25 (4.8)	24 (5.1)	49 (4.9)
Hydrochlorothiazide	25 (4.8)	24 (5.1)	49 (4.9)
Thyroid hormones	36 (6.9)	38 (8.1)	74 (7.5)
Levothyroxine	28 (5.4)	33 (7.1)	61 (6.2)
Vitamin D and analogues	30 (5.7)	26 (5.6)	56 (5.7)

Source: Statistical Reviewer's analysis

Abbreviations: ACE, angiotensin-converting enzyme; ATC, anatomical therapeutic chemical; micro-MITT, microbiological-Modified Intent-to-treat population; N, total number of patients in micro-MITT population; n, number of patients in specified subgroup; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A

As indicated in [Table 88](#), in the micro-MITT population, concomitant medication use was very similar to pre-existing medication use (most numbers were identical). The most common classes were still 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (15.5%), angiotensin-converting enzyme inhibitors (plain) (10.9%), and biguanides (10.9%). The two groups were generally balanced in concomitant medication use.

Table 88. Concomitant Medication in ≥4% of Subjects in Either Group, Micro-MITT Population, Trial 310

ATC Class (Level 3) Medication	Sulopenem (N=522) n (%)	Amoxicillin/ Clavulanate (N=468) n (%)	Total (N=990) n (%)
Number of subjects with at least one medication use	348 (66.7)	297 (63.5)	645 (65.2)
ACE inhibitors, plain	52 (10.0)	56 (12.0)	108 (10.9)
Lisinopril	40 (7.7)	50 (10.7)	90 (9.1)
Angiotensin II receptor blockers (ARBs), plain	55 (10.5)	41 (8.8)	96 (9.7)
Losartan	40 (7.7)	25 (5.3)	65 (6.6)
Benzodiazepine derivatives	21 (4.0)	16 (3.4)	37 (3.7)
Beta blocking agents, selective	28 (5.4)	20 (4.3)	48 (4.8)
Biguanides	59 (11.3)	49 (10.5)	108 (10.9)
Metformin	57 (10.9)	42 (9.0)	99 (10.0)
Dihydropyridine derivatives	29 (5.6)	26 (5.6)	55 (5.6)
Amlodipine	26 (5.0)	21 (4.5)	47 (4.7)
HMG-CoA reductase inhibitors	87 (16.7)	66 (14.1)	153 (15.5)
Atorvastatin	35 (6.7)	34 (7.3)	69 (7.0)
Other antidepressants	24 (4.6)	25 (5.3)	49 (4.9)
Progestogens and estrogens, fixed combinations	37 (7.1)	46 (9.8)	83 (8.4)
Proton pump inhibitors	55 (10.5)	28 (6.0)	83 (8.4)
Omeprazole	31 (5.9)	18 (3.8)	49 (4.9)
Selective beta-2-adrenoreceptor agonists	29 (5.6)	28 (6.0)	57 (5.8)
Selective serotonin reuptake inhibitors	24 (4.6)	26 (5.6)	50 (5.1)
Thiazides, plain	25 (4.8)	24 (5.1)	49 (4.9)
Hydrochlorothiazide	25 (4.8)	24 (5.1)	49 (4.9)
Thyroid hormones	36 (6.9)	38 (8.1)	74 (7.5)
Levothyroxine	28 (5.4)	33 (7.1)	61 (6.2)
Vitamin D and analogues	30 (5.7)	27 (5.8)	57 (5.8)

Source: Statistical Reviewer's analysis

Abbreviations: ACE, angiotensin-converting enzyme; ATC, anatomical therapeutic chemical; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; micro-MITT, microbiological-modified intent-to-treat population; N, total number of subjects in micro-MITT population; n, number of subjects with specified medication use

As indicated in [Table 89](#), in the micro-MITT population, a total of 6.3% of the subjects reported concomitant antibacterial drug use, and administration was comparable in the two treatment groups. The most common class was nitrofurantoin derivatives (2.3%).

Table 89. Concomitant Antibacterial Use in ≥0.5% of Subjects in Either Group, Micro-MITT Population, Trial 310

ATC Class (Level 3) Medication	Sulopenem (N=522) n (%)	Amoxicillin/ Clavulanate (N=468) n (%)	Total (N=990) n (%)
Number of subjects with at least one medication use	32 (6.1)	30 (6.4)	62 (6.3)
Combinations of penicillins, incl. beta-lactamase inhibitors	3 (0.6)	1 (0.2)	4 (0.4)
Amoxicillin trihydrate; clavulanate potassium	3 (0.6)	1 (0.2)	4 (0.4)
Combinations of sulfonamides and trimethoprim, incl. derivatives	7 (1.3)	6 (1.3)	13 (1.3)
Sulfamethoxazole; trimethoprim	7 (1.3)	6 (1.3)	13 (1.3)
First-generation cephalosporins	4 (0.8)	4 (0.9)	8 (0.8)
Cefalexin	4 (0.8)	3 (0.6)	7 (0.7)
Fluoroquinolones	5 (1.0)	8 (1.7)	13 (1.3)
Ciprofloxacin	5 (1.0)	7 (1.5)	12 (1.2)

ATC Class (Level 3) Medication	Sulopenem (N=522) n (%)	Amoxicillin/ Clavulanate (N=468) n (%)	Total (N=990) n (%)
Nitrofurantoin	11 (2.1)	12 (2.6)	23 (2.3)
Nitrofurantoin	10 (1.9)	11 (2.4)	21 (2.1)

Source: Statistical Reviewer's analysis

Abbreviations: ATC, anatomical therapeutic chemical; Incl., including; micro-MITT, microbiological-modified intent-to-treat population; N, total number of patients in micro-MITT population; n, number of subjects with specific medication use

As indicated in [Table 90](#), in the micro-MITT population, about 79% of the subjects reported a prior medical history. The most common system organ classes (SOCs) represented were Surgical and Medical procedures (41.8%), Social circumstances (40%, including post-menopause), and Vascular disorders (33%, including hypertension). The two treatment groups were generally balanced in terms of prior medical history.

Table 90. Medical History in ≥4% of Subjects in Either Group, Micro-MITT Population, Trial 310

System Organ Class Preferred Term	Sulopenem (N=522) n (%)	Amoxicillin/ clavulanate (N=468) n (%)	Total (N=990) n (%)
Number of subjects with any medical history	431 (82.6)	350 (74.8)	781 (78.9)
Blood and lymphatic system disorders	30 (5.7)	21 (4.5)	51 (5.2)
Anemia	28 (5.4)	19 (4.1)	47 (4.7)
Endocrine disorders	48 (9.2)	49 (10.5)	97 (9.8)
Hypothyroidism	39 (7.5)	43 (9.2)	82 (8.3)
Eye disorders	21 (4.0)	14 (3.0)	35 (3.5)
Gastrointestinal disorders	85 (16.3)	58 (12.4)	143 (14.4)
Gastroesophageal reflux disease	58 (11.1)	28 (6.0)	86 (8.7)
Hepatobiliary disorders	25 (4.8)	15 (3.2)	40 (4.0)
Immune system disorders	44 (8.4)	26 (5.6)	70 (7.1)
Seasonal allergy	22 (4.2)	15 (3.2)	37 (3.7)
Infections and infestations	61 (11.7)	44 (9.4)	105 (10.6)
Investigations	29 (5.6)	9 (1.9)	38 (3.8)
Metabolism and nutrition disorders	183 (35.1)	133 (28.4)	316 (31.9)
Hypercholesterolemia	32 (6.1)	24 (5.1)	56 (5.7)
Hyperlipidemia	54 (10.3)	45 (9.6)	99 (10.0)
Obesity	36 (6.9)	30 (6.4)	66 (6.7)
Type 2 diabetes mellitus	82 (15.7)	64 (13.7)	146 (14.7)
Vitamin D deficiency	26 (5.0)	23 (4.9)	49 (4.9)
Musculoskeletal and connective tissue disorders	86 (16.5)	59 (12.6)	145 (14.6)
Osteoarthritis	21 (4.0)	13 (2.8)	34 (3.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	39 (7.5)	22 (4.7)	61 (6.2)
Nervous system disorders	62 (11.9)	42 (9.0)	104 (10.5)
Migraine	26 (5.0)	11 (2.4)	37 (3.7)
Psychiatric disorders	105 (20.1)	94 (20.1)	199 (20.1)
Anxiety	53 (10.2)	40 (8.5)	93 (9.4)
Depression	54 (10.3)	48 (10.3)	102 (10.3)
Insomnia	32 (6.1)	28 (6.0)	60 (6.1)

System Organ Class Preferred Term	Sulopenem (N=522) n (%)	Amoxicillin/clavulanate (N=468) n (%)	Total (N=990) n (%)
Renal and urinary disorders	20 (3.8)	27 (5.8)	47 (4.7)
Reproductive system and breast disorders	36 (6.9)	16 (3.4)	52 (5.3)
Respiratory, thoracic and mediastinal disorders	66 (12.6)	57 (12.2)	123 (12.4)
Asthma	39 (7.5)	37 (7.9)	76 (7.7)
Social circumstances	225 (43.1)	171 (36.5)	396 (40.0)
Menopause	44 (8.4)	26 (5.6)	70 (7.1)
Post-menopause	180 (34.5)	143 (30.6)	323 (32.6)
Surgical and medical procedures	231 (44.3)	183 (39.1)	414 (41.8)
Appendectomy	16 (3.1)	21 (4.5)	37 (3.7)
Caesarean section	39 (7.5)	36 (7.7)	75 (7.6)
Cholecystectomy	34 (6.5)	18 (3.8)	52 (5.3)
Female sterilization	48 (9.2)	22 (4.7)	70 (7.1)
Hysterectomy	74 (14.2)	71 (15.2)	145 (14.6)
Intra-uterine contraceptive device insertion	22 (4.2)	20 (4.3)	42 (4.2)
Vascular disorders	173 (33.1)	154 (32.9)	327 (33.0)
Hypertension	162 (31.0)	144 (30.8)	306 (30.9)

Source: Statistical Reviewer's analysis

Abbreviations: micro-MITT, microbiological - modified intent-to-treat population; N, total number of patients in micro-MITT population; n, number of subjects with specified SOC

As shown in the following [Table 91](#), almost all subjects in the micro-MITT population reported uUTI signs and/or symptoms at baseline. The signs and symptoms were comparable between the two treatment groups.

Table 91. Signs and Symptoms at Baseline, Micro-MITT Population, Trial 310

Signs and Symptoms	Sulopenem (N=522) n (%)	Amoxicillin/Clavulanate (N=468) n (%)	Total (N=990) n (%)
Number of subjects with any signs or symptoms	522 (100.0)	467 (99.8)	989 (99.9)
Burning (dysuria) when passing urine			
Mild	106 (20.3)	83 (17.7)	189 (19.1)
Moderate	223 (42.7)	211 (45.1)	434 (43.8)
No symptom	80 (15.3)	69 (14.7)	149 (15.1)
Severe	113 (21.6)	104 (22.2)	217 (21.9)
Frequency of urination or going to the toilet very often			
Mild	77 (14.8)	88 (18.8)	165 (16.7)
Moderate	261 (50.0)	232 (49.6)	493 (49.8)
No symptom	26 (5.0)	17 (3.6)	43 (4.3)
Severe	158 (30.3)	130 (27.8)	288 (29.1)
Pain or uncomfortable pressure in the lower abdomen/pelvic area			
Mild	122 (23.4)	124 (26.5)	246 (24.8)
Moderate	216 (41.4)	174 (37.2)	390 (39.4)
No symptom	114 (21.8)	105 (22.4)	219 (22.1)
Severe	70 (13.4)	64 (13.7)	134 (13.5)

Signs and Symptoms	Sulopenem (N=522) n (%)	Amoxicillin/ Clavulanate (N=468) n (%)	Total (N=990) n (%)
Urgency of urination or a strong and uncontrollable urge to pass urine			
Mild	93 (17.8)	78 (16.7)	171 (17.3)
Moderate	191 (36.6)	175 (37.4)	366 (37.0)
No symptom	73 (14.0)	75 (16.0)	148 (14.9)
Severe	165 (31.6)	139 (29.7)	304 (30.7)

Source: Table 23 of the Clinical Study Report and Statistical Reviewer's analysis
Abbreviations: micro-MITT, microbiological - modified intent-to-treat population; N, total number of patients in micro-MITT population; n, number of subjects with specific signs and symptoms

Baseline pathogens in the micro-MITT population are shown in [Table 92](#). The most common pathogens were *E. coli* (81.8%), *K. pneumoniae* (10.9%), and *P. mirabilis* (2.7%). The two treatment groups were generally balanced in terms of pathogens.

Table 92. Baseline Pathogen, Micro-MITT Population, Trial 310

Pathogen	Sulopenem N=522 n (%)	Amoxicillin/ Clavulanate N=468 n (%)	Total N=990 n (%)
<i>Citrobacter freundii</i>	5 (1.0)	0	5 (0.5)
<i>Citrobacter koseri</i>	3 (0.6)	2 (0.4)	5 (0.5)
<i>Enterobacter bugandensis</i>	0	1 (0.2)	1 (0.1)
<i>Enterobacter cloacae</i>	1 (0.2)	0	1 (0.1)
<i>Enterobacter hormaechei</i>	4 (0.8)	8 (1.7)	12 (1.2)
<i>Enterobacter kobei</i>	1 (0.2)	0	1 (0.1)
<i>Escherichia coli</i>	423 (81.0)	387 (82.7)	810 (81.8)
<i>Escherichia sp</i>	1 (0.2)	0	1 (0.1)
<i>Klebsiella aerogenes</i>	4 (0.8)	3 (0.6)	7 (0.7)
<i>Klebsiella oxytoca</i>	0	2 (0.4)	2 (0.2)
<i>Klebsiella pneumoniae</i>	58 (11.1)	50 (10.7)	108 (10.9)
<i>Klebsiella sp</i>	1 (0.2)	1 (0.2)	2 (0.2)
<i>Klebsiella variicola</i>	5 (1.0)	1 (0.2)	6 (0.6)
<i>Morganella morganii</i>	2 (0.4)	1 (0.2)	3 (0.3)
<i>Pantoea sp</i>	1 (0.2)	0	1 (0.1)
<i>Proteus mirabilis</i>	14 (2.7)	13 (2.8)	27 (2.7)
<i>Providencia stuartii</i>	2 (0.4)	1 (0.2)	3 (0.3)
<i>Serratia marcescens</i>	3 (0.6)	1 (0.2)	4 (0.4)

Source: Table 24 of the Clinical Study Report and Statistical Reviewer's analysis
Abbreviations: micro-MITT, microbiological -modified intent-to-treat population; N, total number of patients in micro-MITT population; n, number of subjects with specific baseline pathogen

Primary Efficacy Endpoint

As shown in [Table 93](#), in the micro-MITT population, the overall success proportions were 60.9% and 55.6% in the sulopenem and the active control groups, respectively, with a difference of 5.4% and a 95% CI of [-0.8%, 11.5%]. The results could demonstrate NI of sulopenem to the active control, if a -10% NI margin could be used. However, NI in this population may have limited interpretability because it included subjects with pathogens that were resistant to the control drug.

The overall success results were driven by microbiological success, as the clinical success proportions were similar between the two treatment groups.

Table 93. Overall Response (Primary Endpoint), Micro-MITT Population, Trial 310

Response	Sulopenem N=522 n (%)	Amoxicillin/ Clavulanate N=468 n (%)	Difference (95% CI)
Overall response at TOC	318 (60.9)	260 (55.6)	5.4 (-0.8, 11.5)
Overall nonresponse	177 (33.9)	185 (39.5)	
Indeterminate	27 (5.2)	23 (4.9)	
Clinical success at TOC	397 (76.1)	358 (76.5)	-0.4 (-5.7, 4.9)
Microbiologic success at TOC	390 (74.7)	315 (67.3)	7.4 (1.8, 13.1)

Source: Table 48 of the Study Report and Statistical Reviewer's analysis

Abbreviations: micro-MITT, microbiological -modified-intent-to-treat; N, total number of patients in micro-MITT population; n, number of subjects with specific response; TOC, test of cure

In the micro-MITT population, the subgroup analysis results were similar to these in the micro-MITTS population, except that only nominally significant differences in the age >65 years and CrCl <60 mL/min subgroups were observed ([Table 94](#)).

Table 94. Subgroup Analysis of Overall Response at TOC, Micro-MITT Population, Trial 310

Variable	Sulopenem (N=522) n (%)	Amoxicillin/ Clavulanate (N=468) n (%)	Difference (%) (95% CI)
Age, years			
<65	250/400 (62.5)	221/372 (59.4)	3.1 (-3.8, 10)
≥65	68/122 (55.7)	39/96 (40.6)	15.1 (1.7, 27.9)
Race			
American Indian or Alaska Native	1/1 (100.0)	0	
Asian	8/10 (80.0)	7/8 (87.5)	-7.5 (-43.2, 32.9)
Black or African American	47/84 (56.0)	43/84 (51.2)	4.8 (-10.3, 19.6)
Native Hawaiian or other Pacific Islander	0	0/1	
Other	6/8 (75.0)	1/4 (25.0)	
Ethnicity			
Hispanic or Latino	220/333 (66.1)	173/296 (58.4)	7.6 (-0.0, 15.2)
Not Hispanic or Latino	98/189 (51.9)	87/171 (50.9)	1.0 (-9.3, 11.3)
Not reported	0	0/1	
Body mass index (kg/m ²)			
<25	86/132 (65.2)	82/140 (58.6)	6.6 (-5.0, 18)
25-30	125/190 (65.8)	95/157 (60.5)	5.3 (-4.9, 15.5)
>30	107/200 (53.5)	83/171 (48.5)	5.0 (-5.2, 15.1)
Diabetes			
Yes	40/86 (46.5)	29/68 (42.6)	3.9 (-11.9, 19.4)
No	278/436 (63.8)	231/400 (57.8)	6.0 (-0.6, 12.6)
Creatinine clearance (mL/min)			
<60	66/113 (58.4)	37/86 (43.0)	15.4 (1.3, 28.8)
≥60	250/406 (61.6)	221/375 (58.9)	2.6 (-4.2, 9.5)
Missing	2/3 (66.7)	2/7 (28.6)	
Quinolone susceptibility			
Susceptibility	250/392 (63.8)	195/336 (58.0)	5.7 (-1.4, 12.8)
Resistant/nonsusceptible	68/130 (52.3)	65/131 (49.6)	2.7 (-9.4, 14.7)
Missing		0/1	

Variable	Sulopenem (N=522) n (%)	Amoxicillin/ Clavulanate (N=468) n (%)	Difference (%) (95% CI)
ESBL			
Positive	32/52 (61.5)	21/46 (45.7)	15.9 (-4.0, 34.6)
Negative	286/470 (60.9)	239/421 (56.8)	4.1 (-2.4, 10.5)
Missing		0/1	
Baseline pathogen			
<i>Escherichia coli</i>	263/423 (62.2)	219/387 (56.6)	5.6 (-1.2, 12.3)
<i>Klebsiella pneumoniae</i>	31/58 (53.4)	22/50 (44.0)	9.4 (-9.5, 2.8)
<i>Proteus mirabilis</i>	6/14 (42.9)	6/13 (46.2)	-3.3 (-38.7, 32.8)
Other	21/33 (63.4)	15/21 (71.4)	-7.8 (-31.53, 18.65)

Source: Tables 60, 64, 93, and 99 of the Study Report and Statistical Reviewer's analysis

Abbreviations: ESBL, extended spectrum β -lactamase; micro-MITT, microbiological -modified-intent-to-treat; N, total number of patients in micro-MITT population; n, number of subjects with specific variable; TOC, test of cure

16.3. Study Results, ITT Population, Trial 310

Only clinical efficacy analysis results are presented in this section.

Clinical Efficacy Endpoint in the ITT Population

Patient-determined clinical response by visit in the ITT population is summarized in the following [Table 95](#). The proportion of subjects with clinical success increased over time in both groups, although difference between the two treatment groups were small. In the MITT population, the results were very similar, as only 3 subjects in each group were excluded.

Table 95. Patient-Determined Clinical Response by Visit, ITT Population, Trial 310

Visit	Sulopenem N=1111 n (%)	Amoxicillin/ Clavulanate N=1111 n (%)	Difference (%) (95% CI)
EOT (Day 5)	649 (58.4)	683 (61.5)	-3.1 (-7.1, 1.0)
TOC (Day 12)	852 (76.7)	849 (76.4)	0.2 (-3.3, 3.8)
FV (Day 28)	907 (81.6)	911 (82.0)	-0.4 (-4.6, 2.9)

Source: Statistical Reviewer's analysis

Abbreviations: EOT, end of therapy; FV, final visit; ITT, intent-to-treat; N, total number of patients in ITT population; n, number of subjects with clinical response; TOC, test of cure

16.4. Trial 302 for cUTI

Trial 302 was a phase 3, multicenter, double-blind, randomized trial designed to compare the efficacy, tolerability, and safety of IV sulopenem followed by oral sulopenem etzadroxil/probenecid with that of IV ertapenem followed by oral ciprofloxacin or amoxicillin/clavulanate for the treatment of cUTI in both men and women.

Subjects were randomized 1:1 to receive either IV sulopenem 1000 mg once daily for at least 5 days (five doses) followed by oral sulopenem etzadroxil 500 mg co-administered with oral probenecid 500 mg BID to complete 7 to 10 total days of treatment versus ertapenem IV 1000 mg once daily for at least 5 days (five doses) followed by oral ciprofloxacin 500 mg or

amoxicillin/clavulanate 875 mg BID to complete 7 to 10 total days of therapy. Duration of treatment could be extended up to a total of 14 days for patients with bacteremia at baseline.

The primary efficacy endpoint was overall response (resolution of symptoms and clearance of the baseline uropathogen) at Day 21 (TOC). The primary analysis population was the micro-MITT, defined as subjects who received at least a single dose of study medication, had the disease under study (with two of the five baseline cUTI symptoms), and a positive study entry urine culture within 48 h prior to the first dose. The study entry urine culture had to have no more than two species of uropathogens (Enterobacterales only, susceptible to sulopenem [MIC ≤1] and ertapenem [MIC ≤0.5]) at ≥10⁵ CFU/mL, except in the situation where one of the organisms cultured from the urine was also isolated from blood cultures drawn at baseline. Patients with a study pathogen isolated from baseline blood cultures were included in the micro-MITT population regardless of the patient’s baseline urine culture result.

The Applicant’s efficacy results were based on definitions of microbiological responses using the same definition for “persistence” as in Trial 301, i.e., a uropathogen present in baseline urine culture which grew at ≥10³ CFU/mL at TOC with further specification as follows: “The genus/species and susceptibility profiles need to match. For the Baseline and TOC visits, additional molecular testing by pulsed field gel electrophoresis or whole-genome sequencing may be performed for confirmation.” FDA requested reanalysis of the data for Trials 301, 302, and 303 (for cIAI), based on definitions of microbiological response without using additional molecular testing. The results from the two analyses from the initial and updated reports were consistent, but only the results using the initial statistical analysis plan (SAP) are reported here.

The two treatment groups were comparable with respect to demographic characteristics. The majority of subjects were female (about 55%). The mean age was about 59 years (range 18 to 94 years). The majority of subjects had acute pyelonephritis (57.1% in the sulopenem arm; 56.9% in the ertapenem arm). *E. coli* was the most common organism isolated (76.1% on sulopenem; 78.6% on ertapenem).

As shown in the following [Table 96](#), Trial 302 failed to show noninferiority using a -10% noninferiority margin. IV sulopenem followed by oral (PO) sulopenem etzadroxil/probenecid was significantly worse than the active comparator, IV ertapenem followed by PO ciprofloxacin or amoxicillin/clavulanate.

Table 96. Overall Response at TOC, Micro-MITT Population, Trial 302

Response	Sulopenem	Ertapenem	Difference (%) (95% CI)
	(N=444) n (%)	(N=440) n (%)	
Overall response	265 (59.7)	296 (67.3)	-7.6 (-13.9, -1.3)
Overall nonresponse	162 (36.5)	122 (27.7)	
Indeterminate	17 (3.8)	22 (5.0)	

Source: Table 62, updated Study Report

Abbreviations: micro-MITT, microbiological - modified-intent-to-treat; N, total number of patients in micro-MITT population; n, number of subjects with specific response; TOC, test of cure

In the sulopenem group, 87% of all subjects in the micro-MITT population stepped down from IV sulopenem to PO sulopenem etzadroxil/probenecid and the overall response rate in these subjects was 61.2% [i.e., (154+26+53+5)/(248+55+80+6)]; the response rates by ciprofloxacin and amoxicillin/clavulanate susceptibility are shown in [Table 97](#). In the ertapenem group, 67.5%

(297/440) of subjects stepped down to oral therapy with either ciprofloxacin or amoxicillin/clavulanate; of these subjects, 50% (220/440) stepped down to ciprofloxacin PO with an overall response rate of 82.3% (181/220) while 17.5% (77/440) of subjects stepped down to amoxicillin/clavulanate with an overall response rate of 54.5% (42/77). Comparisons of outcomes between subjects who stepped down to oral therapy in the two groups are limited by being post-randomization subgroup analyses. The fact that more subjects stepped down to oral therapy in the sulopenem group suggested that subjects receiving oral sulopenem etzadroxil/probenecid were not necessarily comparable to subjects receiving oral ciprofloxacin or oral amoxicillin/clavulanate at the time of stepdown. Nevertheless, the results in [Table 97](#) suggest that an efficacy decrement of stepdown sulopenem etzadroxil/probenecid compared to stepdown ciprofloxacin in the subgroup with ciprofloxacin-susceptible pathogens may have contributed to the unfavorable trial conclusions. Such an efficacy decrement would be consistent with the Trial 301 results seen for uUTI.

Table 97. Overall Response at TOC by Stepdown Category, Sulopenem IV to PO Sulopenem Etzadroxil/Probenecid, Ertapenem IV to PO Ciprofloxacin, and Ertapenem IV to PO Amoxicillin/Clavulanate, Micro-MITT Population, Trial 302

Overall Response	Ciprofloxacin Susceptible n/N (%)	Ciprofloxacin Resistant, Amoxicillin/ Clavulanate Susceptible n/N (%)	Ciprofloxacin Resistant, Amoxicillin/ Clavulanate Resistant n/N (%)
Sulopenem IV to PO sulopenem etzadroxil/probenecid			
Overall responder	154/248 (62.1)	26/55 (47.3)	53/80 (66.3)
Overall nonresponder	86/248 (34.7)	28/55 (50.9)	27/80 (33.8)
Indeterminate	8/248 (3.2)	1/55 (1.8)	0/80 (0.0)
Ertapenem IV to PO ciprofloxacin			
Overall responder	179/215 (83.3)	0	2/5 (40.0)
Overall nonresponder	27/215 (12.6)	0	3/5 (60.0)
Indeterminate	9/215 (4.2)	0	0/5 (0)
Ertapenem IV to PO amoxicillin/clavulanate			
Overall responder	4/6 (66.7)	37/66 (56.1)	0/2 (0.0)
Overall nonresponder	2/6 (33.3)	27/66 (40.9)	2/2 (100.0)
Indeterminate	0/6 (0)	2/66 (3.0)	0/2 (0.0)

Source: Tables 40 and 42 submitted July 29, 2024, and Statistical Reviewer's analysis

Five of six subjects with missing resistance data were responders.

Abbreviations: IV, intravenous; micro-MITT, microbiological modified intent-to-treat; N, total number of patients in micro-MITT population; n, number of subjects with specific response; PO, oral; TOC, test of cure

Patients who remained on IV sulopenem were either not able to tolerate oral therapy or did not have sufficient resolution of their infection for the investigator to recommend stepdown treatment. Overall response in these patients by ciprofloxacin or amoxicillin/clavulanate susceptibility is shown in [Table 98](#). Twenty-seven (49%) of fifty-five subjects who received only sulopenem IV were overall responders.

Table 98. Overall Response at TOC by Stepdown Category, Sulopenem Group (IV Only), Micro-MITT Population, Trial 302

Overall Response	Ciprofloxacin Susceptible n/N (%)	Ciprofloxacin Resistant, Amoxicillin/Clavulanate Susceptible n/N (%)	Ciprofloxacin Resistant, Amoxicillin/Clavulanate Resistant n/N (%)
Overall responder	18/34 (52.9)	3/5 (60.0)	6/15 (40.0)
Overall nonresponder	10/34 (29.4)	2/5 (40.0)	7/15 (46.7)
Indeterminate	6/34 (17.6)	0/5 (0.0)	2/15 (13.3)

Source: Table 41 submitted July 29, 2024, and Statistical Reviewer's analysis

One subject with missing resistance data was a nonresponder.

Abbreviations: IV, intravenous; micro-MITT, microbiological -modified-intent-to-treat; N, total number of patients in micro-MITT population; n, number of subjects with specific response; TOC, test of cure

As shown in [Table 99](#) for the ertapenem group, 32.0% [(106+35)/440] received IV only, and 51.8% [(58+15)/(106+35)] of these subjects were overall responders.

Table 99. Overall Response at TOC by Stepdown Category, Ertapenem Arm (IV Only), Micro-MITT Population, Trial 302

Overall Response	CIP R/I and AMO/CLAV R/I n/N (%)	CIP R/I and AMO/CLAV R/I As Only Reason for Staying on IV ERT n/N (%)	CIP R/I and AMO/CLAV R/I Plus Another Reason for Staying on IV ERT n/N (%)	NOT CIP R/I and AMO/CLAV R/I n/N (%)
Overall responder	58/106 (54.7)	45/84 (53.6)	13/22 (59.1)	15/35 (42.9)
Overall Nonresponder	45/106 (42.5)	38/84 (45.2)	7/22 (31.8)	12/35 (34.3)
Indeterminate	3/106 (2.8)	1/84 (1.2)	2/22 (9.1)	8/35 (22.9)

Source: Table 43 submitted July 29, 2024, and Statistical Reviewer's analysis

Abbreviations: AMO, amoxicillin; CIP, ciprofloxacin; CLAV, clavulanate; ERT, ertapenem; I, intermediate; IV, intravenous; micro-MITT, microbiological modified intent-to-treat; R, resistant; N, total number of patients in micro-MITT population; n, number of subjects with specific response; TOC, test of cure

[Table 100](#) shows the microbiologic and clinical responses by visit. At the Day 5 and EOT visits, the two treatment groups had similar microbiologic response rates. Only at the TOC visit did a significantly lower treatment effect emerge in the sulopenem group. At each visit, clinical response rates were similar between the two treatment groups.

Table 100. Microbiologic Response and Clinical Response at Day 5, EOT, and TOC, Micro-MITT Population, Trial 302

Outcome	Sulopenem (N=444) n (%)	Ertapenem (N=440) n (%)	Difference (%) (95% CI)
Microbiologic response			
Day 5	429 (96.6)	419 (95.2)	1.4 (-1.3, 4.2)
EOT	413 (93.0)	417 (94.8)	-1.8 (-5.0, 1.4)
TOC	275 (61.9)	308 (70.0)	-8.1 (-14.3, -1.8)
Clinical response			
Day 5	203 (45.7)	196 (44.5)	1.2 (-5.4, 7.7)
EOT	398 (89.6)	399 (90.7)	-1.0 (-5.0, 2.9)
TOC	397 (89.4)	389 (88.4)	1.0 (-3.2, 5.2)

Source: Statistical Reviewer's analysis

Abbreviations: EOT, end of therapy; micro-MITT, microbiological -modified-intent-to-treat; N, total number of patients in micro-MITT population; n, number of subjects with specific outcome; TOC, test of cure

Efficacy Conclusions From Trial 302

Trial 302 did not provide evidence for the efficacy of IV sulopenem followed by oral sulopenem etzadroxil/probenecid for the treatment of cUTI. In the primary efficacy analysis of overall clinical and microbiological response at the TOC visit, IV sulopenem followed by oral sulopenem etzadroxil/probenecid did not demonstrate noninferiority compared to the control group treated with IV ertapenem followed by oral ciprofloxacin or oral amoxicillin/clavulanate. Further, the sulopenem group was statistically inferior to the control group. Results for overall response in the two treatment groups were similar at Day 5 (the minimum duration of IV therapy) and the EOT but differed by the TOC visit on Day 21. The efficacy decrement was driven by a difference in microbiologic response rates, as clinical response rates were similar between the sulopenem and ertapenem treatment groups. There was remaining uncertainty regarding whether any efficacy decrements were due to the intravenous or oral sulopenem because while the randomized comparisons were designed to evaluate intravenous-to-oral regimens, results were suggestive of an efficacy decrement of stepdown sulopenem etzadroxil/probenecid compared to stepdown ciprofloxacin in subjects with ciprofloxacin-susceptible pathogens. Such an efficacy decrement is consistent with the Trial 301 results seen for uUTI where the noninferiority of oral sulopenem etzadroxil/probenecid to oral ciprofloxacin in ciprofloxacin-susceptible isolates was not demonstrated.

16.5. Trial 303 for cIAI

Trial 303 was a phase 3, multicenter, double-blind, randomized trial designed to compare the efficacy, tolerability, and safety of IV sulopenem followed by oral sulopenem etzadroxil/probenecid with that of IV ertapenem followed by oral ciprofloxacin and metronidazole or amoxicillin/clavulanate for the treatment of cIAI.

A total of 674 subjects were randomized (1:1) to receive either IV sulopenem 1000 mg once daily for at least 5 days (five doses) followed by sulopenem etzadroxil 500 mg co-administered with oral probenecid 500 mg twice daily to complete 7 to 10 total days of treatment or ertapenem IV 1000 mg once daily for at least 5 days (five doses) followed by oral ciprofloxacin 500 mg twice daily and metronidazole 500 mg four times a day or amoxicillin/clavulanate 875 mg twice daily to complete 7 to 10 total days of therapy. Duration of treatment could be extended up to a total of 14 days. The results are shown in [Table 101](#). After initial unblinding of the study, imbalances in outcome by treatment were identified by the Applicant. Subsequently, the Applicant conducted a post hoc analysis by re-examining and re-analyzing the data. FDA did not agree with the Applicant's post hoc analysis after the study data were unblinded. Trial 303 failed to show NI using a -10% margin, either based on the primary analysis or the post hoc analysis.

Table 101. Applicant's Analysis of Primary and Post Hoc Results – Clinical Response at TOC, Micro-MITT Population, Trial 303

Clinical Success	Sulopenem (N=249)	Ertapenem (N=266)	Difference (%) (95% CI)
Primary	204 (81.9)	233 (87.9)	-6.0 (-12.2, 0.2)
Post hoc	213 (85.5)	240 (90.2)	-4.7 (-10.3, 1.0)

Source: Study Report

Abbreviations: micro-MITT, microbiological - modified-intent-to-treat; N, total number of patients in micro-MITT population; TOC, test of cure

17. Clinical Safety

17.1. Treatment-Emergent Adverse Events, Trial 310

[Table 102](#) shows the full list of adverse events (AEs) by SOC and preferred term (PT) in the safety population of Trial 310.

Table 102. Subjects With Adverse Events by System Organ Class and Preferred Term, Safety Population, Trial 310

System Organ Class Preferred Term	Sulopenem Etzadroxil/ Probenecid N=1107 n (%)	Amoxicillin/ Clavulanate N=1107 n (%)
Any AE	209 (18.9)	136 (12.3)
Blood and lymphatic system disorders (SOC)	1 (0.1)	2 (0.2)
Anemia	1 (0.1)	2 (0.2)
Cardiac disorders (SOC)	0	1 (0.1)
Palpitations	0	1 (0.1)
Ear and labyrinth disorders (SOC)	3 (0.3)	2 (0.2)
Vertigo	3 (0.3)	2 (0.2)
Gastrointestinal disorders (SOC)	145 (13.1)	84 (7.6)
Diarrhea	90 (8.1)	45 (4.1)
Nausea	48 (4.3)	32 (2.9)
Vomiting	16 (1.4)	4 (0.4)
Gastroesophageal reflux disease	11 (1.0)	1 (0.1)
Constipation	3 (0.3)	1 (0.1)
Abdominal distension	1 (0.1)	0
Feces discolored	1 (0.1)	0
Feces soft	1 (0.1)	0
Flatulence	2 (0.2)	1 (0.1)
Diverticulum	0	1 (0.1)
Food poisoning	0	1 (0.1)
Hemorrhoids	0	1 (0.1)
Dyspepsia	3 (0.3)	5 (0.5)
Abdominal pain	7 (0.6)	11 (1.0)
General disorders and administration site conditions (SOC)	7 (0.6)	3 (0.3)
Fatigue	5 (0.5)	0
Chills	2 (0.2)	0
Chest pain	0	1 (0.1)
Edema peripheral	0	1 (0.1)
Pyrexia	0	1 (0.1)
Immune system disorders (SOC)	1 (0.1)	0
Seasonal allergy	1 (0.1)	0

System Organ Class Preferred Term	Sulopenem Etzadroxil/ Probenecid N=1107 n (%)	Amoxicillin/ Clavulanate N=1107 n (%)
Infections and infestations (SOC)	46 (4.2)	23 (2.1)
Vulvovaginal mycotic infection	33 (3.0)	13 (1.2)
COVID-19	5 (0.5)	2 (0.2)
Gastroenteritis	2 (0.2)	0
Bacterial vaginosis	1 (0.1)	0
Bronchitis	1 (0.1)	0
Lower respiratory tract infection	1 (0.1)	0
Nasopharyngitis	1 (0.1)	0
Pharyngitis streptococcal	1 (0.1)	0
Influenza	1 (0.1)	1 (0.1)
Upper respiratory tract infection	1 (0.1)	1 (0.1)
Chlamydial infection	0	1 (0.1)
Clostridium difficile infection	0	1 (0.1)
Genital herpes	0	1 (0.1)
Herpes zoster	0	1 (0.1)
Sinusitis	0	1 (0.1)
Tooth infection	0	1 (0.1)
Injury, poisoning and procedural complications (SOC)	6 (0.5)	2 (0.2)
Arthropod bite	1 (0.1)	0
Contusion	1 (0.1)	0
Foot fracture	1 (0.1)	0
Muscle strain	1 (0.1)	0
Road traffic accident	1 (0.1)	0
Fall	1 (0.1)	1 (0.1)
Ligament sprain	0	1 (0.1)
Metabolism and nutrition disorders (SOC)	1 (0.1)	2 (0.2)
Polydipsia	1 (0.1)	0
Decreased appetite	0	1 (0.1)
Dehydration	0	1 (0.1)
Musculoskeletal and connective tissue disorders (SOC)	5 (0.5)	6 (0.5)
Myositis	1 (0.1)	0
Neck pain	1 (0.1)	0
Pain in extremity	1 (0.1)	0
Arthralgia	0	1 (0.1)
Back pain	3 (0.3)	4 (0.4)
Musculoskeletal pain	0	1 (0.1)
Nervous system disorders (SOC)	30 (2.7)	23 (2.1)
Headache	24 (2.2)	17 (1.5)
Ageusia	1 (0.1)	0
Dystonia	1 (0.1)	0
Migraine	1 (0.1)	0
Somnolence	1 (0.1)	0
Syncope	1 (0.1)	0
Dysgeusia	0	1 (0.1)
Memory impairment	0	1 (0.1)
Dizziness	2 (0.2)	4 (0.4)

System Organ Class Preferred Term	Sulopenem Etzadroxil/ Probenecid N=1107 n (%)	Amoxicillin/ Clavulanate N=1107 n (%)
Psychiatric disorders (SOC)	1 (0.1)	2 (0.2)
Stress	1 (0.1)	0
Confusional state	0	1 (0.1)
Insomnia	0	2 (0.2)
Renal and urinary disorders (SOC)	4 (0.4)	5 (0.5)
Urine odor abnormal	4 (0.4)	0
Acute kidney injury	0	1 (0.1)
Chromaturia	0	1 (0.1)
Hematuria	0	1 (0.1)
Nephrolithiasis	0	2 (0.2)
Reproductive system and breast disorders (SOC)	3 (0.3)	2 (0.2)
Perineal pain	1 (0.1)	0
Vaginal discharge	2 (0.2)	1 (0.1)
Vulvovaginal pruritus	1 (0.1)	0
Vulvovaginal discomfort	0	1 (0.1)
Respiratory, thoracic and mediastinal disorders (SOC)	2 (0.2)	4 (0.4)
Asthma	1 (0.1)	0
Sneezing	1 (0.1)	0
Cough	0	1 (0.1)
Nasal congestion	0	1 (0.1)
Oropharyngeal pain	1 (0.1)	2 (0.2)
Rhinorrhea	0	1 (0.1)
Skin and subcutaneous tissue disorders (SOC)	5 (0.5)	2 (0.2)
Lichen sclerosis	1 (0.1)	0
Rash	1 (0.1)	0
Rosacea	1 (0.1)	0
Hyperhidrosis	1 (0.1)	1 (0.1)
Pruritus	1 (0.1)	1 (0.1)
Vascular disorders (SOC)	4 (0.4)	2 (0.2)
Flushing	1 (0.1)	0
Hot flush	1 (0.1)	0
Intermittent claudication	1 (0.1)	0
Hypertension	1 (0.1)	1 (0.1)
Peripheral coldness	0	1 (0.1)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any event that occurs or worsens in either intensity or frequency after the first dose of study drug in a period.

Duration is 5 days for each arm.

Abbreviations: AE, adverse event; COVID-19, coronavirus 2019; N, number of patients in treatment arm; n, number of subjects with adverse event; SOC, system organ class

17.2. Treatment-Emergent Adverse Events, Pooled Analysis, Trials 301 and 310

[Table 103](#) shows the full list of AEs by SOC and PT in the integrated safety population of Trials 301 and 310.

Table 103. Subjects With Adverse Events by System Organ Class and Preferred Term, Integrated Safety Population, Trials 301 and 310

System Organ Class Preferred Term	Sulopenem N=1932 n (%)	Amoxicillin/ Clavulanate N=1107 n (%)	Ciprofloxacin N=822 n (%)
Any AE	416 (21.5)	136 (12.3)	115 (14.0)
Blood and lymphatic system disorders (SOC)	1 (0.1)	2 (0.2)	0
Anemia	1 (0.1)	2 (0.2)	0
Cardiac disorders (SOC)	1 (0.1)	1 (0.1)	0
Tachycardia	1 (0.1)	0	0
Palpitations	0	1 (0.1)	0
Ear and labyrinth disorders (SOC)	3 (0.2)	2 (0.2)	1 (0.1)
Vertigo	3 (0.2)	2 (0.2)	1 (0.1)
Eye disorders (SOC)	1 (0.1)	0	1 (0.1)
Conjunctival hemorrhage	1 (0.1)	0	0
Altered visual depth perception	0	0	1 (0.1)
Gastrointestinal disorders (SOC)	285 (14.8)	84 (7.6)	65 (7.9)
Diarrhea	186 (9.6)	40 (3.6)	21 (2.6)
Nausea	80 (4.1)	32 (2.9)	30 (3.6)
Vomiting	29 (1.5)	4 (0.4)	11 (1.3)
Abdominal pain	22 (1.1)	11 (1.0)	9 (1.1)
Gastroesophageal reflux disease	13 (0.7)	1 (0.1)	0
Loose stools	8 (0.4)	5 (0.5)	0
Dyspepsia	7 (0.4)	5 (0.5)	3 (0.4)
Constipation	5 (0.3)	1 (0.1)	1 (0.1)
Feces soft	4 (0.2)	0	3 (0.4)
Flatulence	3 (0.2)	1 (0.1)	0
Dry mouth	2 (0.1)	0	1 (0.1)
Abdominal distension	1 (0.1)	0	0
Abnormal feces	1 (0.1)	0	0
Eructation	1 (0.1)	0	0
Feces discolored	1 (0.1)	0	0
Hemorrhoids	1 (0.1)	1 (0.1)	1 (0.1)
Small intestinal obstruction	1 (0.1)	0	0
Diverticulum	0	1 (0.1)	0
Food poisoning	0	1 (0.1)	0
Toothache	0	0	1 (0.1)
General disorders and administration site conditions (SOC)	17 (0.9)	3 (0.3)	4 (0.5)
Fatigue	7 (0.4)	0	1 (0.1)
Chills	4 (0.2)	0	1 (0.1)
Pyrexia	3 (0.2)	1 (0.1)	1 (0.1)
Asthenia	1 (0.1)	0	2 (0.2)
Chest pain	1 (0.1)	1 (0.1)	0
Cyst	1 (0.1)	0	0
Malaise	1 (0.1)	0	0
Edema peripheral	1 (0.1)	1 (0.1)	0
Pain	1 (0.1)	0	0
Hepatobiliary disorders (SOC)	2 (0.1)	0	1 (0.1)
Cholelithiasis	2 (0.1)	0	0
Hepatomegaly	1 (0.1)	0	0
Bile duct stone	0	0	1 (0.1)

System Organ Class Preferred Term	Sulopenem N=1932 n (%)	Amoxicillin/ Clavulanate N=1107 n (%)	Ciprofloxacin N=822 n (%)
Immune system disorders (SOC)	1 (0.1)	0	2 (0.2)
Seasonal allergy	1 (0.1)	0	0
Drug hypersensitivity	0	0	2 (0.2)
Infections and infestations (SOC)	84 (4.3)	23 (2.1)	21 (2.6)
Vulvovaginal mycotic infection	46 (2.4)	13 (1.2)	7 (0.9)
COVID-19	5 (0.3)	2 (0.2)	0
Bacterial vaginosis	4 (0.2)	0	2 (0.2)
Upper respiratory tract infection	4 (0.2)	1 (0.1)	2 (0.2)
Gastroenteritis	3 (0.2)	0	1 (0.1)
Influenza	3 (0.2)	1 (0.1)	0
Nasopharyngitis	3 (0.2)	0	1 (0.1)
Pharyngitis streptococcal	3 (0.2)	0	0
Rhinitis	3 (0.2)	0	3 (0.4)
Respiratory tract infection	2 (0.1)	0	0
Urinary tract candidiasis	2 (0.1)	0	0
Bronchitis	1 (0.1)	0	0
Candida infection	1 (0.1)	0	1 (0.1)
Conjunctivitis	1 (0.1)	0	0
Gastroenteritis viral	1 (0.1)	0	0
Infectious mononucleosis	1 (0.1)	0	0
Lower respiratory tract infection	1 (0.1)	0	0
Oral herpes	1 (0.1)	0	0
Pyelonephritis acute	1 (0.1)	0	0
Urosepsis	1 (0.1)	0	0
Abscess limb	0	0	1 (0.1)
Chlamydial infection	0	1 (0.1)	0
Clostridium difficile infection	0	1 (0.1)	0
Genital herpes	0	1 (0.1)	0
Gonorrhea	0	0	1 (0.1)
Herpes zoster	0	1 (0.1)	0
Impetigo	0	0	1 (0.1)
Pharyngitis	0	0	1 (0.1)
Pneumonia	0	0	1 (0.1)
Sinusitis	0	1 (0.1)	0
Tooth infection	0	1 (0.1)	0
Injury, poisoning and procedural complications (SOC)	9 (0.5)	2 (0.2)	0
Arthropod bite	3 (0.2)	0	0
Contusion	1 (0.1)	0	0
Fall	1 (0.1)	1 (0.1)	0
Foot fracture	1 (0.1)	0	0
Ligament sprain	1 (0.1)	1 (0.1)	0
Muscle strain	1 (0.1)	0	0
Road traffic accident	1 (0.1)	0	0
Investigations (SOC)	1 (0.1)	0	1 (0.1)
Cardiac murmur	1 (0.1)	0	0
Glycosylated hemoglobin increased	0	0	1 (0.1)

System Organ Class Preferred Term	Sulopenem N=1932 n (%)	Amoxicillin/ Clavulanate N=1107 n (%)	Ciprofloxacin N=822 n (%)
Metabolism and nutrition disorders (SOC)	4 (0.2)	2 (0.2)	1 (0.1)
Vitamin D deficiency	2 (0.1)	0	0
Dehydration	1 (0.1)	1 (0.1)	0
Polydipsia	1 (0.1)	0	0
Decreased appetite	0	1 (0.1)	1 (0.1)
Musculoskeletal and connective tissue disorders (SOC)	13 (0.7)	6 (0.5)	5 (0.6)
Back pain	7 (0.4)	4 (0.4)	2 (0.2)
Pain in extremity	3 (0.2)	0	1 (0.1)
Arthralgia	1 (0.1)	1 (0.1)	2 (0.2)
Flank pain	1 (0.1)	0	0
Myositis	1 (0.1)	0	0
Neck pain	1 (0.1)	0	0
Musculoskeletal pain	0	1 (0.1)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps) (SOC)	1 (0.1)	0	0
Lung adenocarcinoma	1 (0.1)	0	0
Nervous system disorders (SOC)	61 (3.2)	23 (2.1)	23 (2.8)
Headache	42 (2.2)	17 (1.5)	18 (2.2)
Dizziness	11 (0.6)	4 (0.4)	5 (0.6)
Dysgeusia	2 (0.1)	1 (0.1)	0
Migraine	2 (0.1)	0	0
Ageusia	1 (0.1)	0	0
Dystonia	1 (0.1)	0	0
Hypoesthesia	1 (0.1)	0	0
Paresthesia	1 (0.1)	0	0
Presyncope	1 (0.1)	0	0
Somnolence	1 (0.1)	0	0
Syncope	1 (0.1)	0	0
Lumbosacral radiculopathy	0	0	1 (0.1)
Memory impairment	0	1 (0.1)	0
Psychiatric disorders (SOC)	2 (0.1)	2 (0.2)	1 (0.1)
Psychotic disorder	1 (0.1)	0	0
Stress	1 (0.1)	0	0
Anxiety	0	0	1 (0.1)
Confusional state	0	1 (0.1)	0
Insomnia	0	2 (0.2)	0
Renal and urinary disorders (SOC)	16 (0.8)	5 (0.5)	1 (0.1)
Urine odor abnormal	12 (0.6)	0	1 (0.1)
Nephrolithiasis	2 (0.1)	2 (0.2)	0
Acute kidney injury	1 (0.1)	1 (0.1)	0
Hematuria	1 (0.1)	1 (0.1)	0
Hydronephrosis	1 (0.1)	0	0
Renal pain	1 (0.1)	0	0
Chromaturia	0	1 (0.1)	0

System Organ Class Preferred Term	Sulopenem N=1932 n (%)	Amoxicillin/ Clavulanate N=1107 n (%)	Ciprofloxacin N=822 n (%)
Reproductive system and breast disorders (SOC)	7 (0.4)	2 (0.2)	2 (0.2)
Vaginal discharge	5 (0.3)	1 (0.1)	0
Vulvovaginal pruritus	2 (0.1)	0	0
Perineal pain	1 (0.1)	0	0
Pelvic pain	0	0	1 (0.1)
Vulvovaginal burning sensation	0	0	1 (0.1)
Vulvovaginal discomfort	0	1 (0.1)	0
Respiratory, thoracic and mediastinal disorders (SOC)	8 (0.4)	4 (0.4)	4 (0.5)
Cough	2 (0.1)	1 (0.1)	2 (0.2)
Oropharyngeal pain	2 (0.1)	2 (0.2)	0
Asthma	1 (0.1)	0	0
Dyspnea	1 (0.1)	0	0
Pleural effusion	1 (0.1)	0	0
Respiratory disorder	1 (0.1)	0	0
Sinus congestion	1 (0.1)	0	1 (0.1)
Sneezing	1 (0.1)	0	0
Epistaxis	0	0	1 (0.1)
Nasal congestion	0	1 (0.1)	0
Rhinorrhea	0	1 (0.1)	0
Skin and subcutaneous tissue disorders (SOC)	11 (0.6)	2 (0.2)	3 (0.4)
Pruritus	4 (0.2)	1 (0.1)	0
Angioedema	1 (0.1)	0	0
Dermatitis allergic	1 (0.1)	0	0
Hyperhidrosis	1 (0.1)	1 (0.1)	0
Lichen sclerosis	1 (0.1)	0	0
Rash	1 (0.1)	0	1 (0.1)
Rosacea	1 (0.1)	0	0
Skin lesion	1 (0.1)	0	0
Dermal cyst	0	0	1 (0.1)
Erythema	0	0	1 (0.1)
Vascular disorders (SOC)	13 (0.7)	2 (0.2)	4 (0.5)
Hypertension	7 (0.4)	1 (0.1)	4 (0.5)
Hypotension	2 (0.1)	0	0
Flushing	1 (0.1)	0	0
Hot flush	1 (0.1)	0	0
Intermittent claudication	1 (0.1)	0	0
Phlebolith	1 (0.1)	0	0
Peripheral coldness	0	1 (0.1)	0

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as any event that occurs or worsens in either intensity or frequency after the first dose of study drug in a period.

Duration is 5 days for sulopenem or amoxicillin, 3 days for Ciprofloxacin.

Abbreviations: AE, adverse event; COVID-19, coronavirus 2019; N, number of patients in treatment arm; n, number of subjects with adverse event; SOC, system organ class

18. Clinical Virology

Not applicable.

19. Clinical Microbiology

19.1. Nonclinical Microbiology

Please refer to the previous Multidisciplinary Review dated July 22, 2021, for the evaluation of in vitro and in vivo microbiology data presented in the initial NDA submission. No new in vitro and in vivo studies were conducted for this resubmission.

Clinical Studies for the uUTI Indication

The Applicant conducted two phase 3 uUTI clinical trials (IT001-301 or Trial 301 and IT001-310 or Trial 310) to determine the safety and efficacy of oral sulopenem etzadroxil/probenecid for this indication. For the treatment of adult women with uUTI, oral sulopenem etzadroxil/probenecid was compared with oral ciprofloxacin in Trial 301, while in Trial 310, oral sulopenem etzadroxil/probenecid was compared with oral amoxicillin/clavulanate.

Data from Trial 301 were reviewed for the initial NDA submission and are not included in this review. Please refer to the previous Multidisciplinary Review and Evaluation dated July 22, 2021. There are no pooled analyses, as only one phase 3 trial, Trial 310 is included in this resubmission. Therefore, this review only covers the uUTI Trial 310 and the Agency's recommendation on sulopenem broth microdilution MIC and disk diffusion breakpoints (BPs) for the uUTI-indicated Enterobacterales species.

uUTI Phase 3 Clinical Study: IT001-310 or Trial 310

In Trial 310, oral sulopenem etzadroxil/probenecid was compared with oral amoxicillin/clavulanate for the treatment of adult women with uUTI. The primary endpoint was overall response on Day 12 (± 1 day) which was the TOC visit.

Definitions of Analysis Populations

Intent-to-Treat: The ITT population included all randomized patients regardless of whether the patient received study drug.

Modified ITT: The MITT group included all randomized patients who received at least a single dose of study medication. Patients were analyzed according to the treatment group to which they were randomized.

Microbiologic-MITT (or micro-MITT): Micro-MITT patients were MITT patients with a positive study entry urine culture defined as $\geq 10^5$ CFU/mL of a uropathogen (*Enterobacterales* or *S. saprophyticus* only) and no more than two species of microorganisms identified in the study entry urine culture, regardless of colony count.

Micro-MITTS: The micro-MITTS population comprised micro-MITT patients with a baseline uropathogen susceptible to the comparator drug, amoxicillin/clavulanate (defined as MIC $\leq 8/4$ mg/L per Clinical and Laboratory Standards Institute [CLSI] breakpoints [CLSI M100]), and no baseline pathogen non-susceptible to amoxicillin/clavulanate.

Micro-MITTR: The micro-MITTR population comprised micro-MITT patients with a baseline uropathogen non-susceptible (intermediate [MIC 16/8 mg/L per CLSI M100] or resistant [MIC $\geq$ 32/16 mg/L per CLSI M100]) to the comparator drug, amoxicillin/clavulanate.

In the ITT populations, a total of 522/1111 (47%) and 468/1111 (42.1%) patients were in the micro-MITT populations of the sulopenem arm and amoxicillin/clavulanate arm, respectively. The micro-MITT population included both micro-MITTS (patients with a baseline pathogen susceptible to amoxicillin/clavulanate) and micro-MITTR (patients with a baseline pathogen non-susceptible to amoxicillin/clavulanate) populations. In Trial 310, the micro-MITTR population was very small (3% total in both arms) compared to the micro-MITTR (18%) in Trial 301.

Microbiological Sampling

Methods for Microbiological Collection, Culture, and Identification

For microbiological culture and analysis, mid-stream clean-catch urine specimens were collected from patients at Screening (Baseline), Day 3, Day 5 (EOT), Day 12 (TOC), Day 28, and for any study-related visits. Urine samples were received at International Health Management Associates in boric acid tubes within 48 hours of collection, either ambient or refrigerated.

Baseline/screening urine samples were cultured on blood agar plates, and MacConkey plates using a 1 μ L loop. Samples from all other visits were cultured on blood agar plates, CAN, and MacConkey plates using a 1 μ L and a 10 μ L loop. All culture plates were incubated at 35°C for 18 to 24 hours in non-CO₂ incubators.

Target Pathogens

For Study IT001-310, the following organisms were considered a uropathogen when isolated from an acceptable urine culture specimen:

Monomicrobial or polymicrobial infections caused by:

- Enterobacterales
- *Staphylococcus saprophyticus*
- *Pseudomonas aeruginosa*
- *Enterococcus* spp.

The latter two organisms were considered non-target pathogens. All target and non-target pathogens were identified by Matrix-Assisted Laser Desorption Ionization–Time of Flight (MALDI-TOF), had aspartate aminotransferase testing by broth microdilution, and were saved when considered significant. Disk diffusion testing was performed on only Enterobacterales and *S. saprophyticus*. The micro-MITT population for this study only included patients with uUTIs caused by Enterobacterales. A study urine culture that was positive for more than two species of microorganisms was considered contaminated, regardless of colony count.

Microbiological Outcome Measures

The microbiological definitions used in the assessment of the per-pathogen microbiological response at baseline and post-baseline are summarized in [Table 104](#) and [Table 105](#).

Table 104. Microbiological Assessment of Baseline Pathogens at TOC

Response	Definition
Eradication	A urine culture obtained at the timepoint of analysis demonstrated 10^3 CFU/mL of the baseline uropathogen
Persistence	A uropathogen from urine present at baseline regardless of susceptibility grew at $\geq 10^3$ CFU/mL at the timepoint of analysis*.
Persistence with Increasing MIC	A urine culture taken after at least 2 full days of treatment grew $\geq 10^3$ CFU/mL of the baseline uropathogen and displayed ≥ 4 -fold higher MIC to study drug received at the timepoint of analysis.
Indeterminate	Patient was lost to follow-up, or an assessment was not undertaken such that no urine culture was obtained (or culture results could not be interpreted) at the timepoint of analysis (contaminated results are considered a negative culture and therefore an eradication ⁶).

Source: NDA submission

*The genus/species and susceptibility profiles need to match. Additional molecular testing by pulsed field gel electrophoresis or whole genome sequencing was performed as needed for confirmation.

Abbreviations: CFU, colony-forming units; MIC, minimum inhibitory concentration

Table 105. Microbiological Definitions of Post-Baseline Pathogens

Response	Definition
Superinfection	A uropathogen not present at baseline grew with $\geq 10^5$ CFU/mL from the first dose of study drug through the EOT visit in the setting of recurrent/persistent/new uUTI symptoms requiring non-study systemic antibacterial treatment* (patient-determined clinical failure at EOT).
New Infection	Isolation of a non-baseline pathogen from a culture post-EOT visit from a urine culture specimen with $\geq 10^5$ CFU/mL in a patient with one or more new uUTI signs/symptoms requiring new systemic antibacterial treatment* after the EOT visit (patient-determined clinical failure post-EOT).
Recurrence	In a patient with clinical and microbiological success at EOT, isolation of a baseline pathogen from a urine culture specimen with $\geq 10^5$ CFU/mL post-EOT visit, along with new or recurrence of one or more uUTI signs/symptoms requiring new systemic antibacterial treatment* after the EOT visit (patient-determined clinical failure post-EOT).
Colonization	Isolation of a microorganism from the urine culture after EOT in a patient without one or more signs and symptoms of uUTI and not requiring new systemic antibiotic therapy* (patient-determined clinical success post-EOT).

Source: NDA submission

*Excluding linezolid, daptomycin, vancomycin, azithromycin, metronidazole, josamycin, macrolide, nifuratel, tergyran, fluconazole, cystone, butoconazole nitrate, clindamycin hydrochloride, clotrimazole, tinidazole, and clarithromycin, as well as "antibiotics and chemotherapeutics for dermatological use" and "ophthalmologicals" since they have no activity against the pathogens in the study. Abbreviations: CFU, colony-forming units; EOT, end of treatment; uUTI, uncomplicated urinary tract infection

Baseline Pathogens in Trial 310: micro-MITT Population

All urinary pathogens cultured from the micro-MITT population are presented in [Table 106](#). The most frequently isolated pathogens in both treatment arms were *E. coli* (81.8%), *K. pneumoniae* (10.9%), and *P. mirabilis* (2.7%).

Table 106. Pathogens From Urine at Baseline – Micro-MITT Population, Trial 310

	Sulopenem- etzadroxil/ Probenecid (N = 522) n (%)	Amoxicillin/clavulanate (N = 468) n (%)	Total (N = 990) n (%)
Number of Patients with at least one Study Uropathogen at Baseline	522 (100.0)	468 (100.0)	990 (100.0)
<i>Escherichia coli</i>	423 (81.0)	387 (82.7)	810 (81.8)
<i>Klebsiella pneumoniae</i>	58 (11.1)	50 (10.7)	108 (10.9)
<i>Proteus mirabilis</i>	14 (2.7)	13 (2.8)	27 (2.7)
<i>Enterobacter hormaechei</i>	4 (0.8)	8 (1.7)	12 (1.2)
<i>Klebsiella aerogenes</i>	4 (0.8)	3 (0.6)	7 (0.7)
<i>Klebsiella variicola</i>	5 (1.0)	1 (0.2)	6 (0.6)
<i>Citrobacter freundii</i>	5 (1.0)	0 (0.0)	5 (0.5)
<i>Citrobacter koseri</i>	3 (0.6)	2 (0.4)	5 (0.5)
<i>Serratia marcescens</i>	3 (0.6)	1 (0.2)	4 (0.4)
<i>Morganella morganii</i>	2 (0.4)	1 (0.2)	3 (0.3)
<i>Providencia stuartii</i>	2 (0.4)	1 (0.2)	3 (0.3)
<i>Klebsiella oxytoca</i>	0 (0.0)	2 (0.4)	2 (0.2)
<i>Klebsiella spp.</i>	1 (0.2)	1 (0.2)	2 (0.2)
<i>Enterobacter bugandensis</i>	0 (0.0)	1 (0.2)	1 (0.1)
<i>Enterobacter cloacae</i>	1 (0.2)	0 (0.0)	1 (0.1)
<i>Enterobacter kobei</i>	1 (0.2)	0 (0.0)	1 (0.1)
<i>Escherichia spp.</i>	1 (0.2)	0 (0.0)	1 (0.1)
<i>Pantoea spp.</i>	1 (0.2)	0 (0.0)	1 (0.1)

Source: IT001-310 Table 14.1.9.1

Abbreviations: %, 100 x n/N; micro-MITT, microbiological modified intent-to-treat; N, total number of patients in the micro-MITT population; n, number of subjects with specific uropathogen

Monomicrobial And Polymicrobial Infections at Baseline: micro-MITT, Trial 310

About 94% of patients in the micro-MITT population had monomicrobial infections as shown in [Table 107](#).

Table 107. Monomicrobial and Polymicrobial Infections at Baseline – Micro-MITT Population, Trial 310

	Sulopenem- etzadroxil/Probenecid (N = 522) n (%)	Amoxicillin/clavulanate (N = 468) n (%)	Total (N = 990) n (%)
Monomicrobial	483 (92.5)	448 (95.7)	931 (94.0)
Polymicrobial	39 (7.5)	20 (4.3)	59 (6.0)

Source: IT001-310 Table 14.1.10.2

Monomicrobial infection is $\geq 100,000$ CFU/mL in baseline specimen of only 1 Enterobacterales; Polymicrobial infection is $\geq 100,000$ CFU/mL in baseline specimen of any 2 Enterobacterales.

Abbreviations: %, 100 x n/N; micro-MITT, microbiological modified intent-to-treat; N, total number of patients in the micro-MITT population

MIC Data of Baseline Pathogens: micro-MITT, Trial 310

The in vitro MIC₅₀ and MIC₉₀ data of sulopenem and amoxicillin/clavulanate in the micro-MITT populations in both treatment groups (combined) are presented in [Table 108](#). Sulopenem MIC₅₀/MIC₉₀ values were 0.03/0.06 mcg/mL, 0.03/0.06 mcg/mL, and 0.12/0.5 mcg/mL against 809 *E. coli*, 108 *K. pneumoniae*, and 27 *P. mirabilis* isolates, respectively.

Table 108. Activity of Sulopenem and Amoxicillin/Clavulanate Against Baseline Pathogens – Micro-MITT Population – Both Treatment Groups (Combined), Trial 310

Organism Antibiotic	N	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)	CLSI %S/%I/%R
<i>Escherichia coli</i>	809			
Sulopenem		0.03	0.06	0/0/0
Amoxicillin/clavulanate		4	8	95.8/3.0/1.2
<i>Klebsiella pneumoniae</i>	108			
Sulopenem		0.03	0.06	0/0/0
Amoxicillin/clavulanate		1	4	99.1/0.0/0.9
<i>Proteus mirabilis</i>	27			
Sulopenem		0.12	0.5	0/0/0
Amoxicillin/clavulanate		0.5	4	100.0/0.0/0.0
<i>Enterobacter cloacae</i> complex	15			
Sulopenem		0.06	0.25	0/0/0
Amoxicillin/clavulanate		32	32	8.3/33.3/58.3

Source: IT001-310 Table 14.1.18.1

Percentages are calculated as 100 x (n/N); for the %S/%I/%R column there is no breakpoint for CLSI when 0/0/0 appears. Percentages are calculated based on N, where N is the number of patients in the micro-MITT population with respective study uropathogen at baseline with valid MIC values.

Abbreviations: %I, percent of intermediate pathogens; %R, percent of resistant pathogens; %S, percent of susceptible pathogens; CLSI, clinical and laboratory standards institute; MIC, minimum inhibitory concentration; micro-MITT, microbiological modified intent-to-treat; N, total number of patients in the micro-MITT population; µg/mL, microgram per milliliter

Clinical and Microbiological Outcomes, Trial 310

The overall response (combined clinical and microbiological response) and microbiological response at TOC in the micro-MITT (micro-MITTR + micro-MITTS) populations are covered in this section of the review.

Overall Response at TOC: micro-MITT Population, Trial 310

The primary efficacy endpoint for this study was the overall response at the TOC (Day 12) Visit. Overall success was observed in 60.9% of patients receiving sulopenem etzadroxil/probenecid, compared to 55.6% of patients in the amoxicillin/clavulanate treatment group [treatment difference (95% CI): 5.4% (-0.8, 11.5)]. Sulopenem demonstrated noninferiority to amoxicillin/clavulanate in the micro-MITT population and is summarized in [Table 109](#).

Table 109. Overall Response at TOC – Micro-MITT Population, Trial 310

Outcome	Sulopenem etzadroxil/Probenecid (N = 522) n (%)	Amoxicillin/clavulanate (N = 468) n (%)	Difference (95% CI)	p-value
Success	318 (60.9)	260 (55.6)	5.4 (-0.8, 11.5)	0.0437
Failure/Indeterminate	204 (39.1)	208 (44.4)		
Failure	177 (33.9)	185 (39.5)		
Indeterminate	27 (5.2)	23 (4.9)		

Source: IT001-310 Table 14.2.1.1

Success is defined as combined clinical and microbiological success at TOC. Indeterminate responses are considered failures for CI calculation. CI computed using the method proposed without stratification by Miettinen and Nurminen. One-sided p-value corresponding to the lower bound of the 95% CI is reported.

Abbreviations: %, 100 x n/N; micro-MITT, microbiological modified intent-to-treat; N, total number of patients in the micro-MITT population; n, number of subjects with specific outcome; TOC, test of cure

Overall Response at TOC by Key Targeted Baseline Pathogens: micro-MITT, Trial 310

The overall response at TOC by target baseline pathogens in the micro-MITT population is summarized in [Table 110](#). Sulopenem achieved greater response against *E. coli* and *K. pneumoniae* isolates compared to amoxicillin/clavulanate.

Table 110. Overall Response at TOC by Selected Baseline Pathogens – Micro-MITT Population, Trial 310

Baseline Pathogen	Sulopenem etzadroxil/Probenecid (N = 522) m/n (%)	Amoxicillin/clavulanate (N = 468) m/n (%)
<i>Escherichia</i>	263/423 (62.2)	219/387 (56.6)
<i>Escherichia coli</i>	263/423 (62.2)	219/387 (56.6)
<i>Klebsiella</i>	31/58 (53.4)	22/50 (44.0)
<i>Klebsiella pneumoniae</i>	31/58 (53.4)	22/50 (44.0)
<i>Proteus</i>	6/14 (42.9)	6/13 (46.2)
<i>Proteus mirabilis</i>	6/14 (42.9)	6/13 (46.2)
<i>Enterobacter</i>	3/4 (75.0)	8/8 (100.0)
<i>Enterobacter hormaechei</i>	3/4 (75.0)	8/8 (100.0)

Source:IT001-310 Table 14.2.2.1.1

Abbreviations: %, 100 x m/n; micro-MITT, microbiological modified intent-to-treat; m, number of subjects with microbiologic success and with specific study uropathogen; N, number of patients in the micro-MITT population; n, number of patients in the micro-MITT population with specific study uropathogen; TOC, test of cure

Microbiologic Response: micro-MITT Population, Trial 310

The microbiologic response per patient at TOC for the micro-MITT population is presented in [Table 111](#). The microbiologic response rates were higher for patients on sulopenem etzadroxil/probenecid than those on amoxicillin/clavulanate (74.7%, compared with 67.3%).

Table 111. Microbiologic Response Per Patient at TOC and Reasons for Overall Nonresponse at TOC – Micro-MITT Population, Trial 310

Micro-MITT Population/Microbiologic Response per Patient	Sulopenem etzadroxil/Probenecid (N = 522) n (%)	Amoxicillin/clavulanate N = 468 n (%)	Difference (95% CI)
Success (eradication)	390 (74.7)	315 (67.3)	7.4 (1.8, 13.1)
Failure	106 (20.3)	131 (28.0)	
Persistence	106 (20.3)	131 (28.0)	
Persistence with Increasing MIC	0 (0.0)	0 (0.0)	
Indeterminate	26 (5.0)	22 (4.7)	

Source:IT001-310 Table 14.2.6.1.1

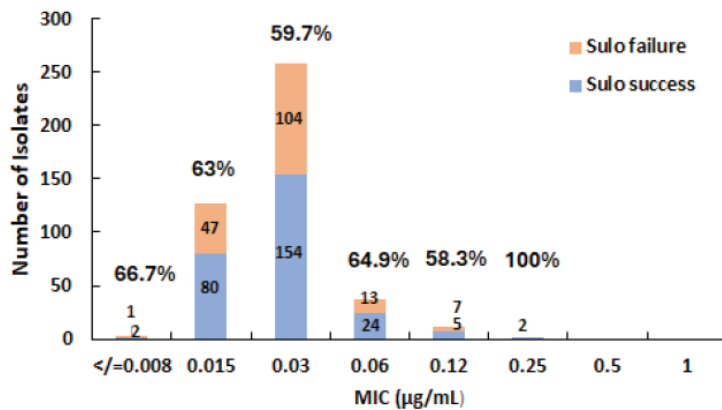
Indeterminate responses are considered failures for CI calculation. CI computed using the method proposed without stratification by Miettinen and Nurminen. Persistence with increasing MIC means a ≥ 4 dilution higher MIC from baseline visit.

Abbreviations: %, 100 x n/N; CI, Confidence Interval; micro-MITT, microbiologic modified intent-to-treat; MIC, minimal inhibitory concentration; N, number of patients in the micro-MITT population; TOC, Test of Cure

Correlation of Overall Response at TOC And Sulopenem Mics of Key Target Pathogens: Micro-MITT Population, Trial 310

The overall response by target pathogens *E. coli* (N = 439), *K. pneumoniae* (N = 60) and *P. mirabilis* (N = 14) and their MICs for sulopenem in the micro-MITT population are shown in [Figure 11](#), [Figure 12](#), and [Figure 13](#), respectively. Against *E. coli*, the overall rate of success was between 58.3 to 100% across an MIC range of ≤0.008 to 0.25 mcg/mL. Against *K. pneumoniae*, an overall success rate of 44.4 to 100% with an MIC range of 0.03 to 0.25 mcg/mL was observed. Against *P. mirabilis*, success rates were observed between 0 and 100% with an MIC range 0.015 to 0.5 mcg/mL.

Figure 11. Overall Response Per Pathogen for MIC to Sulopenem – Micro-MITT Population – *E. coli* (N = 439), Trial 310

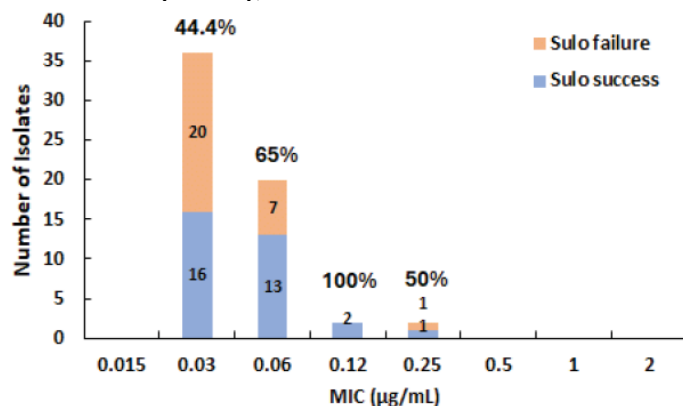


Source: IT001-310 Table 14.2.2.3.1

Overall response at TOC by pathogen for MIC to sulopenem micro-MITT population. % = 100 x n/N

Abbreviations: MIC, minimal inhibitory concentration; micro-MITT, microbiological modified intent-to-treat; N, number of patients in the micro-MITT population; n, number of subjects who achieved overall response with specific pathogen at MIC to sulopenem; sulo, sulopenem; TOC, test of cure

Figure 12. Overall Response Per Pathogen for MIC to Sulopenem – Micro-MITT Population – *K. pneumoniae* (N = 60), Trial 310

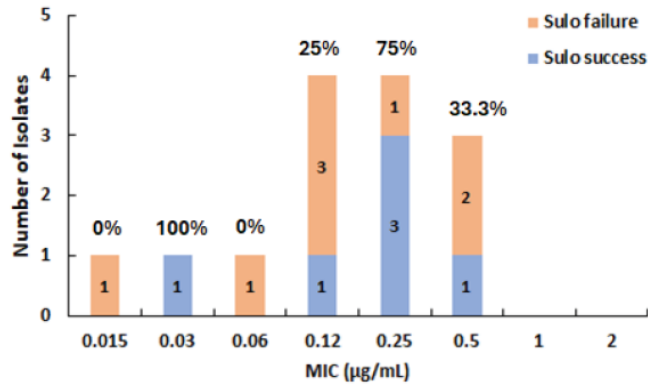


Source: IT001-310 Table 14.2.2.3.1

Overall response at TOC by pathogen for MIC to sulopenem micro-MITT population. % = 100 x n/N

Abbreviations: MIC, minimal inhibitory concentration; micro-MITT, microbiological modified intent-to-treat; N, total number of patients in the micro-MITT population; n, number of subjects who achieved overall response with specific pathogen at MIC to sulopenem; sulo, sulopenem; TOC, test of cure

Figure 13. Overall Response Per Pathogen for MIC to Sulopenem – Micro-MITT Population – *P. mirabilis* (N = 14), Trial 310



Source: NDA submission

Overall response at TOC by pathogen for MIC to sulopenem micro-MITT population. % = 100 x n/N

Abbreviations: MIC, minimal inhibitory concentration; micro-MITT, microbiological modified intent-to-treat; N, number of patients in the micro-MITT population; n, number of subjects achieved overall response with specific pathogen at MIC to sulopenem; sulo, sulopenem; TOC, test of cure

Per Pathogen Microbiologic Response at TOC: micro-MITT, Trial 310

The per-pathogen microbiologic response at TOC for the micro-MITT population is provided in [Table 112](#). The microbiologic response rates for patients with baseline *E. coli* and *K. pneumoniae* isolates was higher in the sulopenem arm compared with the amoxicillin/clavulanate arm.

Table 112. Per-Pathogen Microbiologic Response at TOC – micro-MITT Population, Trial 310

Baseline Pathogen	Sulopenem etzadroxil/Probenecid (N = 522) m/n (%)	Amoxicillin/clavulanate (N = 468) m/n (%)
<i>Escherichia</i>	321/424 (75.7)	265/387 (68.5)
<i>Escherichia coli</i>	320/423 (75.7)	265/387 (68.5)
<i>Escherichia</i> spp.	1/1 (100.0)	0/0 (0.0)
<i>Klebsiella</i>	51/68 (75.0)	32/57 (56.1)
<i>Klebsiella aerogenes</i>	2/4 (50.0)	1/3 (33.3)
<i>Klebsiella oxytoca</i>	0/0 (0.0)	2/2 (100.0)
<i>Klebsiella pneumoniae</i>	43/58 (74.1)	27/50 (54.0)
<i>Klebsiella</i> spp.	1/1 (100.0)	1/1 (100.0)
<i>Klebsiella variicola</i>	5/5 (100.0)	1/1 (100.0)
<i>Proteus</i>	6/14 (42.9)	9/13 (69.2)
<i>Proteus mirabilis</i>	6/14 (42.9)	9/13 (69.2)
<i>Citrobacter</i>	6/8 (75.0)	2/2 (100.0)
<i>Citrobacter freundii</i>	3/5 (60.0)	0/0 (0.0)
<i>Citrobacter koseri</i>	3/3 (100.0)	2/2 (100.0)
<i>Enterobacter</i>	5/6 (83.3)	8/9 (88.9)
<i>Enterobacter bugandensis</i>	0/0 (0.0)	0/1 (0.0)
<i>Enterobacter cloacae</i>	1/1 (100.0)	0/0 (0.0)
<i>Enterobacter hormaechei</i>	3/4 (75.0)	8/8 (100.0)
<i>Enterobacter kobei</i>	1/1 (100.0)	0/0 (0.0)
<i>Providentia</i>	2/2 (100.0)	1/1 (100.0)
<i>Providentia stuartii</i>	2/2 (100.0)	1/1 (100.0)
<i>Serratia</i>	2/3 (66.7)	1/1 (100.0)
<i>Serratia marcescens</i>	2/3 (66.7)	1/1 (100.0)
<i>Morganella</i>	2/2 (100.0)	0/1 (0.0)
<i>Morganella morganii</i>	2/2 (100.0)	0/1 (0.0)
<i>Pantoea</i>	1/1 (100.0)	0/0 (0.0)
<i>Pantoea</i> spp.	1/1 (100.0)	0/0 (0.0)

Source: IT001-310 Table 14.2.6.7.1

% = 100 x m/n

Abbreviations: m, number of subjects with microbiologic success and with specific study uropathogen; micro-MITT, microbiological modified intent-to-treat; N, total number of patients in the micro-MITT population; n, number of subjects with specific study uropathogen; TOC, test of cure

Impact of Treatment on the Distribution of Susceptibility to the Treatment Regimen: Emergence of Resistance During Therapy, Trial 310

In this study, no post baseline isolate was observed with a sulopenem MIC that had increased by ≥ 4 -fold relative to a baseline isolate of the same genus and species.

Correlation of MIC Values of Baseline Isolates to Microbiologic Outcome at TOC: micro-MITT Population, Trial 310

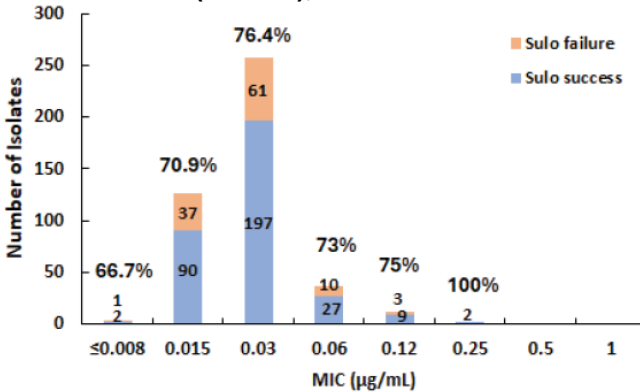
The per pathogen microbiologic response of *E. coli*, *K. pneumoniae*, and *P. mirabilis* at TOC by baseline MIC to sulopenem was determined as percent success for the overall micro-MITT population. Microbiologic response was defined as microbiologic success at TOC in the microbiologically evaluable (ME-TOC) patients. The microbiologic response per pathogen for MIC to sulopenem for *E. coli* (N = 439), *K. pneumoniae* (N = 60), and *P. mirabilis* (N = 14) in

the overall micro-MITT population are shown in [Figure 14](#), [Figure 15](#), and [Figure 16](#), respectively.

E. coli

Against 439 *E. coli* isolates, the rate of microbiologic success ranged from 66.7 to 100% over the MIC range of ≤ 0.008 to 0.25 mcg/mL. No baseline *E. coli* isolates with MIC ≥ 0.5 mcg/mL were available.

Figure 14. Microbiologic Response Per Pathogen for MIC to Sulopenem – Micro-MITT Population Overall – *E. coli* (N = 439), Trial 310



Source: NDA submission

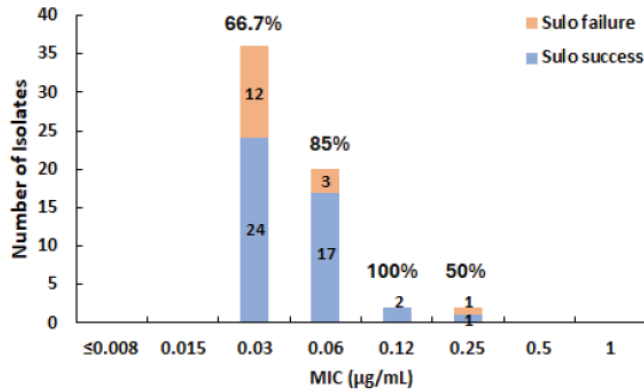
Success is defined as microbiologic success at TOC. % = $100 \times m/n$

Abbreviations: m, number of patients with Eradication response to the specific pathogen and MIC to sulopenem; MIC, minimal inhibitory concentration; micro-MITT, microbiological modified intent-to-treat; N, number of patients in the micro-MITT population; N1, number of patients with specific pathogen; n, number of patients with specific pathogen and MIC to sulopenem; Sulo, sulopenem; TOC, test of cure

K. pneumoniae

Against 60 *K. pneumoniae* isolates, the rate of microbiologic success ranged from 50 to 100% over the MIC range of 0.03 to 0.25 mcg/mL. No baseline *K. pneumoniae* isolates with MIC ≥ 0.5 mcg/mL were available.

Figure 15. Microbiologic Response Per Pathogen for MIC to Sulopenem – Micro-MITT Population Overall – *K. pneumoniae* (N = 60), Trial 310



Source: NDA submission

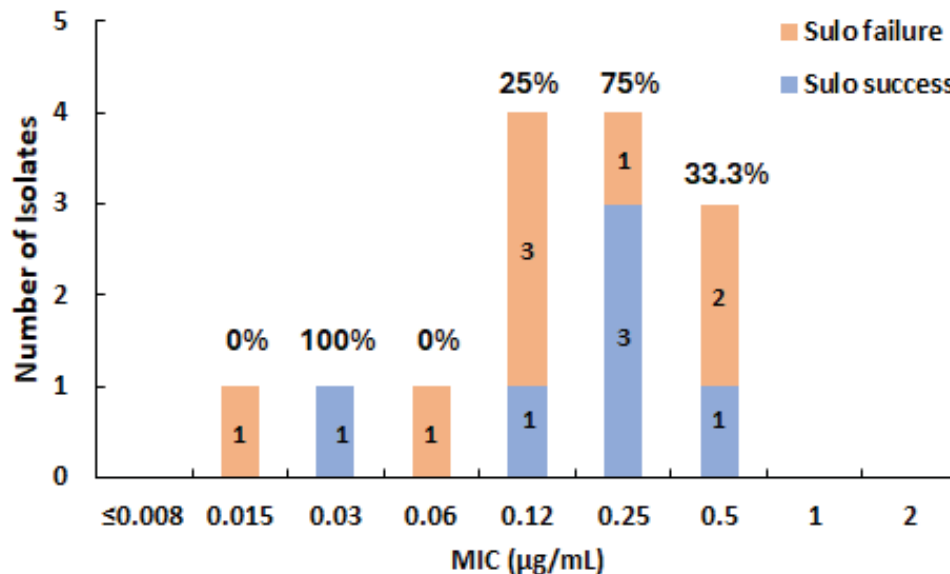
Success is defined as microbiologic success at TOC. % = 100 x m/n

Abbreviations: m, number of patients with Eradication response to the specific pathogen and MIC to sulopenem; MIC, minimal inhibitory concentration; micro-MITT, microbiological modified intent-to-treat; N, number of patients in the micro-MITT population; N1, number of patients with specific pathogen; n, number of patients with specific pathogen and MIC to sulopenem; Sulo, sulopenem; TOC, test of cure

P. mirabilis

The microbiologic response by sulopenem MIC for the baseline *P. mirabilis* population from overall micro-MITT (N = 14) is shown in [Figure 16](#). Against a much smaller number of *P. mirabilis* baseline isolates, the rates of microbiologic success ranged from 0 to 100% over the MIC range of 0.015 to 0.5 mcg/mL.

Figure 16. Microbiologic Response Per Pathogen for MIC to Sulopenem – Micro-MITT Population Overall – *P. mirabilis* (N = 14), Trial 310



Source: NDA submission

Success is defined as microbiologic success at TOC. % = 100 x m/n

Abbreviations: m, number of patients with Eradication response to the specific pathogen and MIC to sulopenem; MIC, minimal inhibitory concentration; micro-MITT, microbiological modified intent-to-treat; N, number of patients in the micro-MITT population; N1, number of patients with specific pathogen; n, number of patients with specific pathogen and MIC to sulopenem; Sulo, sulopenem; TOC, test of cure

Baseline Pathogens in Trial 310: micro-MITTS Population

All urinary pathogens cultured from the micro-MITTS population are presented in [Table 113](#). The most frequently isolated pathogens in both treatment arms were *E. coli* (83.9%), *K. pneumoniae* (11.6%), and *P. mirabilis* (2.8%).

Table 113. Pathogens From Urine at Baseline, Micro-MITTS Population, Trial 310

Pathogen	Sulopenem (N=480) n (%)	Amoxicillin/ Clavulanate (N=442) n (%)	Total (N=922) n (%)
<i>Escherichia coli</i>	400 (83.3)	374 (84.6)	774 (83.9)
<i>Klebsiella pneumoniae</i>	57 (11.9)	50 (11.3)	107 (11.6)
<i>Proteus mirabilis</i>	13 (2.7)	13 (2.9)	26 (2.8)

Source: NDA submission

Abbreviations: micro-MITTS, microbiological modified intent-to-treat susceptible; N, total number of patients in the micro-MITTS population; n, number

Per-Pathogen Microbiological Response in the micro-MITTS Populations, Trial 310

The per-pathogen microbiologic response at TOC for the micro-MITTS population is provided in [Table 114](#). The microbiologic response rates were higher for patients on sulopenem etzadroxil/probenecid than those on amoxicillin/clavunilate arm.

Table 114. Per-Pathogen Microbiologic Response at TOC, ME-TOC Population

Pathogen	Sulopenem (%)	Amoxicillin/ Clavulanate (%)
<i>Escherichia coli</i>	304/400 (76.0)	254/374 (67.9)
<i>Klebsiella pneumoniae</i>	42/ 57 (73.7)	27/ 50 (54.0)
<i>Proteus mirabilis</i>	5/13 (38.5)	9/ 13 (69.2)

Source: NDA submission

Abbreviations: ME-TOC, microbiologically evaluable test of cure; TOC, test of cure

A summary of the overall response at TOC in Trial 310 by sulopenem baseline MIC in the sulopenem-treated micro-MITT population is shown by target pathogen in [Table 115](#).

Table 115. Correlation of Sulopenem MIC at Baseline to Overall Response in Sulopenem-Treated, Micro-MITT Population, Trial 310

Organism	Overall Response Rate at TOC (n/N) by MIC (µg/mL)												
	Total	≤0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	>16
<i>E. coli</i>	269/439 (61.3)	82/130 (63.1)	154/258 (59.7)	24/37 (64.9)	7/12 (58.3)	2/2 (100)							
<i>K. pneumoniae</i>	32/60 (53.3)		16/36 (44.4)	13/20 (65.0)	2/2 (100)	1/2 (50.0)							
<i>P. mirabilis</i>	6/14 (42.9)	0/1 (0.0)	1/1 (100)	0/1 (0.0)	1/4 (25.0)	3/4 (75.0)	1/3 (33.3)						
<i>E. cloacae</i> complex	3/5 (60.0)		1/1 (100)	1/1 (100)	1/1 (100)	1/1 (100)	0/1 (0.0)						
Other Enterobacteriales	12/16 (75.0)		4/6 (66.7)	3/3 (100)	3/4 (75.0)	0/1 (0.0)	2/2 (100)						
Enterobacteriales overall	322/444 (72.5)	82/131 (62.6)	176/302 (58.3)	41/62 (66.1)	14/23 (60.9)	7/9 (77.8)	3/6 (50.0)						

Source: IT001-310 Table 14.2.2.3.1

Abbreviations: MIC, Minimal Inhibitory Concentration; micro-MITT, microbiological modified intent-to-treat; N, total number of patients in the micro-MITTS population; n, number; TOC, test of cure

Clinical microbiology reviewer's comments: In Trial 310, favorable overall responses were observed for patients with baseline isolates of E. coli, K. pneumoniae, and P. mirabilis that had

MIC values ranging from ≤ 0.015 up to 0.25 mcg/mL. No baseline isolates of *E. coli*, and *K. pneumoniae* with MIC ≥ 0.5 mcg/mL were available. Three baseline *P. mirabilis* isolates with MIC 0.5 mcg/mL were available but only one isolate achieved overall success. No baseline *P. mirabilis* isolates with MIC ≥ 1.0 mcg/mL were available.

Sulopenem Activity Against AmpC and ESBL Isolates With Known β -Lactamase (*bla*) Genes in Trials 301 and 310

A total of 336 phenotypically resistant baseline uUTI isolates from Trials 301 and 310 were further analyzed by multiplex PCR to screen for *bla*-genes encoding ESBLs, AmpC β -lactamases, and carbapenemases. [Table 116](#) and [Table 117](#) summarize the clinical and microbiological responses to sulopenem in AmpC- and predominant ESBL-producing isolates in Trials 301 and 310, respectively. Against 208 AmpC and ESBL isolates in Trial 301, sulopenem had MIC₅₀/MIC₉₀ values of 0.06/0.12, 0.03/0.06, and 0.03/0.06 mcg/mL against AmpC (n=12), CTX-M (n=105), and TEM-OSBL (n=38) genotypes, respectively. The clinical responses were 33.3%, 66.7%, and 63.2% and microbiological responses were 50%, 49.5%, and 50% against AmpC, CTX-M, and TEM-OSBL, respectively. Similarly, against 128 AmpC- and ESBL-producing isolates in Trial 310, sulopenem MIC_{50/90} values were 0.06/0.12, 0.03/0.06, 0.03/0.06 mcg/mL against AmpC (n=14), CTX-M (n=78), and TEM-OSBL (n=22) genotypes, respectively. Against AmpC, CTX-M, and TEM-OSBL, the clinical responses were 71.4%, 84.6%, and 72.7% and the microbiological responses were 85.7%, 62.8%, and 50%, respectively. Among all ESBL genotypes, CTX-M-15 was the most frequently identified from 107/336 (31.8%) baseline ESBL-producing isolates.

Table 116. Clinical and Microbiological Response to Sulopenem in AmpC and Predominant ESBL-Producing Isolates at TOC, Micro-MITT Population, Trial 301

Pathogen	<i>bla</i> Type	Total Isolates	MIC Range (mcg/mL)	MIC ₅₀ /MIC ₉₀ (mcg/mL)	Clinical Response n/N (%)	Microbiological Response n/N (%)
<i>E. coli</i>	AmpC	12	0.03-1.0	0.06/0.12	4/12 (33.3)	6/12 (50)
	CTX-M	105	≤ 0.008 -1.0	0.03/0.06	70/105 (66.7)	52/105 (49.5)
	TEM-OSBL	38	0.015-0.25	0.03/0.06	24/38 (63.2)	19/38 (50)
<i>K. pneumoniae</i>	CTX-M	14	0.03-0.5	0.12/0.5	12/14 (85.7)	9/14 (64.3)
	OXA-48	3	4-8		2/3 (66.7)	2/3 (66.7)
	SHV	19	0.03-8	0.12/4	16/19 (84.2)	13/19 (68.4)
	TEM-OSBL	11	0.03-0.5	0.06/0.5	10/11 (90.9)	7/11 (63.6)

Source: NDA submission

Abbreviations: ESBL, extended-spectrum beta-lactamase; MIC, minimum inhibitory concentration; micro-MITT, microbiological modified intent-to-treat; N, total number; n, number; TOC, test of cure

Table 117. Clinical and Microbiological Response to Sulopenem in AmpC and Predominant ESBL-Producing Isolates at TOC, Micro-MITT Population, Trial 310

Pathogen	bla Type	Total Isolates	MIC Range (mcg/mL)	MIC ₅₀ /MIC ₉₀ (mcg/mL)	Clinical Response n/N (%)	Microbiological
						Response n/N (%)
<i>E. coli</i>	AmpC	14	0.03-0.25	0.06/0.12	10/14 (71.4)	12/14 (85.7)
	CTX-M	78	0.015-0.25	0.03/0.06	66/78 (84.6)	49/78 (62.8)
	TEM-OSBL	22	0.015-0.12	0.03/0.06	16/22 (72.7)	11/22 (50)
<i>K. pneumoniae</i>	AmpC	1	0.06-0.06		0/1 (0)	1/1 (100)
	CTX-M	2	0.06-0.25		1/2 (50)	1/2 (50)
	SHV-OSBL	3	0.06-0.25		1/3 (33.3)	2/3 (66.7)
	TEM-OSBL	1	0.06-0.06		1/1 (100)	1/1 (100)
<i>P. mirabilis</i>	CTX-M	2	0.25-0.5		2/2 (100)	2/2 (100)
	TEM-OSBL	2	0.25-0.5		2/2 (100)	2/2 (100)

Source: NDA submission

Abbreviations: ESBL, extended-spectrum beta-lactamase; MIC, minimum inhibitory concentration; micro-MITT, microbiological modified intent-to-treat; N, total number; n, number; TOC, test of cure

Supporting Microbiology Data From Other Phase 3 Studies

As mentioned earlier, the Applicant also conducted two additional phase 3 trials to evaluate the safety and efficacy of sulopenem for the treatment of cUTI and cIAI; both failed to meet their primary endpoints. Microbiology data from both Trial 302 (cUTI) and Trial 303 (cIAI), included by the Applicant in the original NDA submission to support the safety of sulopenem for treatment of uUTI, were reviewed in the Multidisciplinary Review and Evaluation dated July 22, 2021.

Applicant's Proposed Interpretive Criteria for Sulopenem: uUTI Target Pathogens

The Applicant has proposed sulopenem broth microdilution MIC and disk diffusion susceptibility testing interpretive criteria or BPs against Enterobacterales based on the following sulopenem summary data:

- MIC frequency distributions for surveillance study and clinical study isolates for the indicated pathogens;
- PK/PD information including target attainment analysis from Monte-Carlo simulations conducted with phase 3 patient PK data;
- A summary of the correlation between microbiologic outcomes and MIC; and
- The generation of proposed disk diffusion interpretive criteria by correlation between zone diameter and broth microdilution MIC values in scatterplot following the CLSI error-rate bounding analysis.

The Applicant-proposed BPs against Enterobacterales are summarized in the following [Table 118](#).

Table 118. Proposed Broth Microdilution (MIC) and Disk Diffusion Susceptibility Test Criteria for Sulopenem

Organism	MIC (µg/mL)	Zone Diameter ^a (mm)
Enterobacterales		(b) (4)

Source: NDA submission

^a Sulopenem 2-µg disk

Abbreviations: MIC, minimum inhibitory concentration; NA, not applicable

19.2. FDA Recommendations for Breakpoints or Susceptibility Test Interpretive Criteria

The following is a summary of the Agency’s MIC Susceptibility Test Interpretive Criteria (STIC)/ BPs recommendations with rationale for labeling recommendations on the first and second list pathogens pertinent to Section 12.4 “Microbiology of the sulopenem (ORLYNVAH)” PI:

First List / Indicated Pathogens for the uUTI Indication

Sulopenem has been shown to be active against most isolates of the following gram-negative pathogens, both in vitro and in clinical infections. Therefore, we agree to the Applicant’s proposed 1st list of indicated gram-negative uUTI pathogens:

Aerobic Gram-Negative acteria

(b) (4)

- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Proteus mirabilis*

We recommend deleting

(b) (4)

Second List/ in vitro Pathogens Associated With the uUTI Indication

The inclusion of pathogens in the second list has been modified based on relevance to the uUTI indication and having in vitro MIC90 values for sulopenem less than or equal to the FDA recommended susceptible breakpoint (≤ 0.25 mcg/mL) against isolates of similar genus or organism group as the proposed indicated pathogens. We agree to include the following pathogens in the 2nd list for the uUTI indication:

Aerobic Gram-Negative Bacteria

- *Citrobacter freundii*
- *Citrobacter koseri*
- *Enterobacter cloacae* species Complex

- *Klebsiella aerogenes*
- *Klebsiella oxytoca*
- *Proteus vulgaris*
- *Providencia alcalifaciens*
- *Providencia stuartii*

Aerobic Gram-Positive Bacteria

- *Staphylococcus saprophyticus*
- *Streptococcus agalactiae*

Agency’s MIC STIC/BPs Recommendations With Rationales

The Applicant’s proposed broth microdilution MIC BPs were revised for accuracy and clarity. The Agency’s recommended sulopenem broth microdilution MIC BPs for the uUTI-indicated three Enterobacterales species are listed in [Table 119](#).

Table 119. Agency-Recommended Broth Microdilution (MIC) Interpretive Criteria (BPs) for Sulopenem

Indicated Pathogens	Broth Microdilution Method (MIC)		
	Susceptible (S) mcg/mL	Intermediate (I) mcg/mL	Resistant (R) mcg/mL
<i>Escherichia coli</i>	≤0.25	0.5	≥1.0
<i>Klebsiella pneumoniae</i>	≤0.25	0.5	≥1.0
<i>Proteus mirabilis</i>	≤0.25	0.5	≥1.0

Source: Clinical Microbiology Reviewer’s analysis using data from NDA submission
Abbreviations: BPs, break points; MIC, minimum inhibitory concentration

For setting the MIC BPs for sulopenem against *E. coli*, *K. pneumoniae*, and *P. mirabilis*, the Agency relied on:

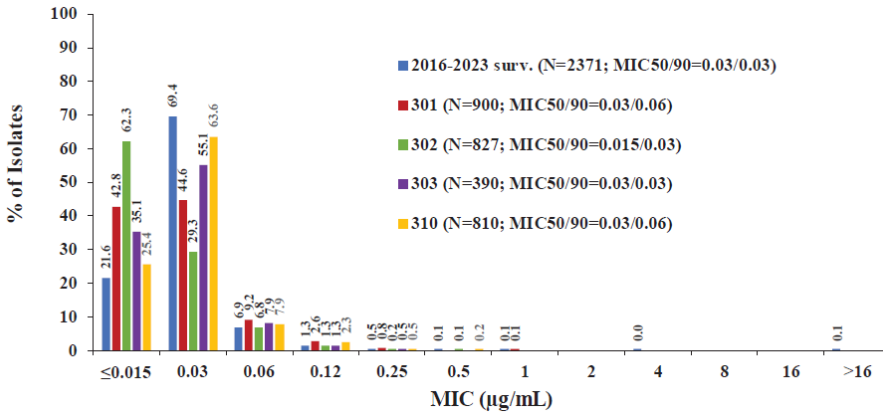
- The overall MIC₉₀ and epidemiological cutoff values (ECV) data from clinical and surveillance study isolates;
- Microbiological eradication rates at each MIC dilution of uUTI clinical study isolates from both uUTI Trials 301 and 310; and
- Of note, the Agency did not consider the Applicant’s PK/PD data since there are general uncertainties with the translatability of PK/PD study results in the setting of uUTI. However, the Agency considered that a sulopenem susceptible BP of 0.25 mcg/mL against Enterobacterales for uUTI seemed to be supported based on the PTA predictions of plasma PK/PD data.
- MIC₉₀ and ECV data – Clinical and Surveillance

The MIC distributions of sulopenem in clinical studies, micro-MITT populations of Trials 301 (uUTI), 302 (cUTI), 303 (cIAI), and 310 (uUTI) and recent surveillance studies (2016-2023 combined) are shown in histograms for uUTI target pathogens *E. coli* ([Figure 17](#)), *K.*

pneumoniae (Figure 18), and *P. mirabilis* (Figure 19). A unimodal distribution was observed for all three pathogens from clinical trials and surveillance isolates.

The MIC₉₀ values against *E. coli* isolates from surveillance and clinical studies were 0.03 and 0.06 mcg/mL, respectively (Figure 17). The ECV was calculated for *E. coli* as 0.0625 mcg/mL (99.9%) against 6,081 isolates from surveillance and clinical studies by using epidemiological cut-off values (ECOFF) finder analysis.

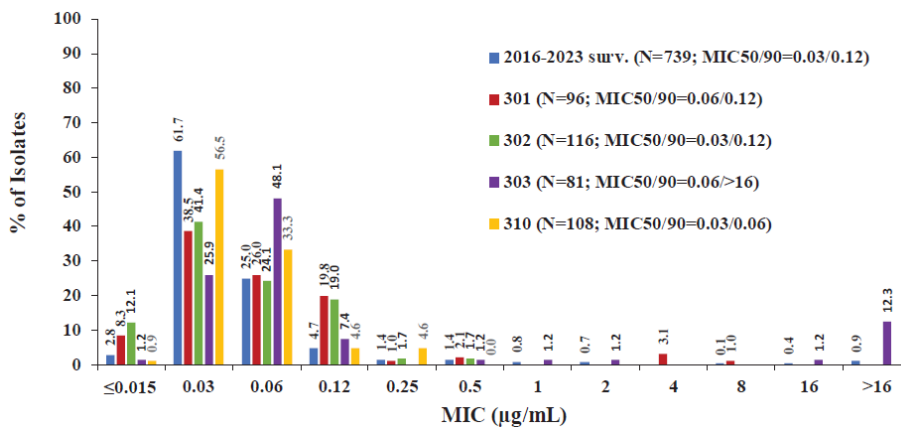
Figure 17. MIC Distribution of Sulopenem for *E. coli* Isolates During Recent Surveillance and Phase 3 Clinical Trials



Source: NDA submission
 Abbreviations: MIC, minimum inhibitory concentration; n, total number of subjects; Surv., surveillance

The MIC₉₀ values against *K. pneumoniae* isolates were 0.12 mcg/mL and 0.06 to 0.12 mcg/mL from surveillance and clinical studies, respectively (Figure 18). The ECV was calculated for *K. pneumoniae* as 0.125 mcg/mL (99.9%) against 1,373 isolates from surveillance and clinical studies by using ECOFF finder analysis (Turnidge et al. 2006).

Figure 18. MIC Distribution of Sulopenem for *K. pneumoniae* Isolates During Recent Surveillance and Phase 3 Clinical Trials

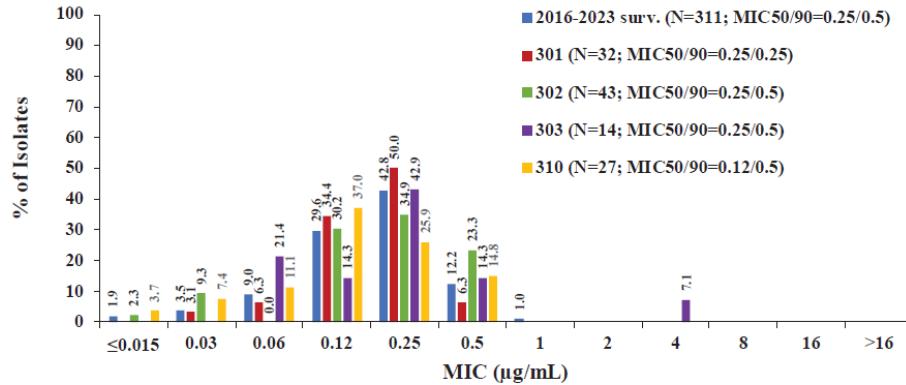


Source: NDA submission
 Abbreviations: MIC, minimum inhibitory concentration; n, total number of subjects; Surv., surveillance

The MIC₉₀ values against *P. mirabilis* isolates from surveillance and clinical studies were 0.5 and 0.25 to 0.5 mcg/mL, respectively (Figure 19). The ECV was calculated for *P. mirabilis* as

0.41 mcg/mL (95.0%), 0.78 mcg/mL (99.5%), and 1.12 mcg/mL (99.5%) against 493 isolates from surveillance and clinical studies by using ECOFF finder analysis ([Turnidge et al. 2006](#)).

Figure 19. MIC Distribution of Sulopenem for *P. mirabilis* Isolates During Recent Surveillance and Phase 3 Clinical Trials



Source: NDA submission

Abbreviations: MIC, minimum inhibitory concentration; n, total number of subjects; Surv, surveillance

Correlation of Microbiological Success to MIC Values of Baseline *E. coli*, *K. pneumoniae*, and *P. mirabilis* Isolates From uUTI Trials 301 and 310

Microbiological success at the TOC visit, in relation to MIC values of total baseline *E. coli*, *K. pneumoniae*, and *P. mirabilis* isolates from the sulopenem treatment group in the micro-MITT population of both uUTI clinical trials (301 and 310), are summarized below:

- Among a total of 876 baseline *E. coli* isolates from Trials 301 and 310, the MIC range was ≤ 0.008 to 1.0 mcg/mL; the MIC₉₀ values against *E. coli* isolates from surveillance and clinical studies were 0.03 and 0.06 mcg/mL, respectively. Overall microbiological eradication/success at TOC was achieved in 661/876 (75.5%) isolates. While the cumulative microbiological success rate of 75.4% (660/875) was achieved up to the highest MIC 0.25 mcg/mL, 5/7 (71.4%) isolates were eradicated at this MIC. No baseline *E. coli* isolates with MIC 0.5 mcg/mL or ≥ 2 mcg/mL were available; only one baseline *E. coli* isolate with sulopenem MIC of 1 mcg/mL was available and eradicated. Therefore, we recommend a susceptible BP of 0.25 mcg/mL as more appropriate to cover most of the *E. coli* population.
- Among a total of 108 baseline *K. pneumoniae* isolates from Trials 301 and 310, the MIC range was 0.015 to 8.0 mcg/mL; the MIC₉₀ values against *K. pneumoniae* isolates were 0.12 mcg/mL and 0.06 to 0.12 mcg/mL from surveillance and clinical studies, respectively. Overall microbiological eradication/success at TOC was achieved in 81/108 (75%) isolates. While the cumulative microbiological success rate of 74.5% (79/106) was achieved up to the highest MIC 0.25 mcg/mL, 1/2 (50%) isolates were eradicated at this MIC. No baseline *K. pneumoniae* isolates with MIC 0.5 and 1.0 mcg/mL were available. However, 2 baseline isolates with MIC 4 mcg/mL and 8 mcg/mL were available and eradicated. Therefore, we recommend a susceptible BP of 0.25 mcg/mL as more appropriate to cover most of the *K. pneumoniae* population.
- Among a total of 31 baseline *P. mirabilis* isolates from Trials 301 and 310, the MIC range was ≤ 0.015 to 0.5 mcg/mL; the MIC₉₀ values against *P. mirabilis* isolates from surveillance and clinical studies were 0.5 and 0.25 to 0.5 mcg/mL, respectively. Overall microbiological

eradication/success at TOC was achieved in 20/31 (64.5%) isolates. While the cumulative microbiological success rate of 67.9% (19/28) was achieved up to the highest MIC 0.25 mcg/mL, 13/14 (92.9%) isolates were eradicated at this MIC. Three baseline *P. mirabilis* isolates with MIC 0.5 mcg/mL were available but only one isolate was eradicated. No baseline *P. mirabilis* isolates with MIC ≥ 1.0 mcg/mL were available. Therefore, we recommend a susceptible BP of 0.25 mcg/mL as more appropriate to cover most of the *P. mirabilis* population.

PK/PD Data and PTA Predictions in Plasma

The lack of an established nonclinical model for uUTIs and uncertainties surrounding: 1) urine specific PK/PD parameters, 2) appropriate bacteriologic endpoint for use in PTA analyses, and 3) the relative importance of plasma versus urine drug concentrations limited the Agency’s reliance on the Applicant’s PK/PD package to support the proposed STIC. Because of concerns with the reliability of the results of the murine thigh infection model PK/PD studies, results of the in vitro PK/PD target determination studies were prioritized in the Agency’s PTA evaluations. PTA analyses showed that the free plasma concentrations associated with the proposed dose regimen resulted in achievement of the in vitro targets in $\geq 90\%$ of simulated subjects up to an MIC 0.25 mcg/mL. In urine, PTA analyses showed achievement of the in vitro targets in $\geq 90\%$ of simulated subjects up to an MIC of 8 mcg/mL. Given the aforementioned knowledge gaps and their implications for the translatability of nonclinical PK/PD findings to clinical efficacy, the Agency prioritized the more conservative findings from plasma-based PTA analysis in support of a sulopenem susceptible BP of 0.25 mcg/mL against Enterobacterales.

In summary, the FDA review team recommends sulopenem Susceptible (S)/Intermediate (I)/Resistant (R) MIC BPs of $\leq 0.25/0.5/\geq 1.0$ mcg/mL against Enterobacterales (*E. coli*, *K. pneumoniae*, and *P. mirabilis* only) that are $\geq$ (b) (4) than the Applicant’s proposed S/I/R BPs of (b) (4) mcg/mL.

The corresponding disk diffusion zone diameter BPs have been calculated by following CLSI error rate criteria. The Agency-recommended broth microdilution (MIC) and disk diffusion interpretive criteria (BPs) for sulopenem are summarized in [Table 120](#).

Table 120. Agency-Recommended Broth Microdilution (MIC) and Disk Diffusion Interpretive Criteria (BPs) for Sulopenem

Indicated Pathogens	Broth Microdilution Method (MIC)			Disk Diffusion Method Zone Diameter		
	Susceptible (S) mcg/mL	Intermediate (I) mcg/mL	Resistant (R) mcg/mL	Susceptible (S) mm	Intermediate (I) mm	Resistant (R) mm
<i>E. coli</i>	≤ 0.25	0.5	≥ 1.0	≥ 19	16-18	≤ 15
<i>K. pneumoniae</i>	≤ 0.25	0.5	≥ 1.0	≥ 19	16-18	≤ 15
<i>P. mirabilis</i>	≤ 0.25	0.5	≥ 1.0	≥ 19	16-18	≤ 15

Source: Clinical Microbiology Reviewer’s analysis using data from NDA submission
 Abbreviation: BPs, break points; MIC, minimum inhibitory concentration

Broth MIC versus Disk Zone Diameter Correlation and Error-Rate Bounding Analysis

The scatterplot analysis was done using the Error-rate bounding method in accordance with CLSI M23 guideline ([Table 121](#)).

Table 121. Acceptable Error Rates in Interpretation Between Test Methods (CLSI M23)

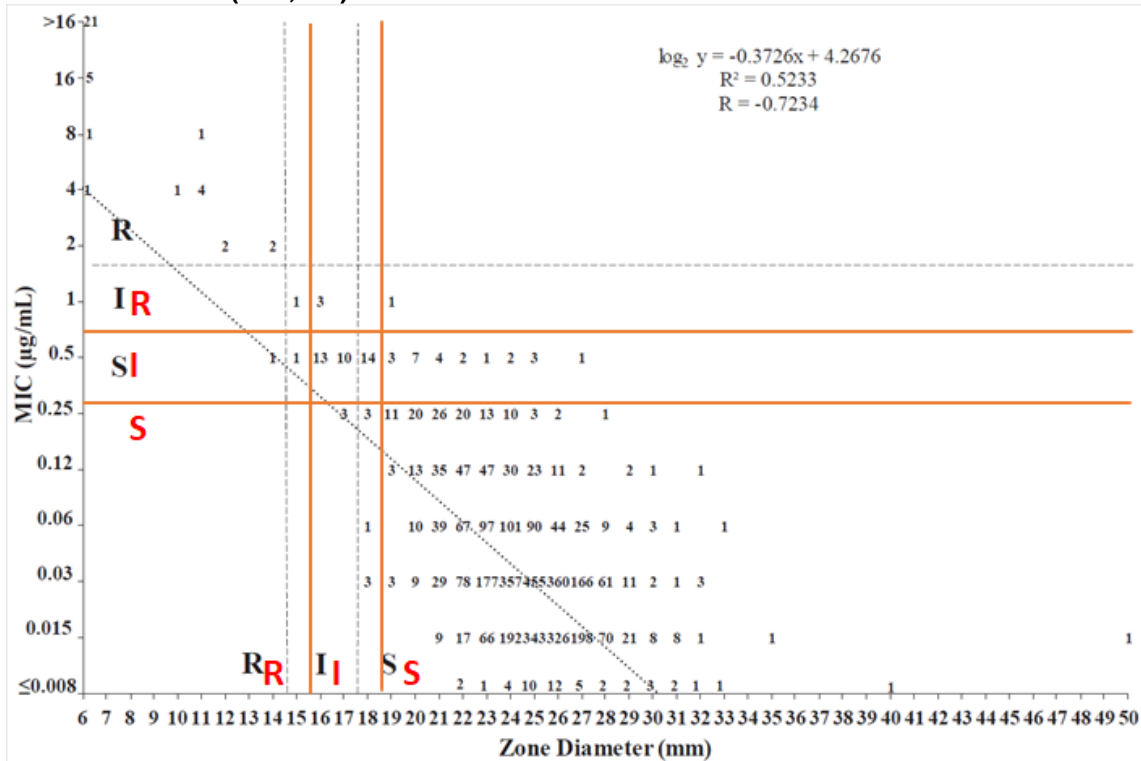
Discrepancy Rates			
I-dilution Intermediate Range	Very Major	Major	Minor
≥ I+2	< 2%	NA	< 5%
I+1 to I-1	< 10%	< 10%	< 40%
≤ I-2	NA	< 2%	< 5%

Source: CLSI M23-A3
 Abbreviations: CLSI, Clinical and Laboratory Standards Institute; I, intermediate; NA, not applicable

The broth microdilution MIC and disk zone correlation are shown by scatterplot for Enterobacteriales (Figure 20/Table 122) and the primary pathogens *E. coli* (Figure 21/Table 123), *K. pneumoniae* (Figure 22/Table 124), and *P. mirabilis* (Figure 23/

Table 125). A reanalysis was conducted for all scatterplots using the Agency recommended MIC BPs for sulopenem (S/I/R of 0.25/0.5/1 mcg/mL). According to the reanalysis, the Agency recommends sulopenem disk interpretive criteria of ≥19 mm susceptible, 16-18 mm intermediate, and ≤15 mm resistant.

Figure 20. Correlation Between Sulopenem Broth MIC Values and Disk Diffusion for Overall Enterobacteriales (N=3,946)



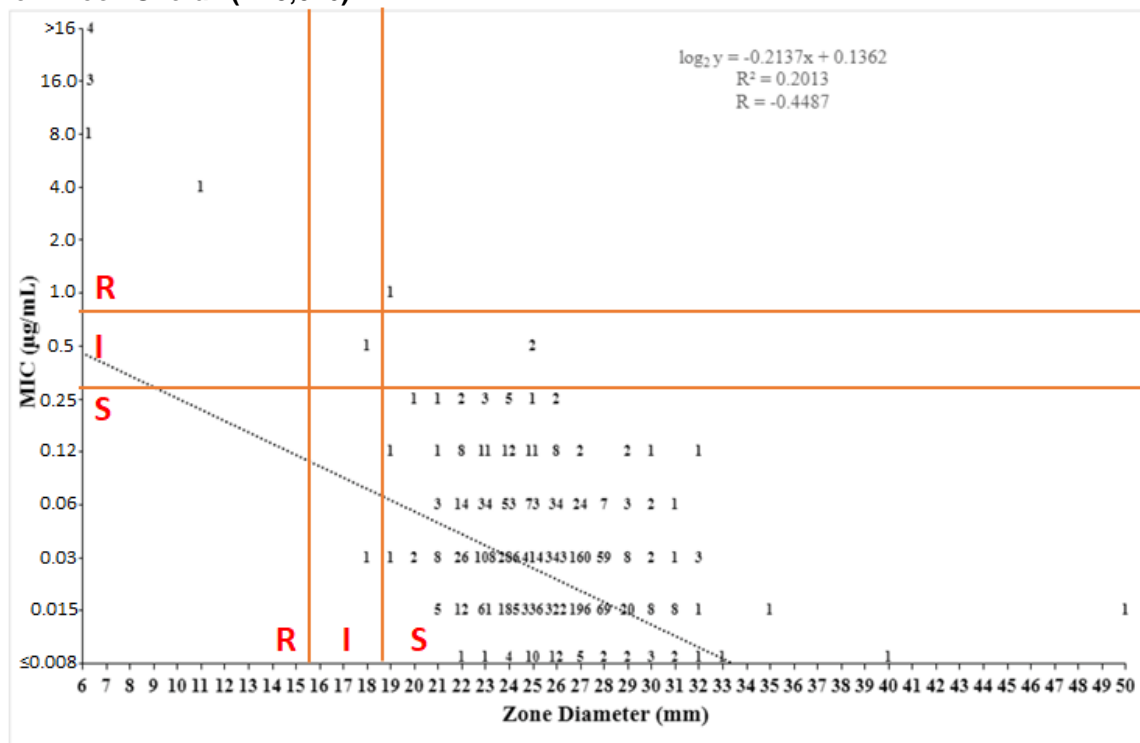
Source: Clinical Microbiology Reviewer's analysis using data from NDA submission
 Abbreviations: MIC, minimum inhibitory concentration

Table 122. Scatterplot Analysis of Broth Microdilution (MIC) and Disk Zone Correlation for Enterobacteriales (N=3,946)

MIC range	N	Discrepancy Rates					
		Very Major		Major		Minor	
		n	(%)	n	(%)	n	(%)
>I+2	38	0	0	NA	NA	0	0
I+1 to I-1	179	1	0.6	0	0	29	16.2
<I-2	3729	NA	NA	0	0	4	0.1
TOTAL	3946	1	0.03	0	0	33	0.8

Source: Clinical Microbiology Reviewer's analysis using data from NDA submission
 Abbreviations: MIC, minimum inhibitory concentration; N, total number; n, number

Figure 21. Correlation Between Sulopenem Broth (MIC) Values and Disk Diffusion Zone Diameters for *E. coli* Overall (N=3,026)



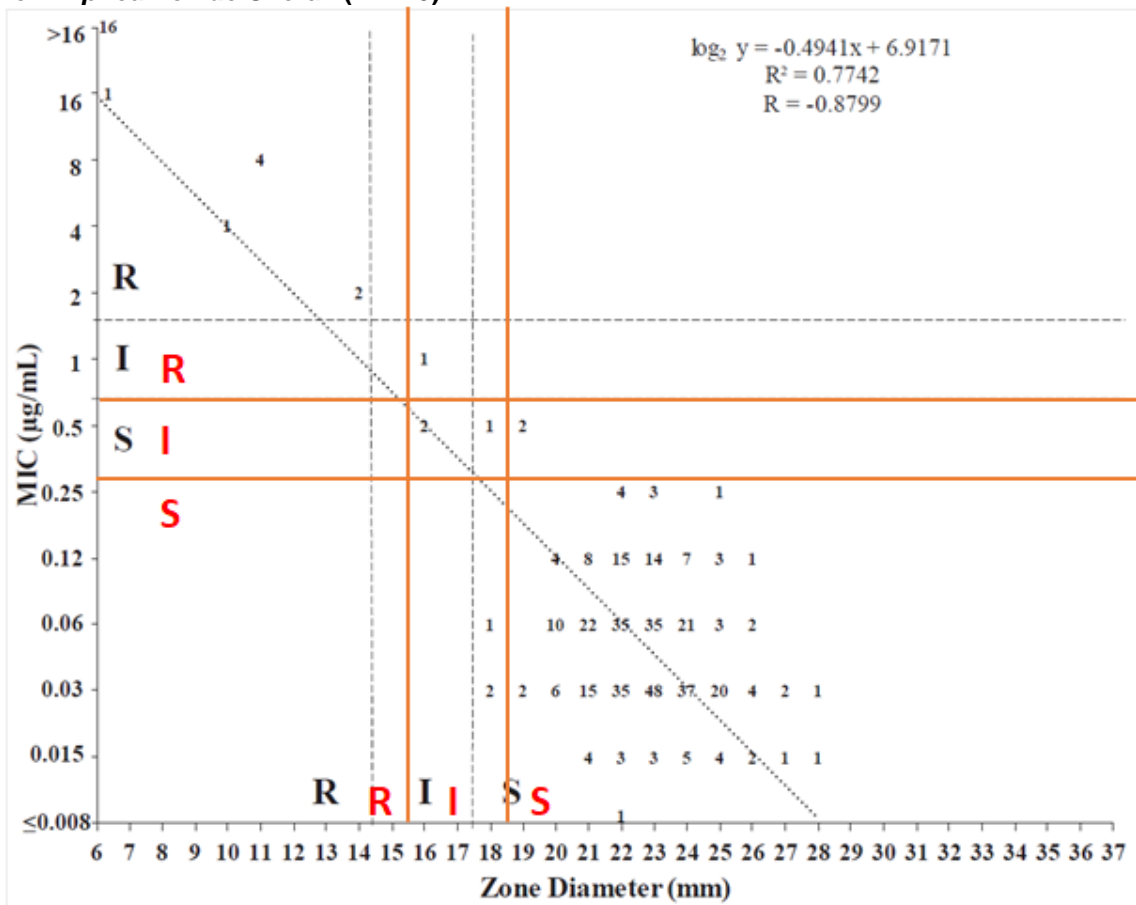
Source: Clinical Microbiology Reviewer's analysis using data from NDA submission
 Abbreviations: MIC, minimum inhibitory concentration; N, total number

Table 123. Scatterplot Analysis of Broth Microdilution (MIC) and Disk Zone Correlation for *E. coli* (N=3,026)

MIC range	N	Discrepancy Rates					
		Very Major		Major		Minor	
		n	(%)	n	(%)	n	(%)
>I+2	9	0	0	NA	NA	0	0
I+1 to I-1	19	1	5.3	0	0	0	0
<I-2	2998	NA	NA	0	0	1	0.03
TOTAL	3026	1	0.03	0	0	1	0.03

Source: Clinical Microbiology Reviewer's analysis using data from NDA submission
 Abbreviations: MIC, minimum inhibitory concentration; N, total number; n, number

Figure 22. Correlation Between Sulopenem Broth (MIC) Values and Disk Diffusion Zone Diameters for *K. pneumoniae* Overall (N=415)



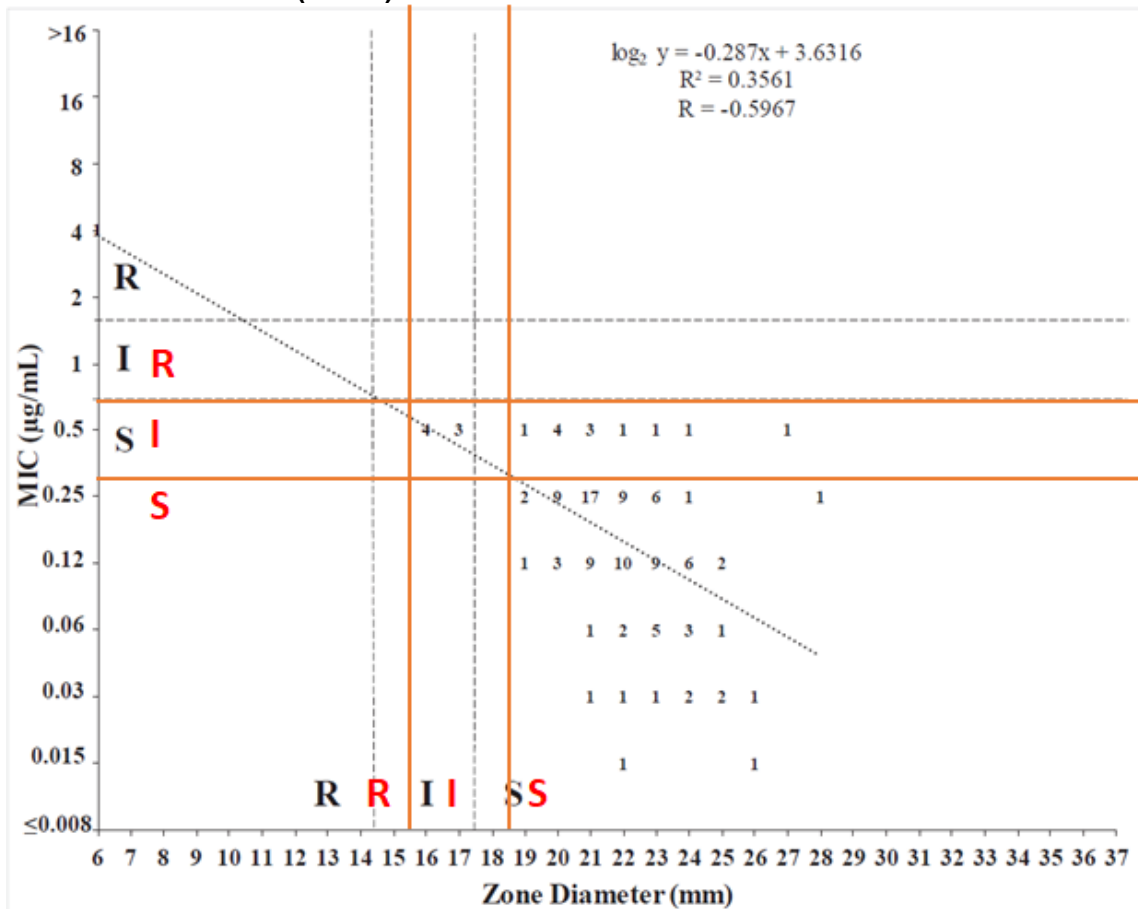
Source: Clinical Microbiology Reviewer's analysis using data from NDA submission
 Abbreviations: MIC, minimum inhibitory concentration; N, total number

Table 124. Scatterplot Analysis of Broth Microdilution (MIC) and Disk Zone Correlation for *K. pneumoniae* (N=415)

MIC range	N	Discrepancy Rates					
		Very Major		Major		Minor	
		n	(%)	n	(%)	n	(%)
>I+2	24	0	0	NA	NA	0	0
I+1 to I-1	14	0	0	0	0	3	21.4
<I-2	377	NA	NA	0	0	3	0.8
TOTAL	415	0	0	0	0	6	1.4

Source: Clinical Microbiology Reviewer's analysis using data from NDA submission
 Abbreviations: MIC, minimum inhibitory concentration; N, total number; n, number

Figure 23. Correlation Between Sulopenem Broth (MIC) Values and Disk Diffusion Zone Diameters for *P. mirabilis* Overall (N=127)



Source: Clinical Microbiology Reviewer's analysis using data from NDA submission
 Abbreviations: MIC, minimum inhibitory concentration; N, total number

Table 125. Scatterplot Analysis of Broth Microdilution (MIC) and Disk Zone Correlation for *P. mirabilis* (N=127)

MIC range	N	Discrepancy Rates					
		Very Major		Major		Minor	
		n	(%)	n	(%)	n	(%)
>I+2	1	0	0	NA	NA	0	0
I+1 to I-1	64	0	0	0	0	12	18.8
<I-2	62	NA	NA	0	0	0	0
TOTAL	127	0	0	0	0	12	9.4

Source: Clinical Microbiology Reviewer's analysis using data from NDA submission
 Abbreviations: MIC, minimum inhibitory concentration; N, total number; n, number; NA, not applicable

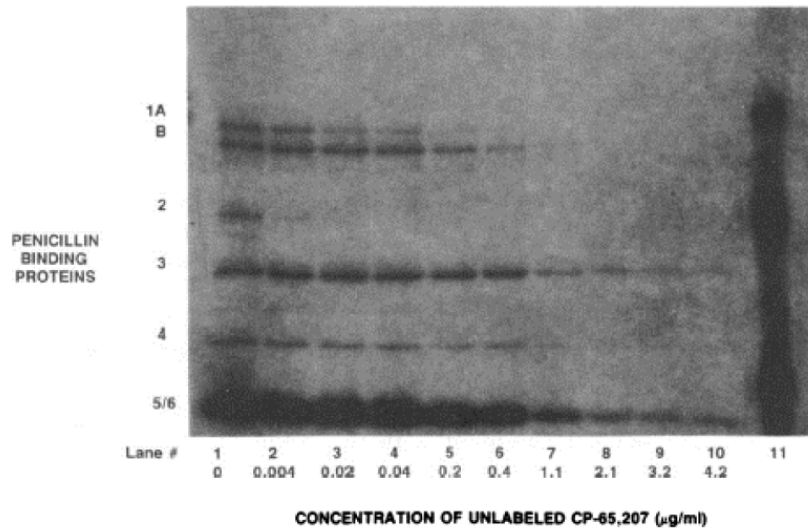
20. Mechanism of Action/Drug Resistance

20.1. Mechanism of Action

Sulopenem is a penem antibacterial drug that inhibits bacterial cell wall synthesis by binding to penicillin-binding proteins (PBPs). A competitive binding assay was conducted with ³H-penicillin in *E. coli* strain W-7 that showed sulopenem (CP-65,207) had the highest affinity for PBP2, with concentrations as low as 0.004 mcg/mL ([Gootz et al. 1989](#)). The assay also showed that the relative order of affinity for PBPs of sulopenem in *E. coli* was PBP2 >PBP1A >PBP1B >PBP4 >PBP3 >PBP5/6. Additionally, it was determined through a hydrolysis study that sulopenem (CP-65207) was highly stable to some cephalosporinases, including plasmid-encoded enzymes TEM-1, SHV-1, and PSE-2.

Similar to other carbapenems, sulopenem showed bactericidal killing by time-kill assay at concentrations $\geq 4X$ the MIC against *E. coli* and *K. pneumoniae*.

Figure 24. Autoradiograph of Competitive Binding of Unlabeled Sulopenem (CP-65,207) vs. ³H-penicillin G for *E. coli* W-7 PBPs



Source: (Gootz et al. 1989) AAC, Figure 3

Lanes 1 through 10, Test system with concentrations of CP-65,207 between 0 and 4.2 pLg/ml; lane 11, radiolabeled molecular weight standards.

Abbreviations: *E. Coli*, *Escherichia coli*; PBP, penicillin-binding proteins

20.2. Drug Resistance

In general, the mechanisms for β -lactam resistance in gram-negative bacteria include the following:

- Hydrolysis by penicillinases, cephalosporinases, oxacillinases and carbapenemases;
- Reduced uptake across the outer membrane due to decreased expression or loss of porin channels;
- Extrusion of drugs by multidrug resistance efflux pumps;
- Mutation of PBP targets (e.g., PBPs).

High-level β -lactam resistance is achieved when multiple mechanisms are combined in a single cell, e.g., production of a carbapenemase in a cell that lacks porin(s) and has overexpressed efflux pumps.

In vitro, development of resistance to sulopenem was evaluated in spontaneous mutation frequency studies using two *E. cloacae* isolates and in serial passage studies using clinical isolates of *E. coli* and *K. pneumoniae*.

In spontaneous mutation frequency studies, sulopenem resistant mutants were selected in vitro at a frequency of 1×10^{-8} with a ≤ 2 -fold MIC increase from the parent *E. cloacae* strain. In the serial passage mutation studies, MIC values increased 16-fold during 15 serial passages in two out of the three tested *E. coli* isolates and were unchanged for the third isolate. MIC values increased 8-fold during serial passage for one of the two *K. pneumoniae* isolates tested, and MIC values increased from 0.5 to 256 mcg/mL for the other isolate.

Similar to other carbapenems, resistance to sulopenem occurs primarily due to enzymatic inactivation by carbapenemases, but also can be caused by β -lactamase production, efflux pump

expression, and changes in porins and/or PBPs ([Papp-Wallace et al. 2011](#); [Harting 2019](#); [Papp-Wallace 2019](#)) Aside from the β -lactam class of antimicrobial drugs, sulopenem is not expected to demonstrate cross-resistance to any other class.

21. Other Drug Development Considerations

Following the complete response of the original NDA application, the Applicant halted development of the IV sulopenem formulation (Please see Sections [3](#) and [8.3](#)).

22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

Please refer to Section [10](#) for a summary of findings from the clinical site inspections. Details of the three clinical site inspections completed by the Office of Scientific Investigations for Trial 310 are presented here. Based on the results of these inspections, Trial 310 (Protocol IT001-310) appears to have been conducted adequately, and the clinical data generated by these clinical sites appear to be reliable in support of this NDA.

The clinical sites were chosen using a risk-based approach primarily based on numbers of enrolled subjects, treatment effect, and prior inspection history. The three sites were Dr. Jodi Sanson (Site 129), Dr. Peyman Banooni (Site 115), and Dr. Moises A. Issa (Site 251).

The inspection results from a Clinical Inspection Summary by Dr. Lee are included below:

1. Jodi L. Sanson, M.D.

Healthstar Research, LLC

661 Airport Road, Suite D

HOT SPRINGS, AK 71913

Inspection Dates: 8/20 – 21, 2024

Protocol IT001-310, Site 129: 27 subjects were screened, all 27 were enrolled, and all 27 completed the study. The study conduct at this clinical investigator site was audited for adherence to the study protocol, institutional review board (IRB) oversight, site monitoring, staff training, study medication disposition, and clinical investigator financial disclosure.

Subject case records were reviewed for all subjects, including detailed review for 15 subjects. The major study data were verified against source records for all enrolled subjects, to include treatment assignment, major efficacy endpoints, AEs, PDs, and use of non-study rescue antibiotics or other concomitant medications.

No significant good clinical practice (GCP) deficiencies or regulatory deviations were observed. Informed consent forms (ICFs) were signed for all subjects. The study records showed complete financial disclosure, adequate AE and PD reporting, and acceptable drug accountability. The primary and the key secondary efficacy and safety endpoint data were verifiable.

2. Peyman Banooni, M.D.

Matrix Clinical Research
1919 West 7th Street
LOS ANGELES, CA 90057

Inspection Dates: July 29, 2024 - August 1, 2024

Protocol IT001-310, Site 115: 41 subjects were screened, 38 were enrolled, and 35 completed the study. The study conduct at this clinical investigator site was audited for adherence to the study protocol, IRB oversight, site monitoring, staff training, study medication disposition, and clinical investigator financial disclosure.

Subject case records were reviewed for all enrolled subjects. The major study data were verified against source records for all enrolled subjects, to include treatment assignment, major efficacy endpoints, AEs, PDs, and use of non-study rescue antibiotics or other concomitant medications.

The observed GCP deficiencies were minor and isolated (typically recordkeeping), of which the most significant example appeared to be not having performed pregnancy testing in one subject because the testing was deemed unnecessary due to the history of a recent miscarriage (potential clinical outcomes and risks discussed).

Significant GCP deficiencies were otherwise not observed. ICFs were signed for all subjects. The study records showed complete financial disclosure, adequate AE and PD reporting, and acceptable drug accountability. The primary and the key secondary efficacy and safety endpoint data were verifiable.

3. Moises A. Issa, M.D.

Zenith Clinical Research
7050 Taft Street
HOLLYWOOD, FL 33024

Inspection Dates: July 29, 2024 – August 2, 2024.

Protocol IT001-310, Site 251: 81 subjects were screened, 77 were enrolled, and 63 completed the study. The study conduct at this clinical investigator site was audited for adherence to the study protocol, IRB oversight, site monitoring, staff training, study medication disposition, and clinical investigator financial disclosure.

Subject case records were reviewed for all subjects, including detailed review for 31 subjects. The major study data were verified against source records for all enrolled subjects, to include treatment assignment, major efficacy endpoints, AEs, PDs, and use of non-study rescue antibiotics or other concomitant medications.

The inspection was noteworthy for documentation of subject selection that appeared to be NOT adequately rigorous, typically for Exclusion Criterion 15 (pregnancy potential). Adequate contraception history and negative pregnancy testing were not consistently documented in as many as one-third (26/77) of the women enrolled.

GCP deficiencies important to study data quality were not observed. ICFs were signed for all subjects. The study records showed complete financial disclosure, adequate AE and PD

reporting, and acceptable drug accountability. The major efficacy and safety endpoint data were verifiable.

Reviewer's [Dr. John Lee's] comment: Specifically, the following GCP deficiencies were observed. All observations appear unlikely to have any impact on the efficacy or safety of the study results.

- *Inclusion Criteria 3 (leukocyte esterase): Six subjects were enrolled based on positive leukocyte esterase urine dipstick testing (LE-UDT) not further specified as 4+ positive (large) LE-UDT.*
- *Exclusion Criteria 15 (pregnancy potential): For all subjects, a negative urine pregnancy test result was obtained, and a screening interview was conducted to verbally confirm (and document) adequate contraception during study participation, but: (1) pregnancy testing was not always obtained within the protocol-specified timeframe, and (2) the specific method of ongoing contraception was often not recorded. All subjects were contacted as needed to retroactively obtain and record the missing information about the specific contraception method. No subject became pregnant during the study.*
- *Exclusion 13 (neutropenia): One subject was enrolled with an absolute neutrophil count (ANC) of $0.99 \times 10^3/\mu\text{L}$, just under (at) the protocol-specified minimum of $1.0 \times 10^3/\mu\text{L}$. Repeat testing (Day 12) confirmed an ANC well above the protocol-specified minimum.*

For further details, please refer to the clinical inspection summary written by Dr. John Lee from Office of Scientific Investigations, dated October 7, 2024, in Document Archiving Reporting and Regulatory Tracking System.

For details regarding inspections conducted for Trial 301, please refer to Section [10](#) of this review and Section 4 of the NDA Multi-Disciplinary Review and Evaluation {NDA 213972} dated July 22, 2021.

23. Labeling: Key Changes

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 April 25, 2024 ([Table 126](#)). The PI was reviewed to ensure that 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.

Based on discussions with the Office of New Drug Policy (ONDP), Regulatory Policy Advisors Team and Labeling Policy Team (email from ONDP dated 9/30/2024), it was noted that due to the specific concerns regarding ORLYNVAH use and possible increase in antimicrobial resistance, ONDP agreed with DAI/OID's position that parts of the language under 21 CFR 201.24 (Labeling for systemic antibacterial drug products) are not appropriate to include in the ORLYNVAH PI. Omission and/or revision of parts of the language under 21 CFR 201.24 seems particularly critical from a public health standpoint for ORLYNVAH given the concerns about inappropriate use of ORLYNVAH (which could lead to drug resistance) and antibacterial drug stewardship. See Table 126 below for descriptions of omissions/revisions made to the language under 21 CFR 201.24 in Section 17 (Patient Counseling Information) and subsections 1.2 (Usage

to Reduce Development of Drug-Resistant Bacteria) and 5.5 (Development of Drug-Resistant Bacteria) of the full prescribing information (FPI). Similar edits were made to the Highlights section of the PI (not shown in Table 126) to align with these edits made to the FPI.

Table 126. 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	Indication statement edited to restrict use of sulopenem based on feedback obtained from the 9/9/2024 Antimicrobial Drugs Advisory Committee (AMDAC) panel regarding the most appropriate use of sulopenem etzadroxil/probenecid: "ORLYNVAH is indicated for the treatment of uncomplicated urinary tract infections (uUTI) caused by the designated microorganisms <i>Escherichia coli</i>, <i>Klebsiella pneumoniae</i>, or <i>Proteus mirabilis</i>, in adult women who have limited or no alternative oral antibacterial treatment options." This revised indication statement was reviewed with the Office of New Drug Policy (ONDP) on 10/1/2024. Concurrence was obtained from ONDP regarding the revised indication statement during a meeting held on 10/16/2024. Deleted "<i>Staphylococcus saprophyticus</i>" as an indicated pathogen due to insufficient microbiological and clinical information. Refer to Section 19.2 of the IA for additional information. Deleted (b) (4) as this is not relevant to this product labeling. Added the following Limitations of Use: "ORLYNVAH is not indicated for the treatment of complicated urinary tract infections (cUTI) or as step-down treatment after intravenous antibacterial treatment of cUTI" and "ORLYNVAH is not indicated for the treatment of complicated intra-abdominal infections (cIAI) or as step-down treatment after intravenous antibacterial treatment of cIAI." These were added to mitigate the risk of off-label use as efficacy of sulopenem etzadroxil/probenecid has not been established for cUTI or cIAI. Refer to Sections 6.2.3, 16.4 and 16.5 of the IA for additional information. The Usage heading was edited from "Usage" to "Usage to Reduce Development of Drug-Resistant Bacteria." In discussion with ONDP, the Usage heading was edited so as not to imply that one could use sulopenem etzadroxil/probenecid for another indication given the strong concerns by AMDAC regarding antibacterial resistance with off-label use and to inform healthcare providers about the restricted indication. Under the "Usage to Reduce Development of Drug-Resistant Bacteria" heading, the following statement in 21 CFR 201.24 (b) regarding prevention and culture and susceptibility information was deleted/revised: 1) "or prevent infections" changed to read as "treat uUTI" 2) deleted "When culture and susceptibility

Full PI Sections ¹	Rationale for Major Changes to Finalized PI ² Compared to Applicant's Draft PI
	information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy." The following text was included: "To reduce the development of drug-resistant bacteria and maintain the effectiveness of ORLYNVAH and other anti-bacterial drugs, ORLYNVAH should be used only to treat uUTI that are proven or strongly suspected to be caused by susceptible bacteria. Culture and susceptibility information should be utilized in selecting or modifying antibacterial therapy [see <i>Warnings and Precautions</i> (5.5)]." These edits were made to remove (b) (4) based on feedback from the AMDAC meeting and were reviewed with ONDP on 10/1/2024. Obtained concurrence from ONDP regarding the final revised usage statement during a meeting held on 10/16/2024.
2 DOSAGE AND ADMINISTRATION	Subsection 2.2 Recommended Dosage in Patients with Renal Impairment: Added recommendation to exclude use of ORLYNVAH in patients with CrCl <15 mL/min and those on hemodialysis. Refer to Section 8.1.2 of the IA for additional details.
4 CONTRAINDICATIONS	Deleted (b) (4) from the hypersensitivity contraindication and specified the contraindication is in patients with a history of hypersensitivity to sulopenem etzadroxil or probenecid or to other beta-lactam antibacterial drugs. (b) (4) Added "patients with known blood dyscrasias" and "patients with known uric acid kidney stones" based on the probenecid PI instead of the Applicant's proposed statement "(b) (4) blood dyscrasias or uric acid kidney stones."
5 WARNINGS AND PRECAUTIONS	Added contraindication of ketorolac based on the ketorolac PI Subsection 5.1 "Hypersensitivity Reactions" was edited to include that cases of angioedema have been reported in patients treated with ORLYNVAH. Added warnings for uric acid kidney stones (subsection 5.3) and exacerbation of gout (subsection 5.4) based on the probenecid PI. Subsection 5.5, the Warning for "Development of Drug-Resistant Bacteria" was edited to reflect the specific indication of ORLYNVAH, i.e., uUTI. The required language for the Warnings and Precautions section for systemic antibacterial drugs under 21 CFR 201.24 was revised, specifically stating susceptible uUTI instead of "bacterial infection" and removing "or a prophylactic indication." These edits were made in consultation with ONDP due to concerns from AMDAC about off-label use of ORLYNVAH and risk of development of penem-resistance in the community and hospital settings leading to difficulty or inability to treat patients with antibacterial drug-resistant infections.

Full PI Sections¹	Rationale for Major Changes to Finalized PI² Compared to Applicant's Draft PI
6 ADVERSE REACTIONS	Added uric acid kidney stones and exacerbation of gout to the list of adverse reactions at the beginning of section 6 Adverse Reactions, described in greater detail in the Warnings and Precautions section. Subsection 6.1 Clinical Trials Experience was edited to present pooled safety data from Trials 301 and 310 given the similarities between the two trials rather than presenting data from each trial separately. Serious adverse reaction frequency and treatment discontinuation frequency were updated to reflect pooled safety data from Trials 301 and 310. Based on the pooled safety data, the following adverse reactions leading to study discontinuation were included: nausea, diarrhea, abdominal pain, gastroesophageal reflux disease, vomiting, and dizziness. Based on the pooled safety data, vulvovaginal mycotic infection and headache were added as adverse reactions occurring at 2% or greater in patients receiving ORLYNVAH. Table 1 was edited to a cutoff of adverse reactions occurring in $\geq 1\%$ from 2% to display a more thorough summary of adverse reactions. Therefore, vulvovaginal mycotic infection, vomiting, and abdominal pain were moved from the paragraph below to the table. Additionally, Table 1 was edited to reflect pooled safety data from Trials 301 and 310. The number of subjects in the safety population were modified to reflect that FDA excluded 13 subjects (8 in the sulopenem arm, 5 in the ciprofloxacin arm) from site 218 of Trial 301. The selected adverse reactions list was updated to be more thorough, including the addition of "elevated transaminases." Adverse reactions not observed in clinical studies of ORLYNVAH that have been observed with probenecid were added from the probenecid PI. Refer to Sections 6.3 and 17 of the IA for additional details on clinical data providing evidence of safety.

Full PI Sections¹	Rationale for Major Changes to Finalized PI² Compared to Applicant's Draft PI
7 DRUG INTERACTIONS	Subsection 7.1 Potential for ORLYNVAH to affect other drugs: Organized drug interactions into a tabular format to improve readability and clarify mitigation strategies. Information on the negative finding from the valproic acid drug-drug interaction study was also added given the observed class effect with other penem antibacterials. Subsection 7.2 Potential for Other Drugs to Affect ORLYNVAH: Added this subsection to describe the potential for OAT3 inhibitors to affect the PK of ORLYNVAH. Subsection 7.3 Drug/Laboratory Interactions: Clarified the type of interference (i.e., with copper sulfate) is the basis for the noted drug/laboratory interaction with urine glucose tests.
8 USE IN SPECIFIC POPULATIONS (e.g., Pregnancy, Lactation, Females and Males of Reproductive Potential, Pediatric Use, Geriatric Use, Renal Impairment, Hepatic Impairment)	Subsection 8.1 Pregnancy: This section was modified to provide additional details regarding effects of sulopenem etzadroxil in pregnant females in embryo-fetal development (EFD) studies in mice, rats, and rabbits. Information about EFD studies in (b) (4) rabbits with intravenous sulopenem was deleted. Also, additional details were added to the description of the pre-postnatal study with sulopenem etzadroxil in rats. Refer to Section 7.4 of this IA and the NDA 213972 Multidisciplinary Review dated July 22, 2021, for additional details. Subsection 8.2 Lactation: This subsection was modified to include information about human and animal data regarding the presence of sulopenem etzadroxil, sulopenem, and probenecid in lactation milk. Subsection 8.4 Pediatric Use: This subsection was modified to include a brief description of the methods and results of the toxicology study in juvenile rats with sulopenem etzadroxil. Subsection 8.6 Renal Impairment: Revised to streamline the description of findings from the dedicated renal impairment study and recommend against use in patients with CrCl <15 mL/min and patients on hemodialysis due to the lack of PK data in these patients.
9 DRUG ABUSE AND DEPENDENCE	Not applicable.
10 OVERDOSAGE	Deleted the following statement (b) (4)

Full PI Sections¹	Rationale for Major Changes to Finalized PI² Compared to Applicant's Draft PI
12 CLINICAL PHARMACOLOGY	Subsection 12.1 Mechanism of action: Clarified the mechanism of action for probenecid and sulopenem etzadroxil. Subsection 12.2 Pharmacodynamics: Clarified the PK/PD index found to best correlate with sulopenem's activity. Subsection 12.3 Pharmacokinetics: Extensive revisions were made throughout this subsection to streamline contents, improve readability and align the format with the FDA Guidance, Clinical Pharmacology for Human Prescription Drug and Biological Products.
13 NONCLINICAL TOXICOLOGY	Subsection 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility: The paragraphs describing genetic toxicity testing for sulopenem etzadroxil, sulopenem, and probenecid under <u>Mutagenesis</u> were modified to include additional details. Information about (b) (4) was deleted. Additional details were added to the description of fertility testing with sulopenem etzadroxil and probenecid. Subsection 13.2 Animal Toxicology and/or Pharmacology: This section was modified to add more details about positive Coomb's results and reductions in red cell counts in the 1-month toxicology study with oral sulopenem etzadroxil in monkeys. (b) (4)
14 CLINICAL STUDIES	Trial 310 was designated as Trial 1, and Trial 301 was designated at Trial 2. The analysis population for Trial 301 was changed to include Site 202 and use the definitions for the analysis population and microbiologic response from the original Statistical Analysis Plan finalized before the unblinded interim analysis. Results were removed for the micro-MITT populations for Trial 301 and Trial 310. (b) (4)

Full PI Sections ¹	Rationale for Major Changes to Finalized PI ² Compared to Applicant's Draft PI
	Subgroup results defined by baseline pathogen were changed to show overall (clinical and microbiological) response (b) (4) for Trial 301 and Trial 310 because this was the primary endpoint in each trial. Sections describing Trial 302 and Trial 303 were added to provide information on the Limitations of Use for cUTI and cIAI that were added to the Indications and Usage section of the PI. The tables were re-configured to add Composite Response and its components (clinical and microbiological response) Refer to Sections 6 and 16 of the IA for additional details on clinical data providing evidence of efficacy.
17 PATIENT COUNSELING INFORMATION	The paragraph on “antibacterial resistance” was modified to emphasize sulopenem’s recommended use (b) (4) who are proven or highly suspected to have a susceptible uUTI. Specifically, the term “bacterial infections” was changed to “proven or strongly suspected susceptible uUTI.” This change from required language (21 CFR 201.24(d)) was reviewed with ONDP and recommended given the AMDAC concerns regarding inappropriate use of ORLYNVAH leading to drug resistance. The required language could be misleading as ORLYNVAH is not indicated for “bacterial infections” but only for a specific subset of patients with uUTI. In addition, “antibacterial drugs” was changed to “ORLYNVAH” in the first sentence and “the medication” was changed to “ORLYNVAH” in the fifth sentence of the required language in 21 CFR 201.24 (d).
Product Quality Sections (i.e., DOSAGE FORMS AND STRENGTHS, DESCRIPTION, HOW SUPPLIED/STORAGE AND HANDLING)	In Subsection 16.1 How Supplied, the description of the drug product was reworded for clarity and accuracy to “<i>ORLYNVAH tablets are supplied as pink, oval-shaped, film-coated, fixed-dose, bilayer combination tablets debossed with SULO on one side and plain on the other side, containing 500 mg of sulopenem etzadroxil and 500 mg of probenecid.</i>”

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): AMDAC, Antimicrobial Drugs Advisory Committee; CFR, Code of Federal Regulations; cIAI, complicated intra-abdominal infections; CrCl, creatinine clearance; cUTI, complicated urinary tract infections; EFD, embryo-fetal development; FDA, Food and Drug Administration; OAT, organic anion transporter; ONDP, Office of New Drugs Policy; PI, Prescribing Information; PK, pharmacokinetics; PK/PD, pharmacokinetic/pharmacodynamic; uUTI, uncomplicated urinary tract infections

23.1. Approved Labeling Types

Upon approval of this application, the following labeling documents will be FDA-approved:

- Prescribing Information (PI)
- Carton Labeling for 10 tablets
- Carton Labeling for 30 tablets

- Container Label for 10 tablets
- Container Label for 30 tablets

24. Postmarketing Requirements and Commitments

Postmarketing Requirements

Required Pediatric Assessments

- Conduct an open label, single-dose study to evaluate the pharmacokinetics, safety, and tolerability of sulopenem etzadroxil/probenecid in pediatric patients aged 12 years to less than 18 years with bacterial infection and receiving background antibacterial therapy.

Draft Protocol Submission: 12/2024
Final Protocol Submission: 03/2025
Study Completion: 06/2026
Final Report Submission: 12/2026

- Conduct an open label, single-dose study to evaluate the pharmacokinetics, safety, and tolerability of sulopenem etzadroxil/probenecid in pediatric patients aged 2 years to less than 12 years with bacterial infection and receiving background antibacterial therapy.

Draft Protocol Submission: 03/2027
Final Protocol Submission: 06/2027
Study Completion: 06/2029
Final Report Submission: 12/2029

- Conduct a randomized, controlled study to evaluate the safety, tolerability, and efficacy of sulopenem etzadroxil/probenecid in pediatric patients aged 2 years to less than 18 years with uncomplicated urinary tract infections (uUTI).

Draft Protocol Submission: 12/2029
Final Protocol Submission: 03/2030
Study Completion: 06/2032
Final Report Submission: 12/2032

PMR Under 505(0):

Conduct a U.S. surveillance study over a five-year period after the introduction of sulopenem etzadroxil/probenecid to the market to determine if resistance or decreased susceptibility to sulopenem etzadroxil/probenecid is occurring in the target population of bacteria identified in the approved sulopenem label.

Draft Protocol Submission: 01/2025
Final Protocol Submission: 05/2025
Interim Report: 08/2026
Interim Report: 08/2027
Interim Report: 08/2028

Interim Report: 08/2029
Study Completion: 06/2030
Final Report Submission: 08/2030

25. Financial Disclosure

Table 127. Covered Clinical Studies, Trial 310

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 171		
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: N/A Significant payments of other sorts: N/A Proprietary interest in the product tested held by investigator: N/A Significant equity interest held by investigator: N/A Sponsor of covered study: N/A		
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): 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Please refer to Table 113 in the NDA Multi-disciplinary Review and Evaluation {NDA 213972} dated July 22, 2021 for financial disclosure related to Trial 301.

26. References

FDA Guidance for Industry *Uncomplicated Urinary Tract Infections: Developing Drugs for Treatment* (August 2019)

Critchley, IA, N Cotroneo, MJ Pucci, and R Mendes, 2019, The burden of antimicrobial resistance among urinary tract isolates of *Escherichia coli* in the United States in 2017, *PLoS One*, 14(12):e0220265.

Dunne, MW, SI Aronin, KC Yu, JA Watts, and V Gupta, 2022, A multicenter analysis of trends in resistance in urinary Enterobacterales isolates from ambulatory patients in the United States: 2011-2020, *BMC Infect Dis*, 22(1):194.

NDA 213972

ORLYNVAH (sulopenem etzadroxil/probenecid)

Gootz, T, J Retsema, A Girard, E Hamanaka, M Anderson, and S Sokolowski, 1989, In vitro activity of CP-65,207, a new penem antimicrobial agent, in comparison with those of other agents, *Antimicrob Agents Chemother*, 33(8):1160-1166.

Gupta, K, TM Hooton, KG Naber, B Wullt, R Colgan, LG Miller, GJ Moran, LE Nicolle, R Raz, AJ Schaeffer, and DE Soper, 2011, International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases, *Clin Infect Dis*, 52(5):e103-120.

Harting, J, 2019, Carbapenem-resistant Enterobacteriaceae Infections: A Review of Epidemiology and Treatment Options, *The University of Louisville Journal of Respiratory Infections*, 3(1, Article 4).

Hooton, TM, 2012, Clinical practice. Uncomplicated urinary tract infection, *N Engl J Med*, 366(11):1028-1037.

FDA Guidance for Industry *In Vitro Drug Interaction Studies — Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions* (January 2020)

Kaye, KS, V Gupta, A Mulgirigama, AV Joshi, NE Scangarella-Oman, K Yu, G Ye, and FS Mitrani-Gold, 2021, Antimicrobial Resistance Trends in Urine Escherichia coli Isolates From Adult and Adolescent Females in the United States From 2011 to 2019: Rising ESBL Strains and Impact on Patient Management, *Clin Infect Dis*, 73(11):1992-1999.

FDA Guidance for Industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998)

FDA Guidance for Industry *Antibacterial Therapies for Patients With an Unmet Medical Need for the Treatment of Serious Bacterial Diseases – Questions and Answers (Revision 1)* (May 2022)

Medina, M and E Castillo-Pino, 2019, An introduction to the epidemiology and burden of urinary tract infections, *Ther Adv Urol*, 11:1756287219832172.

Papp-Wallace, KM, 2019, The latest advances in β -lactam/ β -lactamase inhibitor combinations for the treatment of Gram-negative bacterial infections, *Expert Opin Pharmacother*, 20(17):2169-2184.

Papp-Wallace, KM, A Endimiani, MA Taracila, and RA Bonomo, 2011, Carbapenems: past, present, and future, *Antimicrob Agents Chemother*, 55(11):4943-4960.

FDA Draft Guidance for Industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (September 2019)

FDA Guidance for Industry *Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (September 2023)

Turnidge, J, G Kahlmeter, and G Kronvall, 2006, Statistical characterisation of bacterial wild-type MIC value distributions and the determination of epidemiological cut-off values, *Clin Microbiol Infect*, 12(5):418-425.

Westfall, PH and A Krishen, 2001, Optimally weighted, fixed sequence and gatekeeper multiple testing procedures, *Journal of Statistical Planning and Inference*, 99(1):25-40.

27. Review Team

Table 128. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory project manager	Sheel Shah
Chief, regulatory project management staff	Gregory DiBernardo
Nonclinical reviewer	James Wild
Nonclinical team leader	Amy Nostrandt
OCP reviewer(s)	Henrietta Abodakpi
OCP team leader(s)	Dakshina Chilukuri, Jiajun Liu
Clinical reviewer	Angela Kopack
Clinical team leader	Ramya Gopinath
Clinical Microbiology Reviewer	Jalal Sheikh
Clinical Microbiology Team Leader	Avery Goodwin
Biometrics reviewer	Xianbin Li
Biometrics team leader	Daniel Rubin
Associate Director for Labeling	Abimbola Adebawale
Cross-discipline team leader	Ramya Gopinath
Safety Regulatory Project Manager	Fariba Izadi
Deputy Director for Safety	Mukil Natarajan
Division director (pharm/tox)	Hanan Ghantous
Division director (regulatory)	Maureen Dillon-Parker
Deputy division director (OCP)	Zhixia Yan Danielsen
Division director (OB)	Lei Nie
Deputy division director (clinical)	Dmitri Iarikov
Division director (clinical)	Peter Kim
Office director (or designated signatory authority)	John Farley

Abbreviations: OB, Office of Biostatistics; OCP, Office of Clinical Pharmacology

Table 129. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Dorota Matecka
OPDP	Syed Qumerunnisa
OSI	Phillip Kronstein & John Lee
OSE	Amy Chung
OSE/DEPI	Ikponmwosa Osaghae & Yan Li
OSE/DMEPA	Valerie Vaugh & Deborah Myers
OSE/DRM	Brad Moriyama & Naomi Boston
OSE/DPV	Maya Beganovic & Rachna Kapoor
Office of Product Quality Team	Janell Artis, Karina Zuch, Katherine Windsor, David Claffey, Dorota Matecka, Akshata Nevrekar, Gaetan Ladouceur, Steve Rhieu, Iwona Weidlich, Nathan Davis, Elsbeth Chikhale, Haodan Yuan

Abbreviations: DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DRISK, Division of Risk Management; OPDP, Office of Prescription Drug Promotion; OPQ, Office of Pharmaceutical Quality; OSE, Office of Surveillance and Epidemiology; OSI, Office of Scientific Investigations

27.1. Reviewer Signatures

Table 27-130 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
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: 10/23/2024 9:05 AM EDT		
		GUID: 2024102313512		

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	Xianbin Li OB DBIV	Sections: 6, 15, 16	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Xianbin Li		Digitally signed by Xianbin Li Date: 10/23/2024 9:05 AM EDT GUID: 2024102313552		

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, 15, 16, 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: 10/23/2024 9:06 AM EDT GUID: 2024102313659		

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: 10/23/2024 9:07 AM EDT		
		GUID: 2024102313755		

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	Jiajun Liu OCP DPM	Sections: 5,6,7,8,14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Jiajun Liu		Digitally signed by Jiajun Liu		
		Date: 10/23/2024 9:09 AM EDT		
		GUID: 202410231396		

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	Henrietta Abodakpi OCP DIDP	Sections: 5, 6, 8, 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Henrietta Abodakpi Digitally signed by Henrietta Abodakpi Date: 10/23/2024 9:10 AM EDT GUID: 20241023131036				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharmacometrics Reviewer Discipline Primary Reviewer	Henrietta Abodakpi OCP DIDP	Sections: 5,6,8,14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Henrietta Abodakpi Digitally signed by Henrietta Abodakpi Date: 10/23/2024 9:11 AM EDT GUID: 20241023131140				

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	Angela Kopack OID DAI	Sections: 1, 2, 3, 4, 7, 8, 10, 11, 12, 15, 16, 17, 21, 22, 23, 24, 25, 26	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Angela Kopack		Digitally signed by Angela Kopack Date: 10/23/2024 9:12 AM EDT GUID: 2024102313123		

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	Henrietta Abodakpi OCP DIDP	Sections: 5,6,8,14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Henrietta Abodakpi		Digitally signed by Henrietta Abodakpi Date: 10/23/2024 9:12 AM EDT GUID: 20241023131235		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharmacometrics Reviewer Discipline Secondary Reviewer	Jiajun Liu OCP DPM	Sections: 5,6,8,14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Jiajun Liu		Digitally signed by Jiajun Liu Date: 10/23/2024 9:21 AM EDT GUID: 2024102313215		

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	Jalal Sheikh OID DAI	Sections: 19, 20	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Jalal Sheikh		Digitally signed by Jalal Sheikh Date: 10/23/2024 9:22 AM EDT GUID: 20241023132228		

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	James Wild 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: James Wild		Digitally signed by James Wild		
		Date: 10/23/2024 9:32 AM EDT GUID: 2024102313324		

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 Secondary Reviewer	Abimbola Adebawale OID DAI	Sections: 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Abimbola Adebawale		Digitally signed by Abimbola Adebawale		
		Date: 10/23/2024 9:34 AM EDT GUID: 20241023133410		

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	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Abimbola Adebowale Digitally signed by Abimbola Adebowale Date: 10/23/2024 9:36 AM EDT GUID: 2024102313363				

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	Sheel Shah ORO DROID	Sections: 1.1	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Sheel Shah Digitally signed by Sheel Shah Date: 10/23/2024 9:45 AM EDT GUID: 20241023134539				

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: 10/23/2024 10:53 AM EDT GUID: 20241023145324				

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: Contributed to sections 5, 6, 8 and 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Dakshina Chilukuri Digitally signed by Dakshina Chilukuri Date: 10/23/2024 11:25 AM EDT GUID: 2024102315256				

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: 1,2,3,4,7,8,10,11,12,15,17,21,22,23,24,25,26	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: 10/23/2024 11:40 AM EDT GUID: 20241023154047		

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	Amy Nostrandt 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: Amy Nostrandt		Digitally signed by Amy Nostrandt Date: 10/23/2024 11:56 AM EDT GUID: 20241023155624		

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	Dorota Matecka OPQAI DPQAIIII	Sections: 9	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	Signing on behalf of OPQ Team
Signature: Dorota Matecka		Digitally signed by Dorota Matecka Date: 10/23/2024 12:02 PM EDT GUID: 2024102316243		

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 Dibernardo Date: 10/23/2024 12:03 PM EDT GUID: 2024102316311		

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	Dorota Matecka OPQAI DPQAIIII	Sections: 9	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	Signing on behalf of OPQ Team
Signature: Dorota Matecka		Digitally signed by Dorota Matecka		
		Date: 10/23/2024 12:04 PM EDT		
		GUID: 202410231645		

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	Zhixia Danielsen OCP DIDP	Sections: 5, 6.1, 8.1, 8.2, 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Zhixia Danielsen		Digitally signed by Zhixia Danielsen		
		Date: 10/23/2024 2:59 PM EDT		
		GUID: 20241023185917		

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 DROID	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 Parker Date: 10/23/2024 3:28 PM EDT GUID: 20241023192849				

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 Tertiary Reviewer	Dmitri Iarikov OID DAI	Sections: 1-23	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: 10/24/2024 7:32 AM EDT GUID: 20241024113252				

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/

RAMYA GOPINATH
10/24/2024 08:11:47 AM

PETER W KIM
10/24/2024 08:51:43 AM

JOHN J FARLEY
10/24/2024 09:11:58 AM

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	NDA
Application Number(s)	213972
Priority or Standard	Priority
Submit Date(s)	November 25, 2020
Received Date(s)	November 25, 2020
PDUFA Goal Date	July 25, 2021
Division/Office	DAI/OID
Review Completion Date	July 9, 2021
Established/Proper Name	Sulopenem etzadroxil/probenecid
Pharmacologic Class	Penem antibacterial drug combined with a renal tubular transport blocking agent
Code Name	PF-03709270/probenecid
Applicant	Iterum Therapeutics
Doseage Form	Tablet (500 mg sulopenem etzadroxil and 500 mg probenecid)
Applicant-Proposed Dosing Regimen	One tablet orally twice daily for 5 days
Applicant Proposed Indication(s)/Population(s)	Adult women ≥ 18 years of age for the treatment of uncomplicated urinary tract infections caused by the designated susceptible microorganisms proven or strongly suspected to be nonsusceptible to a quinolone: <i>Escherichia coli</i> , <i>Klebsiella pneumoniae</i> and <i>Proteus mirabilis</i>
Applicant Proposed SNOMED CT Indication Disease Term for Each Proposed Indication	68566005 Urinary tract infectious disease (disorder)
Recommendation on Regulatory Action	Complete Response

Table of Contents

Table of Tables	5
Table of Figures.....	15
Reviewers of Multi-Disciplinary Review and Evaluation.....	18
Glossary	23
1. Executive Summary.....	25
1.1. Product Introduction.....	25
1.2. Conclusions on the Substantial Evidence of Effectiveness.....	25
1.3. Benefit-Risk Assessment	26
1.4. Patient Experience Data.....	31
2. Therapeutic Context	32
2.1. Analysis of Condition.....	32
2.2. Analysis of Current Treatment Options.....	33
3. Regulatory Background.....	35
3.1. U.S. Regulatory Actions and Marketing History	35
3.2. Summary of Presubmission/Submission Regulatory Activity.....	35
4. Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety.....	36
4.1. Office of Scientific Investigations	36
4.2. Product Quality	39
4.2.1. Comments on Novel Excipients	39
4.2.2. Comments on Impurities/Degradants of Concern.....	40
4.2.3. Comments on Impurities/Degradants of Concern in Probenecid.....	43
4.3. Clinical Microbiology	43
4.3.1. Mechanism of Action.....	43
4.3.2. Antimicrobial Spectrum of Activity.....	43
4.3.3. Resistance	44
4.3.4. Clinical Study.....	44
4.3.5. Breakpoints or Susceptibility Test Interpretive Criteria (STIC) for Sulopenem.....	44
4.4. Devices and Companion Diagnostic Issues.....	46
5. Nonclinical Pharmacology/Toxicology	46
5.1. Executive Summary	46
5.2. Referenced NDAs, BLAs, DMFs.....	49
5.3. Pharmacology.....	49

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

5.4. ADME/PK	51
5.5. Toxicology.....	66
5.5.1. General Toxicology	66
5.5.2. General Toxicology; Additional Studies	70
5.5.3. Genetic Toxicology.....	74
5.5.4. Carcinogenicity	77
5.5.5. Reproductive and Developmental Toxicology	77
5.5.6. Other Toxicology Studies	91
6. Clinical Pharmacology	99
6.1. Executive Summary	99
6.2. Summary of Clinical Pharmacology Assessment	100
6.2.1. Pharmacology and Clinical Pharmacokinetics.....	100
6.2.2. General Dosing and Therapeutic Individualization	100
6.3. Comprehensive Clinical Pharmacology Review	102
6.3.1. General Pharmacology and Pharmacokinetic Characteristics	102
6.3.2. Clinical Pharmacology Questions.....	103
7. Sources of Clinical Data and Review Strategy.....	115
7.1. Table of Clinical Studies.....	115
7.2. Review Strategy.....	118
8. Statistical and Clinical Evaluation.....	118
8.1. Review of Relevant Individual Trials Used To Support Efficacy.....	118
8.1.1. IT001-301 for Treatment of Uncomplicated Urinary Tract Infection.....	118
8.1.2. Study Results.....	128
8.1.3. Assessment of Efficacy Across Trials.....	141
8.1.4. Integrated Assessment of Effectiveness	144
8.2. Review of Safety	144
8.2.1. Safety Review Approach	144
8.2.2. Review of the Safety Database	145
8.2.3. Adequacy of Applicant’s Clinical Safety Assessments.....	148
8.2.4. Safety Results.....	149
8.2.5. Analysis of Submission-Specific Safety Issues.....	165
8.2.6. Clinical Outcome Assessment Analyses Informing Safety/Tolerability	166
8.2.7. Safety Analyses by Demographic Subgroups	166
8.2.8. Specific Safety Studies/Clinical Trials.....	168
8.2.9. Additional Safety Explorations.....	168

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

8.2.10. Safety in the Postmarket Setting	169
8.2.11. Integrated Assessment of Safety	169
8.3. Statistical Issues	170
8.4. Conclusions and Recommendations	171
9. Advisory Committee Meeting and Other External Consultations.....	172
10. Pediatrics	172
11. Labeling Recommendations.....	173
11.1. Prescription Drug Labeling	173
12. Risk Evaluation and Mitigation Strategies	174
13. Postmarketing Requirements and Commitment	174
14. Deputy Division Director (DAI) Comments	175
15. Office Director (OID) Comments.....	175
16. Appendices	175
16.1. References.....	175
16.2. Financial Disclosure	176
16.3. OCP Appendices (Technical Documents Supporting OCP Recommendations).....	178
16.4. Additional Safety Analyses	232
16.5. Clinical Microbiology	240
16.5.1. In Vitro Information.....	240
16.5.2. Animal Infection Model Studies.....	256
16.5.3. Pharmacokinetics/Pharmacodynamics Studies	259
16.5.4. Clinical Study For Sulopenem: uUTI.....	259
16.5.5. Supporting Microbiology Data From Other Phase 3 Studies	281
16.5.6. Applicant's Proposed Interpretive Criteria for Sulopenem: uUTI Target Pathogens.....	287
16.5.7. Recommended BPs for Sulopenem Against Target uUTI Pathogens	287

Table of Tables

Table 1. Summary of Current Treatment Options for uUTI	33
Table 2. Excipient Quantity Per Unit, Maximum Daily Intake and Oral Maximum Potency per Unit Dose	40
Table 3. Nonclinical Qualification of the Specified Impurities in the Sulopenem Etzadroxil Drug Substance	41
Table 4. Nonclinical Qualification of the Specified Impurities in the Sulopenem Etzadroxil Drug Product	42
Table 5. Recommended Broth Microdilution (MIC) and Disk Diffusion Interpretive Criteria (BPs) for Sulopenem.....	46
Table 6. ADME/PK Findings.....	51
Table 7. Mean Toxicokinetic Parameters for CP-70429 in Male Rats After a Single Oral Administration of PF-03709270	51
Table 8. Mean Toxicokinetic Parameters for CP-70429 in Male Monkeys After a Single Oral Administration of PF-03709270.....	52
Table 9. Plasma Metabolites in Sprague-Dawley Rats Following 400 mg/kg Oral Administration of [¹⁴ C]CP-70429	53
Table 10. Plasma Metabolites of PF-03709270 in Sprague-Dawley Rats Following 400 mg/kg Oral Administration of [¹⁴ C]PF-03709270 (Head Label).....	54
Table 11. Plasma Metabolites of PF-03709270 in Sprague-Dawley Rats Following 400 mg/kg Oral Administration of [¹⁴ C]PF-03709270 (Tail Label).....	54
Table 12. Percentage of Plasma Metabolites of CP-70429 in Male and Female Monkeys Following IV Administration of [¹⁴ C]CP-70429	55
Table 13. Toxicokinetic Parameters for CP-70429 in Rats Administered Daily Oral PF-03709270 for 30 Days	57
Table 14. Toxicokinetic Parameters for 2-EBA in Rats Administered Daily Oral PF-03709270 for 30 Days.	57
Table 15. Mean Toxicokinetic Parameters for PF-03709270 in Monkeys After Oral Administration of PF-03709270 for a Single Day	58
Table 16. Mean Toxicokinetic Parameters for CP-70429 in Monkeys After Oral Administration of PF-03709270 for 30 Days.....	59
Table 17. Mean Toxicokinetic Parameters for 2-EBA in Monkeys After Oral Administration of PF-03709270 for 30 Days.....	59
Table 18. Toxicokinetic Parameters for CP-70429 in the 14-Day Combination Toxicology Study in Rats	61

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

Table 19. Toxicokinetic Parameters for 2-EBA in the 14-Day Combination Toxicology Study in Rats	61
Table 20. Toxicokinetic Parameters for Probenecid in the 14-Day Combination Toxicology Study in Rats	61
Table 21. Summary of Mean Toxicokinetic Parameters for CP-70429 in Mice After Administration of Oral PF-03709270	61
Table 22. Summary of Mean Toxicokinetic Parameters for 2-EBA in Mice After Administration of Oral PF-03709270	62
Table 23. Mean Toxicokinetic Parameters for CP-70429 in Pregnant Rats on GD 17 After Oral Administration of PF-03709270	62
Table 24. Mean Toxicokinetic Parameters for 2-EBA in Pregnant Rats on GD 17 After Oral Administration of PF-03709270	62
Table 25. Mean Toxicokinetic Parameters for PF-03709270 on GD 19 in Pregnant Rabbits Administered Oral PF-03709270	62
Table 26. Toxicokinetic Parameters for CP-70429 on GD 19 in Pregnant Rabbits Administered Oral PF-03709270	62
Table 27. Mean Toxicokinetic Parameters for 2-EBA on GD 19 in Pregnant Rabbits Administered Oral PF-03709270	63
Table 28. Summary of Sulopenem Toxicokinetic Parameters in Maternal Plasma Collected and in Pooled Fetal Plasma Collected on GD 21 Following IV Maternal Dosing of Sulopenem in Cohort I	63
Table 29. Sulopenem Concentrations (ng/ml) in Plasma and Milk and Milk to Plasma Ratios for Dams Following Once Daily IV Administration of Sulopenem – LD 14 Collection of Maternal Blood and Lactation Milk	63
Table 30. Summary of Sulopenem Toxicokinetic Parameters in Maternal Plasma Collected and in Pooled Fetal Plasma Collected on GD 21 Following Oral Maternal Dosing of PF-03709270 in Cohort II	64
Table 31. Sulopenem Concentrations (ng/ml) in Plasma and Milk and Milk to Plasma Ratios for Dams Following Once Daily Oral Gavage Administration of PF-03709270 – LD 14 Collection of Maternal Blood and Lactation Milk	64
Table 32. Summary of 2-EBA Toxicokinetic Parameters in Maternal Plasma Collected and in Pooled Fetal Plasma Collected on GD 21 Following Oral Maternal Dosing of PF-03709270 in Cohort II	64
Table 33. Summary of Sulopenem Toxicokinetic Parameters in Juvenile Rat Plasma Following IV Administration of Sulopenem	65
Table 34. Summary of Sulopenem Toxicokinetic Parameters in Juvenile Rat Plasma Following Oral Gavage Administration of PF-03709270	65

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

Table 35. Summary of 2-EBA Toxicokinetic Parameters in Juvenile Rat Plasma Following Oral Gavage Administration of PF-03709270	66
Table 36. Methods for Study No.: 06GR278	67
Table 37. Observations and Results: Changes From Control (Study No.: 06GR278).....	67
Table 38. Methods for Study No.: 06GR263	68
Table 39. Observations and Results: Changes From Control (Study No.: 06GR263).....	69
Table 40. Methods for Study No.: 18IT001-(b) (4)-417503-02	71
Table 41. Observations and Results: Changes From Control (Study No.: 18IT001-(b) (4)-417503-02).....	72
Table 42. Absolute and Relative Kidney Weights for Males on Day 15 in the PF-03709270/Probenecid Combination Toxicology Study.....	73
Table 43. Absolute and Relative Kidney Weights for Females on Day 15 in the PF-03709270/Probenecid Combination Toxicology Study.....	73
Table 44. Methods for Study No.: 08GR017	78
Table 45. Observations and Results (Study No.: 08GR017)	78
Table 46. Methods for Study No.: 09GR119	80
Table 47. Observations and Results (Study No.: 09GR119)	80
Table 48. Summary of Fetal Weights in Study No.: 09GR119	81
Table 49. Methods for Study No.: 08GR040	83
Table 50. Observations and Results (Study No.: 08GR040)	84
Table 51. Methods for Study No.: 08GR037	85
Table 52. Observations and Results (Study No.: 08GR037)	85
Table 53. Methods for Study No.: 18IT001-8383180-02	87
Table 54. Observations and Results (Study No.: 18IT001-8383180-02).....	89
Table 55. Methods for Study No.: 18IT001-8383182-02	92
Table 56. Observations and Results: Changes From Control (Study No.: 18IT001-8383182-02; Cohort I).....	93
Table 57. Sulopenem-Related Effects on Kidney Weights at the End of the Dosing Period.....	94
Table 58. The Incidence and Severity of Sulopenem-Related Histology Findings in the Kidney at the End of the Dosing Period	95
Table 59. The Incidence and Severity of Sulopenem-Related Histology Findings in the Kidney at the End of the Recovery Period	95
Table 60. Observations and Results: Changes From Control (Study No.: 18IT001-8383182-02; Cohort II).....	96

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

Table 61. PF-03709270-Related Effects on Kidney Weights at the End of the Dosing Period.....	97
Table 62. The Incidence and Severity of PF-03709270-Related Histology Findings in the Kidney at the End of the Dosing Period.....	98
Table 63. The Incidence and Severity of PF-03709270-Related Histology Findings in the Kidney at the End of the Recovery Period.....	98
Table 64. Summary of OCP's Recommendations and Comments on Key Issues.....	99
Table 65. Summary of the Pharmacokinetic Properties of Sulopenem.....	100
Table 66. General Pharmacology and Pharmacokinetic Characteristics.....	102
Table 67. Summary of Statistical Analyses for Sulopenem Food Effect for the Bilayer Tablet.....	109
Table 68. Treatment-Emergent Clinically Significant Diarrhea in the Phase 3 uUTI Study 301 by Fed/Fasted Status.....	110
Table 69. Listing of Clinical Trials Relevant to This NDA.....	115
Table 70. Study 301: Microbiological Response Definition From Protocol.....	122
Table 71. Applicant's Revised Definition of Microbiological Response.....	127
Table 72. Study 301: Disposition of Patients by Treatment, ITT Population (Excluding 2 Sites).....	129
Table 73. Study 301: Analysis Populations by Treatment Using the Initial SAP, ITT Population (Including Site 202).....	130
Table 74. Study 301: Demographic and Baseline Characteristics, MMITTR Population (Including Patients From Site 202).....	131
Table 75. Study 301: Pathogens from Urine at Baseline, MMITTR Population (Including Patients From Site 202).....	132
Table 76. Study 301: Concomitant Medication Use in Antibacterial Therapy and Categories with 10 or More Subjects, MMITTR Population (Including Patients From Site 202).....	133
Table 77. Study 301: Medical History in Conditions With 10 or More Patients, MMITTR Population (Including Patients From Site 202).....	133
Table 78. Study 301: Overall Response at TOC Using Revised vs. Original SAP, MMITTR Population.....	135
Table 79. Study 301: Applicant's and FDA's Analysis Overall Response Using Original SAP, Including Site 202, MMITTR Population.....	135
Table 80. Study 301: Clinical Response, Microbiological Response Per Patient, And Microbiological Response Per Selected Pathogen at TOC Using Original SAP, MMITTR Population.....	137

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

Table 81. Analysis of Overall Response by Visit Using the Original SAP, MMITTR Population (Including Patients From Site 202)	137
Table 82. FDA’s Analysis of Overall Response at TOC, Contaminated Urine Culture as Failure in the Definition of Microbiological Success, MMITTR Population	138
Table 83. FDA’s Analysis of Overall Response at TOC Using Complete Eradication as Definition of Microbiological Success, MMITTR Population	138
Table 84. Change in Applicant’s Overall Response Results from Subjects Included in the Interim Analysis, MMITTR Population	139
Table 85. FDA’s Subgroup Analyses of the Overall Response by Age, Race, and Country, MMITTR Population, Including Patients From Site 202	140
Table 86. Study 301: Subgroup Analysis of Overall Response at TOC by Creatinine Clearance, MMITTR Population (Including Patients From Site 202)	140
Table 87. Study 301: Applicant’s Analysis Results - Overall Response at TOC Using the Revised vs. Original SAP, MMITTS Population (Excluding/Including Site 202).....	141
Table 88. Study 302: Overall Response at TOC, MMITT Population	142
Table 89. Study 303: Applicant’s Analysis Primary and Post-Hoc Results - Clinical Response at TOC, MMITT Population	144
Table 90. Safety Database for Sulopenem.....	145
Table 91. Demographic and Other Baseline Patient Characteristics of the Study 301 Safety Population.....	146
Table 92. Demographic and Other Baseline Patient Characteristics of Integrated Phase 3 Safety Population	147
Table 93. Deaths in the Integrated Phase 3 Safety Population.....	149
Table 94. SAEs Occurring in Study 301.....	151
Table 95. SAEs in the Integrated Phase 3 Safety Population by SOC	152
Table 96. SAEs in the SOC of Infections and Infestations in the Integrated Phase 3 Safety Population.....	152
Table 97. TEAEs Leading to Study Drug Discontinuation in Study 301	153
Table 98. Discontinuations Due to Nonserious AEs in Studies 302 and 303.....	154
Table 99. TEAEs by System Organ Class in Study 301	156
Table 100. TEAEs Occurring in >0.5% of Subjects in Either Treatment Arm in Study 301	156
Table 101. TEAEs by System Organ Class in the Integrated Phase 3 Safety Population .	157
Table 102. TEAEs Occurring in >0.5% of Subjects in Either Treatment Arm in the Integrated Phase 3 Safety Population.....	158
Table 103. Peak ALT Elevations in Study 301	160

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

Table 104. ALT Values for Subjects in 301 With Any Postbaseline ALT Elevation >2x ULN	160
Table 105. Peak AST Elevations in Study 301	161
Table 106. Peak ALT Elevations in the Integrated Phase 3 Safety Population	161
Table 107. Peak AST Elevations in the Integrated Phase 3 Safety Population	161
Table 108. Maximum Diarrhea Severity Among Subjects in Study 301	166
Table 109. Duration of Diarrhea Among Subjects in Study 301	166
Table 110. Subjects With At Least One TEAE by Demographic and Other Baseline Patient Characteristics in Study 301	167
Table 111. Subjects With the TEAE of Diarrhea by Demographic and Other Baseline Patient Characteristics in Study 301	167
Table 112. Significant High-Level Labeling Changes (Not Direct Quotations).....	173
Table 113. Covered Clinical Study (Name and/or Number): IT001-301	176
Table 114. Covered Clinical Study (Name and/or Number): IT001-302.....	177
Table 115. Covered Clinical Study (Name and/or Number): IT001-303.....	178
Table 116. Summary of Bioanalytical Method Validation Reports	178
Table 117. Individual Clinical Pharmacology Reports Reviewed.....	183
Table 118. Treatments Received in Cohorts 1 and 2	184
Table 119. Mean ($\pm$ SD) PK Parameters for Sulopenem Following Dosing With PF-03678685 or PF-03709270 (Sulopenem Etzadroxil).....	185
Table 120. Analysis of Dose Proportionality for Dose Range of 400 to 2000 mg.....	185
Table 121. Dosing in Cohort 1 (Single Ascending Dose).....	186
Table 122. Dosing Scheme in Cohorts 2 to 6 (Multiple Ascending Dose)	186
Table 123. Summary of Sulopenem Plasma PK Parameter Values Following Single Oral Dose Administration of Sulopenem Etzadroxil.....	187
Table 124. Summary of Sulopenem Plasma PK Parameter Values Following Multiple Dose Administration With and Without Probenecid	188
Table 125. Treatment Sequence of the Four Cohorts in Study IT001-105.....	189
Table 126. Comparison of Sulopenem Exposures for Subjects With eGFR <90 mL/min to Those With eGFR $\geq$ 90 mL/min in Cohort 1	190
Table 127. Absolute Bioavailability Analysis and Comparison of Plasma Sulopenem PK Parameters for Cohort 1 – Bilayer Tablet (Fasted)	191
Table 128. Absolute Bioavailability Analysis and Comparison of Plasma Sulopenem PK Parameters With Redosing for Cohort 1 – PK Parameter Population – Bilayer Tablet (Fed State).....	192

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

Table 129. Period Effect Analysis of Plasma Sulopenem PK Parameters for Cohort 2 ...	192
Table 130. Effect of Food on Plasma Sulopenem PK Parameters for IV Sulopenem	193
Table 131. Individual Values and Descriptive Statistics of Plasma Probenecid PK Parameters by Cohort	194
Table 132. Mean Cumulative Amount ($\pm$ SD) of Total Radioactivity Excreted in Urine and Feces Independently, as Well as Combined, Following a Single Oral Dose of [¹⁴ C] PF-03709270 in Healthy Male Subjects	195
Table 133. PK Parameters Following Oral Administration of 1000 mg Sulopenem Etzadroxil in Renal Function Groups	201
Table 134. Statistical Analysis of Sulopenem PK Parameters for Primary Study	203
Table 135. Statistical Analysis of Sulopenem PK for Probenecid Sub-Study	203
Table 136. Summary of Treatment Groups for Study IT001-101	205
Table 137. Effect of 500 mg Probenecid on Sulopenem PK Parameters Under Fed Conditions	206
Table 138. Summary of Sulopenem Cumulative Urine PK Parameters Following Administration of Sulopenem Etzadroxil With and Without Probenecid Day 1 (Left) and Day 7 (Right) under Fed Conditions.....	207
Table 139. Effect of Itraconazole on Plasma Sulopenem PK Parameters for Cohort 2...208	
Table 140. Effect of Itraconazole on Plasma Sulopenem PK Parameters for Cohort 3...209	
Table 141. Effect of Sulopenem Etzadroxil Alone on Valproic Acid Plasma PK Parameters.....	211
Table 142. Effect of Sulopenem Etzadroxil/Probenecid Combination on Valproic Acid Plasma PK Parameters	212
Table 143. Drug Administration Schedule for Study Cohorts	212
Table 144. Summary of Statistical Analysis for Administration of Sulopenem Etzadroxil With Gastric pH Modifiers.....	213
Table 145. Sulopenem PK Parameters Following Coadministration of Sulopenem Etzadroxil With Probenecid Doses of 500 mg and 1000 mg	214
Table 146. Sulopenem PK/PD Endpoint Summary of TAMIC Estimates Using q3h, q6h, q12h and q24h Dosage Regimens in Immunocompetent (IC) or Immunosuppressed (IS) Thigh Infection Model.....	218
Table 147. PK/PD Summary – TAMIC Estimates for q6h Regimens of Sulopenem or Meropenem vs. <i>K. Pneumoniae</i> 1116 in an Immunosuppressed Thigh Infection Model.....	219
Table 148. Trials Included in the Population PK Analysis.....	221

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

Table 149. Summary of Baseline Demographic Covariates for Analysis- Phase 1 Studies	223
Table 150. Summary of Baseline Demographic Covariates for Analysis- Phase 3 Studies	224
Table 151. Parameter Estimates (RSE) and Median (95% CI) for the Final Model.....	226
Table 152. Summary of AUC _{0-12h} and Cmax by Study and Route	231
Table 153. TEAEs Occurring in <0.5% of Subjects in Study 301	232
Table 154. TEAEs Occurring in <0.5% of Subjects in the Integrated Phase 3 Safety Population.....	234
Table 155. Strains Used in Uppsala Time-Kill Study and Sulopenem MIC Values.....	241
Table 156. Broth Microdilution MIC Values of Sulopenem and Ertapenem Against Organisms Used in the JMI Time-Kill Study.....	242
Table 157. Summary of the Minimum and Maximum FICI Values Observed During Checkerboard Testing of Sulopenem With a Variety of Agents Against <i>E. Coli</i> and <i>K. Pneumoniae</i>	244
Table 158. MIC50/90 Values (µg/mL) of Sulopenem Against Aerobic Gram-Negative Bacteria – Surveillance.....	247
Table 159. MIC50/90 Values (µg/mL) of Sulopenem Against Aerobic Gram-Positive Bacteria – Surveillance.....	248
Table 160. Types of Carbapenemases Evaluated by Enterobacterales Species.....	251
Table 161. Effect of Divalent Cation Concentration on Sulopenem Activity	252
Table 162. Effect of Test Medium pH on Sulopenem Activity	253
Table 163. Effect of Inoculum Density on Sulopenem Activity	253
Table 164. Effect of Supplementation of Test Medium With Lysed Horse Blood and Incubation in CO ₂ on Sulopenem Activity.....	254
Table 165. Summary of QC Ranges for the Broth Microdilution Testing of Sulopenem Against Aerobes	255
Table 166. Sulopenem and Ertapenem PAE and PA-SME Values Against <i>E. Coli</i> and <i>K. Pneumoniae</i>	256
Table 167. Quantification of Metabolites of Sulopenem-Etzadroxil During Incubation in Human Blood	256
Table 168. Efficacy (PD50 in mg/kg) of Sulopenem, Sulopenem Etzadroxil and Comparators Against Murine Systemic Infections.....	257
Table 169. Efficacy (PD50 in mg/kg) of Sulopenem, Sulopenem-Etzadroxil and Comparators Against Murine Pulmonary Infections.....	258

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

Table 170. Efficacy (ED50 in mg/kg) of Sulopenem, Sulopenem-Etzadroxil and Comparators Against Gerbil Otitis Media	258
Table 171. Summary of Designs for Key Studies in Support of Sulopenem-Etzadroxil NDA.....	259
Table 172. Baseline Pathogens	263
Table 173. Post-Baseline Pathogens	264
Table 174. Monomicrobial and Polymicrobial Infections at Baseline – MMITTR Population.....	264
Table 175. Activity of Sulopenem and Ciprofloxacin Against Baseline Pathogens – MMITTR Population – Sulopenem Treatment Group	265
Table 176. Activity of Sulopenem and Ciprofloxacin Against Baseline Pathogens – MMITTR Population – Ciprofloxacin Treatment Group	265
Table 177. Activity of Sulopenem and Ciprofloxacin Against Baseline Pathogens – MMITTR Population – Both Treatment Groups (Combined)	265
Table 178. Pathogens From Urine at Baseline – MMITTS Population	266
Table 179. Monomicrobial and Polymicrobial Infections at Baseline – MMITTS Population.....	266
Table 180. Activity of Sulopenem and Ciprofloxacin Against Baseline Pathogens – MMITTS Population – Sulopenem Treatment Group	267
Table 181. Activity of Sulopenem and Ciprofloxacin Against Baseline Pathogens – MMITTS Population – Ciprofloxacin Treatment Group	267
Table 182. Activity of Sulopenem and Ciprofloxacin Against Baseline Pathogens – MMITTS Population – Both Treatment Groups	268
Table 183. Pathogens From Urine at Baseline – MMITT Population	269
Table 184. Monomicrobial and Polymicrobial Infections at Baseline – MMITT Population.....	269
Table 185. Activity of Sulopenem and Ciprofloxacin Against Baseline Pathogens – MMITT Population – Sulopenem Treatment Group	270
Table 186. Activity of Sulopenem and Ciprofloxacin Against Baseline Pathogens – MMITT Population – Ciprofloxacin Treatment Group	270
Table 187. Activity of Sulopenem and Ciprofloxacin Against Baseline Pathogens – MMITT Population – Both Treatment Groups	271
Table 188. Summary of Patients in the MMITT Population With PCR Assignment to Study Population Due to Baseline Isolate Discordance of Ciprofloxacin Susceptibility by Culture	272
Table 189. Distribution of Study Uropathogens at Baseline – ITT Population.....	275

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

Table 190. Pathogens From Urine at Baseline – MMITT Population	283
Table 191. Pathogens From Blood at Baseline – MMITT Population.....	284
Table 192. Activity of Sulopenem and Ertapenem Against Baseline Pathogens – Micro- MITT Population – Both Treatment Groups	284
Table 193. Proposed Broth Microdilution and Disk Diffusion Susceptibility Test Criteria for Sulopenem.....	287
Table 194. Recommended Broth Microdilution (MIC) and Disk Diffusion Interpretive Criteria (BPs) for Sulopenem.....	291
Table 195. Acceptable Error Rates in Interpretation Between Test Methods (CLSI M23).....	291

Table of Figures

Figure 1. Mean and Standard Error of Sulopenem in Urine – Study IT001-301.....	108
Figure 2. Change in Bacterial Burden vs. PK/PD Indices for a Strain of <i>K. Pneumoniae</i> ..	114
Figure 3. Liver Test Plot for Subject IT001-302/ (b) (6)	163
Figure 4. Liver Test Plot for Subject IT001-303/ (b) (6)	164
Figure 5. Proposed Metabolic Pathways of PF-03709270 (Sulopenem Etzadroxil) in Humans	197
Figure 6. Mean Plasma Concentration-Time Profiles for [¹⁴ C]Sulopenem Etzadroxil and Sulopenem	197
Figure 7. Study IT001-104 Outline	210
Figure 8. Determination of PK/PD Index of Sulopenem From Dose Fractionation Studies Using <i>S. Pneumoniae</i> in a Murine Thigh Infection Model	216
Figure 9. Scheme of Model Structure of the Final PopPK Model.....	225
Figure 10. Goodness-of-Fit Plots for Final Covariate Model	228
Figure 11. VPC Plots for Final Covariate Model – Phase 3 Studies Only	229
Figure 12. Effect of Covariates Included in the Final PK Model on Sulopenem Exposure	230
Figure 13. ETA of TM -Covariate Plots	230
Figure 14. Autoradiograph of Competitive Binding of Unlabeled CP-65,207 Versus 3HPenicillin G for <i>E. coli</i> W-7 PBPs.....	241
Figure 15. Time-Kill Kinetic Activity for Sulopenem Against <i>E. Coli</i> and <i>K. Pneumoniae</i> Isolates – Uppsala	242
Figure 16. Time-Kill Curves for Sulopenem and Ertapenem Against <i>E. Coli</i> and <i>K. Pneumoniae</i> Isolates – JMI.....	243
Figure 17. Sulopenem MIC Distribution Against FQ-S and FQ-R <i>E. Coli</i>	249
Figure 18. Sulopenem MIC Distribution Against Non-ESBL and ESBL <i>E. Coli</i>	249
Figure 19. Sulopenem MIC Distribution Against Non-ESBL and ESBL <i>K. Pneumoniae</i>	250
Figure 20. Sulopenem MIC Distribution against CSE and CRE <i>K. Pneumoniae</i>	250
Figure 21. Sulopenem MIC Distribution Against Genetically Characterized CRE (N=300)	251
Figure 22. Flow Chart of Microbiology Procedures for the IT001-301 Study: US Sites (Top Figure); Ex-US Sites (Bottom Figure).....	262
Figure 23. Overall Response Per Pathogen for MIC to Sulopenem – MMITT Population – <i>E. coli</i> (N=437).....	275

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

Figure 24. Overall Response Per Pathogen for MIC to Sulopenem – MMITT Population – <i>K. pneumoniae</i> (N=48)	276
Figure 25. Overall Response Per Pathogen for MIC to Sulopenem – MMITT Population – <i>P. mirabilis</i> (N=17)	276
Figure 26. Microbiologic Response Per Pathogen for MIC to Sulopenem – MMITT Population Overall – <i>E. coli</i> (N=437)	277
Figure 27. Microbiologic Response Per Pathogen for MIC to Sulopenem – MMITTS Population – <i>E. coli</i> (N=310).....	278
Figure 28. Microbiologic Response Per Pathogen for MIC to Sulopenem – MMITTR Population – <i>E. coli</i> (N=127).....	278
Figure 29. Microbiologic Response Per Pathogen for MIC to Sulopenem – MMITT Population Overall – <i>K. pneumoniae</i> (N=48).....	279
Figure 30. Microbiologic Response Per Pathogen for MIC to Sulopenem – MMITTS Population – <i>K. pneumoniae</i> (N=36)	279
Figure 31. Microbiologic Response Per Pathogen for MIC to Sulopenem – MMITTR Population – <i>K. pneumoniae</i> (N=12).....	280
Figure 32. Microbiologic Response Per Pathogen for MIC to Sulopenem – MMITT Population Overall – <i>P. mirabilis</i> (N=17)	281
Figure 33. IT001-302 Microbiology Sample Flow Chart	282
Figure 34. Microbiologic Response Per Pathogen From Urine or Blood at TOC for MIC to Sulopenem – MMITT Population, <i>E. coli</i>	285
Figure 35. Microbiologic Response Per Pathogen From Urine or Blood at TOC for MIC to Sulopenem – MMITT Population, <i>K. pneumoniae</i>	286
Figure 36. Microbiologic Response Per Pathogen From Urine or Blood at TOC for MIC to Sulopenem – MMITT Population, <i>P. mirabilis</i>	286
Figure 37. MIC Distribution of Sulopenem for <i>E. Coli</i> Isolates During Recent Surveillance and Phase 3 Clinical Trials.....	288
Figure 38. MIC Distribution of Sulopenem for <i>K. Pneumoniae</i> Isolates During Recent Surveillance and Phase 3 Clinical Trials.....	289
Figure 39. MIC Distribution of Sulopenem for <i>P. Mirabilis</i> Isolates During Recent Surveillance and Phase 3 Clinical Trials.....	289
Figure 40. Correlation Between Sulopenem Broth MIC Values and Disk Diffusion for Overall Enterobacteriales (N=2856)	292
Figure 41. Correlation Between Sulopenem Broth MIC Values and Disk Diffusion Zone Diameters for <i>E. Coli</i> Overall (N=2148)	292
Figure 42. Correlation Between Sulopenem Broth MIC Values and Disk Diffusion Zone Diameters for <i>K. Pneumoniae</i> Overall (N=302)	293

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

Figure 43. Correlation Between Sulopenem Broth MIC Values and Disk Diffusion
Zone Diameters for *P. Mirabilis* Overall (N=89) 294

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NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

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NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

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Glossary

ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the curve
BID	twice daily
BMI	body mass index
BP	breakpoint
CFU	colony forming units
cIAI	complicated intraabdominal infection
CL	clearance
CLcr	clearance creatinine
CLSI	Clinical Laboratory Standard Institute
CRE	carbapenem-resistant Enterobacterales
CRO	Contract Research Organization
cUTI	complicated urinary tract infection
DDI	drug-drug interaction
DMC	data monitoring committee
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EOT	end-of-treatment
F	bioavailability
FDA	Food and Drug Administration
FQ	fluoroquinolone
FV	final visit
GI	gastrointestinal
GLP	good laboratory practice
GOF	goodness of fit
HPLC	high-performance liquid chromatography
ICH	International Conference on Harmonisation
IHMA	International Health Management Associates
IIV	inter individual variability
IND	Investigational New Drug
IP	intraperitoneal
IR	immediate release
ITT	intent to treat
IV	intravenous
LC-MS/MS	liquid chromatography with mass spectrometry
LLOQ	lower limit of quantification

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

MAD	multiple ascending doses
MIC	minimum inhibitory concentration
MITT	modified intent-to-treat
MMITT	microbiological modified intent-to-treat
MMITTR	microbiological modified intent-to-treat resistant
MMITTS	microbiological modified intent-to-treat susceptible
MNPCE	micronucleated polychromatic erythrocytes
(b) (4)	(b) (4)
MTD	maximally tolerated dose
MTT1	mean transit time for first transit chain
NDA	new drug application
NMT	not more than
NOAEL	no observed adverse effect level
OSI	Office of Scientific Investigation
PAE	post-antibiotic effect
PBP	penicillin-binding protein
PCR	polymerase chain reaction
PD	pharmacodynamics
PDUFA	Prescription Drug User Fee Act
PFGE	pulse-field gel electrophoresis
PIB	powder-in-bottle
PK	pharmacokinetics
PO	orally
PopPK	population pharmacokinetics
PPI	proton pump inhibitor
PSAQ	Patient Symptom Assessment Questionnaire
PTA	probability of target attainment
QC	quality control
RSE	relative standard error
SAD	single ascending doses
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
TEAE	treatment emergent adverse event
TOC	test-of-cure
ULN	upper limit of normal
uUTI	uncomplicated urinary tract infection
VPC	visual predictive check
WBC	white blood cell
WGS	whole genome sequencing

1. Executive Summary

1.1. Product Introduction

Sulopenem etzadroxil/probenecid bilayer oral tablet is a fixed-dose combination of a penem antibacterial prodrug (sulopenem etzadroxil) and a renal tubular transport blocking drug (probenecid). The role of probenecid is to increase the systemic exposure of the antibacterial drug, sulopenem. Each tablet contains 500 mg sulopenem etzadroxil and 500 mg probenecid. Sulopenem etzadroxil is a new molecular entity while probenecid was approved in the 1950s. The Applicant's proposed indication is the treatment of adult women ≥ 18 years of age with uncomplicated urinary tract infections (uUTI) caused by designated susceptible microorganisms proven or strongly suspected to be nonsusceptible to a quinolone. The proposed dose is one tablet orally (PO) administered twice daily (BID) for 5 days.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has not provided substantial evidence of effectiveness for sulopenem for the treatment of uUTI. In the prespecified subgroup of subjects with uUTI caused by a ciprofloxacin-nonsusceptible pathogen in Study 301, sulopenem was found to be superior to ciprofloxacin based on the primary endpoint of overall response (clinical response and microbiological response). However, in the prespecified subgroup of subjects with uUTI caused by a ciprofloxacin-susceptible pathogen in Study 301, sulopenem was inferior to ciprofloxacin. As clinicians usually do not obtain urine cultures when treating uUTI, it may be difficult to identify patients who may benefit from therapy with sulopenem. Additionally, in the related indications of complicated urinary tract infections (cUTI) (Study 302) and complicated intraabdominal infections (cIAI) (Study 303), sulopenem was not noninferior to the active comparator based on the primary efficacy endpoints in each trial. Of note, sulopenem was inferior to the active comparator in Study 302. Nonclinical PK/PD data suggest that the Applicant's proposed dose of sulopenem is suboptimal which may provide an explanation for the Phase 3 study results.

In order to provide substantial evidence of effectiveness, the Applicant should conduct at least one additional successful study in uUTI and consider using a different active comparator drug in the study(ies) that is more reflective of currently recommended treatment for uUTI. Additionally, the Agency recommends that the Applicant conduct further investigation to determine the optimal sulopenem dosing regimen for the proposed treatment indication(s).

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

In this NDA, the Applicant seeks approval of sulopenem etzadroxil/probenecid bilayer oral tablet for the treatment of adult women ≥ 18 years of age with uncomplicated urinary tract infections (uUTI) caused by designated susceptible microorganisms proven or strongly suspected to be nonsusceptible to a quinolone. uUTI is a common infection that affects most women at least once in their lives. Although there are many antibacterial drugs approved to treat uUTI, antimicrobial resistance may limit their use in certain patients. In addition, many of the antibacterial drugs available to treat resistant pathogens are only available for intravenous administration while oral therapy is preferred in the treatment of uUTI.

In uUTI Study 301, sulopenem was found to be superior to ciprofloxacin with respect to overall response (clinical response and microbiological response) in the prespecified subgroup of subjects with a ciprofloxacin-nonsusceptible pathogen. Overall response was attained by 77/160 (48%) of sulopenem subjects and 49/149 (33%) of ciprofloxacin subjects with a difference of 15% (95% CI, 4.4% to 26.1%; p-value 0.0062). However, among subjects with a ciprofloxacin-susceptible pathogen, sulopenem was found to be inferior to ciprofloxacin. The overall response was 218/365 (60%) for sulopenem and 296/410 (72%) for ciprofloxacin with a difference of -12.5% (95% CI, -19.1% to -5.9%). Of note, clinicians usually do not obtain urine cultures when treating uUTI. As a result, the role of sulopenem in treating uUTI is unclear and also raises concerns about how to distinguish an appropriate patient population. In addition, in the related indications of complicated urinary tract infections (cUTI) and complicated intraabdominal infections (cIAI), sulopenem was not noninferior to the active comparator based on the primary efficacy endpoints in each trial. Nonclinical PK/PD data suggest that the Applicant's proposed dose of sulopenem is suboptimal which may explain the results of the Phase 3 studies. Overall, there is insufficient evidence to support the findings of benefit for sulopenem in patients with a uUTI caused by a ciprofloxacin-nonsusceptible pathogen.

The primary safety database for this NDA consisted of 825 sulopenem subjects with uUTI from Study 301. This database was supported by the safety findings from the cUTI Study 302 and the cIAI Study 303; a total of 1855 subjects were exposed to sulopenem in the three Phase 3 trials. Taken together, there was an adequate safety database for this NDA. In Study 301, gastrointestinal adverse reactions, including diarrhea, nausea, and abdominal pain, were common among subjects taking oral sulopenem/probenecid. In particular, diarrhea occurred in 12% of sulopenem subjects in Study 301. However, the diarrhea and other GI adverse events were generally mild and not treatment-limiting. Elevations in ALT, generally less than 5x the upper limit of normal, occurred more commonly among sulopenem subjects compared to ciprofloxacin subjects in Study 301. However, there were no cases that met Hy's Law criteria in Study 301. Hypersensitivity reactions, including angioedema involving the face, were noted uncommonly in the studies. The identified safety issues (e.g., hypersensitivity reactions, GI adverse

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

reactions, and elevations in transaminases) can be addressed through labeling and do not preclude approval. Overall, there is an acceptable safety profile for sulopenem/probenecid.

In summary, while the safety profile for sulopenem is acceptable, there is insufficient evidence to support the effectiveness of sulopenem for the treatment of uUTI. In order to provide substantial evidence of effectiveness, the Applicant should conduct at least one additional successful study in uUTI and consider using a different active comparator drug in the study(ies) that is more reflective of currently recommended treatment for uUTI. Additionally, the Agency recommends that the Applicant conduct further investigation to determine the optimal sulopenem dosing regimen for the proposed treatment indication(s).

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• uUTI is an acute infection of the bladder in women with normal anatomy of the urinary tract and is characterized by symptoms of lower abdominal discomfort, dysuria, and urinary frequency. • Progression of the infection to the kidney (pyelonephritis) is uncommon, but if it occurs could necessitate hospitalization. • The most common bacterial cause of uUTI is <i>Escherichia coli</i> (75-95%); other less common pathogens associated with uUTI are <i>Staphylococcus saprophyticus</i>, <i>Klebsiella</i> species, and <i>Proteus</i> species. • uUTIs are common; up to 80 to 90% of women will have at least one uUTI during their life. Risk factors for uUTI include recent sexual intercourse, use of spermicides, and history of prior UTI.	uUTI is a common infection with more than 80% of women experiencing a uUTI at least once in their lives.
Current Treatment Options	• There are many FDA-approved antibacterial drugs for the treatment of uUTI including trimethoprim/sulfamethoxazole, nitrofurantoin, fosfomycin, fluoroquinolones, and cephalosporins. • Some of the available antibacterial drugs have known adverse reactions including hypersensitivity reactions, QT prolongation, tendonitis, and neuropathy.	There are many approved antibacterial drugs available for the treatment of uUTI. Therapy is typically chosen empirically since cultures are not usually obtained. Of note, antibacterial drug resistance may limit treatment options.

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	- The decision of which antibacterial drug to use to treat uUTI is often made empirically as cultures are not usually obtained when treating uUTI. - Antibacterial drug resistance in urinary pathogens has been increasing over time. If a patient is found to have a uUTI caused by a drug-resistant pathogen, clinicians may need to change the chosen treatment. In some cases, an IV drug may be needed which would necessitate placement of an IV catheter and may require hospitalization.	
Benefit	- The efficacy of sulopenem for the treatment of uUTI was only demonstrated in a prespecified subgroup of a single adequate and well-controlled trial (Study 301). - Sulopenem was superior to ciprofloxacin in patients with ciprofloxacin-nonsusceptible pathogens using the primary efficacy endpoint of overall response (clinical response and microbiological response). The overall response was 77/160 (48%) for sulopenem and 49/149 (33%) for ciprofloxacin with a difference of 15% (95% CI, 4.4% to 26.1%; p-value 0.0062). - Among patients with uUTI caused by a ciprofloxacin-susceptible pathogen, sulopenem was not noninferior to ciprofloxacin. The overall response was 218/365 (60%) for sulopenem and 296/410 (72%) for ciprofloxacin with a difference of -12.5% (95% CI, -19.1% to -5.9%). Sulopenem was inferior compared to ciprofloxacin based on the overall response. - In the related indications of cUTI and cIAI, sulopenem was not noninferior to the active comparator based on the primary efficacy endpoints in each trial. - In the cUTI trial (Study 302), sulopenem (IV to oral step down) was inferior compared to the active comparator (IV ertapenem with step down to oral	There is insufficient evidence of benefit for sulopenem for the treatment of uUTI as the only positive result was in the ciprofloxacin-nonsusceptible population. Sulopenem was inferior to ciprofloxacin in the ciprofloxacin-susceptible population of Study 301. In clinical practice, as urine cultures are not routinely obtained for patients with uUTI, the role of sulopenem in treating uUTI is unclear. In addition, there is no supportive evidence of benefit as the cUTI and cIAI trials failed to show that sulopenem was noninferior to the active comparator. The chosen dose of sulopenem may be suboptimal as it was based on $T > MIC$ as the target while nonclinical PK/PD data suggest

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	ciprofloxacin or amoxicillin/clavulanate) based on the primary endpoint of overall response. The overall response was 265/444 (60%) for sulopenem and 296/440 (67%) for the comparator with a difference of -7.6% (95% CI, -13.9, -1.3). • In the cIAI trial (Study 303), sulopenem (IV to oral step down) was not noninferior compared to the active comparator (IV ertapenem with step down to oral ciprofloxacin/metronidazole or amoxicillin/clavulanate) based on the primary endpoint of clinical response. The clinical response was 204/249 (82%) for sulopenem and 233/266 (88%) for the comparator with a difference of -6.0% (95% CI, -12.2, 0.2). • There are inadequate data to support the use of T > MIC in target attainment analyses to justify the dose selection and susceptibility breakpoint determination. • The results of the nonclinical PK/PD studies are not definitive but suggest that sulopenem exhibits concentration-dependent killing against pathogens relevant to uUTI, cUTI, and cIAI.	sulopenem exhibits concentration-dependent killing against uropathogens. If sulopenem's activity against uropathogens is indeed concentration dependent, dosing for the uUTI trial (Study 301) may be suboptimal. Further delineation of the relevant PK/PD driver for sulopenem's activity is needed.
Risk and Risk Management	• The primary safety population consisted of 825 subjects with uUTI from a single Phase 3 trial who received the proposed dosing regimen of sulopenem/probenecid. • Additional safety data were reviewed from Study 302 in cUTI and Study 303 in cIAI which included use of both the IV and oral formulations of sulopenem. A total of 1855 subjects received sulopenem between the three Phase 3 trials. • Hypersensitivity reactions, including angioedema involving the face, were observed in two patients taking oral sulopenem/probenecid.	The three Phase 3 trials in uUTI, cUTI, and cIAI provided an adequate safety database for the currently proposed dosing regimens. The identified safety issues (e.g., angioedema, GI adverse reactions, and elevations in transaminases) do not preclude approval. Overall, there was an acceptable risk profile for sulopenem/probenecid.

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Gastrointestinal adverse reactions, including diarrhea, nausea, and abdominal pain, were common among subjects taking oral sulopenem/probenecid. In particular, diarrhea occurred in 12% of sulopenem subjects. However, the diarrhea and other GI adverse events were generally mild and not treatment-limiting. • Elevations in ALT, generally less than 5x the upper limit of normal, were more common among sulopenem subjects compared to ciprofloxacin subjects in Study 301. There were no cases of Hy's Law in Study 301. One subject in Study 302 met Hy's Law criteria on Day 5, but subsequently had normal liver enzyme tests. • Other nonserious adverse events that occurred uncommonly, but more frequently among sulopenem subjects compared to the comparator subjects include dizziness, rash, abnormal urine odor, and vulvovaginal yeast infection.	Hypersensitivity reactions, gastrointestinal adverse reactions, and elevations in transaminases were noted in the Phase 3 trials. Other nonserious adverse reactions including dizziness, rash, abnormal urine odor, and vulvovaginal yeast infection were also noted in the trials. All these adverse reactions are included in the proposed labeling. Hypersensitivity reaction is also included in the Warnings and Precautions section of the proposed labeling.

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

☒	The patient experience data that were submitted as part of the application include:	Section of review where discussed, if applicable
☒	Clinical outcome assessment (COA) data, such as	
☒	Patient reported outcome (PRO)	8.1.1
☐	Observer reported outcome (ObsRO)	
☐	Clinician reported outcome (ClinRO)	
☐	Performance outcome (PerfO)	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Natural history studies	
☐	Patient preference studies (e.g., submitted studies or scientific publications)	
☐	Other: (Please specify):	
☐	Patient experience data that were not submitted in the application, but were considered in this review:	
☐	Input informed from participation in meetings with patient stakeholders	
☐	Patient-focused drug development or other stakeholder meeting summary reports	
☐	Observational survey studies designed to capture patient experience data	
☐	Other: (Please specify):	
☐	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Uncomplicated urinary tract infections are characterized by local signs and symptoms including lower abdominal discomfort, dysuria, and urinary frequency that is associated with pyuria and a microbial pathogen on urine culture. uUTI, also referred to as acute cystitis, occur in females with normal anatomy of the urinary tract and are not accompanied by systemic signs or symptoms, such as fever greater than 38 degrees Celsius or costovertebral angle pain/tenderness. Urinary tract infections associated with systemic signs or symptoms, such as fever, and those occurring in males are referred to as cUTI.

uUTIs are common in women with normal genitourinary tracts. Up to 80 to 90% of women will have at least one uUTI during their life. Risk factors for uUTI include recent sexual intercourse, use of spermicides, and a history of prior UTI.

The most common bacterial cause of uUTI is *Escherichia coli* (75-95%); other less common pathogens associated with uUTI are *Staphylococcus saprophyticus*, *Klebsiella* species, and *Proteus* species. Rates of antibacterial drug resistance for *E. coli* have been increasing worldwide (see Section 2.2). It is important to note that in clinical practice uUTIs are often diagnosed based on symptoms and, if available, a dipstick urinalysis positive for leukocyte esterase or nitrites; urine culture is not regularly obtained unless there are risk factors for a drug-resistant pathogen.

Although baseline or follow up urine cultures are not usually obtained in the treatment of uUTI, clinicians generally expect that antibacterial drug treatment will result in eradication of the causative pathogen and sterilization of the urine. The goal of treatment in uUTI is to resolve the acute symptoms but also to reduce the risk of infection progression, including the development of pyelonephritis. Persistent bacteriuria following treatment is generally considered treatment failure. In two randomized studies of antibacterial drugs compared to NSAIDs, the rate of pyelonephritis in patients with uUTIs who were not treated with antibacterial drugs was between 2 to 5% compared to 0 to 0.4% in patients treated with antibacterial drugs (Gagyor et al. 2015; Kronenberg et al. 2017).

The association between bacteriuria, even when asymptomatic, and infectious complications has been shown in pregnant women. In studies from the 1960s and 1970s, between 20% to 30% of pregnant women with untreated asymptomatic bacteriuria developed pyelonephritis later in the course of pregnancy (Nicolle 2015). In a more recent study from the Netherlands (Kazemier et al. 2015), pyelonephritis occurred in 2.4% of pregnant women with asymptomatic bacteriuria who were not treated with antibacterial drugs, and in only 0.6% among pregnant women who did not have asymptomatic bacteriuria. Among the patients who were treated for asymptomatic bacteriuria, there were no cases of pyelonephritis. A similar finding is noted in the renal transplant literature. In a study of renal transplant patients from a transplant center in New York (Lee et al. 2013), having ≥ 10 bacterial colony forming units (CFU)/mL in the urine

during the 3 months post-transplant was an independent risk factor for subsequent bacteremia (hazard ratio 2.4, 95% CI 1.2-4.8).

2.2. Analysis of Current Treatment Options

The decision of which antibacterial drug to use to treat uUTI is often made empirically. However, if culture results are available, they are used to guide treatment choice. When making an empiric treatment choice, clinicians need to consider the local rates of antibacterial drug resistance. Determining the local rate of resistant pathogens for uUTI may be challenging as resistance rates obtained from passive surveillance may overestimate resistance as cultures are obtained more often from patients with risk factors for having a resistant pathogen (Ti et al. 2003). Still, passive surveillance from microbiology laboratories can be helpful, especially in detecting changes in resistance patterns. Two studies found that drug-resistant *E. coli* are becoming more common. In a U.S.-based study from 2000 to 2010, rates of *E. coli* resistance from outpatient urine cultures increased for ciprofloxacin (3% to 17%), TMP/SMX (18% to 24%), nitrofurantoin (0.8% to 1.6%), and ceftriaxone (0.2% to 2.3%) (Sanchez et al. 2012). In Olmsted County, Minnesota from 2005 to 2009, the rate of *E. coli* resistance identified from urine cultures increased for ampicillin (39% to 43%; P=.02), cefazolin (4% to 7%; P<.001), trimethoprim-sulfamethoxazole (17% to 25%; P<.001), fluoroquinolones (7% to 16%; P<.001), fluoroquinolone plus trimethoprim-sulfamethoxazole (4% to 10%; P<.001), gentamicin (3% to 7%; P<.001), and extended-spectrum cephalosporins (1% to 3%; P<.001). The rate of nitrofurantoin-resistance did not increase (Swami et al. 2012).

Table 1 below summarizes the currently available treatment options for uUTI. Clinical efficacy for all the listed treatment options are generally high if the pathogen is susceptible to the antibacterial drug. Current treatment guidelines recommend trimethoprim/sulfamethoxazole, nitrofurantoin, or fosfomycin as first-line options for the treatment of uUTI.

Table 1. Summary of Current Treatment Options for uUTI

Product Name	Relevant Indication	Year of Approval	Dosing/ Administration	Important Safety and Tolerability Issues
Nitrofurantoin	Acute uncomplicated urinary tract infection	1953	100 mg PO bid	Pulmonary reactions, hepatotoxicity, neuropathy, hemolytic anemia
Trimethoprim/sulfamethoxazole	Urinary tract infections	1973	1 DS tablet PO bid	Hypersensitivity reactions
Trimethoprim	Uncomplicated urinary tract infections	1980	100 mg PO q 12 hr	Hypersensitivity reactions
Fosfomycin	Uncomplicated urinary tract infections	1996	3 gram sachet, single dose PO	Diarrhea

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

Product Name	Relevant Indication	Year of Approval	Dosing/ Administration	Important Safety and Tolerability Issues
Ciprofloxacin	Acute uncomplicated cystitis	1987	250 mg PO bid x 3 days	Tendinopathy, peripheral neuropathy, CNS adverse reactions, aortic aneurysm, QT prolongation, blood glucose disturbances
Ofloxacin	Uncomplicated cystitis	1990	200 mg PO q 12 hr	Same as ciprofloxacin
Levofloxacin	Uncomplicated UTI	1996	250 mg PO daily x 3 days	Same as ciprofloxacin
Aztreonam	Uncomplicated urinary tract infections	1986	500-1000 IV q 8-12 hr	Hypersensitivity reactions
Amoxicillin/clavulanate	Urinary tract infections	1984	500-875 mg PO q 12 hr or 250-500 mg PO q 8 hr	Hypersensitivity reactions, hepatic dysfunction
Imipenem/cilastatin	Uncomplicated urinary tract infections	1985	500 mg IV q 6 hr	Hypersensitivity reactions, seizures
Cephalexin	Genitourinary tract infections	1971	250 mg PO q 6 hr	Hypersensitivity reactions, seizure potential
Ceftriaxone	Uncomplicated urinary tract infections	1984	1 g IV/IM daily	Hypersensitivity reactions
Ceftazidime	Uncomplicated urinary tract infections	1985	250 mg IV q 12h	Hypersensitivity reactions
Cefuroxime	Uncomplicated urinary tract infections	1987	250 mg PO q 12 hr	Hypersensitivity reactions
Cefixime	Uncomplicated urinary tract infections	1989	400 mg PO daily	Hypersensitivity reactions
Cefpodoxime	Uncomplicated urinary tract infections	1992	100 mg PO q 12 hr x 7 days	Hypersensitivity reactions
Cefepime	Uncomplicated urinary tract infections	1996	0.5-1 g IV q 12 hr	Hypersensitivity reactions, neurotoxicity

Source: Reviewer Table

Abbreviations: bid, twice daily; uUTI, uncomplicated urinary tract infections.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Sulopenem is a new molecular entity and has not been approved in the United States or any other country.

3.2. Summary of Presubmission/Submission Regulatory Activity

The development program was conducted under IND 129834 (intravenous [IV] sulopenem; opened 02 Mar 2016), IND 129849 (sulopenem etzadroxil/probenecid; opened 02 Mar 2016),

(b) (4)
The Division granted sulopenem qualified infectious disease product designation for uUTI, cUTI, and cIAI on 29 Jul 2016 and fast track designation for these same indications on 15 Mar 2019.

The Division and Iterum met in July 2017 to discuss the clinical trial design for Study 301 for the treatment of uUTI. The Division emphasized that the clinical response component of the overall response endpoint (combined clinical and microbiological responses) should be defined as the resolution of all UTI symptoms that were present at baseline. The Division also noted that for a noninferiority trial it is essential that only patients with pathogens susceptible to the comparator (ciprofloxacin) be included in the efficacy analysis. The Sponsor was concerned that excluding patients with a ciprofloxacin-resistant pathogen would remove a significant population from their study. In November 2017, Iterum submitted a proposal for statistical hypothesis testing for the uUTI trial in which there would be two analysis populations, one for subjects with a ciprofloxacin-susceptible pathogen at baseline (microbiological modified intent-to-treat susceptible [MMITTS]) and another for subjects with a ciprofloxacin-nonsusceptible pathogen at baseline (microbiological modified intent-to-treat resistant [MMITTR]). Superiority testing would be used in the MMITTR population while noninferiority testing using a 10% margin would be used in the MMITTS population. The following comment was sent to Iterum in response to this study design.

We agree with the proposed framework for hypothesis testing and interim analysis. Because the analyses in the MMITTS and MMITTR populations can be viewed as answering separate research questions, we agree that it is not necessary to use alpha sharing or hierarchical testing to control the overall Type I error rate for the two primary analyses at the one-sided alpha =0.025 level. However, it is important to note that discordant results in the two primary analyses, for example, if the trial is only able to demonstrate that sulopenem is superior to ciprofloxacin in the MMITTR population, but is not able to demonstrate that sulopenem is noninferior to ciprofloxacin in the MMITTS population can be problematic. We will need to understand the reasons for the discrepant findings. Also, the discordant results may have significant labeling implications, such as, limited use language, limitation of use/warning regarding

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

empiric use. For a clinical condition such as uUTI, where therapy is generally empiric, the utility of a product for which efficacy is not demonstrated in the MMITTS population could be limited.

A pre-NDA meeting was held on 28 Sep 2020. The Division reiterated their concern regarding the discordant results between the MMITTS and MMITTR populations and that the results did not support the use of sulopenem for uUTI caused by ciprofloxacin-susceptible isolates. In addition, the Division noted that there are limitations to exploratory analyses of studies that failed to meet their primary endpoint and that the data from Study 302 could not support a labeled indication for cUTI.

4. Significant Issues From Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations

Routine PDUFA surveillance inspections were conducted for four clinical investigators, Drs. Fernandez, Sorkin-Wells, Rodriguez de la Torre, and Thomas, and the study sponsor, Iterum Therapeutics International, in support of NDA 213972. In addition, combined PDUFA/for-cause inspections were conducted on two clinical investigators, Drs. Oporta and Terrelonge. All of the inspections covered one clinical study, IT001-301.

The source records documenting the overall response criteria (i.e., survival status, concomitant non-study antibacterial therapy, urine culture and susceptibility testing results, and Patient Symptom Assessment Questionnaire [PSAQ] responses) and the investigator's assessment of clinical response (i.e., resolution of pre-therapy signs and symptoms of the index infection and whether additional antibacterial drugs were required) were reviewed and verified against the Applicant's data line listings, with only minor discrepancies noted. The data generated by Site 219 (Dr. Fernandez), Site 103 (Dr. Sorkin- Wells), Site 150 (Dr. Rodriguez de la Torre), and Site 200 (Dr. Thomas) appear acceptable in support of the uUTI indication. However, data reliability concerns were identified during the routine PDUFA inspection of the Applicant as follows:

1. The statistical analysis plan (SAP) was amended after a pre-planned interim analysis conducted by an unblinded statistician. The SAP amendment specifically changed overall response criteria to state that the genus/species and susceptibility profiles of the urinary isolate needed to match [to incorporate results from whole genome sequencing (WGS) and pulse-field gel electrophoresis (PFGE)].
2. WGS and PFGE test results (which were used to place subjects in subgroups of susceptible and resistant populations and to determine overall response) were incorporated after the study was unblinded (i.e., study was unblinded on 19 June 2020; WGS and PFGE were incorporated on 29 June 2020).

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

This is concerning because there was a potential for bias to be introduced into the study results because the Applicant's statisticians and data management staff had prior knowledge of the subjects' treatment assignment and overall response. Despite these concerns, the reanalysis of study data (generated in Protocol IT001-301) as requested by the review division adequately addresses the concerns regarding the changes to the SAP and use of WGS and PFGE results after unblinding of the study.

In addition, the combined PDUFA/for-cause inspections of Drs. Terrelonge (Site 202) and Oporta (Site 218) were conducted to address the Applicant's specific data reliability concerns that they used as a basis to exclude the patient data from these two sites from all efficacy analyses.

Regarding Site 202, the Applicant noted several reasons that they excluded this site: (1) PFGE analysis of some urinary isolates identified from the baseline urine bacterial cultures were either genetically indistinguishable or closely related, (2) that there was a high contamination rate of urine samples, and (3) artificial intelligence software suggested intentional patient non-adherent behavior. Regarding these cited reasons, the inspection found the following.

1. Documentation was available in the subjects' source records for review related to the urine collection, handling, processing, and shipping, and dosing of the study drug. However, it was not possible to confirm whether urine samples sent to the laboratory belonged to the subject identified on the sample. In addition, the inspector attempted to contact 10 subjects and was able to reach 3 of them who confirmed their participation in the study. Overall, it could not be confirmed that urine samples from one subject were used to enroll multiple subjects.
2. There were issues reported during the conduct of the study with the collection, handling, processing, and shipping of the urine samples. For example, numerous samples were allegedly contaminated, urine samples were possibly sent on dry ice instead of at ambient temperature, urinalyses were not run by the central laboratory, and samples were not received by the central laboratory. Based on the microbiology urine culture and susceptibility reports, these issues appear to have started as early as October 2018. The Contract Research Organization (CRO) reviewed the site's laboratory processes and procedures in November and December 2018 and January 2019 and found no deficiencies. In addition, the study monitor noted that the site appeared to have appropriately collected, processed, labeled, and shipped all necessary biospecimen samples in a timely manner to the central laboratories as outlined in the current Covance, (b) (4) and International Health Management Associates (IHMA) study central laboratory manuals. The CRO retrained the site staff on the collection, handling, and processing of urine samples on 12 Dec 2018. Despite the retraining, the issues continued, and the sponsor placed the site on enrollment hold on 4 Apr 2019. The FDA inspector reviewed the standard operating procedures for sample collection and processing and found no issues. The Office of Scientific Investigations (OSI) reviewer noted that the site did not have any formal documentation from the sponsor informing them of their enrollment hold, nor did they have documentation regarding the results of the June 2019 audit, which appears to not

have been communicated or provided to the site. Only the final report of the second audit conducted in October 2019 was communicated and provided to the site, and this report did not address the issue of contaminated urine samples. It also does not appear that the sponsor and CRO conducted a formal root-cause analysis and implemented a sufficient corrective and preventative action plan (other than the re-training that occurred in December 2018 and the subsequent enrollment hold). Based on the lack of a formal root cause analysis of these issues and a lack of a formal letter informing the site of their enrollment hold, it was not clear which issues were the result of problems at the site and which were the result of potential problems at the central laboratory. Most importantly, it should be noted that these reportedly high contamination rates, whatever the cause (site vs. laboratory), would not necessarily justify removing all of the efficacy data from this site from the primary analysis.

3. The Applicant reported to FDA that the dosing of 27 out of 68 subjects was classified with red and/or orange flags by the software (i.e., red flag means strong visual proof of intentional non-adherence behavior and orange flag means intentional non-adherence behavior is highly likely). In an email correspondence to the study site's research coordinator, the Applicant identified 10 subjects for follow-up by the site staff as having their dosing classified as red. Documentation was available in the source records that confirmed that all of these 10 subjects subsequently took the dose that was classified as red by the software after initially spitting the dose out. The reasons noted in the source records for subjects taking the medication out of their mouth included the large size of the dose, the medication made them feel nauseous, and difficulty using the application while at the same time trying to take the medication. The OSI reviewer noted that although many subjects may have initially spit out the medication during the recording of the videos for various reasons, at least 10 of the 27 subjects later confirmed that they took the medication after initially spitting out or removing the dose from their mouth, with the dosing information being well-documented in the source records at the site.

M.O. Comment: There does not appear to be sufficient cause to exclude all data from Site 202. The FDA inspection could not confirm that a single urine sample was used to enrolled multiple subjects at Site 202. In addition, it appears the medication adherence software results may have been misinterpreted as many patients with "red flag" events were well-documented to have taken the dose. Finally, the decision to exclude Site 202 was made late in the analysis of the study which may have allowed the Applicant to know how it could affect the results.

Regarding Site 218, the Applicant informed FDA that they deemed the data from this site unreliable because 13 patients at the site had a positive baseline culture for both *Escherichia coli* and *Klebsiella pneumoniae*, and PFGE analysis showed that all the *Escherichia coli* and *Klebsiella pneumoniae* isolates were either genetically indistinguishable or closely related (1-2 band differences). They also reported that urine leukocyte esterase and nitrite dip stick results differed from central lab results in 10 of the 13 patients. (b) (7)(A)

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

(b) (7)(A) a post hoc sensitivity analysis should be conducted, excluding all the subjects from this site.

M.O. Comment: Given the concerning findings from Site 218, (b) (7)(A) it appears justifiable to exclude this site from the analyses.

4.2. Product Quality

The NDA, as amended, has provided sufficient Chemistry, Manufacturing, and Controls information to assure the identity, strength, purity, and quality of the proposed drug product, sulopenem etzadroxil and probenecid tablets. The drug product is a pink, oval-shaped, film-coated, immediate release, bilayer tablet, containing 500 mg sulopenem etzadroxil and 500 mg probenecid. The drug product formulation contains conventional excipients of compendial grade. The proposed commercial packaging configurations for the drug product include high density polyethylene bottles (10-count and 30-count) and aluminum foil blisters ((b) (4)-count). The stability information submitted in the NDA supports the 24-month expiration dating for the drug product to be stored in the proposed commercial packaging systems at room temperature (20-25°C). Overall, the information provided in the NDA for the drug product (sulopenem etzadroxil and probenecid tablets) and both drug substances (sulopenem etzadroxil and probenecid) was found to be adequate. The manufacturing and testing facilities for this NDA are deemed acceptable and an overall "Approve" recommendation was entered into Panorama by the Office of Pharmaceutical Manufacturing Assessment on May 4, 2021.

The NDA is recommended for approval by the Office of Pharmaceutical Quality. For details, please refer to the Office of Pharmaceutical Quality Integrated Quality Assessment dated June 1, 2021 in DARRTS.

4.2.1. Comments on Novel Excipients

There are no novel excipients. All of the excipients included in the maximum daily intake of two tablets per day have been used in higher amounts in previously approved products (Table 2).

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

Table 2. Excipient Quantity Per Unit, Maximum Daily Intake and Oral Maximum Potency per Unit Dose

Component	Amount per unit (mg/tablet)	Total Daily Intake (mg)	Oral IID Limit Maximum Potency per Unit Dose (mg) ¹
Microcrystalline cellulose			(b) (4)
Lactose monohydrate			
Hydroxypropyl cellulose			
Croscarmellose sodium			
Magnesium stearate			
(b) (4) Components			
Polyvinyl alcohol			
Titanium dioxide			
Talc			
Lecithin (soya)			
Xanthan gum			
Carmines			

¹Inactive Ingredients Database - maximum unit dose for oral dosage route
 Source: Table 3.2.P.1-5 from 3.2.P.1: Description and Composition of the Drug Product
 Abbreviations: IID, inactive ingredient database.

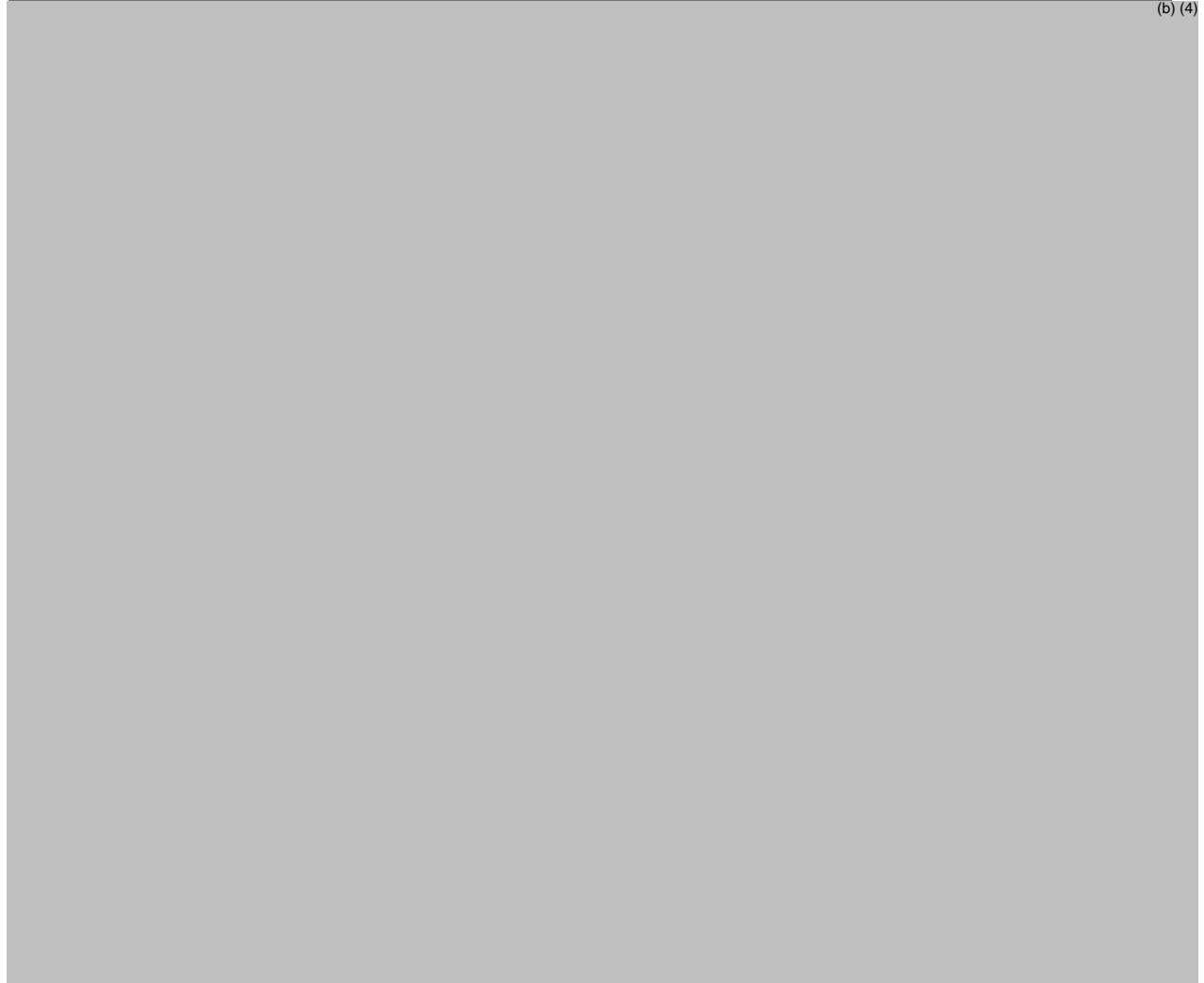
4.2.2. Comments on Impurities/Degradants of Concern

Drug Substance

The impurities in the sulopenem drug substance that exceeded International Conference on Harmonisation (ICH) limits were all adequately qualified for safety in nonclinical toxicology studies (Table 3).

Table 3. Nonclinical Qualification of the Specified Impurities in the Sulopenem Etzadroxil Drug Substance

(b) (4)



Drug Product

The impurities in the sulopenem drug product that exceeded ICH limits were adequately qualified for safety in nonclinical toxicology studies (Table 4).

Table 4. Nonclinical Qualification of the Specified Impurities in the Sulopenem Etzadroxil Drug Product

(b) (4)



Potential Genotoxic Impurities

All the impurities will be controlled at levels that are individually or in combination below the limit of (b) (4) µg/day recommended for drugs with a dosing duration of ≤1 month. There were no potential genotoxic impurities of concern.

Residual Solvents

There were no residual solvents of concern. The residual solvents included in the sulopenem etzadroxil drug substance and their acceptance criteria, are (b) (4) (not more than [NMT] (b) (4) ppm), (b) (4) (NMT (b) (4) ppm), (b) (4) (NMT (b) (4) ppm) and (b) (4) (NMT (b) (4) ppm). The acceptance criteria for (b) (4) are consistent with the recommended levels in the ICH Q3C (R6) Guidance. (b) (4) is controlled at the accepted ICH Q3C(R6) limit for (b) (4) a structurally related compound.

Elemental Impurities

(b) (4) were identified as the only elemental impurities (b) (4) of the sulopenem etzadroxil drug substance. (b) (4) is controlled according to the recommendations in the ICH Q3D (R1) Guidance with a permitted daily exposure limit for (b) (4) of (b) (4) µg/day ((b) (4) ppm for a 1 g oral daily dose of sulopenem etzadroxil). (b) (4) will be controlled at levels of (b) (4) µg/1 gram of sulopenem etzadroxil/day which is much less than the provisional maximum daily intake for (b) (4) mg/kg body weight) established in World Health Organization Guidelines. All other potential elemental impurities were assessed to present a negligible risk of contamination to the drug substance.

4.2.3. Comments on Impurities/Degradants of Concern in Probenecid

All of the impurities in the probenecid drug substance will be adequately controlled according to the specifications for the listed probenecid reference product as described in DMF (b) (4)

4.3. Clinical Microbiology

Microbiological response analyses related to pathogen isolation, identification, and susceptibility testing with standard culture methods are covered in Section 16.5 of this review. A summary of the clinical microbiology review and recommendations is presented below:

4.3.1. Mechanism of Action

Sulopenem, a penem antibacterial drug, inhibits bacterial cell wall synthesis by binding to penicillin-binding proteins (PBPs) resulting in cell death. In *Escherichia coli*, the relative order of affinity towards PBPs was PBP2>PBP1A > PBP1B > PBP4>PBP3>PBP5/6. Similar to other carbapenems, sulopenem showed bactericidal killing by time-kill assay at concentrations ≥4X the minimum inhibitory concentration (MIC) against *E. coli* and *K. pneumoniae*.

4.3.2. Antimicrobial Spectrum of Activity

Sulopenem demonstrates in vitro activity against both aerobic and anaerobic gram-positive and gram-negative bacteria. The in vitro MIC_{50/90} values (inhibits the growth of ≥50% and ≥90% of the isolates) were determined for sulopenem against isolates of relevant pathogens from 3 recent surveillance studies (North American and European isolates) and a single uUTI clinical study (IT001-301). Against *E. coli* isolates, sulopenem had MIC_{50/90} values of 0.03/0.03-0.06 µg/mL; against *K. pneumoniae* isolates, sulopenem had MIC_{50/90} values of 0.03-0.06/0.06-0.12 µg/mL; and against *P. mirabilis* isolates, sulopenem had MIC_{50/90} values of 0.12-0.25/0.25-0.5 µg/mL reported.

4.3.3. Resistance

Sulopenem resistant mutants were selected by conducting in vitro spontaneous mutation frequency studies using two *E. cloacae* isolates at a frequency of 1×10^{-8} with a ≤ 2 -fold MIC. In serial passage mutation studies, MIC values to sulopenem were observed to increase 16-fold during 15 serial passages in two of the three *E. coli* isolates tested and were unchanged for the third isolate. MIC values increased 8-fold during serial passage for one of the two *K. pneumoniae* isolates tested, and MIC values increased from 0.5 to 256 $\mu\text{g/mL}$ for the other isolate. Resistance occurs primarily due to enzymatic inactivation of carbapenems by carbapenemases, but also can be caused by β -lactamase production, efflux pump expression, and changes in porins and/or PBPs. No instance of antagonism was observed in vitro between sulopenem and other routinely used antibacterial drugs against tested *E. coli* and *K. pneumoniae* isolates.

4.3.4. Clinical Study

A single Phase 3 clinical study (IT001-301) was conducted to determine the safety and efficacy of a 5-day course of oral sulopenem etzadroxil/probenecid versus a 3-day course of oral ciprofloxacin (comparator arm) for the treatment of women (≥ 18 years of age) with uUTI. The microbiological modified intent-to-treat (mMITT) population comprised all subjects who had at least one or a maximum of two baseline urinary bacterial pathogen(s) identified from urine with $\geq 10^5$ CFU/mL. Bacterial urinary pathogens were identified from microbiological culture of acceptable urine specimens collected at baseline, and subsequent visits.

In the mMITT population, uUTIs were predominantly caused by *E. coli* (56.0% in sulopenem treatment group and 58.4% in ciprofloxacin treatment group), *K. pneumoniae* (6.5% in sulopenem treatment group and 6.0% in ciprofloxacin treatment group), and *P. mirabilis* (2.2% in sulopenem treatment group and 2.1% in ciprofloxacin treatment group).

4.3.5. Breakpoints or Susceptibility Test Interpretive Criteria (STIC) for Sulopenem

The following is a summary of the Clinical Microbiology team's proposed breakpoints (BPs) rationale and labeling recommendations:

For setting the MIC BPs for sulopenem against *E. coli*, *K. pneumoniae*, and *P. mirabilis*, the Clinical Microbiology team relied primarily on microbiological eradication rates at each MIC dilution of clinical isolates, and the in vitro MIC data from clinical and surveillance isolates. The pharmacokinetics/pharmacodynamics (PK/PD) target index for sulopenem was predicted to be either $T > \text{MIC}$ or $C_{\text{max}}/\text{MIC}$ based on plasma concentration; however, the results are not definitive. Typically, beta-lactam drugs exhibit $T > \text{MIC}$. The Clinical Pharmacology team has concerns with the validity of PK/PD study results. The microbiological success in relation to MIC values of baseline *E. coli*, *K. pneumoniae*, and *P. mirabilis* isolates from the sulopenem treatment group in mMITT population at test-of-cure (TOC) visit are summarized below:

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

- Among 437 baseline *E. coli* isolates with an MIC range of 0.015 to 1.0 µg/mL, the overall microbiological eradication rate at TOC was 76.4%. The highest sulopenem MIC corresponding to microbiological success was 0.25 µg/mL and 3/5 (60%) isolates were eradicated. There was only one baseline *E. coli* isolate with sulopenem MIC of 1 µg/mL and it was associated with microbiological persistence. No baseline isolate with an MIC ≥2 µg/mL was observed. The MIC_{50/90} was 0.03/0.06 µg/mL against all *E. coli* isolates from both surveillance and clinical studies. Therefore, a susceptible BP of 0.25 µg/mL appears reasonable and will cover most of the *E. coli* population.
- Among 48 baseline *K. pneumoniae* isolates with an MIC range 0.015 to 8.0 µg/mL, the overall microbiological eradication rate at TOC was 77.1%. The highest sulopenem MIC that corresponded to a favorable microbiological outcome was 0.12 µg/mL and 7/8 (87.5%) isolates at this MIC were eradicated. No baseline isolates were observed with MIC values between 0.25 to 2.0 µg/mL. However, 2 baseline isolates with MIC values of 4 and 8 µg/mL were identified and eradicated. The MIC_{50/90} was 0.03/0.12 µg/mL against all *K. pneumoniae* isolates from the surveillance and clinical studies. Therefore, a susceptible BP of 0.25 µg/mL appears reasonable and will cover most of the *K. pneumoniae* population.
- Among 17 baseline *P. mirabilis* isolates with an MIC range of 0.03 to 0.25 µg/mL, the overall microbiological eradication rate at TOC was 82.4%. The highest sulopenem MIC that corresponded to microbiological success was 0.25 µg/mL and 10/10 (100%) isolates at this MIC were successfully eradicated. No baseline isolate was available with MIC values ≥0.5 µg/mL. Against *P. mirabilis* isolates from both surveillance and clinical studies, the MIC_{50/90} values were between 0.12/0.25 to 0.25/0.5 µg/mL. Therefore, a susceptible BP of 0.25 µg/mL appears reasonable and should cover most *P. mirabilis* isolates.

In summary, microbiological success was observed in patients with baseline isolates of *E. coli* and *P. mirabilis* that had MIC values of ≤0.015 to 0.25 µg/mL. No baseline *E. coli* isolate had an MIC of 0.5 µg/mL but a single isolate at an MIC of 1.0 µg/mL was associated with microbiological failure. No baseline *P. mirabilis* isolate had an MIC ≥0.5 µg/mL. Microbiological success was observed in patients with baseline *K. pneumoniae* isolates that had MIC values of ≤0.015 to 0.12 µg/mL. No baseline *K. pneumoniae* isolates with MIC values between 0.25 to 2 µg/mL were observed; however, two isolates at MIC 4 and 8 µg/mL were observed and eradicated. Therefore, susceptible (S)/intermediate (I)/resistant (R) MIC BPs of ≤0.25/0.5/≥1.0 µg/mL against all three uUTI pathogens appeared to be reasonable and will cover most isolates.

The Applicant proposed sulopenem MIC BPs (S/I/R) of (b) (4) µg/mL for Enterobacteriales. However, as noted above, the Clinical Microbiology team recommends the revised MIC BPs (S/I/R) of ≤0.25/0.5/≥1.0 µg/mL for sulopenem against *E. coli*, *K. pneumoniae*, and *P. mirabilis* for uUTI indication. The disk diffusion zone diameter BPs have been calculated accordingly. The Clinical Microbiology team's recommended sulopenem MIC and disk diffusion BPs are summarized in Table 5.

Table 5. Recommended Broth Microdilution (MIC) and Disk Diffusion Interpretive Criteria (BPs) for Sulopenem

Indicated pathogens	Broth dilution method (MIC)			Disk diffusion method (zone diameter)		
	Susceptible (S) µg/mL	Intermediate (I) µg/mL	Resistant (R) µg/mL	Susceptible (S) mm	Intermediate (I) mm	Resistant (R) mm
<i>E. coli</i>	≤0.25	0.5	≥1.0	≥19	16-18	≤15
<i>K. pneumoniae</i>	≤0.25	0.5	≥1.0	≥19	16-18	≤15
<i>P. mirabilis</i>	≤0.25	0.5	≥1.0	≥19	16-18	≤15

Source: Reviewer's table

Abbreviations: BP, breakpoint; MIC, minimum inhibitory concentration.

We agree with the inclusion of *E. coli*, *K. pneumoniae* and *P. mirabilis* in the first list pathogens of 12.4 Microbiology section of the proposed sulopenem labeling. However, inclusion of pathogens in the second list has been modified based on relevance to the uUTI indication and having an in vitro MIC₉₀ of ≤0.25 µg/mL. The recommendation is that the following organisms to be included in the second list: *Staphylococcus saprophyticus*, *Streptococcus agalactiae*, *Citrobacter freundii*, *Citrobacter koseri*, *Enterobacter cloacae species complex*, *Klebsiella aerogenes*, *Klebsiella oxytoca*, *Proteus vulgaris*, *Providencia alcalifaciens*, and *Providencia stuartii*.

Please see Section 16.5.7 "Recommended BPs for Sulopenem Against Target uUTI Pathogens" in the Appendix of this review for a discussion regarding our recommendations and rationale for the breakpoints.

4.4. Devices and Companion Diagnostic Issues

Not applicable for this NDA.

5. Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The proposed product is a bilayer oral tablet that consists of a fixed dose combination of sulopenem etzadroxil and probenecid. Sulopenem etzadroxil (PF-03709270) is a prodrug that is rapidly cleaved upon intestinal absorption to generate its active metabolite, sulopenem (CP-70429) which is a penem antibacterial drug. Penem antibacterial drugs are known to be degraded quickly by human renal dipeptidase, and an inhibitor of this enzyme, probenecid, is included in the fixed dose combination to prolong the actions of sulopenem. The product if approved is intended for the treatment of uUTI with a treatment regimen of one bilayer tablet containing 500 mg sulopenem etzadroxil and 500 mg probenecid administered twice a day for 5 days.

Pivotal toxicology studies that were conducted in support of the NDA in adult animals included 1-month toxicology studies in rats and monkeys with sulopenem etzadroxil and a 14-day combination toxicology study with sulopenem etzadroxil and probenecid in rats. There were no

toxicity findings of concern, but renal changes were observed in rats. The primary finding observed in adult rats in the 1-month toxicology study was a low incidence of regeneration of proximal tubular epithelium in the kidney accompanied by minimal vacuolation of the renal tubular epithelium, renal tubular hypertrophy, and increased kidney weights. The renal findings are not considered to be clinically relevant due to the limited scope and severity of the findings. The lowest sulopenem etzadroxil dose in rats associated with the kidney findings was 400 mg/kg/day which was associated with a mean plasma area under the curve (AUC) exposure for sulopenem of approximately 9 times the mean clinical AUC exposure for sulopenem following a single oral administration of the bilayer tablet. In the combination sulopenem etzadroxil/probenecid toxicology study, kidney weights were increased with an oral sulopenem etzadroxil dose of 800 mg/kg/day administered for 14 days to adult rats, but renal histopathology findings were not observed. These results suggest the duration of sulopenem etzadroxil dosing may influence the severity of renal findings.

In the definitive juvenile toxicity study, oral administration of sulopenem etzadroxil to juvenile rats for 85 days beginning on postnatal day 5 and continuing to postnatal day 90, was associated with more varied and severe renal histopathology findings compared to the findings in adult rats in the 14-day and 1-month toxicology studies. Renal histopathology in juvenile male and/or female rats included slight degeneration of tubular epithelium, renal infarcts, and intratubular concretions. The findings in juvenile rats occurred at lower sulopenem etzadroxil doses and exposures than the doses associated with renal findings in adult rats in the 1-month study, and the findings were poorly reversible or, in the case of tubular concretions, irreversible after a 2-week recovery period. The renal toxicology results in juvenile rats suggest longer durations of repeated sulopenem etzadroxil dosing may result in more varied and severe renal toxicity with potential clinical relevance. The results are also consistent with a potential for more severe renal toxicity in juvenile rats compared to adults. The sulopenem etzadroxil/probenecid bilayer tablet will not be approved for pediatric patients until clinical trials in this population are completed. The results from the juvenile toxicology study suggest increased monitoring of renal toxicity should be considered for future clinical pediatric studies.

Additional sulopenem etzadroxil-related findings were observed in gastrointestinal (GI) tissues in the 14-day combination toxicology study in rats (mixed cell infiltrates, hyperplasia of glandular epithelium and edema in the large intestine) and the 1-month study in monkeys (minimal mucosal hyperplasia). These effects were reversible and are not considered to be a likely source of serious adverse events (SAEs) for clinical dosing for 5 days with the bilayer tablet. Monkeys also exhibited positive Coombs test results that tended to increase with sulopenem etzadroxil dose and likely contributed to antibody mediation of minimal erythrocyte loss and compensatory erythropoiesis in monkeys. Should a similar reaction to sulopenem etzadroxil occur in humans, it is not expected to produce serious adverse effects over a short 5-day course of treatment with the bilayer tablet, but more concern may be warranted for repeated courses of treatment.

Both sulopenem etzadroxil and sulopenem were shown to inhibit hERG potassium channels *in vitro* with estimated IC₅₀ values of 33.4 mcM (15.9 µg/ml) and 300 mcM (104.8 µg/ml),

respectively. However, concern for inhibition of hERG potassium channels and possible QT prolongation in the clinic is minimal because the 2.64 µg/ml plasma C_{max} for sulopenem associated with administration of a single bilayer tablet containing 500 mg sulopenem etzadroxil in fed patients is approximately 6-fold and 40-fold lower than the hERG IC_{50} values for sulopenem etzadroxil and sulopenem, respectively. Also, in a Phase 1 study where no QT prolongation was observed, a single IV dose of 2800 mg sulopenem was associated with a mean plasma C_{max} value (109.7 µg/ml) for sulopenem that was approximately 40 times greater than the expected clinical sulopenem C_{max} associated with oral administration of a single bilayer tablet.

In vitro and *in vivo* genetic toxicology testing was conducted with sulopenem etzadroxil and sulopenem with a similar pattern of results for both compounds. Both compounds were shown to be negative for mutagenicity in Ames assays and sulopenem was negative for mutagenicity in an *in vitro* CHO HGRPT forward mutation assay. However, both compounds produced positive results for clastogenesis in several *in vitro* assays in mammalian cells including an *in vitro* micronucleus assay and human lymphocyte assay with sulopenem etzadroxil and a chromosome aberration assay with sulopenem. These results were balanced by negative results for both compounds *in vivo* in micronucleus assays in bone marrow cells from rats (both compounds) and mice (sulopenem). Based on the negative results in the *in vitro* mutagenicity assays and the *in vivo* micronucleus assays, the weight of evidence supports a negative potential for genotoxicity for sulopenem etzadroxil.

Sulopenem etzadroxil did not inhibit fertility in male and female rats and was not associated with fetal malformations in embryo-fetal studies in rats and rabbits. However, in mice, a higher litter and fetal incidence of cleft palate in fetuses occurred at a sulopenem etzadroxil dose associated with sulopenem exposures approximately 46-times the mean clinical exposure following a single oral dose of the bilayer tablet. In a pre-postnatal study in rats, sulopenem etzadroxil was not associated with changes in the viability, physical development, neurological development, or reproductive capacity of first-generation offspring.

Sulopenem and 2-ethylbutyric acid (2-EBA) are released by hydrolysis of sulopenem etzadroxil, and during hydrolysis the formation of formaldehyde is anticipated. However, measurable quantities of formaldehyde were not observed in any of the rat or monkey toxicology studies, although the lower limit of quantitation for formaldehyde in these studies was high, (b) (4) µg/ml. According to the Applicant, the theoretical maximum amount of formaldehyde expected to form with a 1000 mg dose of sulopenem etzadroxil is (b) (4) mg which is substantially lower than the daily body burden of 36 g/day formaldehyde expected to be ingested and formed endogenously. Because the amount of formaldehyde formed through hydrolysis of sulopenem etzadroxil is expected to be much smaller than the normal body burden, the formation of formaldehyde is not a safety concern. The other major metabolite of sulopenem etzadroxil, 2-EBA, had plasma exposures in the nonclinical toxicology studies that often exceeded exposures for sulopenem. 2-EBA is considered to be qualified for safety by its substantial exposures in the general toxicology studies, *in vivo* genetic toxicology studies, and developmental and reproductive toxicology studies with sulopenem etzadroxil. Similarly, two metabolites that

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

occur disproportionately in humans, M1a and M1b, are considered qualified for safety in the rat toxicology studies based on their high percentages in rat plasma.

Probenecid was first approved in 1951 as BENEMID followed by a number of generic probenecid drug products including the listed probenecid product referenced by the Applicant, PROBENECID by Actavis Pharma, Inc., which is approved for oral doses of up to 1000 mg/day for chronic treatment of gout. In the 14-day combination toxicology study, increasing doses of sulopenem etzadroxil were associated with proportional decreases in probenecid exposure when the two compounds were administered concomitantly. In the same study, probenecid was not associated with notable toxicity and coadministration of probenecid with sulopenem etzadroxil did not substantially change sulopenem AUC exposures in plasma or augment sulopenem etzadroxil-related toxicity. The general toxicity of probenecid is further qualified by its extensive use in FDA-approved products. Information on the product label for the listed probenecid product including warnings, drug interactions, and adverse reactions for probenecid will be included in the labeling for the current product. Information that is missing from the product label for the listed product including information on the nonclinical fertility, embryo-fetal, and pre-postnatal effects of probenecid will also be absent on the product label for the current product.

Considering the nonclinical results as a whole, NDA 213972 is considered approvable from a Pharmacology/Toxicology perspective.

5.2. Referenced NDAs, BLAs, DMFs

INDs 73463 and 129834 for intravenous sulopenem and INDs 77881 and 129849 for sulopenem etzadroxil plus probenecid.

5.3. Pharmacology

Study Title: Safety Pharmacology – Neurofunctional Assessment of PF-03709270 and PF-03678685 in Sprague Dawley Rats. Study No.: 05GR036.

Methods: This good laboratory practice (GLP)-compliant study was conducted by (b) (4) in 2006. Separate groups (6/group of Male Sprague Dawley rats were administered single doses of vehicle (0.5% methylcellulose) or 2000 mg/kg PF-03709270 and PF-03678685 by oral gavage. One hour after dosing, individual animals were evaluated in a functional observational battery including assessments of central nervous system activity and excitability, autonomic nervous system function, neuromuscular function, and sensorimotor function. Locomotor activity and body temperature were also assessed in separate measurements.

Results: PF-03709270 had no effect on any of the functional observational battery or locomotor assessments and no effect on body temperature compared to control values.

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

Study Title: Effect of PF-03709270 on hERG Potassium Channels Stably Expressed in HEK293 Cells. Study No.: PF3709270/GP/0506/HERG

Methods: This non-GLP compliant study was conducted in 2006 by (b) (4). PF-03709270 dissolved in DMSO was incubated with HEK293 cells stably transfected with hERG encoded potassium channels in concentrations of 3, 30, and 100 mcM. A positive control agent was not tested.

Results: PF-03709270 inhibited HERG currents by $5.1 \pm 1.6\%$, $48.3 \pm 2.2\%$ and $75.8 \pm 2.6\%$ at 3, 30 and 100 mcM, respectively. The inhibition observed was dose dependent. Using these values, an IC_{50} value of 33.4 mcM was determined for hERG inhibition by PF-03709270.

Study Title: Effect of CP-70,429 and PF-398,899 on hERG current stably expressed in CHO cells. Study No.: 03-2696-02

Methods: This non-GLP study was conducted in 2004 by Pfizer Global Research and Development in Groton, Connecticut, USA. CP-70429 was incubated in concentrations of 30, 100, and 300 mcM with CHO cells stably transfected with hERG and the effects on hERG-mediated potassium channels was evaluated using whole-cell patch clamp analysis. A positive control agent, dofetilide (30 nM) was tested under the same conditions.

Results: At concentrations of 30, 100, and 300 mcM, CP-70429 inhibited hERG potassium currents in a concentration-dependent manner by $4.9 \pm 3.6\%$, $20.3 \pm 8.5\%$, and $49.2 \pm 5.9\%$ respectively. The IC_{50} value was approximately 300 mcM (104.8 µg/ml).

Study Title: Cardiovascular Assessment of PF-03709270 & PF-03678685 Administered Orally in Instrumented Cynomolgus Monkeys. Study No.: 05GR027

Methods: This non-GLP study was conducted by (b) (4) in 2006. Single doses of vehicle (0.5% methylcellulose), 1000 mg/kg PF-02709270 and 1000 mg/kg PF-03678685 (another sulopenem prodrug) were administered by oral gavage in single doses to fasted Cynomolgus monkeys (4/sex). Administrations followed a cross-over design with a 1-week washout period between administrations. Before dosing, monkeys were implanted with radio-telemetry transmitters. In addition to clinical signs and toxicokinetic measurements (whole blood was collected pre-dose and approximately 8 hours after dosing), telemetry measurements of heart rate, systemic arterial blood pressure (systolic, diastolic, and mean blood pressure) and electrocardiogram parameters (resting rate, PR, QRS, and QT intervals) were measured predose and at approximately 1, 2, 4, 6, 8, 12, and 22 hours after dosing. The method for calculating QTc values was not identified in the study report.

Results: PF-03709270 treated animals experienced emesis within 8 hours of dosing (6/8 animals) and all animals had loose stool beginning at 24 hours after dosing with normal stool returning by 96 hours after dosing. In animals treated with PF-03709270, there was a significant decrease in the mean PR interval from baseline (-6 msec) at 22 hours after dosing compared to control values (-1 msec from baseline). This finding may have been related to a nonsignificant $\approx$

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

7% mean increase in heart rate (compared to vehicle control values) that occurred 22 hours after dosing. None of the other cardiovascular parameters were significantly changed. The plasma concentrations of PF-03709270 and CP-70429 measured 8 hours after dosing were, respectively, 3.55 ± 1.16 ng/ml and 3750 ± 1750 ng/ml.

Study Title: Pulmonary Assessment of PF-03678685 and PF-03709270 in Male Sprague Dawley Rats by Whole Body Plethysmography. Study No.: 05GR040

Methods: This GLP-compliant study was conducted by Pfizer Global Research & Development in Groton Connecticut, USA in 2006. Vehicle (0.5% methylcellulose), or PF-03709270 and PF-03678685 in doses of 2000 mg/kg were administered by oral gavage in single doses to three separate groups of male Sprague-Dawley rats (6/group). Pulmonary function was assessed in each rat via whole body plethysmography in BUXCO chambers beginning immediately after dosing and continuing for 2 hours. Measured parameters included tidal volume, respiratory rate, and minute volume with averages collected every 20 minutes

Results: PF-03709270 was not associated with changes in tidal volume, respiratory rate, or minute volume for 2 hours after dosing compared to vehicle control values.

5.4. ADME/PK

Table 6. ADME/PK Findings

Type of Study	Major Findings
<i>Absorption</i>	
Acute Oral Toxicity Study of PF-03709270 in Rats/ Study No.: 05GR008	PF-03709270 was administered as a single dose by oral gavage to male Sprague Dawley rats (9/group) in doses of 50, 400, or 2000 mg/kg and plasma concentrations of CP-70429 were measured. <u>Dose Proportionality</u> : Plasma C_{max} values increased in a less than dose-proportional manner for all doses, and plasma AUC values increased in a more than dose-proportional manner between the LD and MD groups and in a less than dose-proportional manner between the MD and HD groups (Table 7).

Table 7. Mean Toxicokinetic Parameters for CP-70429 in Male Rats After a Single Oral Administration of PF-03709270

Dose (mg/kg)	Sex	C_{max} (ng/mL)	t_{max} (h)	AUC ₀₋₂₄ (ng·h/mL)
50	Male	971	1.00	2560
400	Male	2350	1.00	32700
2000	Male	5670	24.0	81700

Source: Study Report

Acute Oral Toxicity Study of PF-03709270 and PF-03678685 in Monkeys/ Study No.: 05GR023	PF-03709270 and another prodrug of CP-70429, PF-03678685, were administered by oral gavage to male Cynomolgus monkeys (3/group) in single doses of 1000

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

Type of Study	Major Findings
	mg/kg. Plasma concentrations of the prodrugs and CP-70429 were measured. PF-03709270 was rapidly metabolized to CP-70429 (Table 8).

Table 8. Mean Toxicokinetic Parameters for CP-70429 in Male Monkeys After a Single Oral Administration of PF-03709270

Compound	Dose (mg/kg)	Sex	C _{max}			t _{max}			AUC ₀₋₂₄		
			(ng/mL)			(h)			(ng·h/mL)		
			Mean	S.D.	n	Mean	S.D.	n	Mean	S.D.	n
PF-03709270	1000 mg/kg of PF-03709270	Male	64.0	101	3	1.67	0.577	3	117	112	3
PF-03678685	1000 mg/kg of PF-03678685	Male	6.23	NC	1	8.00	NC	1	76.1	NC	1
CP-70,429	1000 mg/kg of PF-03709270	Male	6860	3900	3	1.00	0.00	3	52000	13800	3
	1000 mg/kg of PF-03678685	Male	5560	1650	3	1.67	0.577	3	48200	17200	3

NC = Not calculated

Source: Study Report

Distribution

Study Title: Tissue Distribution of PF-03709270 in Long-Evans Male Rats/ Study No.: DM2007-03709270-021
The binding of sulopenem to plasma proteins was determined by ultrafiltration in human, monkey, dog, rat, rabbit, and mouse plasma over a concentration range of 1 to 100 µg/ml. The mean percent of sulopenem bound to plasma was 10.7%, 15.2%, 9.3%, 29.4%, 58.9%, and 0% in plasma from humans, monkeys, dogs, rats, rabbits, and mice, respectively. Plasma-protein binding was independent of concentration under the study conditions.

Binding of CP-70429 to Human, Monkey, Dog, Rat, Rabbit, and Mouse Plasma Proteins./ Study No.: DM2004-070429-013
The tissues with the highest AUC exposures to radioactivity over a period of 168 hours after dosing were in descending order: kidney, liver, lung, skin, pancreas, spleen, and blood. Tissues with intermediate exposure included heart, thyroid, thymus, bone marrow, adrenal gland, lacrimal gland, testes, and skeletal muscle. The tissues with the lowest exposures included brain, spinal cord, and seminal vesicles.

Metabolism

Effect of CP-070,429 on Human Drug Metabolizing Enzymes In Vitro./ Study No.: DM2006-070429-029
CP-70429 was incubated in seven concentrations ranging from 0.159 to 50.0 mcM with pooled human liver microsomes and substrates specific for different CYP isozymes. CP-70429 demonstrated little or no inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A.

In Vitro Characterization of Sulopenem and Sulopenem Etzadroxil as Inhibitors of Cytochrome P450 Enzymes in Human Liver Microsomes/ Study No.: 17081086ITX
Sulopenem and sulopenem etzadroxil were separately incubated in concentrations ranging from 0.206 to 150 mcM with pooled human liver microsomes and substrates for specific CYP isozymes in assays measuring direct and time-dependent CYP enzyme activity. Sulopenem did not inhibit any of the tested CYP isozymes (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP3A4/5) directly or in a time-dependent manner at any concentration. Sulopenem etzadroxil showed weak direct inhibition of CYP3A4/5 at the highest concentrations tested and the IC₅₀ was estimated to be >150 mcM. Also, at the highest concentrations, sulopenem etzadroxil demonstrated a weak time-dependent inhibition of CYP3A4/5.

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

Type of Study	Major Findings
Mass Balance, Routes of Excretion and Metabolism of CP-70,429 and its Pro-Drug, PF-03,709,270 Following Intravenous Administration of [¹⁴ C]CP-70,429 and Oral Administration of [¹⁴ C]PF-03,709,270 to Sprague-Dawley Rats./ Study No.: DM2007-03709270-027	The metabolism of CP-70429 and PF-03709270 was studied in rats (2/sex/group) following intravenous administration of [¹⁴C]CP-70429 or oral administration of [¹⁴C]PF-03709270 with a ¹⁴C label at two different positions (head and tail) on PF-03709270. For IV administration of labeled CP-70429, a total of 8 metabolites and CP-70429 were detected in plasma (Table 9). All of the identified metabolites were derived from CP-70429. The most abundant metabolite was the M1a metabolite which accounted for a mean 39.9% of the administered dose followed by M1b comprising a mean percentage of 14.7%. M1a and M1b were two diastereomeric products resulting from hydrolysis of the β-lactam cyclic amide bond followed by dehydrogenation.

Table 9. Plasma Metabolites in Sprague-Dawley Rats Following 400 mg/kg Oral Administration of [¹⁴C]CP-70429

Metabolite (#)	m/z	Rt (min)	Male (%Radioactivity)	Female (%Radioactivity)	Mean
Unknown		2.0	14.4	8.9	11.7
M4a	264	5.0	4.3	0.6	2.5
M1a	366	13.5	34.3	45.5	39.9
M1b	366	14.7	17.9	11.5	14.7
M2	322	17.2	3.4	3.3	3.4
CP-70,429	350	17.8	13.6	18.1	15.9
M6	348	21.9	5.1	0.8	3.0
M3a	350	26.2	5.1	9.4	7.3
M5a	306	29.8	1.9	1.8	1.9

Source: Study Report

For the head labeled PF-03709270, a total of 8 metabolites and CP-70429 were detected in plasma (Table 10). All of the identified metabolites were derived from CP-70429, but the metabolic profile was not exactly the same as that following CP-70429 IV administration. The same major metabolites that occurred following IV administration of CP-70429, M1a and M1b, were also the major plasma metabolites following oral administration of PF-03709270 and these metabolites accounted for mean plasma percentages of 28.8% and 17.7% of radioactivity, respectively. The M1a and M1b metabolites were also identified in human plasma as disproportionate metabolites of sulopenem etzadroxil accounting for 21.8% and 43.6%, respectively, of the total dose in humans. The respective mean plasma percentages of 28.8% and 17.7% in the current study allow calculation of the NOAEL exposures for the two metabolites in the 1-month toxicology study with oral PF-03709270 in rats (Study No.: 06GR278). The safe exposures for each metabolite in Study No.: 06GR278 exceeded the plasma exposures for the M1a and M1b metabolites expected with the maximum recommended dose of sulopenem etzadroxil in humans.

Type of Study Major Findings

Table 10. Plasma Metabolites of PF-03709270 in Sprague-Dawley Rats Following 400 mg/kg Oral Administration of [¹⁴C]PF-03709270 (Head Label)

Metabolite (#)	m/z	Rt (min)	Male	Female	Mean
			(%Radioactivity)		
M1a	366	13.8	22.7	34.9	28.8
M1b	366	14.9	20.7	14.7	17.7
CP-70,429	350	17.9	18.5	14.8	16.7
M6	348	24.6	6.9	1.3	4.1
M3a	350	26.5	10.4	15.6	13.0
M5a	306	28.5	6.0	10.3	8.2
M5b	306	29.8	4.8	3.7	4.3
M8	332	31.6	10.0	4.7	7.4

Source: Study Report

For the tail labelled PF-03709370, a total of 7 metabolites including the primary metabolite, 2-ethylbutyric acid (2-EBA), were detected in plasma (Table 11). All metabolites identified were derived from 2-EBA, suggesting a complete hydrolysis of the PF-03709270 ester bond.

Table 11. Plasma Metabolites of PF-03709270 in Sprague-Dawley Rats Following 400 mg/kg Oral Administration of [¹⁴C]PF-03709270 (Tail Label)

Metabolite (#)	m/z (+/-)	Rt (min)	Male	Female	Mean
			(%Radioactivity)		
MIV	-131	16.4	2.7	6.9	4.8
MIII	-129	17.0	3.9	3.8	3.9
MVI	-190	20.8	1.5	1.0	1.3
MII	172	21.5	4.3	4.4	4.4
MV	174	22.6	1.4	2.1	1.8
MI	-291	23.8	10.3	10.3	10.3
2EBA	-115	30.9	61.8	58.9	60.4

-negative ion mode

Source: Study Report

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

Type of Study	Major Findings
Profiling and Identification of Metabolites in Urine and Plasma Following Intravenous Administration of [¹⁴ C]CP-70,429 to Cynomolgus Monkeys/ Study No.: DM2006-070429-027	One female and one male Cynomolgus monkey were administered a single dose of 200 mg/kg [¹⁴ C]CP-70429 by intravenous injection. Urine, feces, and plasma were collected at different timepoints over a total period of 88 hours. Approximately 78.5% of the dose was recovered in urine with less than 3% recovered in feces. Four metabolites were identified in plasma from both males and females with similar percentages in both sexes (Table 12). The primary metabolite in plasma was M2 which comprised more than 30% of the total radioactivity in plasma in both sexes. The major primary metabolic pathways included β-lactam cyclic amide hydrolysis, sulfoxide reduction, and sulfide cleavage.

Table 12. Percentage of Plasma Metabolites of CP-70429 in Male and Female Monkeys Following IV Administration of [¹⁴C]CP-70429

Metabolite			Percent of Radioactivity					
#	m/z	Retention Time (min)	Males			Females		
			1001	1002	Mean	1103	1104	Mean
M1	322	30.7	7.76	8.75	8.26	13.8	16.3	15.0
M2	264	33.3	35.0	31.6	33.3	38.6	36.2	37.4
M3	322	35.1	16.3	23.8	20.1	18.0	-	8.99
CP-70,429	350	40.1	7.74	9.27	8.51	-	12.1	6.04
M6	350	41.6	2.91	-	1.46	-	5.98	2.99

Source: Study Report

<i>Excretion</i>	
Determination of Radiolabeled Routes of Excretion of [¹⁴ C]PF-03709270 Prodrug A in Sprague-Dawley Rat/ Study No.: PDMK2007-019SR	[¹⁴ C]PF-03709270 was administered in a single oral dose of 400 mg/kg to Sprague Dawley rats (2/sex) and routes of excretion were assessed over a period of 96 hours. The mean total recovery of radioactivity was 91.7±0.53% for all rats over 96 hours. Mean radioactivity recovered in male and female urine was 51.6% and 57.8%, respectively. Mean radioactivity recovered in male and female feces was 37.7% and 29.5%, respectively.
Determination of Radiolabeled Profile in Plasma and Routes of Excretion of [¹⁴ C]PF-03709270 Prodrug A in Cynomolgus Monkeys./ Study NO.: PDMK2007-020SR	[¹⁴ C]PF-03709270 was administered in a single oral dose of 400 mg/kg to one male and one female Cynomolgus monkey and routes of excretion were assessed over a period of 168 hours. Over a period of 168 hours, recovery of radioactivity was 88.2% in the male monkey and 90.5% in the female monkey. Radioactivity recovered in the urine accounted for 28.07% in the male and 30.47% in the female. Radioactivity recovered in the feces accounted for 35.65% in the male and 33.55% in the female.

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

Type of Study	Major Findings
<i>TK Data From General Toxicology Studies</i>	
1-Month Oral Toxicokinetic Study of PF-03709270 in Rats/ Study No.: 07KL014	Rats were administered PF-03709270 by oral gavage once daily for 30 days in doses of 100, 400, and 2000 mg/kg/day. PF-03709270 Plasma Toxicokinetics: PF-03709270 disappeared from plasma rapidly and toxicokinetic measurements were not obtained.
This toxicokinetic study provided toxicokinetic data for the general toxicity study: 1-Month Oral Toxicity and Micronucleus Study of PF-03709270 in Rats/ Study No.: 06GR278	Formaldehyde: There were no quantifiable concentrations of formaldehyde detected in plasma from control and HD animals. CP-7029 Plasma Toxicokinetics (Table 13) <u>Accumulation:</u> Plasma C _{max} and AUC values for CP-70429 on Day 30 were generally 1.5- to 2-fold higher than the Day 1 values consistent with plasma accumulation of CP-70429. <u>Dose proportionality:</u> On Day 30, plasma C _{max} values increased in a less than dose-proportional manner for all doses and plasma AUC values increased in a more than dose-proportional manner between the LD and MD and in a less than dose-proportional manner between the MD and HD. 2-Ethylbutyric Acid (2-EBA) Plasma Toxicokinetics (Table 14) <u>Accumulation:</u> Similar to the pattern with CP-70429, plasma C _{max} and AUC values for 2-EBA were higher (1.5- to 2.5-fold) compared to values on Day 1 consistent with plasma accumulation with repeated dosing. <u>Dose proportionality:</u> On Day 30, plasma C _{max} values for 2-EBA increased in a roughly dose-proportional manner between the LD and MD, but then did not increase at all between the MD and HD. Plasma AUC values increased in a more than dose-proportional manner between the LD and MD and in a less than dose-proportional manner between the MD and HD. Ratio of CP-70429 to 2-EBA: Plasma C _{max} values for 2-EBA were 1.6- to 3.5-fold higher than comparable CP-70429 values, and plasma AUC values for 2-EBA were 1.3- to 1.6-fold higher than CP-70429 AUC values at the same dose.

Type of Study Major Findings

Table 13. Toxicokinetic Parameters for CP-70429 in Rats Administered Daily Oral PF-03709270 for 30 Days

Dose (mg/kg)	Study Day	Gender	Cmax (ng/mL)	Tmax (h)	AUC(0-24) (ng*h/mL)
100	1	Male	1470	1.0	11800
		Female	1740	1.0	5190
		Overall	1610	1.0	7900
	30	Male	2060	1.0	7930
		Female	1730	1.0	6530
		Overall	1900	1.0	7240
400	1	Male	2430	6.0	33400
		Female	2520	6.0	51300
		Overall	2480	6.0	42400
	30	Male	5530	2.0	58100
		Female	6950	1.0	72300
		Overall	5710	1.0	65200
2000	1	Male	3140	6.0	63100
		Female	8870	24	121000
		Overall	5590	24	92000
	30	Male	10900	1.0	144000
		Female	13400	6.0	180000
		Overall	11100	6.0	162000

Overall = combined Male plus Female

Source: Study Report

Table 14. Toxicokinetic Parameters for 2-EBA in Rats Administered Daily Oral PF-03709270 for 30 Days.

Dose (mg/kg)	Study Day	Gender	Cmax (ng/mL)	Tmax (h)	AUC(0-24) (ng*h/mL)
100	1	Male	923	1.0	2600
		Female	3190	1.0	5730
		Overall	2050	1.0	4050
	30	Male	2310	1.0	4410
		Female	8900	1.0	14700
		Overall	5610	1.0	9560
400	1	Male	7070	1.0	36300
		Female	10900	1.0	61800
		Overall	8970	1.0	49000
	30	Male	10900	1.0	93600
		Female	29400	1.0	117000
		Overall	20200	1.0	105000
2000	1	Male	6400	1.0	79500
		Female	9550	1.0	160000
		Overall	7980	1.0	120000
	30	Male	13100	1.0	174000
		Female	23600	1.0	296000
		Overall	18300	1.0	235000

Overall = combined Male plus Female

Source: Study Report

1-Month Oral Toxicity Study of PF-03709270 in Monkeys/ Study No.: 06GR263

Cynomolgus monkeys were administered PF-03709270 by oral gavage once daily for 30 days in doses of 50, 400, and 1000 mg/kg/day.

Type of Study	Major Findings

PF-03709270 Plasma Toxicokinetics (Table 15): Only low levels of PF-03709270 were detected in plasma, and toxicokinetic measurements were only obtained on Day 1.

Formaldehyde: There were no quantifiable concentrations of formaldehyde in plasma from control and HD animals.

CP-7029 Plasma Toxicokinetics (Table 16)

Accumulation: Plasma C_{max} and AUC values for CP-70429 on Day 30 were generally 1.5- to 2-fold higher than the Day 1 values consistent with plasma accumulation of CP-70429 with repeated dosing.

Dose proportionality: On Day 30, plasma C_{max} and AUC values increased in a less than dose-proportional manner for all doses.

2-Ethylbutyric Acid (2-EBA) Plasma Toxicokinetics (Table 17)

Accumulation: Plasma C_{max} and AUC values for 2-EBA were higher (1.0- to 2.5-fold) compared to values on Day 1 consistent with plasma accumulation with repeated dosing.

Dose proportionality: On Day 30, plasma C_{max} values for 2-EBA increased in a roughly dose-proportional manner between the LD and MD, and in a less than dose-proportional manner between the MD and HD groups. Plasma AUC values increased in a more than dose-proportional manner for all dose groups.

Ratio of CP-70429 to 2-EBA: Plasma C_{max} and AUC values for 2-EBA were lower than comparable CP-70429 values by 1.5 to 5-fold for the LD and MD groups, but of a similar magnitude in the HD group.

Table 15. Mean Toxicokinetic Parameters for PF-03709270 in Monkeys After Oral Administration of PF-03709270 for a Single Day

Dose (mg/kg)	Study Day	Gender	C _{max} (ng/mL)			T _{max} (h)			AUC ₍₀₋₂₄₎ (ng*h/mL)		
			Mean	S.D.	n	Mean	S.D.	n	Mean	S.D.	n
50	1	Male	2.05	1.82	3	1.0	1.0	3	NR	NR	3
		Female	3.96	0.503	3	24	0.0	3	NR	NR	3
		Overall	3.00	1.59	6	13	13	6	NR	NR	6
400	1	Male	2.43	2.59	3	3.3	4.2	3	22.1	38.2	3
		Female	16.0	5.49	3	9.7	13	3	156	66.8	3
		Overall	9.20	8.35	6	6.5	9.0	6	88.8	87.8	6
1000	1	Male	50.9	56.8	3	10	12	3	232	116	3
		Female	13.6	11.6	3	11	12	3	96.3	48.3	3
		Overall	32.3	42.0	6	10	11	6	164	108	6

Overall = Combined mean male and female values
 NR = AUC not reported due to n<2 consecutive data points per animal
¹Day 30 TK parameters were not calculated due to quantifiable concentrations in the control samples

Source: Study Report

Type of Study Major Findings

Table 16. Mean Toxicokinetic Parameters for CP-70429 in Monkeys After Oral Administration of PF-03709270 for 30 Days

Dose (mg/kg)	Study Day	Gender	Cmax (ng/mL)			Tmax (h)			AUC(0-24) (ng*h/mL)		
			Mean	S.D.	n	Mean	S.D.	n	Mean	S.D.	n
50	1	Male	2540	1390	3	1.3	0.58	3	7520	3340	3
		Female	3130	770	3	1.3	0.58	3	11600	2220	3
		Overall	2840	1050	6	1.3	0.52	6	9580	3390	6
	30	Male	4930	1860	3	1.0	0.00	3	11900	3100	3
		Female	4330	1210	3	1.3	0.58	3	10300	1240	3
		Overall	4630	1440	6	1.2	0.41	6	11100	2290	6
400	1	Male	5910	591	3	1.7	0.58	3	64400	17600	3
		Female	6010	2700	3	1.0	0.00	3	57200	12100	3
		Overall	5960	1750	6	1.3	0.52	6	60800	14100	6
	30	Male	13200	3900	3	1.0	0.00	3	82700	15900	3
		Female	10600	4250	3	2.3	1.5	3	106000	33400	3
		Overall	11900	3900	6	1.7	1.2	6	94600	26700	6
1000	1	Male	8820	1110	3	1.3	0.58	3	80400	28400	3
		Female	8080	955	3	1.0	0.00	3	45000	38300	3
		Overall	8450	1010	6	1.2	0.41	6	62700	35800	6
	30	Male	23700	6190	3	1.3	0.58	3	183000	45200	3
		Female	17600	4320	3	2.3	1.5	3	145000	27000	3
		Overall	20700	5830	6	1.8	1.2	6	164000	39400	6

Overall = Combined mean male plus female

Source: Study Report

Table 17. Mean Toxicokinetic Parameters for 2-EBA in Monkeys After Oral Administration of PF-03709270 for 30 Days

Dose (mg/kg)	Study Day	Gender	Cmax (ng/mL)			Tmax (h)			AUC(0-24) (ng*h/mL)		
			Mean	S.D.	n	Mean	S.D.	n	Mean	S.D.	n
50	1	Male	947	820	3	1.0	1.00	3	1710	1510	3
		Female	913	510	3	1.7	0.58	3	1980	1440	3
		Overall	930	611	6	1.3	0.82	6	1840	1330	6
	30	Male	1560	920	3	1.0	0.00	3	2080	1270	3
		Female	1900	786	3	1.0	0.00	3	3560	1030	3
		Overall	1730	788	6	1.0	0.00	6	2820	1320	6
400	1	Male	4130	1410	3	3.3	1.20	3	39200	10700	3
		Female	4690	3620	3	5.3	2.30	3	45800	29000	3
		Overall	4410	2480	6	4.3	2.00	6	42500	19900	6
	30	Male	7720	467	3	1.7	0.58	3	40400	7610	3
		Female	6980	2480	3	1.7	0.58	3	47300	16800	3
		Overall	7350	1650	6	1.7	0.52	6	43900	12300	6
1000	1	Male	13400	7780	3	5.3	2.30	3	86100	20800	3
		Female	4610	1490	3	4.3	3.5	3	35400	15000	3
		Overall	9010	6950	6	4.8	2.7	6	60700	32100	6
	30	Male	24900	6980	3	2.0	0.00	3	169000	84100	3
		Female	24700	5620	3	2.7	1.20	3	190000	82600	3
		Overall	24800	5670	6	2.3	0.82	6	179000	75400	6

Overall = Combined mean male plus female

Source: Study Report

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

Type of Study	Major Findings
A 14-Day Oral Gavage Toxicity Study of PF-03709270 With and Without Probenecid in Rats with a 14-Day Recovery Period/ Study No.: 18IT001-(b) (4)-417503-02	Sprague-Dawley rats were administered vehicle or PF-03709270 with and without probenecid in the following groups in daily oral gavage doses for 14 days: Group 1 (vehicle for PF-03709270), Group 2 (vehicle and 200 mg/kg probenecid), Group 3 (100 mg/kg PF-03709270), Group 4 (800 mg/kg PF-03709270), Group 5 (100 mg/kg PF-03709270 and 200 mg/kg probenecid), Group 6 (800 mg/kg PF-03709270 and 200 mg/kg probenecid). CP-70429 Plasma Toxicokinetics (Table 18) <u>Dose Proportionality:</u> Plasma AUC values for CP-70429 increased in an approximately dose-proportional manner and plasma C_{max} values increased in a less than dose-proportional manner. <u>Plasma Accumulation:</u> AUC values were relatively similar after the first dose compared to after 14 days of dosing consistent with limited plasma accumulation with repeated dosing. 2-Ethylbutyric Acid (2-EBA) Plasma Toxicokinetics (Table 19) <u>Dose Proportionality:</u> Plasma AUC values for 2-EBA increased in a more than dose-proportional manner and plasma C_{max} values increased in a less than dose-proportional manner. <u>Plasma Accumulation:</u> AUC values were relatively similar after the first dose compared to after 14 days of dosing suggesting a limited plasma accumulation of 2-EBA with repeated dosing. Ratio of CP-70429 to 2-EBA: Plasma AUC values for CP-70429 were as much as 2-fold lower than those for 2-EBA. Probenecid Plasma Toxicokinetics (Table 20) <u>Plasma Accumulation:</u> Probenecid C_{max} and AUC values were generally similar on Days 1 and 14 with little evidence of plasma accumulation. Effect of Concomitant Probenecid on CP-70429 Exposures: Plasma AUC exposures to CP-70429 in males and females were approximately 1.5 higher for both sexes in the 800:200 mg/kg/day PF-03709270:probenecid group (Group 6) compared to the 800 mg/kg/day PF-03709270 group (Group 4). However the AUC exposure for the lower-dose combination group, 100:200 PF-03709270:probenecid (Group 5) was the same or less than comparable exposures for males and females in the 100 mg/kg/day PF-03709270 group (Group 3). This pattern is consistent with probenecid having a slightly more pronounced effect on the renal elimination of higher plasma exposures of CP-70429. Effect of Concomitant PF-03709270 on Probenecid Exposures: Probenecid exposures reduced in a PF-03709270 dose-dependent manner. This pattern suggests PF-03709270 may have increased the plasma clearance of probenecid.

Type of Study **Major Findings**

Table 18. Toxicokinetic Parameters for CP-70429 in the 14-Day Combination Toxicology Study in Rats

Treatment	Dosage	AUC(0-t) (ng•hr/mL)		Cmax (ng/mL)		Tmax (hr)	
		Day 1	Day 14	Day 1	Day 14	Day 1	Day 14
Males							
PF-03709270	100 mg/kg/day	11.200	13.100	4610	5850	0.25	0.25
	800 mg/kg/day	59.800	109.000	5330	15800	0.25	0.25
PF-03709270: Probenecid	100:200 mg/kg/day	8100	8200	3440	3520	0.5	0.5
	800:200 mg/kg/day	124.000	146.000	7250	12.200	24	0.5
Females							
PF-03709270	100 mg/kg/day	12.400	12.700	6720	11.900	0.5	0.25
	800 mg/kg/day	92.200	91.700	9410	19.300	0.5	0.25
PF-03709270: Probenecid	100:200 mg/kg/day	7260	12.300	5620	5090	0.25	0.5
	800:200 mg/kg/day	124.000	129.000	10.200	17.600	0.5	0.25

Source: Study Report

Table 19. Toxicokinetic Parameters for 2-EBA in the 14-Day Combination Toxicology Study in Rats

Treatment	Dosage	AUC(0-t) (ng•hr/mL)		Cmax (ng/mL)		Tmax (hr)	
		Day 1	Day 14	Day 1	Day 14	Day 1	Day 14
Males							
PF-03709270	100 mg/kg/day	5550	3420	3110	2370	0.5	0.5
	800 mg/kg/day	36.400	46.000	7940	12.000	2	0.5
PF-03709270: Probenecid	100:200 mg/kg/day	3120	3460	1730	1720	0.5	0.5
	800:200 mg/kg/day	242.000	118.000	20.500	14.400	24	0.5
Females							
PF-03709270	100 mg/kg/day	10.400	9330	7030	6670	0.5	0.5
	800 mg/kg/day	231.000	172.000	15.600	18.200	1	1
PF-03709270: Probenecid	100:200 mg/kg/day	5060	10.700	3080	3530	0.25	0.5
	800:200 mg/kg/day	230.000	207.000	11.500	16.200	1	0.5

Source: Study Report

Table 20. Toxicokinetic Parameters for Probenecid in the 14-Day Combination Toxicology Study in Rats

Treatment	Dosage	AUC(0-t) (ng•hr/mL)		Cmax (ng/mL)		Tmax (hr)	
		Day 1	Day 14	Day 1	Day 14	Day 1	Day 14
Males							
Vehicle:Probenecid	0:200 mg/kg/day	2,040,000	1,730,000	151,000	142,000	4	4
PF-03709270: Probenecid	100:200 mg/kg/day	1,240,000	1,110,000	92,400	101,000	4	4
	800:200 mg/kg/day	697,000	756,000	50,000	75,700	0.5	0.5
Females							
Vehicle:Probenecid	0:200 mg/kg/day	2,540,000	2,160,000	198,000	153,000	6	6
PF-03709270: Probenecid	100:200 mg/kg/day	1,910,000	2,550,000	138,000	170,000	6	6
	800:200 mg/kg/day	664,000	1,290,000	41,000	66,800	4	4

Source: Study Report

TK Data From Reproductive Toxicology Studies

Table 21. Summary of Mean Toxicokinetic Parameters for CP-70429 in Mice After Administration of Oral PF-03709270

Dosage (mg/kg/day)	Day of Gestation	Cmax (ng/mL)	Tmax (h)	AUC0-24 (ng•h/mL)
100	15	2660	1.0	4600
400	15	11300	1.0	38700
2000	15	70800	1.0	342000

Source: Study Report

Type of Study Major Findings

Table 22. Summary of Mean Toxicokinetic Parameters for 2-EBA in Mice After Administration of Oral PF-03709270

Dosage (mg/kg/day)	Day of Gestation	Cmax (ng/mL)	Tmax (h)	AUC0-24 (ng•h/mL)
100	15	42.7	1.0	42.7
400	15	11600	1.0	13100
2000	15	108000	1.0	166000

Source: Study Report

Oral Embryo-fetal Development Study of PF-03709270 in Rats/ Study No.: 08GR040

Table 23. Mean Toxicokinetic Parameters for CP-70429 in Pregnant Rats on GD 17 After Oral Administration of PF-03709270

Dose (mg/kg/day)	Cmax (ng/mL)			tmax (h)			AUC(0-24) (ng•h/mL)		
	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
100	1530	620	5	1.0	0.0	5	6170	1930	5
400	5380	1020	4	1.3	0.50	4	29300	8630	4
2000	7690	2790	5	3.4	2.4	5	81100	15900	5

Source: Study Report

Table 24. Mean Toxicokinetic Parameters for 2-EBA in Pregnant Rats on GD 17 After Oral Administration of PF-03709270

Dose (mg/kg/day)	Cmax (ng/mL)			tmax (h)			AUC(0-24) (ng•h/mL)		
	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.	N
100	5120	3530	5	1.2	0.45	5	10000	3870	5
400	21400	9990	4	1.3	0.50	4	75000	25100	4
2000	32500	7610	5	4.2	2.5	5	327000	107000	5

Source: Study Report

Oral Embryo-Fetal Development Study of PF-03709270 in Rabbits/ Study No.: 08GR037

Table 25. Mean Toxicokinetic Parameters for PF-03709270 on GD 19 in Pregnant Rabbits Administered Oral PF-03709270

Dose (mg/kg/day)	Dosing Day	Gender	Cmax (ng/mL)			tmax (h)			AUC(0-24) (ng•h/mL)		
			Mean	S.D.	n	Mean	S.D.	n	Mean	S.D.	n
5	12 (GD 19)	Female	4.94	11.0	5	2.0	NA	1	12.4	27.6	5
15	12 (GD 19)	Female	0.478	1.07	5	NR	NA	0	4.54	10.2	5
50	12 (GD 19)	Female	0.505	1.01	4	6.0	NA	1	5.55	11.1	4

NA = Not applicable as Watson does not report S.D. for BLQ data.

NR – Not reportable (no concentrations above BLQ)

Source: Study Report

Table 26. Toxicokinetic Parameters for CP-70429 on GD 19 in Pregnant Rabbits Administered Oral PF-03709270

Dose (mg/kg/day)	Dosing Day	Gender	Cmax (ng/mL)			tmax (h)			AUC(0-24) (ng•h/mL)		
			Mean	S.D.	n	Mean	S.D.	n	Mean	S.D.	n
5	12 (GD 19)	Female	439	161	5	1.0	0.0	5	1870	760	5
15	12 (GD 19)	Female	614	459	5	1.2	0.45	5	3520	1110	5
50	12 (GD 19)	Female	2900	675	4	1.3	0.50	4	16000	5650	4

Source: Study Report

Type of Study Major Findings

Table 27. Mean Toxicokinetic Parameters for 2-EBA on GD 19 in Pregnant Rabbits Administered Oral PF-03709270

Dose (mg/kg/day)	Dosing Day	Gender	C _{max} (ng/mL)			t _{max} (h)			AUC(0-24) (ng*h/mL)		
			Mean	S.D.	n	Mean	S.D.	n	Mean	S.D.	n
5	12 (GD 19)	Female	24.4	54.6	5	1.0	NA	1	24.4	54.6	5
15	12 (GD 19)	Female	90.4	85.4	5	3.0	2.6	3	447	521	5
50	12 (GD 19)	Female	815	269	4	1.3	0.50	4	4660	2350	4

NA = Not applicable as Watson does not report S.D. for BLQ data.
 NR – Not reportable (no concentrations above BLQ)

Source: Study Report

Effects on Pre- and Post-Natal Development, Including Maternal Function, with Sulopenem via Intravenous Injection and PF-03709270 via Oral Gavage in Sprague-Dawley Rats/ Study No.: 18IT001-8383180-02

Cohort I: IV administration of 100, 300, and 1000 mg/kg/day Sulopenem

Table 28. Summary of Sulopenem Toxicokinetic Parameters in Maternal Plasma Collected and in Pooled Fetal Plasma Collected on GD 21 Following IV Maternal Dosing of Sulopenem in Cohort I

Familial Status	Dose Group	Dose Level (mg/kg/day)	C ₀ (ng/mL)	C _{max} (ng/mL)	DN C _{max} [(ng/mL)/(mg/kg/day)]		T _{max} (h)	T _{1/2} (h)	AUC _{0-t} (h*ng/mL)	AUC ₀₋₂₄ (h*ng/mL)	DN AUC ₀₋₂₄ [(h*ng/mL)/(mg/kg/day)]		Fetal:Dam	
					C _{max}	T _{max}					C _{max}	AUC ₀₋₂₄	C _{max}	AUC ₀₋₂₄
Dam	2	100	363000	235000	2350	0.0830	1.00	NR	NR	NR	NR	NA	NA	
	3	300	1110000	783000	2610	0.0830	1.00	NR	NR	NR	NR	NA	NA	
	4	1000	NR	2860000	2860	0.0830	0.0830	NR	NR	NR	NR	NA	NA	
Pooled Fetal	2	100	NA	1720	17.2	0.0830	1.00	NR	NR	NR	NR	0.00732	NA	
	3	300	NA	8060	26.9	0.0830	1.00	NR	NR	NR	NR	0.0103	NA	
	4	1000	NA	50700	50.7	1.00	1.00	NR	NR	NR	NR	0.0177	NA	

GD Gestation day.
 NA Not applicable.
 NR Values not reported.

Source: Study Report

Table 29. Sulopenem Concentrations (ng/ml) in Plasma and Milk and Milk to Plasma Ratios for Dams Following Once Daily IV Administration of Sulopenem – LD 14 Collection of Maternal Blood and Lactation Milk

Group	Dose (mg/kg/day)	Milk Concentration (ng/ml)	Plasma Concentration (ng/ml)	Milk:Plasma Ratio
2	100 (N=6)	Mean	1550	55.6
		SD	342	43.8
3	300 (N=8)	Mean	3760	66.5
		SD	1060	46.5
4	1000 (N=7)	Mean	21400	44.0
		SD	9600	31.7

Source: Study Report

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

Type of Study	Major Findings
	Cohort II: Oral Administration of 100, 300, and 1000 mg/kg/day PF-03709270

Table 30. Summary of Sulopenem Toxicokinetic Parameters in Maternal Plasma Collected and in Pooled Fetal Plasma Collected on GD 21 Following Oral Maternal Dosing of PF-03709270 in Cohort II

Familial Status	Dose Group	Dose Level (mg/kg/day)	C _{max} (ng/mL)	DN C _{max} [(ng/mL)/(mg/kg/day)]		T _{max} (h)	T _{last} (h)	AUC ₀₋₄ (h*ng/mL)	AUC ₀₋₂₄ (h*ng/mL)	DN AUC ₀₋₂₄ [(h*ng/mL)/(mg/kg/day)]	M:P		Fetal:Dam	
				C _{max}	AUC ₀₋₂₄						C _{max}	AUC ₀₋₂₄		
Dam	6	100	6880	68.8	1.00	24.0	26100	26100	261	NA	NA	NA	NA	
	7	300	20800	69.3	1.00	24.0	114000	114000	381	1.90	1.48	NA	NA	
	8	1000	50500	50.5	1.00	6.00	NR	NR	NR	1.68	NA	NA	NA	
Pooled Fetal	6	100	8170	81.7	1.00	24.0	NR	NR	NR	1.70 ^a	NA	1.19	NA	
	7	300	24700	82.2	1.00	6.00	NR	NR	NR	174	NA	1.19	NA	
	8	1000	55300	55.3	6.00	6.00	NR	NR	NR	179	NA	1.10	NA	

GD Gestation day.
 NR Values not reported due to less than three measureable concentrations in the profile.
 a Immediately following oral administration of PF-03709270, very high sulopenem concentrations were observed. These values were included in descriptive statistics and TK analysis as no in-life or bioanalytical reason could be identified to explain these values. However, interpretation of trends based on these data should be interpreted with caution.

Source: Study Report

Table 31. Sulopenem Concentrations (ng/ml) in Plasma and Milk and Milk to Plasma Ratios for Dams Following Once Daily Oral Gavage Administration of PF-03709270 – LD 14 Collection of Maternal Blood and Lactation Milk

Group	Dose (mg/kg/day)	Milk Concentration (ng/ml)	Plasma Concentration (ng/ml)	Milk:Plasma Ratio
6	100 (N=7)	Mean	781	0.536
		SD	500	0.682
7	300 (N=8)	Mean	1110	1.08
		SD	731	1.13
8	1000 (N=8)	Mean	2360	0.503
		SD	1250	0.360

Source: Study Report

Table 32. Summary of 2-EBA Toxicokinetic Parameters in Maternal Plasma Collected and in Pooled Fetal Plasma Collected on GD 21 Following Oral Maternal Dosing of PF-03709270 in Cohort II

Familial Status	Dose Group	Dose Level (mg/kg/day)	C _{max} (ng/mL)	DN C _{max} [(ng/mL)/(mg/kg/day)]		T _{max} (h)	T _{last} (h)	AUC ₀₋₄ (h*ng/mL)	AUC ₀₋₂₄ (h*ng/mL)	DN AUC ₀₋₂₄ [(h*ng/mL)/(mg/kg/day)]	Fetal:Dam	
				C _{max}	AUC ₀₋₂₄						C _{max}	AUC ₀₋₂₄
Dam	7	300	10900	36.5	1.00	24.0	77400	77400	258	NA	NA	
	8	1000	30100	30.1	1.00	6.00	NR	NR	NR	NA	NA	
Pooled Fetal	6 ^a	100 ^a	4790	47.9	1.00	1.00	NR	NR	NR	NA	NA	
	7	300	142	0.473	1.00	6.00	NR	NR	NR	0.0130	NA	
	8	1000	309	0.309	1.00	6.00	NR	NR	NR	0.0103	NA	

GD Gestation day.
 NR Values not reported due to less than three measureable concentrations in the profile.
 a Immediately following oral administration of PF-03709270, very high sulopenem concentrations were observed. These values were included in descriptive statistics and TK analysis as no in-life or bioanalytical reason could be identified to explain these values. However, interpretation of trends based on these data should be interpreted with caution.

Source: Study Report

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

Type of Study	Major Findings																																																												
Juvenile Toxicity and Toxicokinetic Oral Gavage and Intravenous Injection Study with Sulopenem and PF-03709270 in Sprague-Dawley Rats with up to a 4 Week Recovery Period/ Study No.: 181T001-8383182-02	Table 33. Summary of Sulopenem Toxicokinetic Parameters in Juvenile Rat Plasma Following IV Administration of Sulopenem <table border="1"> <thead> <tr> <th>Interval</th> <th>Dose Group</th> <th>Dose Level (mg/kg/day)</th> <th>Sex</th> <th>C_{max} (ng/mL)</th> <th>T_{max} (h)</th> <th>AUC₀₋₂₄ (h*ng/mL)</th> <th>t_{1/2} (h)</th> </tr> </thead> <tbody> <tr> <td rowspan="9">PND 21</td> <td rowspan="3">2</td> <td rowspan="3">60</td> <td>M</td> <td>66600</td> <td>0.0830</td> <td>20600</td> <td>NC</td> </tr> <tr> <td>F</td> <td>66800</td> <td>0.0830</td> <td>21200</td> <td>NC</td> </tr> <tr> <td>MF</td> <td>66700</td> <td>0.0830</td> <td>20800</td> <td>NC</td> </tr> <tr> <td rowspan="3">3</td> <td rowspan="3">200</td> <td>M</td> <td>162000</td> <td>0.0830</td> <td>62200</td> <td>NC</td> </tr> <tr> <td>F</td> <td>176000</td> <td>0.0830</td> <td>62500</td> <td>NC</td> </tr> <tr> <td>MF</td> <td>169000</td> <td>0.0830</td> <td>62300</td> <td>NC</td> </tr> <tr> <td rowspan="3">4</td> <td rowspan="3">800</td> <td>M</td> <td>974000</td> <td>0.0830</td> <td>315000</td> <td>NC</td> </tr> <tr> <td>F</td> <td>950000</td> <td>0.0830</td> <td>321000</td> <td>NC</td> </tr> <tr> <td>MF</td> <td>962000</td> <td>0.0830</td> <td>318000</td> <td>NC</td> </tr> </tbody> </table>	Interval	Dose Group	Dose Level (mg/kg/day)	Sex	C _{max} (ng/mL)	T _{max} (h)	AUC ₀₋₂₄ (h*ng/mL)	t _{1/2} (h)	PND 21	2	60	M	66600	0.0830	20600	NC	F	66800	0.0830	21200	NC	MF	66700	0.0830	20800	NC	3	200	M	162000	0.0830	62200	NC	F	176000	0.0830	62500	NC	MF	169000	0.0830	62300	NC	4	800	M	974000	0.0830	315000	NC	F	950000	0.0830	321000	NC	MF	962000	0.0830	318000	NC
Interval	Dose Group	Dose Level (mg/kg/day)	Sex	C _{max} (ng/mL)	T _{max} (h)	AUC ₀₋₂₄ (h*ng/mL)	t _{1/2} (h)																																																						
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	3	200	M	162000	0.0830	62200	NC																																																						
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			MF	962000	0.0830	318000	NC																																																						

NC Not calculated due to the inability to characterize the elimination phase per SOP criteria.
 Notes: All surviving animals in Groups 1 through 4 were sacrificed due to poor condition of the tail on PND 77.
 Combined male and female (MF) parameters were calculated by combining concentration data for all animals (male and female) at each dose level on each interval and using these data as a separate composite profile for TK analysis. These parameters are not an average of the values calculated for males and females separately.

Source: Study Report

Table 34. Summary of Sulopenem Toxicokinetic Parameters in Juvenile Rat Plasma Following Oral Gavage Administration of PF-03709270

Interval	Dose Group	PF-03709270		Sex	C _{max} (ng/mL)	T _{max} (h)	AUC ₀₋₂₄ (h*ng/mL)	t _{1/2} (h)	
		Dose Level (mg/kg/day)							
PND 5	6	25		M	654	0.500	827	0.936	
				F	450	0.500	714	1.03	
				MF	572	0.500	779	0.771	
	7	75			M	1410	1.00	3800	1.77
					F	1070	1.00	4060	1.55
					MF	1240	1.00	3950	1.63
	8	225			M	2240	0.500	11700	3.01
					F	1920	1.00	13400	3.62
					MF	2050	0.500	12500	3.37
	PND 90	6	25		M	4130	0.500	4230	NC
					F	7740	0.250	5170	NC
					MF	5740	0.250	4700	NC
7		75			M	9400	0.250	18800	NC
					F	12300	0.500	21100	NC
					MF	9660	0.250	19100	NC
8		225			M	13200	0.500	57400	NC
					F	19900	0.500	71800	NC
					MF	16600	0.500	64600	NC

NC Not calculated due to the inability to characterize the elimination phase per SOP criteria.
 Note: Combined male and female (MF) parameters were calculated by combining concentration data for all animals (male and female) at each dose level on each interval and using these data as a separate composite profile for TK analysis. These parameters are not an average of the values calculated for males and females separately.

Source: Study Report

Type of Study **Major Findings**

Table 35. Summary of 2-EBA Toxicokinetic Parameters in Juvenile Rat Plasma Following Oral Gavage Administration of PF-03709270

PF-03709270							
Interval	Dose Group	Dose Level (mg/kg/day)	Sex	C _{max} (ng/mL)	T _{max} (h)	AUC ₀₋₂₄ (h*ng/mL)	t _{1/2} (h)
PND 5	6	25	M	544	0.500	3840	NC
			F	691	1.00	3580	NC
			MF	552	0.500	3750	NC
	7	75	M	3430	1.00	20400	NC
			F	2520	1.00	22200	NC
			MF	2970	1.00	21100	NC
	8	225	M	8890	2.00	88700	11.4
			F	8890	1.00	94700	NC
			MF	8780	1.00	91400	11.6
PND 90	6	25	M	1400	0.500	894	NC
			F	4610	0.250	2800	NC
			MF	2640	0.250	1850	NC
	7	75	M	3830	0.250	7280	NC
			F	7700	0.500	16600	NC
			MF	5230	0.500	9710	NC
	8	225	M	11300	1.00	40700	NC
			F	22800	0.500	87300	NC
			MF	16900	1.00	64000	NC

NC = Not calculated due to the inability to characterize the elimination phase per SOP criteria.

Notes: Combined male and female (MF) parameters were calculated by combining concentration data for all animals (male and female) at each dose level on each interval and using these data as a separate composite profile for TK analysis. These parameters are not an average of the values calculated for males and females separately.

Gender differences were observed, with exposure greater than 2-fold in females on PND 90. Therefore, MF combined results are presented for informational purposes only.

Source: Study Report

Abbreviations: ADME, absorption, distribution, metabolism, and excretion; AUC, area under the curve; C_{max}, maximum serum concentration; HD, high dose; IV, intravenous; LD, low dose; MD, mid dose; NOAEL, no observed adverse effect level

5.5. Toxicology

5.5.1. General Toxicology

Study title/ number: 1-Month Oral Toxicity and Micronucleus Study of PF-03709270 in Rats/
 Study No: 06GR278

- Based on minimal vacuolation of the renal tubular epithelium, renal tubular hypertrophy, and a low incidence of tubular regeneration that occurred primarily in high-dose males and females and to a lesser extent in mid-dose males, the low-dose of 100 mg/kg/day was identified as a no observed adverse effect level (NOAEL) in this study.
- The plasma AUC_{0-24h} for CP-70429 (sulopenem) associated with the NOAEL dose of PF-03709270 on Day 30 was 7240 ng•hr/ml.
- The oral administration of PF-03709270 to rats did not induce micronuclei in the polychromatic bone marrow erythrocytes at ≤2000 mg/kg.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

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 {sulopenem etzadroxil/probenecid}

Table 36. Methods for Study No.: 06GR278

Method	Details
Dose and frequency of dosing:	Once per day doses of 0 (vehicle), 100, 400, and 2000 mg/kg/day
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% methylcellulose
Species/Strain:	Sprague-Dawley rats
Number/Sex/Group:	10/sex/group
Age:	9 weeks old
Satellite groups/ unique design:	6 toxicokinetics animals/sex/group
Deviation from study protocol affecting interpretation of results:	No

Table 37. Observations and Results: Changes From Control (Study No.: 06GR278)

Parameters	Major Findings
Mortality	One HD male was euthanized on Day 23 due to body weight loss and clinical signs including rough fur, stained fur, decreased skin turgor, and noisy labored respiration observed on Days 19 to 23.
Clinical Signs	In the HD group, clinical signs included stained fur of the muzzle, urogenital and/or anogenital region in 7/20 animals, noisy respiration in 3/20 animals, and loose stools in 1/20 animals. The observations were observed sporadically with low incidence throughout the study.
Body Weights	No PF-03709270-related effects on body weight were observed.
Feed Consumption	Except on Day 8 where slight decreases in mean food consumption (-11% to -12%) were observed in MD and HD females and HD males, no changes in food consumption occurred.
Ophthalmoscopy	No PF-03709270-related ophthalmoscopy findings were observed.
Hematology	Day 31 HD males: +40% mean prothrombin time** The increased mean prothrombin time occurred only in HD males and was not considered to be toxicologically important.
Clinical Chemistry	No toxicologically relevant changes in serum chemistry were observed. Mean values for ALT and AST were statistically significantly decreased compared to control values in HD and/or MD males and HD females.
Urinalysis	No toxicologically relevant urinalysis findings were observed
Gross Pathology	Gross pathology findings included enlarged cecum and/or pale multi-focal discoloration of the kidney in 1/10 LD males, 4/10 MD males, 2/10 MD females, and 9/10 HD males. In 9/10 HD females, enlarged cecum was observed including one female with dilation of the duodenum.
Organ Weights	Kidney: Relative kidney weights (relative to body weight) were increased approximately 10% and 40% in both sexes in the MD and HD groups respectively compared to control values. The increased kidney weights correlated with renal tubular hypertrophy observed microscopically. Liver: Mean absolute and relative liver weights were increased 10% -20% in both sexes in the HD group compared to control values. Spleen: Absolute and relative spleen weights were significantly decreased by 13-14% in HD females compared to control values. Prostate: Absolute and relative prostate weights were decreased approximately 20% in MD and HD males. In the absence of histologic correlates, the changes in liver, spleen, and prostate weights were not considered to be toxicologically important.

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 {sulopenem etzadroxil/probenecid}

Parameters	Major Findings
Histopathology Adequate battery: Yes	Minimal focal vacuolation of segmental tubular epithelial cells in the renal cortex occurred in 5/10 HD males and 5/10 HD females and in 1/10 MD females. All HD males and 5/10 HD females at 2000 mg/kg exhibited minimal to mild tubular hypertrophy of the outer stripe of the medullary zone of the kidney. The tubular hypertrophy was characterized by mild dilation of the tubular lumina with increased amounts of epithelial cytoplasm sometimes accompanied by multiple foci of epithelial regeneration. The severity was minimal to mild in HD males and mild in HD females. Fewer males (2/10) and females (1/10) in the MD group and 1/10 male in the LD group exhibited this same change. Tubular hypertrophy correlated with the increased kidney weights for males and females at the two highest dose levels. Immunohistochemical staining for P450 enzymes 3A1, 2B6, and 2E1 in kidney sections from one control male and one HD male showed increased intensity of staining in the hypertrophic outer stripe zone in the HD male consistent with metabolic enzyme induction.
[Other evaluations]	Micronucleus assay: see Section 5.5.3 Toxicokinetics: see Section 5.4

** : statistically significantly different than the mean control value; $p \leq 0.01$

Abbreviations: HD, high dose; LD, low dose; MD, mid dose; ALT, alanine aminotransferase; AST, aspartate aminotransferase

Study title/ number: 1-Month Oral Toxicity Study of PF-03709270 in Monkeys/ Study No: 06GR263

- PF-03709270 administered by oral gavage to Cynomolgus monkeys at ≥ 400 mg/kg caused positive Coombs' test, decreased red blood cell parameters, and GI side effects.
- The low-dose of 50 mg/kg was considered to be the NOAEL and was associated with a plasma AUC_{0-24h} for CP-70429 (sulopenem) of 11100 ng•hr/ml on Day 30 of dosing.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 38. Methods for Study No.: 06GR263

Method	Details
Dose and frequency of dosing:	Animals were dosed once per day for 30 days in doses of 0 (vehicle), 50, 400, and 1000 mg/kg/day.
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% methylcellulose
Species/Strain:	Cynomolgus monkeys
Number/Sex/Group:	3/sex/group
Age:	3 to 3.5 years of age
Satellite groups/ unique design:	No separate toxicokinetic animals or recovery animals were included in the study.
Deviation from study protocol affecting interpretation of results:	No

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

Table 39. Observations and Results: Changes From Control (Study No.: 06GR263)

Parameters	Major Findings
Mortality	No mortality occurred during the study period.
Clinical Signs	PF-03709270-related clinical signs included loose/liquid stools and emesis, and with a lower incidence, distended abdomen. Loose/liquid stools were observed beginning on Day 1 in all dose groups and persisted with dose-dependent increases in incidence and severity throughout the dosing period. Sporadic emesis was observed in all dose groups between Day 1 and 26. Abdominal distention was observed in one MD male (Days 30-31), and two HD males (Days 5-12 and 16-31 for one animal and Days 2-12 for the other) and one HD female (Days 28-30). Hunched posture was observed in one HD male (Days 8-9 and 11-12) and one HD female (Day 10) possibly secondary to the gastrointestinal observations.
Body Weights	Body weights were decreased at the end of the dosing period in HD males and females by approximately 16% and 9%, respectively, compared to control values.
Feed Consumption	Delays in eating and decreases in food consumption (qualitatively assessed) were observed beginning on Day 2 in MD and HD males and females.
Ophthalmoscopy	No PF-03709270-related ophthalmoscopy findings were observed.
ECG	No PF-03709270-related changes in any ECG parameters, blood pressure, or heart rate were observed.
Hematology	On Day 15, minimal to mild decreases in RBC, HGB, and/or HCT (reduced 15% to 19% compared to pretreatment values) were observed in individual HD monkeys. On Day 30, slightly greater, but generally mild, decreases in group mean values for these parameters (reduced 14% to 23% compared to pretreatment values) were noted in HD monkeys and in MD females as well as increased RDW (red cell distribution width, 10-20% higher than pretreatment values) and absolute and percent reticulocytes (240% to 550% increases compared to pretreatment values). Direct Coomb's testing on Days 15 and 30 demonstrated positive reactions for polyspecific anti-human globulin and anti-IgG, but not anti-C3b/C3d, in all MD and HD animals and the strength of the reaction tended to increase with dose. These results were consistent with antibody-mediated red blood cell loss with compensatory erythropoiesis. Slightly increased platelet counts (40% to 60% increase compared to pretreatment values) on Days 15 and 30 in male HD monkeys was consistent with thrombocytosis secondary to antibody-mediated red cell turnover.
Clinical Chemistry	In HD males and females, slight reductions in mean serum albumin (reductions of 14% to 18% compared to pretreatment values) were observed. The reduction in serum albumin coupled with slightly increased serum globulin in HD females (+10% compared to pretreatment values) resulted in a decreased albumin/globulin ratio (-24% compared to pretreatment). These systemic responses may have been associated with immune-mediated red cell turnover.
Urinalysis	On Day 31, urine pH was slightly decreased to ≤ 8.0 in 0/6, 1/6, 4/6, and 3/6 animals (both male and female) in control, LD, MD, and HD groups, respectively. A white precipitate, possibly related to the alkaline urine was observed on Day 31 in urine samples from three HD females. The sediment had a microscopic appearance of amorphous granular material consisting of round, oval and irregularly shaped refractile bodies. The origin and toxicological significance of the granular material is unknown.
Gross Pathology	Dilation of the colon was observed in 2/3 HD males.

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

Parameters	Major Findings
Organ Weights	In males and females in the HD group, absolute and relative (to body weight) liver weights were increased by approximately 10-30% compared to control values. Also absolute and relative kidney weights were increased by approximately 8-9% in HD males. All of the changes were not statistically significant and no histological correlates corresponded with the increased liver and kidney weights. Mean absolute and relative (to body weight) adrenal weights were increased by 10 to 40% in MD and HD males and in females at all PF-03709270 dose levels. In HD animals increased adrenal weights were associated with cortical hypertrophy. Also absolute and relative thymus weights were decreased by 26% to 72% compared to control values in MD and HD males and females. The decreased thymus weights correlated with histological findings of lymphoid depletion in the thymus. The increased adrenal weights and decreased thymus weights are consistent with treatment-related stress.
Histopathology	No liver or kidney histopathology was reported. GI tract: In the jejunum and, to a lesser extent, the ileum, minimal mucosal hyperplasia was noted in HD animals. The effects were subtle and likely reflected a slight increase in cell loss from villi and increased proliferation of crypt epithelium. Adrenal Glands and Thymus: Decreased cortical hypertrophy in HD animals and lymphoid depletion in HD males (minimal to marked) and females (moderate to marked) was consistent with a treatment-related stress response.
<u>[Other evaluations]</u>	Toxicokinetics: See Section 5.4

Abbreviations: HD, high dose; HCT, hematocrit; HGB, hemoglobin; LD, low dose; MD, mid dose; RBC, red blood cell

5.5.2. General Toxicology; Additional Studies

Study title/ number: 14-Day Oral Gavage Toxicity Study of PF-03709270 with and without Probenecid in Rats with a 14-Day Recovery Period/ Study No: 18IT001-(b) (4) - 417503-02

- In male and female rats administered 800 mg/kg PF-03709270 with and without probenecid, histopathology findings included accumulations of seromucinous secretions along with degeneration of the nasal epithelium and slight osteolysis of turbinate bones. The nasal findings were reduced for incidence and severity after the recovery period and may have been related to nasal reflux exposure to gavage fluids.
- Histopathology findings in the large intestine of male and female rats receiving 800 mg/kg/day PF-03709270 with or without probenecid included infiltrates of mixed inflammatory cells and hyperplasia of the glandular epithelium. The large intestine findings were fully reversible after the recovery period.
- Concomitant administration of 200 mg/kg/day probenecid with 800 mg/kg/day PF-03709270 did not substantially change PF-03709270-related findings.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

Table 40. Methods for Study No.: 18IT001-(b) (4)-417503-02

Method	Details
Dose and frequency of dosing:	Animals were dosed once per day for 14 days in the following groups and doses: Group 1 (vehicle for PF-03709270); Group 2 (vehicle and 200 mg/kg/day probenecid); Group 3 (100 mg/kg/day PF-03709270); Group 4 (800 mg/kg/day PF-03709270); Group 5 (100 mg/kg/day PF-03709270 and 200 mg/kg/day probenecid; and Group 6 (800 mg/kg/day PF-03709270 and 200 mg/kg/day probenecid)
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% methylcellulose
Species/Strain:	Cynomolgus monkeys
Number/Sex/Group:	10/sex/group
Age:	7 weeks old
Satellite groups/ unique design:	Toxicokinetic animals (3/sex/group for Group 1 and 9/sex/group for Groups 2-6) and recovery animals (5/sex/group). Main Study animals were administered vehicle or test articles once per day by oral gavage for 14 days before the planned termination on Day 15. Recovery animals were maintained for an additional 2 weeks without additional dosing until the planned termination on Day 29.
Deviation from study protocol affecting interpretation of results:	No

Table 41. Observations and Results: Changes From Control (Study No.: 18IT001-(b) (4)-417503-02)

Parameters	Major Findings
Mortality	All animals survived until the scheduled euthanasia date.
Clinical Signs	No clinical signs related to PF-03709270 or probenecid were observed.
Body Weights	Body weights were similar in all groups for males and females.
Feed Consumption	No change in food consumption was observed.
Ophthalmoscopy	No toxicologically relevant ophthalmoscopy findings were observed.
Hematology	No changes related to test-article administration were observed.
Clinical Chemistry	Urea Nitrogen: Statistically significantly lower urea nitrogen levels in serum were observed in males and females in Groups 4 (800 mg/kg PF-03709270) and Group 6 (800 mg/kg PF-03709270:200 mg/kg probenecid) at the end of dosing on Day 15. In males, urea nitrogen levels were decreased by 29% and 25% in Groups 4 and 6, respectively, and in females urea nitrogen levels were decreased by 20% and 25% in the same respective groups. At the end of the recovery period on Day 30, urea nitrogen levels were similar in all groups. Creatinine: Serum creatinine was statistically significantly increased in Groups 5 (100 mg/kg PF-03709270: 200 mg probenecid) and 6 in males and females at the end of dosing on Day 15. In males, serum creatinine levels were 28% and 32% increased, and in females creatine levels were approximately 9% and 6% increased respectively in Groups 5 and 6 on Day 15. On Day 30 after the recovery period, creatine levels were similar in all groups. Renal impairment generally results in increased circulating levels of both urea nitrogen and creatinine. In this case urea nitrogen levels were reduced in the groups receiving the highest doses of PF-03709270. Reductions in urea nitrogen might indicate that less is being produced by the liver. Given the reversibility of the findings and in the absence of histological correlates in the liver or kidney, the toxicological relevance of the findings is not clear.
Urinalysis	Urine specific gravity was significantly higher for females in Group 6 (1.050) compared to the mean control value (1.025) at the end of dosing on Day 15. However, a similar effect was not observed in males in Group 6 or in the other treatment groups on Day 15 and specific gravity values were similar in all groups for both sexes at the end of the recovery period on Day 29.
Gross Pathology	No gross pathology findings were considered to be related to administration of PF-03709270 or probenecid or the combination.

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{sulopenem etzadroxil/probenecid}

Parameters	Major Findings
Organ Weights	Absolute and relative kidney weights were statistically significantly increased at the end of dosing on Day 15 in Groups 4, 5 and 6 with smaller percentage increases in Group 5 in both males and females compared to vehicle control values (Table 42 and Table 43). However, in the absence of histological correlates, the basis of the increased kidney weights is not clear. At the end of the recovery period on Day 30, kidney weights were similar in all groups.

Table 42. Absolute and Relative Kidney Weights for Males on Day 15 in the PF-03709270/Probenecid Combination Toxicology Study

Parameter	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Terminal Body Weight	271.5	275.6	279.9	273.5	286.1	268.3
Absolute Brain Weight	1.8934	1.9570	1.9816	1.9662	1.9952	1.928
Absolute Kidney Weight (g)	2.1860	2.3213	2.4090	2.678** (+22.5%)	2.512* (+14.9%)	2.573** (+17.7%)
RBW Kidney	0.80478	0.84231	0.86015	0.9833** (+22.2%)	0.8771* (+9.0%)	0.9599** (+19.3%)
RbrW Kidney	115.43	118.68	121.59	136.47** (+18.3%)	125.52 (+8.7%)	133.53** (+15.7%)

Source: Data from the Study Report
Statistically significant compared to Group 1 control values: * p ≤ 0.05; ** p ≤ 0.01
Abbreviations: RBW, relative to body weight; RbrW, relative to brain weight

Table 43. Absolute and Relative Kidney Weights for Females on Day 15 in the PF-03709270/Probenecid Combination Toxicology Study

Parameter	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Terminal Body Weight	206.9	203.6	202.2	197.8	209.3	200.1
Absolute Brain Weight	1.8749	1.870	1.8673	1.863	1.874	1.846
Absolute Kidney Weight (g)	1.7141	1.680	1.7641	1.931** (+12.7%)	1.828 (+6.6%)	1.895* (+10.6%)
RBW Kidney	0.82914	0.8262	0.8728	0.9768** (+17.8%)	0.8723 (+5.2%)	0.9474** (+14.3%)
RBrW Kidney	91.42	89.95	94.58	103.63** (+13.4%)	97.55 (+6.7%)	102.71** (+12.4%)

Source: Data from the Study Report
Statistically significant compared to Group 1 control values: * p ≤ 0.05; ** p ≤ 0.01
Abbreviations: RBW, relative to body weight; RbrW, relative to brain weight

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

Parameters	Major Findings
Histopathology Adequate battery: Yes	Large Intestine: PF-03709270-related microscopic findings were noted in the large intestine (cecum, colon, and/or rectum) of both sexes. Findings were more prevalent and severe in the females. Intestinal changes (infiltrates of mixed inflammatory cells, hyperplasia of the glandular epithelium, and edema) and were most prevalent in females in Group 4 (800 mg/kg/day PF-03709270) and in the males and females in Group 6 (800:200 mg/kg/day PF-03709270: probenecid) with a slight increase in incidence and severity in Group 6. Nasal Findings: Histologic changes in the nose consisted of accumulations of seromucinous secretions along with degeneration of the nasal epithelium and slight osteolysis of turbinate bones. Nasal findings were most prevalent in both sexes administered 800 mg/kg/day PF-03709270 (Group 4) and 800:200 mg/kg/day PF-03709270:probenecid (Group 6). However, nasal alterations were occasionally noted in both sexes administered lower dose concentrations of PF-03709270 alone or in combination with probenecid. The nasal findings were reduced for incidence and severity after the recovery period and may have been related to nasal reflux exposure to gavage fluids.
<i>[Other evaluations]</i>	Toxicokinetics: See Section 5.4

5.5.3. Genetic Toxicology

In Vitro Reverse Mutation Assay in Bacterial Cells (Ames)

Study title/ number: PF-03709270: Bacterial Mutagenicity Assay/ Study No.: 05GR022

Key Study Findings:

- In the presence of S9 activation, cytotoxicity for some tester strains occurred at low concentrations of PF-03709270 (≥ 1.5 $\mu\text{g}/\text{plate}$) thus limiting the range of noncytotoxic concentrations that were suitable for mutagenicity testing.
- PF-03709270 did not produce a significant dose-related increase in the number of revertant colonies compared to the negative controls with any of the tester strains with and without S9 activation in the test conditions.

GLP compliance: Yes

Test system: *Salmonella typhimurium* strains TA 1535, TA 1537, TA 98, and TA 100 and *Escherichia coli* strain WP2 uvrA pKM101.

Study is valid: Yes, but limited by the range of nontoxic doses that could be tested.

Study title/ number: Mutagenicity Studies of CP-70429/ Study No.: 90-70429-ames

Key Study Findings:

- Cytotoxicity occurred at low concentrations of PF-03709270 thus limiting the range of noncytotoxic concentrations that were suitable for mutagenicity testing.
- CP-70429-2 was not mutagenic in bacteria in an Ames assay in the testing conditions.

GLP compliance: Yes

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

Test system: *Salmonella typhimurium* strains TA-1535, TA-1537, TA-98 and TA-100; *Escherichia coli* strain WP2uvrA

Study is valid: Yes, , but limited by the range of nontoxic doses that could be tested.

In Vitro Assays in Mammalian Cells

Study title/ number: CHO HGPRT Forward Mutation Assay With a Confirmed Assay With CP-70,429 and Degraded CP-70,429 Solution/ Study No.: 04-688-07.

Key Study Findings:

- CP-70,429 and degraded CP-70,429 solution were considered to be negative for inducing forward mutations at the HGPRT locus in CHO cells with and without metabolic activation under the conditions used in this study.

GLP compliance: Yes

Test system: CHO-K1-BH₄ Chinese hamster ovary (CHO) cells.

Study is valid: Yes

Study title/ number: Exploratory In Vitro Micronucleus Assay of PF-03709270-00/ Study No.: PF-03709270-00-2005-3QM-GN

Key Study Findings:

- PF-03709270 was positive in the presence and absence of S9 activation in this *in vitro* cytogenetic assay.

GLP compliance: No

Test system: CHO-WBL Chinese hamster ovary cells.

Study is valid: Yes

Study title/ number: Genetic Toxicology Report: PF-03709270 Human Lymphocyte Assay/ Study No.: 06GR288

Key Study Findings:

- PF-03709270 was positive for abnormal cells and polyploidy in the absence of S9 activation in an *in vitro* cytogenetic assay.

GLP compliance: Yes

Test system: Cultured human lymphocytes from a healthy adult donor

Study is valid: Yes

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Study title/ number: Chromosome Aberration Assay of CP-70,429/ Study No.: 90-70429-chrom

Key Study Findings:

- CP-70,429-2, with and without S9 mix, was associated with a significant increase in the frequency of cells with chromosome aberrations. Based on these results, CP-70,429-2 induced chromosome aberrations of V79 cells under the stated conditions in this study.

GLP compliance: Yes

Test system: V79 cells derived from Chinese hamster lungs.

Study is valid: Yes

In Vivo Clastogenicity Assay in Rodent (Micronucleus Assay)

Study title/ number: 1-Month Oral Toxicity and Micronucleus Study of PF-03709270 in Rats/
Study No.: 06GR263

Key Study Findings:

- None of the PF-03709270 doses were associated with reductions in polychromatic erythrocytes or increases in micronuclei in polychromatic erythrocytes in rat bone marrow.

GLP compliance: Yes

Test system: Sprague-Dawley rats [CrI: CD(SD)], 9 weeks old, administered doses of 0 (vehicle), 100, 400, and 2000 mg/kg PF-03709270 by oral gavage for 30 days. On Day 31, animals (5/sex/group) were euthanized and polychromatic erythrocytes in bone marrow were evaluated for micronuclei.

Study is valid: Yes, all the negative and positive control values were within the historical control range.

Study title/ number: Micronucleus Assay of CP-70,429-2/ Study No.: 90-70429-micron

Key Study Findings:

- CP-70,429-2 did not induce micronucleus formation in mouse bone marrow cells under the stated conditions. There was also no evidence of toxicity to bone marrow hematopoietic function.

GLP compliance: Yes

Test system: Male ICR mice (SPF, Slc), 8 weeks old were administered single intraperitoneal injections of 0, 500, 1000, and 2000 mg/kg CP-70429-2. Animals were euthanized 30 hours after dosing and the number of micronucleated polychromatic erythrocytes (MNPCE) were determined in 1000 bone marrow cells.

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Study is valid: Yes. Although no historical control data was provided, the positive control group had a very high percentage of MNPCE and the negative control group had a low percent MNPCE value (0.06%).

Study title/ number: In vivo Micronucleus Assay/ Study No.: 05-688-11

Key Study Findings:

- CP-70,429 administered by intravenous injection in doses up to 2000 mg/kg did not induce micronuclei in rat bone marrow polychromatic erythrocytes under the stated conditions in this study.

GLP compliance: Yes

Test system: Sprague-Dawley rats/ Crl: CD(SD); 5-7/sex/group administered vehicle (0.225% NaCl) or 500, 100, and 2000 mg/kg/day CP-70,429 as single IV boluses for two consecutive days. Animals were euthanized 24 hours after the last dose and 2000 polychromatic erythrocytes in bone marrow were counted and evaluated for MNPCE.

Study is valid: Yes. The positive controls produced a significant increase in the number of MNPCE. The number of MNPCE from vehicle controls was within the historical control range.

5.5.4. Carcinogenicity

No carcinogenicity studies have been conducted for sulopenem etzadroxil or sulopenem.

5.5.5. Reproductive and Developmental Toxicology

Fertility and Early Embryonic Development

Study title/ number: Oral Fertility and Early Embryonic Development Study of PF-03709270 in Male and Female Rats With Concurrent Dosing/ Study No.: 08GR017

Key Study Findings

- No PF-03709270-related effects on the copulation index, fertility index, sperm motility or sperm concentration was observed in male rats.
- There were no significant PF-03709270-related effects on the copulation and fertility indexes in females or on the number of corpora lutea, implantation sites, resorptions, and pre- and post-implantation losses.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 44. Methods for Study No.: 08GR017

Method	Details
Dose and frequency of dosing:	0 (Group 1, vehicle control), 100 (Group 2, low-dose), 400 (Group 3, mid-dose), and 2000 (Group 4, high-dose) mg/kg administered once per day
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% methylcellulose
Species/Strain:	Sprague Dawley Rats
Number/Sex/Group:	20/sex/group
Satellite groups:	No toxicokinetic animals were included, but a single blood sample was collected from each animal 1 hour before dosing on Gestation Day (GD) 12.
Study design:	This study was initiated on February 6, 2008. Doses of PF-03709270 were administered orally by gavage once daily. Females were dosed for 14 days prior to mating, throughout the cohabitation period, and continuing through GD 7. Males were dosed for a minimum of 63 days, beginning 28 days prior to cohabitation. Males in each group were mated with females in the same group. All surviving maternal animals were euthanized on GD 14. Following a minimum of 63 days of dosing, all surviving males were euthanized.
Deviation from study protocol affecting interpretation of results:	No

Table 45. Observations and Results (Study No.: 08GR017)

Parameters	Major Findings
Mortality	Two males (euthanized on Days 18 and 57) and four females (euthanized on Days 5, 6, 10, and 29) in the HD group were euthanized in extremis for what were considered treatment related causes. The animals demonstrated rapid weight loss, and dyspnea. At the time of necropsy, the animals demonstrated cecum enlargement and dilated gastrointestinal tracts.
Clinical Signs	PF-03709270-related loose stools were noted in 16 males and 1 female in the HD group and 4 males in the MD group. Also, in the HD group, one female displayed dyspnea, and one male and one female exhibited noisy respiration.
Body Weights	Males: Mean body weights for HD males were statistically significantly reduced on Treatment Day 4 (6-14% compared to the vehicle control group). Mean male body weights in the MD group were statistically significantly reduced compared to the vehicle control group by 3-4% on Treatment Days 8, 11, and 15. Females: Mean body weights in HD females were not affected during the pre-mating phase, but mean body weights were decreased 6-12% on Gestation Days 7, 10, and 14 compared to the vehicle control group. Maternal body weight gains during Gestation Day intervals 0-7 (treatment period) and 7-14 (post-treatment period) were reduced 45% and 21%, respectively, relative to the vehicle control group in HD females.

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

Parameters	Major Findings
Feed Consumption	Males: HD males demonstrated treatment-related, statistically significant decreased food consumption of up to 42% compared to animals in the vehicle control group. MD males also experienced transient decreases (13-22%) in food consumption on Treatment Days 4 and 8. Females: Female rats in the HD group experienced treatment-related statistically significant decreases in food consumption of 10-49% compared to controls on pre-mating Days 4, 8, and 11 and Gestation Day 3. Also, in MD females, there was a transient reduction in food consumption of 21% on pre-mating Day 4.
Necropsy findings [Mating/Fertility Index, Corpora Lutea, Preimplantation Loss, etc.]	Males: No PF-03709270-related effects on the copulation index, fertility index, sperm motility or sperm concentration was observed. A statistically significant decrease in the absolute weight of the male accessory sex organs (prostate, seminal vesicles and coagulating glands weighed as a unit) was noted in HD males. However, absolute testes weights were not decreased, and there was no differences from control when expressed as a ratio of body weight (as the body weight also decreased) suggesting the results were influenced by decreased terminal body weights in HD males. Females: There were no significant PF-03709270-related effects on the copulation and fertility indexes in females. HD females demonstrated a statistically significant increase in estrous cycle length (4.44 days compared to 4.05 days for the controls), and a decrease in the number of estrous cycles (3.38 estrous cycles compared to 3.75 estrous cycles in the controls). The Applicant did not consider the changes to be toxicologically meaningful because they were within historical value ranges, and there were no effects on the number of cohabitation days, copulation rates, and subsequent reproductive functions. There were no significant PF-03709270-related effects on the number of corpora lutea, implantation sites, resorptions, and pre- and post-implantation losses. HD females experienced a statistically significant decrease in the number of viable fetuses (14.7 compared to 16.4 in the vehicle controls), however both numbers fell within historical control range (12.4 to 16.7).

Abbreviations: HD, high dose; LD, low dose; MD, mid dose

Embryo-Fetal Development

Study title/ number: Oral (Gavage) Developmental Toxicity Study of PF-03709270 in Mice/
Study No.: 09GR119

Key Study Findings

- Cleft palate was increased in the high-dose group for litter and fetal incidence compared to the concurrent control and the historical control range.
- In the HD group, 10/25 pregnant female mice died or were prematurely euthanized and death was generally preceded by clinical signs including decreased motor activity, signs of respiratory distress, abdominal distention, mild to severe dehydration and hunched posture.

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
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- The NOAEL for maternal toxicity and fetal toxicity was considered to be the mid dose of 400 mg/kg/day.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 46. Methods for Study No.: 09GR119

Method	Details
Dose and frequency of dosing:	0 (Group 1, vehicle control), 100 (Group 2, low-dose), 400 (Group 3, mid-dose) and 2000 (Group 4, high-dose) mg/kg/day administered once per day from Gestation Day (GD) 6 to GD 15.
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% methylcellulose (4000 centipoise)
Species/Strain:	Mice/ CrI:CD1(ICR)
Number/Sex/Group:	25 pregnant females per group in the Main Study
Satellite groups:	For toxicokinetic analysis: 9 pregnant females in Group 1 and 15 pregnant females each in Groups 2-4.
Study design:	The study was conducted in 2009. Male rats were used only for breeding and were not considered to be part of the test system. Pregnant female mice were administered the test article or vehicle once daily on GDs 6 through 15. All surviving female mice were euthanized on GD 18 and Caesarean section and necropsy was performed. Caesarean section parameters were evaluated and fetuses were evaluated for external, visceral, and skeletal malformations and variations.
Deviation from study protocol affecting interpretation of results:	No

Table 47. Observations and Results (Study No.: 09GR119)

Parameters	Major Findings
Mortality	In the HD group, 10/25 pregnant female mice died or were prematurely euthanized between GD 11 and GD 16 prior to the scheduled termination. The incidence of mortality was statistically significantly increased in the HD group compared to the vehicle control group. Death was generally preceded by decreased motor activity, signs of respiratory distress, abdominal distention, mild to severe dehydration, and hunched posture. At necropsy, each mouse had gaseous distention of the stomach and/or the intestines. The deaths was attributed to PF-03709270.
Clinical Signs	Clinical signs were observed in HD females including signs of respiratory distress (rales, dyspnea, gasping, open mouth breathing, and bradypnea), abdominal distention, decreased motor activity, cold to touch, mild to severe dehydration, pale and/or dark red appearance to one or more body parts (mouth, eyes, ears, paws and/or tail), ptosis, hunched posture, ungroomed coat, soft or liquid feces and red perivaginal substance. The clinical signs occurred primarily in the HD females that died or were prematurely euthanized. PF-03709270-related clinical signs were not observed in LD or MD females.

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

Parameters	Major Findings
Body Weights	Mean maternal body weight was statistically significantly reduced by 6% to 8% in HD females on GDs 13, 14, and 15 compared to the vehicle control mean value. Mean body weight gain in HD females was significantly reduced by 16% for the entire dosage period (GD 6 to GD 16) relative to the mean vehicle control value and also for the GD 9 to GD 12 (-41%) and the GD 12 to GD 16 (-23%) intervals. After the end of dosing and before the scheduled caesarean section on GD 18, body weight gains in the HD group were reduced by 14% compared to control values in the GD 16 to GD 18 interval. Gravid uterine weights in the HD group were 11% lower than control values. Mean body weights and body weight gains in the LD and MD groups were similar to vehicle control values.
Necropsy findings Cesarean Section Data	In pregnant females that survived until the scheduled euthanasia, no gross lesions were attributed to PF-03709270 administration even in the HD group. In the HD females that died or were prematurely euthanized, the incidence of gaseous distension of the stomach and/or the intestines was significantly increased relative to vehicle control values. Enlarged gallbladder was also observed in two of the HD females with enlarged stomachs/intestines. Pregnancy occurred in 23/25, 25/25, 24/25, and 22/25 female mice in the vehicle control, LD, MD, and HD groups, respectively. Because 9/22 pregnant females in the HD group died or were euthanized in extremis prematurely, only 13/22 HD females underwent Caesarean section on GD 18. No caesarean section parameters were affected by dosages of PF-03709270 as high as 2000 mg/kg/day. The litter averages for corpora lutea, implantations, litter sizes, live fetuses, early and late resorptions, the percentage of resorbed conceptuses, and the percentage of live male fetuses were similar in all groups. There were no dead fetuses and all placenta appeared normal.
Necropsy findings Offspring	Mean fetal weights at birth were significantly reduced for male and female offspring and for pooled results for both sexes in the HD group. All of the HD values were at or below the nadir of the historical control range (Table 48).

Table 48. Summary of Fetal Weights in Study No.: 09GR119

Parameter	0 (Vehicle) MKD	100 MKD	400 MKD	2000 MKD	Historical Control Data (2004 to 2008) ^a
Combined Fetal Body Weights/Litter (g)	1.31	1.28	1.26	<u>1.21</u>	1.32 (1.22-1.41)
Male Fetuses	1.34	1.30	1.30	<u>1.23</u>	1.35 (1.23-1.44)
Female Fetuses	1.29	1.25	1.23	<u>1.19</u>	1.30 (1.20-1.38)

MKD = mg/kg/day

g = grams

a. Mean and range based on 29 studies conducted at the Testing Facility from June 2004 to June 2008.

Bold and underlined = test article-related.

Source: Study Report

External Alterations: No external malformations were considered to be increased in the PF-03709270 dose groups except for a significant increase in the HD group for the percent litter incidence (23.1%) and percent fetal incidence (8.1%) of cleft palate compared to the vehicle control group (litter incidence of 4.3% and fetal incidence of 0.4%). The litter and fetal incidence for cleft palate in HD fetuses also exceeded the highest incidences in the historical control data which had a range of 0 – 17.6% for litter incidence and 0 – 3.2% for fetal incidence of cleft palate. Cleft palate occurred with similar litter and fetal incidences in the 100 and 400 mg/kg/day groups compared to the vehicle control group. Exclusive of cleft palate, only one additional external

Parameters	Major Findings
	malformation, rotated fore and/or hindlimb occurred in the MD (litter incidence of 12.5% and fetal incidence of 1.0%) and HD (litter incidence of 15.4% and fetal incidence of 1.2%) groups with a higher litter and fetal incidence compared to the vehicle control group (litter incidence of 4.3% and fetal incidence of 0.4%). However, the litter and fetal incidences for this malformation in the MD and HD groups were within the historical control range (litter incidence range of 0.0 to 45.0%; fetal incidence range of 0.0% to 3.5%). <u>Visceral Alterations:</u> A clear PF-03709270-related visceral malformation was cleft palate. Cleft palate detected as a visceral malformation was statistically significantly increased for litter (23.1%) and fetal incidence (10.5%) compared to the control group (litter incidence of 4.3% and fetal incidence of 0.8%). Also, the litter and the fetal incidence for the HD group were outside the historical control range for visceral cleft palate (0 - 5.9% for litter incidence and 0 - 1.9% for fetal incidence). No other visceral malformations were increased for litter or fetal incidence compared to the vehicle control group. No visceral variations were observed in any group. <u>Skeletal Alterations:</u> The litter and fetal incidence of the skeletal malformation, incompletely ossified palate, was significantly increased in the HD group (litter incidence of 23.1%, fetal incidence of 7.1%) compared to the vehicle control group (litter incidence of 0.0%; fetal incidence of 0.0%). The HD values were also above the highest values in the historical control range (litter incidence range of 0 - 17.6% and fetal incidence range of 0 - 4.5%). Incompletely ossified palate was also observed in a single MD fetus (litter incidence of 4.2%; fetal incidence of 0.6%) but the incidence values were not statistically significantly higher than incidences in the vehicle control group or outside the historical control range. Other skeletal malformations, incompletely ossified frontals and parietals, and absence of ossified interparietals, occurred only in a single vehicle control fetus. Other skeletal alterations were considered to be variations and were not increased for incidence in any of the PF-03709270 treatment groups compared to the vehicle control group. <u>Fetal Ossification Sites:</u> The mean numbers (ossification sites per fetus per litter) of ossified caudal vertebrae, forelimb metacarpals and phalanges, and hindlimb tarsals and phalanges were reduced in the HD group compared to vehicle control values, but statistical significance was only achieved for the mean number of ossified hindlimb tarsals. The mean value for ossified hindlimb tarsals (0.48) was within the historical range; however, the mean number for ossified caudal vertebrae (7.04), forelimb metacarpals (3.92), forelimb phalanges (10.34) and hindlimb phalanges (9.38) were below the lowest value in the historical range. The delays in skeletal ossification in the HD group were consistent with maternal toxicity and reductions in fetal body weights in the HD group.

Abbreviations: HD, high dose; LD, low dose; MD, mid dose

Study title/ number: Oral Embryo-fetal Development Study of PF-03709270 in Rats/ Study No.: 08GR040

Key Study Findings

- PF-03709270-related clinical signs in most of the animals in the high-dose group consisted of alopecia, stained fur, hunched stance, and noisy respiration. Significant reductions in maternal body weight and body weight gain were observed in the mid- and high-dose groups.
- The number of viable fetuses were non-significantly decreased and mean fetal body weights were significantly reduced by 11% in the high-dose group compared to control values.
- No PF-03709270-related external, visceral, or skeletal malformations were observed, but two skeletal variations, unossified cervical centrum and unossified metatarsal, were increased in high-dose fetuses, and the increased variations were considered to be related to maternal toxicity.
- The NOAEL values for maternal and fetal toxicity were considered to be the low-dose (100 mg/kg/day) and the mid-dose (400 mg/kg/day) respectively.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 49. Methods for Study No.: 08GR040

Method	Details
Dose and frequency of dosing:	0 (Group 1; vehicle control), 100 (Group 2, low-dose), 400 (Group 3, mid-dose), and 2000 (Group 4; high-dose) mg/kg PF-03709270 was administered once per day from Gestation Day (GD) 6 to GD 17.
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% methylcellulose
Species/Strain:	Rat/ Sprague-Dawley
Number/Sex/Group:	20 females/group
Satellite groups:	Toxicokinetic analysis: 3 females for Group 1 and 5 females/group for Groups 2-4
Study design:	The study was conducted in 2008. Doses were administered orally by gavage once daily from Gestation Days (GD) 6 to GD 17 except for 4 rats from each group in the Main Study which were dosed from GD 5-17. Dams received cesarean sections and were euthanized on Day 21.
Deviation from study protocol affecting interpretation of results:	No

Table 50. Observations and Results (Study No.: 08GR040)

Parameters	Major Findings
Mortality	Deaths considered to be related to PF-03709270 administration included one HD female euthanized on GD 10 due to excess body weight loss and one HD female found dead on GD 19.
Clinical Signs	PF-03709270-related clinical signs in most HD females consisted of alopecia, stained fur, hunched stance, and noisy respiration. In the MD group, the only treatment-related clinical sign was noisy respiration in 2 animals.
Body Weights	Statistically significant PF-03709270-related reductions in maternal body weight and body weight gain were noted in the MD and HD groups. In the HD group, body weight gain over the dosing period (GD 6-18) was reduced by 42% and mean body weights were significantly reduced from GD 8 to GD 21 by 4-14% compared to control values. The effect was less pronounced in the MD group where body weight gain over the dosing period (GD 6-18) was significantly reduced by 17%, and mean body weights were significantly reduced from GD 14 to GD 21 by 3-6%. In the LD group, body weight gain over the entire treatment period (GD 6-18) was greater than that noted in the control group.
Feed Consumption	PF-03709270-related decreases in food consumption were noted in the MD and HD groups with significant 12% and 30% reductions over the treatment period for the two dose groups respectively. In the LD group a statistically significant decrease in food consumption was noted from GD 7-9 (11% reduction compared to control), however, food consumption over the entire treatment period was comparable to controls.
Necropsy findings Cesarean Section Data	No PF-03709270-related gross pathology findings were observed. Gravid uterus weights were significantly decreased in the MD and HD groups, and in the same groups, non-significant PF-03709270-related increases in the number of early resorptions and post-implantation losses and decreases in the number of viable fetuses were noted. Also, mean fetal body weights were significantly reduced by 11% in the HD group (5.09 g) compared to the mean control value (5.72 g). There were no treatment-related effects on any Cesarean section parameters in the LD group.
Necropsy findings Offspring	<u>External Alterations:</u> The only reported external malformation was an omphalocele in a single LD fetus. <u>Visceral Alterations:</u> None of the visceral malformations were statistically significantly increased for litter or fetal incidence in the PF-03709270-treatment groups compared to control values. Two malformations that did not occur in the vehicle control group occurred in single fetuses in the MD (single fetus with situs inversus) and the HD groups (single fetus with retroesophageal aortic arch). There were no PF-03709270-related increases in visceral variations. <u>Skeletal Alterations:</u> No skeletal malformations were reported. Two skeletal variations, unossified cervical centrum and unossified metatarsal, were statistically significantly increased for litter incidence in the HD group compared to the vehicle control group.

Abbreviations: GD, gestation day; HD, high dose; LD, low dose; MD, mid dose

Study title/ number: Oral Embryo-Fetal Development Study of PF-03709270 in Rabbits/ Study No.: 08GR037

Key Study Findings

- Maternal body weight gains were significantly reduced in a dose-dependent manner in all the PF-03709270 treatment groups. Average maternal food consumption was statistically

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significantly reduced daily from Gestation Day (GD) 8-22 in the mid- and high-dose groups and from GD 11-22 in the low-dose group.

- Post-implantation loss, the number of viable fetuses, gravid uterine weights, and mean fetal body weights were significantly reduced in the mid- and high-dose groups compared to control values.
- No external, visceral, or skeletal malformations were considered to be related to PF-03709270 administration.
- The NOAEL for maternal toxicity was considered to be <5 mg/kg/day. The NOAEL for fetal toxicity was considered to be the low dose of 5 mg/kg/day.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 51. Methods for Study No.: 08GR037

Method	Details
Dose and frequency of dosing:	PF-03709270 doses of 0 (Group 1, vehicle control), 5 (Group 2, LD), 15 (Group 3, MD), and 50 (Group 4, HD) mg/kg/day were administered once per day from Gestation Day (GD) 7 through GD 19.
Route of administration:	Oral Gavage
Formulation/Vehicle:	0.5% methylcellulose in water
Species/Strain:	Rabbits/ New Zealand White
Number/Sex/Group:	20 females/group
Satellite groups:	Toxicokinetic animals: 3 females in Group 1, and 4 females/group in Groups 2-4.
Study design:	This study was initiated on 2/14/2008. Pregnant female rabbits were administered vehicle or PF-03709270 by oral gavage from Gestation Day (GD) 7 through GD 19 followed by caesarean section and necropsy on GD 29.
Deviation from study protocol affecting interpretation of results:	No

Table 52. Observations and Results (Study No.: 08GR037)

Parameters	Major Findings
Mortality	One HD female was euthanized on GD 13 after displaying serious clinical signs (decreased activity, dehydration, dyspnea, loose or liquid stools with mucus, and fur stained in the anogenital regions) and experiencing 19% weight loss.
Clinical Signs	In surviving animals, no clinical signs were considered related to PF-03709270 administration.

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Parameters	Major Findings
Body Weights	No significant differences in mean body weights were observed for any of the PF-03709270 treatment groups. In HD dams, there were statistically significant decreases in body weight gain over the gestation intervals of GD 7 to GD 10 (reduced 133% compared to control values), GD 20 to GD 23 (reduced 83% compared to control values), and for the entire dosing period from GD 7 to GD 20 (reduced 60% compared to control values). In the MD group, a statistically significant decrease in body weight gain was noted over the gestation interval of GD 20 to GD 23 (reduced 50% compared to control values) and for the entire dosing period GD 7 to 20 (reduced 36% compared to control values). In the LD group, body weight gains were significantly decreased over the entire dosing period from GD 7-20 (reduced 28% compared to control values).
Feed Consumption	Average maternal food consumption in the MD and HD groups was statistically significantly reduced daily from GD 8-22 and over the intervals of 8-10, 11-13, 14-16, 17-20, and 8-20. In the LD group, food consumption was significantly reduced daily from GD 13-22 and over the intervals of 8-10, 14-16, 17-20, and 8-20. Average daily food consumption was significantly reduced in all the PF-03709270 treatment groups over the dosing period (GD 8 to GD 20) with dose-dependent reductions in daily food intake of 15%, 36% and 44% compared to control values for the LD, MD, and HD groups, respectively. For the GD 23 to 29 interval, food consumption was similar in all groups.
Necropsy findings Cesarean Section Data	No maternal necropsy findings were considered related to PF-03709270 administration. In the MD and HD groups, late resorptions were increased compared to control values with statistical significance achieved for the HD group. Also, post-implantation loss was significantly increased and the number of viable fetuses, and gravid uterine weights were significantly reduced in the MD and HD groups compared to control values. Mean fetal body weights were significantly reduced by approximately 9% and 7% in the MD and HD groups respectively with mean values of 39.75, 39.50, 36.30, and 37.09 grams for the control, LD, MD, and HD groups, respectively.
Necropsy findings Offspring	<u>External Alterations:</u> No external malformations were considered related to administration of PF-03709270. Two external malformations were reported: exencephaly in one vehicle control fetus and omphalocele in one MD fetus. <u>Visceral Alterations:</u> No visceral malformations were reported. Multiple visceral variations occurred with similar incidences in all groups. <u>Skeletal Malformations:</u> There were no PF-03709270-related skeletal malformations. Malformations (fused frontal, nasal, rib, and sternebra; absent interparietal, supraoccipital, and thoracic arch; hemicentric thoracic centrum; and misshapen parietal) were either seen only in the concurrent control group or at incidence levels comparable to or below the concurrent control group. <u>Skeletal Variations:</u> Multiple skeletal variations were observed but only one variation was increased for incidence in a dose-dependent manner. The litter incidence of unossified forepaw phalanx was statistically significantly increased in both the MD group (litter incidence of 72.2%) and HD group (litter incidence of 84.6%) compared to the LD (litter incidence of 23.5%) and control (litter incidence of 21.1%) groups. This variation may have resulted from maternal toxicity and is consistent with the reduced fetal body weights observed in the MD and HD groups in this study.

Abbreviations: GD, gestation day; HD, high dose; LD, low dose; MD, mid dose

5.5.5.1. Prenatal and Postnatal Development

Study title/ number: Effects on Pre- and Post-Natal Development, Including Maternal Function, With Sulopenem Via Intravenous Injection and PF-03709270 via Oral Gavage in Sprague-Dawley Rats/ Study No.: 18IT001-8383180-02

Key Study Findings

Cohort I: IV Administration with Sulopenem

- Limited maternal toxicity was characterized by minimal reductions in body weight gains during the gestation period.
- F1 offspring did not experience sulopenem-related changes in viability, physical development, neurological development, or reproductive capacity.
- The NOAEL value for fetal development was considered to be the high-dose of 1000 mg/kg/day sulopenem.

Cohort II: Oral administration with PF-03709270

- Limited maternal toxicity was characterized by minimal reductions in body weights and/or body weight gains during the gestation period.
- F1 offspring did not experience PF-03709270-related changes in viability, physical development, neurological development, or reproductive capacity.
- The NOAEL value for fetal development was considered to be the high-dose of 1000 mg/kg/day PF-03709270.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

Table 53. Methods for Study No.: 18IT001-8383180-02

Method	Details
Dose and frequency of dosing:	Cohort I: Intravenous sulopenem (CP-70429) doses of 0 (Group 1, IV vehicle control), 90 (Group 2, IV low-dose), 300 (Group 3, IV mid-dose) and 1000 mg/kg/day (Group 4, IV high-dose); administered once per day from Gestation Day (GD 6) to Lactation Day (LD) 20 to maternal F0 females Cohort II: Oral PF-03709270 doses of 0 (Group 5, oral vehicle control), 100 (Group 6, oral low-dose), 300 (Group 7, oral mid-dose) and 1000 mg/kg/day (Group 8, oral high-dose); administered once per day from GD 6 to LD 20 to maternal F0 females
Route of administration:	Cohort I: Intravenous dosing of sulopenem Cohort II: Oral gavage dosing of PF-03709270
Formulation/Vehicle:	Cohort I: 0.225% physiologic saline for injection in sodium bicarbonate Cohort II: 0.5% methylcellulose 400 cps in deionized water.
Species/Strain:	Rat/ Sprague Dawley
Number/Sex/Group:	24 females per group for both cohorts

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 {sulopenem etzadroxil/probenecid}

Method	Details
Satellite groups:	Toxicokinetic animals: On GD 21 in both cohorts, blood was collected from 3 maternal females/group and their fetuses. On LD 14 in both cohorts, blood and lactation milk were collected from 8 F0 maternal females in each group and their fetuses.
Study design:	This study was initiated on June 7, 2018. F0 maternal females were dosed from GD 6 through LD 20 either intravenously with vehicle (0.225% physiologic saline) or CP-70429 (sulopenem, Cohort I) or via oral gavage with vehicle (0.5% methylcellulose) or PF-03709270 (sulopenem etzadroxil, Cohort II). At weaning, one first generation (F1) male and one female from each litter were selected to continue to the maturation phase. In the maturation phase, F1 animals were assessed for growth, sexual development, locomotor activity, reflex development, learning and memory, and reproductive capability (through GD 13 Cesarean sections for F1 females).
Deviation from study protocol affecting interpretation of results:	No

Abbreviations: GD, gestation day; IV, intravenous; LD, low dose

Table 54. Observations and Results (Study No.: 18IT001-8383180-02)

Generation	Major Findings
F0 Dams	Cohort I: IV Dosing with Sulopenem <u>Survival:</u> No sulopenem-related mortality occurred. <u>Clinical signs:</u> No sulopenem-related clinical signs were observed during gestation or during the lactation period. <u>Body Weight</u> Gestation Period: Mean maternal body weights were similar in all groups from GD 6 to GD 20. HD dams had significantly lower mean body weight gains during the intervals of GD 8 to GD 10 (-23.5%) and GD 14 to GD 16 (-18.1%) compared to control values. However, body weight gains in high-dose dams were significantly increased compared to control values after the end of dosing from GD 18 to GD 20 (+17.4%) and body weight gains from the beginning of dosing until GD 20 were similar in all groups. Lactation Period: No sulopenem-related effects on mean body weight gain or mean body weight for F0 dams were observed during the lactation period. <u>Uterine Content:</u> Dams in all groups delivered naturally on GD 23. No sulopenem-related effects on delivery or litter data were observed. Mean values for duration of delivery, gestation index, post-implantation loss and the number of mated and pregnant females, females with liveborn pups, pups delivered, and implantation sites was similar in all groups. Cohort II: Oral Dosing with PF-03709270 <u>Survival:</u> No mortality was considered to be related to PF-03709270 administration. <u>Clinical signs:</u> No PF-03709270-related clinical signs were observed during gestation or during the lactation period. <u>Body Weight</u> Gestation Period: Mean maternal body weights for the MD and HD groups were decreased by 3.9% and 3.7%, respectively, compared to the mean control body weight on GD 20. The MD group had significantly lower mean body weight gain by ≈51% in the GD 8 to GD 10 interval and by approximately 14% for the entire gestation period (GD 6 through 20). The HD group had significantly lower mean body weight gain by ≈28% in the GD 8 to GD 10 interval, by ≈18% in the GD 10 to GD 12 interval, by ≈39% in the GD 12 to GD 14 interval as well as by approximately 13% for the entire gestation period (GD 6 through 20) compared to control values. Lactation Period: Mean body weights for the entire lactation period (lactation day 0 to 21) for dams were significantly increased by 57% and 52% in the MD and HD groups, respectively, compared to the mean control value. <u>Uterine Content:</u> Females in all the groups delivered naturally on GD 23. No PF-03709270-related effects on delivery or any of the litter parameters were observed.

Generation	Major Findings
F1 Generation	Cohort I: IV Dosing With Sulopenem <u>Survival:</u> Survival and the viability index for F1 offspring was similar in all groups at birth, LD 4, and on LD 21. <u>Clinical signs</u> Lactation Phase: No sulopenem-related clinical signs were observed in F1 offspring. Maturation Phase: In the male and female F1 offspring retained for the reproduction study, no sulopenem-related clinical signs were observed during pre-mating, the mating period, or after mating. <u>Body Weight</u> Lactation Phase: Body weights for male and female F1 offspring were not statistically significantly different between groups at birth on LD 0, and on LDs 4, 7, 14, and 21. Maturation Phase: In the male and female F1 offspring retained for the reproduction study, no sulopenem-related body weight changes were observed during pre-mating, the mating period, or after mating. Gestation Period: In pregnant female F1 offspring included in the F1 reproduction assessment, body weight gain was significantly lower in the LD and HD groups compared to the mean control value during the GD 7 through GD 10 interval. However, the reduced weight gain did not occur in a dose-proportional manner and was not considered to be toxicologically relevant because weight gain was not reduced for the entire gestational period (from GD 0 until GD 13 when caesarean sections were performed), and body weight values were not affected. <u>Physical Development:</u> CP-70429 had no statistically significant effect on the measured physical development parameters in males (time to balanopreputial cleavage) or females (time to vaginal opening). <u>Neurological Assessment</u> No CP-70429-related effects on locomotor activity, acoustic startle responses, or water maze test results were considered related to CP-70429 administration. <u>Reproduction</u> Males: No CP-70429-related changes in the mating, fecundity, or fertility indexes were observed in males. Females: The mean number of estrous cycles and cycle length was similar in all groups. No CP-70429-related changes in the mating, fecundity, or fertility indexes were observed in females. All of the Caesarean section parameters were similar in all groups except the percent pre-implantation loss was nonsignificantly increased by 38.5% in the HD group. Cohort II: Oral Dosing With PF-03709270 <u>Survival:</u> Pup survival was similar in all groups with values between 90% and 100% in all groups for the livebirth index, the LD 4 viability index, and the LD 21 weaning index. <u>Clinical signs:</u> No clinical signs were attributed to PF-03709270 administration during the lactation period or the maturation period. <u>Body Weight</u> Lactation Phase: Body weights for male and female F1 offspring were not statistically significantly different between groups at birth on LD 0, and on LDs 4, 7, 14, and 21. Maturation Phase: No PF-03709270-related effects on mean body weight gain or mean body weight were observed in either sex during maturation or pairing. Gestation Period: Female F1 offspring that became pregnant in the reproduction assessment were maintained until GD 13 when caesarean sections were performed. Pregnant F1 females in the HD group had a non-significant 14% reduction in body weight gain for the period from GD 0 to GD 13 and mean body weights were non-significantly lower by 5.5% and 6.3% on GD 10 and GD 13 respectively compared to

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{sulopenem etzadroxil/probenecid}

Generation	Major Findings
	control values. The weight loss was considered to be PF-03709270-related but not substantially adverse. <u>Physical Development:</u> PF-03709270 had no statistically significant effect on the measured physical development parameters in males (time to balanopreputial cleavage) or females (time to vaginal opening). <u>Neurological Assessment</u> No statistically significant changes in locomotor activity, acoustic startle responses or water maze results were associated with PF-03709270 administration. <u>Reproduction</u> Males: No PF-03709270-related effects on mating, fecundity, or fertility indexes were observed for males. Females: No statistically significant changes in estrous cycle parameters and no PF-03709270-related effects on mating, fecundity, or fertility indices were observed for females. A nonsignificant increase in percent preimplantation loss occurred in the HD group, and because the mean value was outside the historical control range, this effect was considered to be likely related to PF-03709270 administration. All other caesarean section values including the numbers of: corpora lutea, implantation sites, litters with preimplantation loss, early resorptions, late resorptions, postimplantation loss, litters with live fetuses, and the percent postimplantation loss were not significantly different in the PF-03709270-treatment groups compared to control values.
F2 Generation	No data for F2 offspring was provided.

Abbreviations: GD, gestation day; HD, high dose; IV, intravenous; LD, low dose; MD, mid dose

5.5.6. Other Toxicology Studies

Study title/ number: Juvenile Toxicity and Toxicokinetic Oral Gavage and Intravenous Injection Study With Sulopenem and PF-03709270 in Sprague-Dawley Rats With up to a 4 Week Recovery Period/ Study No.: 181T001-8383182-02

Key Findings

- Kidney histopathology including tubular epithelial degeneration and tubular concretions occurred in juvenile rats with the lowest administered dose of sulopenem IV dose (60 mg/kg/day). Tubular concretions were present after a 2-week recovery period. The same pattern of kidney histopathology was evident with the lowest administered dose of oral PF-03709270 (25 mg/kg/day).
- No effects on sexual maturation and bone development, were caused by IV sulopenem doses up to 200 mg/kg/day or by oral PF-03709270 in doses up to 225 mg/kg/day. Neurological function in juvenile rats was also unaffected except for a delayed reduction in overall movement that occurred weeks after the end of dosing.
- Because poorly reversible kidney histopathology was evident with the lowest administered doses of IV sulopenem and oral PF-03709270 in juvenile rats, no NOAEL values were assigned in this study.

Conducting laboratory and location: (b) (4)

GLP compliance: Yes

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 {sulopenem etzadroxil/probenecid}

Table 55. Methods for Study No.: 181T001-8383182-02

Method	Details
Dose and frequency of dosing:	Cohort I: Group 1 (vehicle control I), Group 2 (60 mg/kg/day sulopenem; low-dose sulopenem), Group 3 (200 mg/kg/day sulopenem; mid-dose sulopenem), Group 4 (800 mg/kg/day sulopenem; high-dose sulopenem). Doses were administered from Postnatal Day (PND) 21 through PND 90. Cohort II: Group 5 (vehicle control II) Group 6 (25 mg/kg/day PF-03709270; low-dose PF-03709270), Group 7 (75 mg/kg/day PF-03709270; mid-dose PF-03709270); and Group 8 (225 mg/kg/day PF-03709270; high-dose PF-03709270). Doses were administered from PND 5 to PND 90.
Route of administration:	Cohort I: Intravenous (IV) injection of sulopenem Cohort II: Oral gavage of PF-03709270
Formulation/Vehicle:	Cohort I: Vehicle I for IV dosing: 0.225% Physiologic Saline for Injection in Sodium Bicarbonate. Cohort II: Vehicle II for oral gavage dosing: 0.5% methylcellulose 400 cps in deionized water
Species/Strain:	Rat/ Sprague Dawley, CrI:CD(SD)
Number/Sex/Group:	15/sex/group for both Cohorts
Age:	Cohort I: PND 21 at the start of dosing Cohort II: PND 5 at the start of dosing
Satellite groups/ unique design:	<u>Toxicokinetic animals</u> Cohort I: 6/sex in Group 1 and 15/sex/group in Groups 2-4. Cohort II: 12/sex in Group 5 and 30/sex/group in Groups 6-8. <u>Recovery animals:</u> 10/sex/group for both cohorts <u>Unique Design:</u> This GLP-compliant study was initiated on July 20, 2018. Male and female juvenile rats were administered IV sulopenem from Postnatal Day (PND) 21 up to PND 90 via intravenous injection (Cohort I) or PF-03709270 by oral gavage from PND 5 to PND 90. For the Main Study, sulopenem was administered in doses of 60, 200, or 800 mg/kg/day and PF-03709270 was administered in doses of 25, 75, or 225 mg/kg/day. Due to drug-related tail damage all the Cohort I animals receiving 800 mg/kg/day IV sulopenem were euthanized prematurely before the end of dosing.
Deviation from study protocol affecting interpretation of results:	No

Table 56. Observations and Results: Changes From Control (Study No.: 181T001-8383182-02; Cohort I)

Cohort I: IV Dosing With Sulopenem	
Parameters	Major Findings
Mortality	One HD male receiving 800 mg/kg/day sulopenem was euthanized on PND 59 due to clinical observations of convulsions, ataxia, hyperreactivity and vocalization. The cause of the clinical signs was not certain. Two females and one female in the control group were found dead on PND 27 or PND 62 (the 2 males) and PND 59 (the female). All the remaining males and females in the HD group (800 mg/kg/day) including recovery animals were euthanized prematurely on PNDs 39, 46, 55, or 60 due to severely damaged tails with findings of hyperkeratosis, exudate, and/or epidermal necrosis.
Clinical Signs	Males and females in the control group and in all the sulopenem treatment groups exhibited tail injection-site reactions that included scabs, scaly skin, red or pale discoloration, swollen, or sores beginning on PND 30 (9 days after dosing initiation) and lasting until euthanization. The incidence and severity of the tail effects increased in a sulopenem dose-dependent manner. After the recovery period, the incidence of tail observations decreased in both sexes with a 10-20% incidence remaining in surviving animals in the LD, MD, and control groups.
Body Weights	No sulopenem-related reductions in mean body weight gain or mean body weight were observed for either sex during the dosing or recovery periods.
Feed Consumption	No sulopenem related effects on food consumption was observed during the dosing or recovery periods.
Ophthalmoscopy	No sulopenem-related ophthalmology findings were observed during the dosing or recovery periods.
Hematology	The hematology changes that were observed were not considered to be toxicologically relevant.
Clinical Chemistry	None of the changes in serum chemistry were considered to be toxicologically relevant.
Sexual Maturation	Sulopenem had no effect on the observed dates of balanopreputial separation or vaginal opening at any of the administered doses compared to control values.
Neurobehavioral Assessment	The few changes in locomotor activity, acoustic startle response, and Morris Water Maze parameters were not considered to be toxicologically relevant.
Bone Evaluation	Sulopenem administration had no effect on femur length or bone mineral density in males or females during the dosing and recovery periods.
Gross Pathology	Gross pathology findings mirrored clinical signs and consisted of scaly or discolored skin/subcutis/tails in animals receiving ≥ 60 mg/kg/day sulopenem. The gross pathology findings correlated with hyperkeratosis, exudate, and epidermal necrosis in the tails of afflicted animals.

Cohort I: IV Dosing With Sulopenem

Organ Weights Increased kidney weights in males and females in the 200 mg/kg/day group correlated with histology findings of hyperplasia and hypertrophy of tubule epithelial cells. In males and females, the absolute kidney weights and kidney weights relative to body and brain weights were all significantly increased compared to control values. Absolute kidney weights and kidney weights relative to brain weight were also significantly increased in females administered 60 mg/kg/day sulopenem (Table 57).

Table 57. Sulopenem-Related Effects on Kidney Weights at the End of the Dosing Period

Dose Level (mg/kg/day)	Sex	Sulopenem					
		Males			Females		
		0	60	200	0	60	200
Kidney	Absolute Weight (g)	2.9537	104	112*	1.7447	104*	105*
	Body Weight Ratio (%)	0.6591	108	119*	0.6581	107	113*
	Brain Weight Ratio (%)	138.892	105	113*	88.4024	103*	106*

* = Statistically significant difference (absolute or relative) compared with respective control mean value.

Note: Values for absolute weight and ratio of organ weights (relative to body or brain) for Sulopenem-treated groups expressed as a percentage of the control mean value.

Source: Study Report

After the recovery period, kidney weights remained increased in males (absolute and relative to brain weight) in the 200 mg/kg/day group and females (absolute and relative to brain and body weight) in the 60 and 200 mg/kg/day groups. However, the magnitude of the increased kidney weights was reduced after the recovery period consistent with a degree of reversal.

Cohort I: IV Dosing With Sulopenem

Histopathology Adequate battery: Yes Sulopenem-related histology findings included hyperplasia and/or hypertrophy of tubule epithelial cells in males in the 200 mg/kg/day group and females in the 60 and 200 mg/kg/day groups (Table 58). These findings correlated with increased kidney weights in the same groups. Minimal tubule degeneration occurred at a low incidence in males administered 60 or 200 mg/kg/day but not in females. Degeneration was characterized by vacuolation, granular cytoplasm, or increased apoptotic cells.

Table 58. The Incidence and Severity of Sulopenem-Related Histology Findings in the Kidney at the End of the Dosing Period

Dose Level (mg/kg/day)	Sex	Sulopenem					
		Males			Females		
		0	60	200	0	60	200
Kidney	Number Examined	14	15	15	14	15	15
Hyperplasia, tubule cell	Minimal	0	0	4	0	0	0
Hypertrophy, tubule cell	Minimal	0	0	9	0	1	1
Degeneration, tubule	Minimal	0	1	3	0	0	0
Basophilic tubule	Minimal	11	8	8	2	1	2

Source: Study Report

After the recovery period, microscopic findings in the kidney persisted generally with decreased severity (Table 59). However, some findings, such as tubule hyperplasia in 4/10 males in the 60 mg/kg/day group and 1/10 females in the 200 mg/kg/day group occurred in groups where the same finding was not reported at the end of the dosing period. Also, an incidence of minimal intratubular concretions occurred in male and female animals in the 60 or 200 mg/kg/day groups, but the same finding was not reported for any group in the necropsy at the end of the dosing period.

Table 59. The Incidence and Severity of Sulopenem-Related Histology Findings in the Kidney at the End of the Recovery Period

Dose Level (mg/kg/day)	Sex	Sulopenem					
		Males			Females		
		0	60	200	0	60	200
Kidney	Number Examined	9	10	10	10	10	10
Degeneration tubule	Minimal	0	0	2	0	0	0
Hyperplasia, tubule cell	Minimal	0	4	2	0	0	1
	Slight	0	0	2	0	0	0
Concretion, tubule	Minimal	1	6	5	0	1	2

Source: Study Report

[Other evaluations] **Toxicokinetics:** See Section 5.4

Abbreviations: LD, low dose; MD, mid dose; HD, high dose; PND, postnatal day

Table 60. Observations and Results: Changes From Control (Study No.: 181T001-8383182-02; Cohort II)

Cohort II: Oral Dosing With PF-03709270	
Parameters	Major Findings
Mortality	One male and two females in the HD group (225 mg/kg/day) were euthanized in a moribund condition on PND 7. Clinical observations on the day of euthanasia included thin appearance, hypoactive, irregular respiration, and pale body. Two HD males and one female were found dead on PND 7 and one HD male was found dead on PND 16.
Clinical Signs	No PF-03709270-related clinical signs other than those noted for the HD animals that were euthanized in moribund condition were observed during the dosing or recovery period.
Body Weights	In male rats, no statistically significant reductions in body weight or body weight gain were considered related to PF-03709270 administration except for a significant reduction in body weight on PNDs 8 to 13 ($\leq -10\%$) and a significant reduction in body weight gain on PNDs 5-6 (-33%) and PNDs 7-8 (-37%) in HD males compared to control values. In females, no significant reductions in body weight or body weight gain were observed in the PF-03709270 groups except HD females had significantly lower mean body weights on PND 6 to PND 13 ($\leq -10\%$) and significantly lower body weight gain during the PND 5-6 interval (-33%) compared to control values. For the entire dosing period (PND 5 through PND 90), no effect on body weight or body weight gain in HD males or females was observed compared to control values. During the recovery period, no significant reductions in body weights or body weight gains were observed in the PF-03709270-treatment groups compared to control values.
Feed Consumption	No PF-03709270 related reductions in food consumption were observed during the dosing or recovery periods.
Ophthalmoscopy	No PF-03709270-related ophthalmology findings were observed during the dosing or recovery periods.
Hematology	PF-03709270-related hematology effects included statistically significantly lower absolute neutrophil counts in males administered ≥ 25 mg/kg/day (-34% to -39%) and females administered 25 (-34%) or 225 mg/kg/day (-30%) compared to control values. Also, platelet counts in females were significantly lower at doses ≥ 75 mg/kg/day (-13% to -19%) compared to control values. Both effects were partially reversed at the end of the recovery period. Statistically significant reductions in activated partial thromboplastin time (APTT) on PND 91 in females administered 75 (-11%) and 225 (-10%) mg/kg/day PF-03709270 was not considered to be toxicologically relevant because of the small magnitude of changes, absence of a dose relationship, lack of a similar finding in males, and total reversibility after the recovery period.
Clinical Chemistry	PF-03709270-related clinical chemistry effects that reached statistical significance compared to control values included an 18% reduction in globulin concentration and a 26% higher albumin:globulin ratio in females administered 225 mg/kg/day. Similar effects were not observed in males. Both clinical chemistry effects in females exhibited partial reversal after the recovery period.
Sexual Maturation	PF-03709270 administration had no effect on the time at which balanopreputial separation or vaginal opening occurred.

Cohort II: Oral Dosing With PF-03709270

Parameters	Major Findings
Neurobehavioral Assessment	Locomotor Activity: During the dosing period on PND 82, a significant reduction in X-Y ambulations occurred in females administered 75 (-21%) or 225 (-14%) mg/kg/day compared to control values, but males and pooled values in PF-03709270 treatment groups were not significantly affected. In the recovery period on PND 105, a significant, dose-responsive decrease in basic movements was observed during the recovery phase for the pooled analysis of animals administered 25 (-10%) or 225 (-23%) mg/kg/day compared to control values as well as a non-significant decrease in animals administered 75 mg/kg/day (-14%). In addition, a decrease in X+Y ambulations was observed in the pooled analysis at 225 mg/kg/day (-25%). These results suggest that PF-03709270 was associated with a reduction in overall movement that occurred in a delayed fashion during the recovery period. Acoustic Startle Response: No PF-03709270-related effects on acoustic startle responses were observed in either sex during the dosing or recovery periods. Morris Water Maze: During the dosing period, no PF-03709270-related effects were observed in either sex for any Morris Water Maze measurements. Isolated changes during the recovery period were not considered to be toxicologically relevant.
Bone Evaluation	No PF-03709270-related effects were observed in either sex for femur length or bone mineral density during the dosing or recovery periods.
Gross Pathology	No PF-03709270-related gross pathology findings were reported.
Organ Weights	At the end of dosing, increased kidney weight occurred in a PF-03709270-related manner in animals administered $\geq$ 25 mg/kg/day PF-03709270 (Table 61). Increased kidney weight correlated with hypertrophy of tubule epithelial cells.

Table 61. PF-03709270-Related Effects on Kidney Weights at the End of the Dosing Period

	Sex	PF-03709270							
		Males				Females			
Dose Level (mg/kg/day)	0	25	75	225	0	25	75	225	
Kidney									
Absolute Weight (g)	3.029	114*	119*	132*	1.9882	106	119*	118*	
Body Weight Ratio (%)	0.5757	105*	99	118*	0.6402	101	103	117*	
Brain Weight Ratio (%)	138.952	114*	116*	138*	98.7195	108	118*	125*	

* = Statistically significant difference (absolute or relative) compared with respective control mean value.

Note: Values for absolute weight and ratio of organ weights (relative to body or brain) for PF-03709270-treated groups expressed as a percentage of the control mean value.

Source: Study Report

After the recovery period, increased mean kidney weight (absolute or relative to brain weight) remained in animals administered $\geq$ 25 mg/kg/day PF-03709270. In general, the increases in kidney weights at the end of the recovery period were of a lesser magnitude than the increased kidney weights at the end of the dosing period consistent with a trend toward reversal.

Histopathology	PF-03709270-related microscopic findings occurred in the kidney of animals administered $\geq$ 25 mg/kg/day PF-03709270 (Table 62). Minimal to slight tubule degeneration occurred in males administered 75 and 225 mg/kg/day PF-03709270 but not in females at any dose. Minimal to slight tubule cell hypertrophy and hyperplasia occurred in males and females administered $\geq$ 25 mg/kg/day PF-03709270 and hypertrophy correlated with increased kidney weight. An increase in the incidence and/or severity of renal infarcts occurred in females administered $\geq$ 25 mg/kg/day PF-03709270. Increased incidence and/or severity of intratubular concretions occurred in males administered 225
Adequate battery: Yes	

Cohort II: Oral Dosing With PF-03709270

Parameters	Major Findings
	mg/kg/day PF-03709270 and females administered $\geq$ 25 mg/kg/day PF-03709270. The concretions were characterized by pale amphophilic to basophilic laminated bodies within the lumen of tubules and occurred in control males and PF-03709270-treated males and females.

Table 62. The Incidence and Severity of PF-03709270-Related Histology Findings in the Kidney at the End of the Dosing Period

Dose Level (mg/kg/day)	Sex	PF-03709270							
		Males				Females			
		0	25	75	225	0	25	75	225
Kidney	Number Examined	15	15	15	15	15	15	15	15
Degeneration, tubule	Minimal	0	0	1	5	0	0	0	0
	Slight	0	0	0	2	0	0	0	0
Hyperplasia, tubule cell	Minimal	0	2	7	6	0	2	1	1
	Slight	0	0	0	5	0	0	0	0
Hypertrophy, tubule cell	Minimal	0	5	8	4	0	4	2	7
	Slight	0	0	0	1	0	0	0	0
Basophilic tubule	Minimal	10	8	7	12	3	5	8	3
	Slight	0	0	0	1	0	0	0	0
Infarct	Minimal	1	3	1	2	0	2	5	4
	Slight	0	0	0	0	0	1	0	0
Concretion, tubule	Minimal	7	6	11	6	0	3	6	5
	Slight	0	0	0	1	0	0	0	0

Source: Study Report

After the recovery period, PF-03709270-related microscopic findings remained in the kidney, with generally decreased incidence and/or severity compared with the terminal sacrifice at the end of the dosing period (Table 63). Minimal to slight degeneration of tubule cells and minimal to slight hyperplasia of tubule cells remained in some males in all the PF-03709270-treatment groups, but not in females. An increased incidence of minimal intra-tubular concretions remained in male and female animals in all the PF-03709270 treatment groups but not in control animals.

Table 63. The Incidence and Severity of PF-03709270-Related Histology Findings in the Kidney at the End of the Recovery Period

Dose Level (mg/kg/day)	Sex	PF-03709270							
		Males				Females			
		0	25	75	225	0	25	75	225
Kidney	Number Examined	10	9	10	6	10	10	10	7
Degeneration, tubule	Minimal	0	1	0	2	0	0	0	0
	Slight	0	0	0	1	0	0	0	0
Hyperplasia, tubule cell	Minimal	0	4	8	2	0	0	0	0
	Slight	0	0	2	1	0	0	0	0
Hypertrophy, tubule cell	Minimal	0	1	3	1	0	0	1	2
	Slight	0	0	0	0	0	0	0	0
Concretion, tubule	Minimal	0	3	7	4	0	2	1	2
	Slight	0	0	0	0	0	0	0	0

Source: Study Report

[Other evaluations] **Toxicokinetics:** See Section 5.4

Abbreviations: HD, high dose; PND, postnatal day

Study Title/Number: Ototoxicity Study of CP-70,429 in Rats./ Study No.: 93-70429-RAT-OTO

Methods: This non-GLP study was conducted in 1993 by the (b) (4)
The effects of sulopenem (CP-70,429) on ototoxicity was tested in a non-GLP study of rats administered 0, 200, or 800 mg/kg/day intravenously for 4 weeks. Kanamycin (400 mg/kg/day) was administered to an additional group of rats as a positive control as it has been previously shown to cause ototoxicity. Rats were tested for activation of the pinna reflex with auditory tones ranging from 0.5 to 20 kHz, and the ears were dissected upon necropsy at the end of the study to evaluate pathology and histopathology.

Results: No ototoxicity was observed. Treatment with 200 mg/kg or 800 mg/kg sulopenem did not result in statistically or biologically significant changes in pinna reflex or inner ear pathology compared to the control group. Changes in pinna reflex were seen in the some of the positive control animals as were adverse histopathology changes including hair-cell loss in the inner-ear.

6. Clinical Pharmacology

6.1. Executive Summary

The Office of Clinical Pharmacology (Division of Infectious Disease Pharmacology and Division of Pharmacometrics) has reviewed the information contained in NDA 213972. See Table 64 for a summary of clinical pharmacology-related recommendations and comments on key review issues.

Table 64. Summary of OCP's Recommendations and Comments on Key Issues

Review Issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The pivotal evidence of effectiveness for sulopenem in patients with uncomplicated urinary tract infections (uUTI) comes from one Phase 3 trial (IT001-301).
General dosing instructions	The proposed dosing regimen is one bilayer tablet (500 mg sulopenem etzadroxil/500 mg probenecid) administered orally with food twice daily for 5 days. Probenecid increases the plasma exposures of sulopenem while decreasing its renal clearance. Because of the importance of urine drug concentrations in the treatment of uUTI, use of probenecid in combination with sulopenem etzadroxil may not be appropriate for the proposed indication. Nonclinical PK/PD studies also suggest the proposed dosage regimen may not be optimal.
Dosing in patient subgroups (intrinsic and extrinsic factors)	No dosage adjustment is needed in patients with hepatic impairment. Use is not recommended in patients with CL _{cr} ≤60 mL/min due to reduced effectiveness. Use is also not recommended in subjects on hemodialysis due to the unknown impact of hemodialysis on the disposition of sulopenem.
Labeling	The contents and format of the proposed labeling language are not aligned with the current guidance and will be revised.

Abbreviations: CL_{cr}, creatinine clearance; PD, pharmacodynamics; PK, pharmacokinetics

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

Table 65. Summary of the Pharmacokinetic Properties of Sulopenem

Absorption	
Sulopenem etzadroxil is a prodrug that is rapidly hydrolyzed to sulopenem, the microbiologically-active moiety, following oral administration. Only the pharmacokinetic profile of sulopenem is discussed further because sulopenem etzadroxil is not detected in plasma following oral administration. The absolute bioavailability of sulopenem following administration of a single dose of 500 mg sulopenem etzadroxil and 500 mg probenecid as the oral bilayer tablet under fasted conditions was 40%. Peak plasma concentrations are achieved within 1 h under fasted conditions and 2 h under fed conditions. A high fat meal increased the oral bioavailability of sulopenem to 64%.	
Distribution	
% bound to human plasma protein	10.7%
Volume of distribution (L) ^a	75 L (following intravenous administration) and 134 L (apparent Vd after oral administration)
Elimination	
The half-life of sulopenem is approximately 1.2 hours.	
Metabolism	
Sulopenem etzadroxil is rapidly hydrolyzed after oral administration to sulopenem in the intestines and in systemic circulation. Sulopenem and two inactive metabolites formed by β -lactam cyclic amide bond hydrolysis (M1a and M1b) are the major circulating entities. Sulopenem, M1a and M1b accounted for 32%, 21.8% and 43.6%, respectively, of circulating radioactivity in the mass balance study. No metabolism of sulopenem was observed <i>in vitro</i> with recombinant CYP or UGT enzymes.	
Excretion	
Following oral administration of a 2000 mg dose of [¹⁴ C] sulopenem etzadroxil, 85.1% of the radiolabeled dose was recovered in urine (44.3%) and feces (40.8%) as unchanged sulopenem and metabolites. Sulopenem accounted for 26.9% and 3.1% of the administered dose in urine and feces, respectively.	

^a Mean value based on a single dose of 500 mg sulopenem etzadroxil/500 mg probenecid in healthy volunteers for apparent volume of distribution after oral administration

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The Applicant's proposed dosage regimen is one bilayer tablet (containing 500 mg sulopenem etzadroxil/500 mg probenecid) administered orally twice daily for 5 days based on the expectation that as a β -lactam, sulopenem should exhibit time dependent killing. However, data from the Applicant's nonclinical PK/PD studies suggest that sulopenem's activity against uropathogens may be concentration dependent, which would imply that the proposed dosage regimen is not optimal. If sulopenem's activity is indeed concentration dependent, a higher dose would be expected to be more efficacious than the proposed dosage regimen.

Therapeutic Individualization

No clinically significant differences in the PK of sulopenem were observed based on age, gender, or body weight.

Hepatic Impairment

The effect of hepatic impairment on the PK of sulopenem was not studied. However, because sulopenem does not undergo significant hepatic metabolism or biliary excretion, hepatic impairment is not expected to impact the PK of sulopenem.

Renal Impairment

The sulopenem etzadroxil/probenecid fixed-dose combination is not recommended in patients with CLcr $\leq$ 60 mL/min and patients on hemodialysis.

The dedicated renal impairment study showed AUC values of sulopenem for subjects with mild, moderate and severe renal impairment were 2.0-, 3.0- and 7.4-fold higher, respectively, than the corresponding exposure in subjects with normal renal function after receiving a single 1000 mg oral dose of sulopenem etzadroxil. These increases in sulopenem plasma exposure paralleled a progressive decrease in sulopenem renal clearance with worsening renal impairment. However, because sulopenem has a short half-life (~1 h), the cumulative amount of sulopenem recovered in urine over a 24 h period was comparable across renal function groups. Although the effect of probenecid on sulopenem exposure was not evaluated in this study, probenecid's functionality as an OAT3 inhibitor is attenuated in the setting of renal impairment, and thus is not expected to yield significant increases in sulopenem exposures in subjects with renal impairment. The effects of kidney failure (CLcr <15 mL/min) and hemodialysis on the PK of sulopenem were not studied.

Given the proposed uUTI indication, renal impairment has implications for both safety and efficacy. The safety assessment for subjects across renal function groups indicated that no additional treatment-emergent adverse events (TEAEs) were observed in the various renal impairment groups compared with subjects with normal renal function. The AUC observed in subjects with severe renal impairment was comparable to the AUC associated with the maximally tolerated dose (MTD) in single ascending doses (SAD) studies, and ~28% higher than the AUC observed for the MTD in multiple ascending doses (MAD) studies. Nonetheless, given sulopenem's short half-life and the proposed treatment duration of 5 days, 500 mg sulopenem administered with 500 mg probenecid is expected to be safe in subjects with severe renal impairment. This was confirmed in the Phase 3 uUTI trial, where no additional TEAEs were observed in subjects with severe renal impairment (See Section 8.2).

Based on the available safety information, the fixed-dose combination is not recommended in patients with CLcr <15 mL/min and patients on hemodialysis because the safety of sulopenem has not been studied in these subpopulations.

In the Phase 3 uUTI trial, the efficacy of sulopenem was lower in subjects with CLcr $\leq$ 60 mL/min compared to subjects with CLcr >60 mL/min (See Section 8.1.2). This decreased response to sulopenem may be partly due to the reduced renal clearance of sulopenem (and subsequently, lower urine sulopenem concentrations especially early in the dosing interval) in subjects with CLcr $\leq$ 60 mL/min. Therefore, the fixed-dose combination is not recommended in patients with CLcr $\leq$ 60 mL/min due to sulopenem's reduced effectiveness in this subpopulation.

Outstanding Issues

None

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Information pertaining to the general pharmacology and pharmacokinetic characteristics of sulopenem are summarized in Table 66. Relevant clinical pharmacology information is also summarized for sulopenem etzadroxil and probenecid in Table 66.

Table 66. General Pharmacology and Pharmacokinetic Characteristics

Characteristic	Summary
Mechanism of Action	Sulopenem etzadroxil is an oral prodrug that is rapidly cleaved to release the active compound, sulopenem. Sulopenem belongs to the penem (β-lactam) class of antibacterial drugs. Sulopenem inhibits bacterial cell wall synthesis by binding to essential penicillin-binding proteins (PBP). Probenecid is a uricosuric and renal tubular blocking agent that inhibits the OAT3-mediated excretion of sulopenem, thereby providing increased plasma concentrations of sulopenem.
Active Moieties	Sulopenem
QT Prolongation	At a concentration of 40 times or greater than that achieved after a single 500 mg dose, sulopenem does not prolong the QTc interval to any clinically relevant extent.
Bioanalysis	Multiple LC-MS/MS assays were developed and validated to determine concentrations of sulopenem in human plasma and urine. All bioanalytical methods met the requirements for accuracy, precision, sensitivity, and specificity.
Drug exposure at the therapeutic dosing regimen for uUTI	The mean (%CV) of AUC_{0-inf} and C_{max} following single dose administration of 500 mg sulopenem etzadroxil with 500 mg probenecid in healthy subjects were 5.00 (25.3%) $\mu\text{g}\cdot\text{h}/\text{mL}$ and 1.84 (39.1%) $\mu\text{g}/\text{mL}$, respectively, under fasted conditions. AUC_{0-inf} and C_{max} increased to 7.41 (22.7%) $\mu\text{g}\cdot\text{h}/\text{mL}$ and 2.66 (43.6%) $\mu\text{g}/\text{mL}$, respectively, under fed conditions. Based on a population pharmacokinetic analysis, model predicted AUC_{0-12h} and C_{max} following administration of a single dose containing 500 mg sulopenem etzadroxil with 500 mg probenecid in uUTI patients were 4.87 (33.9%) $\mu\text{g}\cdot\text{h}/\text{mL}$ and 1.39 (30.6%) $\mu\text{g}/\text{mL}$, respectively. Of note, the model-predicted sulopenem AUC and C_{max} for Phase 3 uUTI patients are based on composite PK data from subjects reported as having received the fixed-dose bilayer tablet in either the fed or fasted state. Fed status was poorly defined in the Phase 3 study and food intake was not reported for all subjects. Because food increases bioavailability and food intake was variable, delineating the influence of infection on sulopenem exposures is confounded by this lack of uniformity in study drug administration.

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

Characteristic	Summary
Range of effective dose or exposure	No dose-ranging studies were conducted. The Phase 3 uUTI study evaluated a single regimen of 500 mg sulopenem etzadroxil/500 mg probenecid twice a day.
Maximally tolerated dose (MTD) or exposure	4000 mg is considered the maximally tolerated single dose based on SAD studies. 1200 mg sulopenem etzadroxil in combination with 1000 mg probenecid administered BID for 10 days was the maximally tolerated dose in MAD studies.
Dose Proportionality	The AUC of sulopenem increased in an approximately dose proportional manner for single doses of 400 mg to 2000 mg. C_{max} increased less than dose proportionally with increasing doses.
Variability	For the to-be-marketed bilayer tablet, inter-subject variability (%CV) in AUC_{0-inf} and C_{max} were 25.3% and 39.1%, respectively, for single dose administration of 500 mg sulopenem etzadroxil in combination with 500 mg probenecid in healthy subjects under fasted conditions. Under fed conditions, %CV in AUC_{0-inf} and C_{max} were 22.7% and 43.6%, respectively. Based on population pharmacokinetic analysis, model predicted %CV in AUC_{0-12h} and C_{max} were 33.9% and 30.6%, respectively, in uUTI patients administered a single dose of 500 mg sulopenem in combination with 500 mg probenecid.
Food effect	Coadministration of the to-be-marketed sulopenem etzadroxil bilayer tablet with a high fat meal increases sulopenem AUC_{0-inf} and C_{max} by 48% and 45%, respectively.
Inhibition/Induction of metabolism [in vitro]	Although sulopenem etzadroxil is not detected in plasma following oral administration, it has the potential to inhibit CYP enzymes and transporters located in the gut. In vitro, sulopenem etzadroxil is an inhibitor of CYP3A4/5. However, because it is rapidly hydrolyzed to sulopenem, clinically relevant DDIs are not expected with CYP3A4/5 substrates.
Substrate transporter systems [in vitro]	Sulopenem is a substrate of OAT3. Probenecid is a substrate of BCRP. Sulopenem etzadroxil is a substrate of P-gp. In a clinical DDI study with a P-gp inhibitor (itraconazole), the effect on the AUC and C_{max} of sulopenem was not clinically significant.
Inhibition/Induction of transporter systems	Sulopenem etzadroxil is an inhibitor of BCRP and P-gp. Because it is rapidly hydrolyzed to sulopenem, clinically relevant DDIs are not expected with BCRP and P-gp substrates. Probenecid is an inhibitor of OAT3 and BCRP in vitro.

Abbreviations: AUC, area under the curve; BID, twice daily; C_{max} , maximum serum concentration; CV, coefficient of variations; DDI, drug-drug interaction; LC-MS/MS, liquid chromatography with tandem mass spectrometry; MAD, multiple ascending dose; PK, pharmacokinetics; SAD, single ascending dose; uUTI, uncomplicated urinary tract infection

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

The primary evidence of efficacy of sulopenem in the treatment of uUTI was provided by one Phase 3 trial (IT001-301). In accordance with the FDA guidance on drug development for the treatment of uUTI, the Applicant evaluated sulopenem urine concentrations in a subpopulation of patients enrolled in the Phase 3 trial. Based strictly on comparison of the mean urine

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

concentrations from uUTI patients to the proposed susceptible breakpoint of 0.5 µg/mL, the Applicant asserts that sulopenem urine concentrations exceed this threshold concentration for at least 80% of the dosing interval. However, no formal target attainment analyses were conducted based on urinary concentrations to support this assertion or illustrate that adequate sulopenem concentrations are achieved at the site of action.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

The proposed oral dosing regimen for adults is 500 mg sulopenem etzadroxil with 500 mg probenecid (one bilayer tablet as a fixed-dose combination) administered twice daily for 5 days for the treatment of uUTI caused by susceptible microorganisms proven or strongly suspected to be non-susceptible to a quinolone. This dosing regimen may not be appropriate because only a subset of the population in the Phase 3 uUTI trial met the predefined margin for demonstration of efficacy relative to ciprofloxacin, which is further corroborated by nonclinical PK/PD findings.

Sulopenem Etzadroxil Dosing

As with other β-lactam antibacterials, the efficacy of sulopenem was expected to be driven by the duration of time that plasma concentrations exceed MIC (i.e., $T > MIC$). To support the proposed dosage regimen for the treatment of uUTI, the Applicant conducted PK/PD studies in a murine thigh infection model. These studies were intended to: 1) delineate the relevant PK/PD index for sulopenem, and 2) estimate the magnitude of this index required for various microbiologic endpoints (i.e., bacterial stasis, 1-log, and 2-log CFU/mL reduction in bacterial burden). Per the Applicant's interpretation of the data from these studies, sulopenem's activity was characterized as time dependent. Therefore, a 500 mg dose of sulopenem etzadroxil in combination with 500 mg probenecid every 12 hours was expected to achieve the $T > MIC$ target associated with antimicrobial activity over the range of epidemiological MIC_{90} values observed for target pathogens. However, the Clinical Pharmacology team's assessment of the nonclinical PK/PD studies determined that there was insufficient evidence for the use of $T > MIC$ as the relevant index for sulopenem. Although not definitive, the overall data trend suggested that sulopenem exhibits concentration-dependent killing against uropathogens (for details, see response to the question regarding clinical pharmacology information to support the proposed breakpoint in this section). If sulopenem's activity is indeed concentration dependent as suggested by these studies, the proposed dosing regimen of 500 mg sulopenem etzadroxil administered twice daily (in combination with 500 mg probenecid) may be suboptimal. A higher dose of sulopenem etzadroxil would be expected to yield higher urine concentrations of sulopenem and thus be more efficacious for the treatment of uUTI.

Probenecid Dosing

Because the bilayer tablet includes probenecid, a marketed drug, and the Applicant relied on information described in the FDA-approved labeling for the listed drug, the probenecid

component of the formulation was bridged to a commercial probenecid tablet. To this end, the Applicant illustrated that probenecid plasma exposures were comparable following administration of the bilayer tablet and probenecid, USP tablet (an FDA-approved generic drug version of the reference listed drug, Benemid) in Study IT001-105.

Probenecid lacks antimicrobial activity; instead, it increases plasma exposures of β -lactams by decreasing the renal clearance of these drugs. As an adjuvant to β -lactam therapy, the recommended daily dose of probenecid is 2000 mg administered in divided doses. For the uUTI drug development program, probenecid dose selection was informed by Studies A8811018 and IT001-101, two Phase 1 studies which evaluated the effect of probenecid doses of 250 mg, 500 mg, and 1000 mg on sulopenem exposure. In Study IT001-101, sulopenem AUCs following administration of sulopenem etzadroxil with either 250 mg or 500 mg probenecid were comparable. In both Studies A8811018 and IT001-101, increasing the dose of probenecid from 500 mg to 1000 mg of probenecid (i.e., a 2-fold increase in dose) resulted in only an additional 1.3 to 1.4-fold increase in sulopenem AUC. The Applicant noted that this additional fold increase in exposure would not result in a clinically relevant increase in $T > MIC$ at MICs of 0.5 $\mu\text{g/mL}$ and 1 $\mu\text{g/mL}$ (b) (4)

Therefore, 500 mg probenecid was expected to be sufficient.

In Study IT001-102, it was determined that simultaneous administration of a single 500 mg dose of probenecid with sulopenem etzadroxil results in higher plasma sulopenem exposures than either staggering the administration of sulopenem etzadroxil and probenecid, or administering probenecid as 2 divided doses. Based on these findings, 500 mg probenecid was selected for co-formulation with sulopenem etzadroxil.

When administered as a single 500 mg dose, probenecid increased the plasma AUC of sulopenem by ~1.3 to 1.4-fold compared to administration of 500 mg sulopenem etzadroxil alone. Additionally, multiple dose administration of 500 mg probenecid with 500 mg sulopenem etzadroxil decreased renal clearance of sulopenem by 1.9-fold and increased sulopenem AUC by 1.8-fold under fed conditions (See Appendix 16.3). The cumulative amount of sulopenem recovered in urine over a 24 h period was comparable in the presence or absence of probenecid. However, because probenecid increases plasma exposures of sulopenem at the expense of diminished renal clearance, its use for the treatment of uUTI may not be appropriate if sulopenem's activity is concentration dependent (as suggested by nonclinical PK/PD studies). Instead, concurrent use of probenecid may promote subtherapeutic urine concentrations of sulopenem and thus contribute to treatment failure.

Sulopenem Etzadroxil With Probenecid Dosing

The proposed dosing regimen for the treatment of uUTI was evaluated in the Phase 3 uUTI trial, IT001-301, in which adult females with signs and symptoms of uUTI were randomized to receive either 500 mg sulopenem etzadroxil with 500 mg probenecid as a fixed-dose combination or ciprofloxacin. The primary study endpoint of overall response (a composite of clinical and microbiological response) was evaluated in 2 separate patient populations: patients who presented with a quinolone-susceptible pathogen at baseline (MMITTS), and patients who

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

presented with a quinolone-resistant pathogen at baseline (MMITTR). In the MMITTR population, sulopenem showed superiority to ciprofloxacin in the treatment of uUTI. However, in the MMITTS population, sulopenem failed to demonstrate noninferiority to ciprofloxacin (See Section 8). Failure to meet the noninferiority margin in the MMITTS population may be indicative of suboptimal dosing of sulopenem etzadroxil as suggested by the nonclinical PK/PD studies. Furthermore, because probenecid may decrease urinary concentrations of sulopenem, its use for a uUTI indication may be inappropriate.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

No clinically significant differences in the PK of sulopenem were observed based on age, gender or body weight based on popPK modeling. Hepatic impairment is also not expected to impact the PK of sulopenem. However, use of the sulopenem etzadroxil/probenecid fixed-dose combination tablet is not recommended in subjects with CLcr $\leq$ 60 mL/min due to safety and efficacy concerns in this subpopulation (as described below).

Hepatic Impairment

The effect of hepatic impairment on the PK of sulopenem was not studied. In vitro, sulopenem was not metabolized by recombinant CYP or UGT enzymes. Additionally, the mass balance study (Study A8811006) indicated that biliary excretion does not play a role in sulopenem elimination. In the Phase 3 uUTI trial, 20 subjects in the sulopenem arm of the study had a history of liver disease and the incidence of adverse events (AEs) in this subset of subjects (30%) was comparable to that of the general population (25%). In the Phase 3 cUTI trial, 29 subjects with a history of liver disease were identified and in this study, a higher percentage (i.e., 38%) of patients receiving sulopenem experienced adverse events compared to the overall study population (15%). However, given the small number of subjects with hepatic impairment and possible variability in severity of hepatic impairment in the cUTI trial, the safety implications of this difference in the incidence of adverse events are unknown. Based on the totality of available information, hepatic impairment is not expected to significantly impact the PK of sulopenem. Therefore, the proposed dose is expected to be safe in patients with hepatic impairment.

Renal Impairment

In the mass balance study, following oral administration of a 2000 mg dose of [¹⁴C]sulopenem etzadroxil, approximately 26.9% of total radioactivity was recovered in urine as unchanged sulopenem. Based on population PK modeling of data from all Phase 3 trials, a 2-fold increase in AUC was observed with decreasing CLcr following administration of the bilayer tablet. However, multiple confounders may preclude reliable estimation of the effect of renal impairment on sulopenem exposure using population PK modeling (See Appendix 16.3). Ultimately, renal impairment was not associated with an increased incidence of adverse events in the Phase 3 uUTI trial.

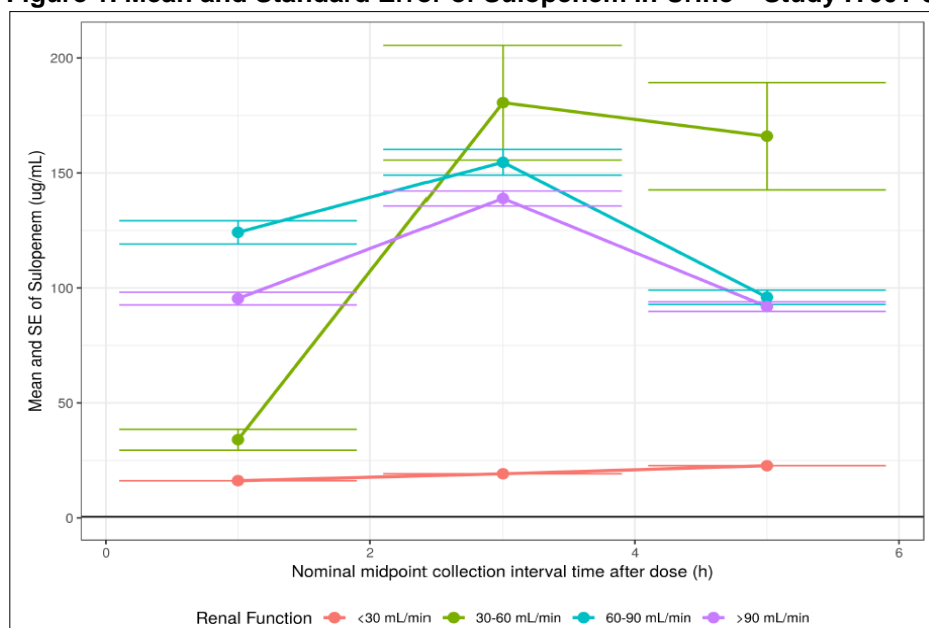
NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

In the dedicated renal impairment study (Study A8811009), following administration of a 1000 mg dose of sulopenem etzadroxil, sulopenem plasma $AUC_{0-\infty}$ increased 2.0-, 3.0- and 7.4-fold for subjects with mild, moderate, and severe renal impairment, respectively, compared with subjects with normal renal function. However, these higher exposures were not associated with a higher incidence of TEAEs in subjects with mild, moderate, or severe renal impairment compared to subjects with normal renal function. Notably, PK in patients with $CL_{Cr} < 15$ mL/min and the effect of dialysis were not assessed in the renal impairment study.

The renal impairment study did not evaluate the effects of coadministration of probenecid on sulopenem exposure in the various renal function groups. According to the referenced probenecid labeling, the effects of probenecid as an OAT3 inhibitor are diminished in the setting of chronic renal impairment (particularly when estimated glomerular filtration rate is ≤ 30 mL/min) due to functional decline of tubular secretion. Therefore, coadministration of probenecid is not expected to increase sulopenem exposure to a significant extent in the setting of severe renal impairment and renal failure. The single 1000 mg dose of sulopenem etzadroxil used in the renal impairment study is expected to be administered as divided doses of 500 mg twice daily for the treatment of uUTI. Because the AUC of sulopenem increased approximately dose proportionally within the sulopenem etzadroxil dose range of 400 to 2000 mg in SAD studies, the estimated sulopenem AUC for a 500 mg dose in subjects with severe renal impairment is approximately 24.0 $\mu\text{g}\cdot\text{h/mL}$. This exposure is comparable to that of the MTD (4000 mg) in SAD studies (i.e., 26.9 $\mu\text{g}\cdot\text{h/mL}$). The MTD in MAD studies was 1200 mg sulopenem etzadroxil in combination with 1000 mg probenecid BID, which was associated with an AUC of 18.8 $\mu\text{g}\cdot\text{h/mL}$. Although this AUC is ~28% lower than the anticipated AUC for a 500 mg dose of sulopenem etzadroxil in subjects with severe renal impairment, the proposed dose is expected to be safe in subjects with severe renal impairment given sulopenem's short half-life even in the setting of severe renal impairment (i.e., 2.75 h) and the short treatment duration of 5 days.

As indicated in the FDA guidance on drug development for the treatment of uUTIs, urinary exposures are important for the efficacy of drugs intended for the treatment of uUTI. Subgroup efficacy analyses for the MMITTR population in the Phase 3 uUTI trial showed a lower response rate in subjects with $CL_{Cr} \leq 60$ mL/min in both the sulopenem and ciprofloxacin arms (See Section 8.1.2). The underlying causes of reduced efficacy in subjects with $CL_{Cr} \leq 60$ mL/min could be multifactorial, with failure to achieve adequate drug exposures in urine as a contributing factor. In the Phase 3 uUTI trial, Day 1 urine concentrations were evaluated in 117 subjects in the sulopenem arm. Of these, only 7 subjects had $CL_{Cr} \leq 60$ mL/min. Study results suggested that compared to subjects with normal renal function, subjects with severe renal impairment ($CL_{Cr} < 30$ mL/min) exhibited significantly lower sulopenem urine concentrations across the entire 6 h urine collection period as shown in Figure 1. Sulopenem urine concentrations in patients with $CL_{Cr} 30$ to ≤ 60 mL/min were also low for the first 2 h collection interval, and increased thereafter.

Figure 1. Mean and Standard Error of Sulopenem in Urine – Study IT001-301



Source: Applicant's Population PK Study Report
Abbreviations: SE, standard error

Due to the limited number of subjects with urine PK data who had $CL_{cr} \leq 60$ mL/min (and especially those with severe renal impairment, where $N=1$), it is unclear if these observations are representative of the expected difference in sulopenem urine concentrations when compared to subjects with normal renal function. Nonetheless, if the efficacy of sulopenem is concentration dependent, the slower renal clearance (and consequently, lower urine concentrations of sulopenem especially early in the dosing interval) in subjects with moderate and severe impairment may have contributed to the reduced efficacy rate observed in this population.

Based on the totality of information, the proposed dose is expected to be safe in patients with mild, moderate, or severe renal impairment. Because subjects with $CL_{cr} < 15$ mL/min and subjects on hemodialysis were excluded from the renal impairment study, the safety of sulopenem in this population cannot be ascertained. Additionally, since the drug product is supplied as a fixed-dose combination, dosage reduction (if needed) would not be feasible for such patients. From an efficacy perspective, the proposed dose appears to be less efficacious in subjects with $CL_{cr} \leq 60$ mL/min. Furthermore, administration of a higher dose in this population may be infeasible, especially in patients with $CL_{cr} < 30$ mL/min, whose sulopenem plasma exposure following a 500 mg dose of sulopenem etzadroxil is expected to approximate that of the MTD in single and multiple ascending dose studies.

Because of the above-stated safety and efficacy concerns, administration of the 500 mg sulopenem etzadroxil/500 mg probenecid fixed-dose combination tablet is not recommended in patients with $CL_{cr} \leq 60$ mL/min and in patients on hemodialysis.

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

Yes, food intake increases the bioavailability of sulopenem and may moderately improve the tolerability of sulopenem. Therefore, the sulopenem etzadroxil/probenecid bilayer tablet should be administered with food. No clinically relevant drug-drug interactions (DDIs) were observed with sulopenem etzadroxil, sulopenem or probenecid.

Food Effect

Following administration of the to-be-marketed sulopenem etzadroxil/probenecid bilayer tablet formulation to healthy adult volunteers, AUC_{inf} and C_{max} increased 48% and 45%, respectively, with a high fat meal (800-1000 calories; 50% fat) compared to fasted conditions (Table 67).

Table 67. Summary of Statistical Analyses for Sulopenem Food Effect for the Bilayer Tablet

Formulation (Cohort) ^a	Parameter	n	Geometric Mean		Fed:Fasted GMR (%) ^b	90% CI
			Fed	Fasted		
Bilayer tablet (Cohort 1)	AUC_{last} ($\mu\text{g}\cdot\text{h}/\text{mL}$)	13	7.29	4.82	151	141, 163
	AUC_{inf} ($\mu\text{g}\cdot\text{h}/\text{mL}$)	12	7.41	5.00	148	138, 160
	C_{max} (g/mL)	13	2.66	1.84	145	120, 175

Source: Table 12 of Applicant's Study IT001-105

Abbreviations: AUC, area under the curve; C_{max} , maximum serum concentration; GMR, geometric mean ratio

The Applicant proposed that the bilayer tablet should be taken with food (b) (4). The Applicant's rationale for this recommendation is that food increases the oral bioavailability of sulopenem and based on the results of the Phase 3 uUTI trial, the incidence of diarrhea is significantly decreased with food intake. Although food intake was reported in the Phase 3 uUTI study, the type of food consumed and caloric contents were not recorded. Furthermore, the timing of food intake and definition of fed state were not clearly defined. Based on the available information, the incidence of treatment-emergent diarrhea was comparable under fed (7.1%) and fasted conditions (7.4%) as summarized in Table 68. Nonetheless, administration of study drug with food appeared to decrease the mean duration of treatment-emergent diarrhea from 5.6 days to 3.7 days. The lack of a notable difference in the incidence of diarrhea is consistent with the safety findings from the dedicated food effect study, IT001-105, where the incidence of GI-related TEAEs following administration of the bilayer tablet were identical (7.1%) in the fed and fasted states; however, no diarrhea was reported under either fed or fasted conditions.

Table 68. Treatment-Emergent Clinically Significant Diarrhea in the Phase 3 uUTI Study 301 by Fed/Fasted Status

Parameter	Sulopenem	
	Fasted	Fed
Total number of patients with treatment-emergent clinically significant diarrhea	32/430 (7.4)	28/396 (7.1)
Intensity ^[1]		
Mild	26/430 (6.0)	20/396 (5.1)
Moderate	6/430 (1.4)	8/396 (2.0)
Severe	0	0
Drug relationship ^[2]		
Related	30/430 (7.0)	24/396 (6.1)
Not related	2/430 (0.5)	4/396 (1.0)
Total number of episodes of diarrhea	511	306
Duration of treatment- emergent diarrhea (days)		
N ^[3]	32	28
Mean (SD)	5.6 (4.00)	3.7 (2.61)
Median	5.0	3.0
Min, max	1, 22	1, 11
Duration of study drug related treatment-emergent diarrhea (days)		
N*	30	24
Mean (SD)	5.4 (4.10)	4.0 (2.67)
Median	5.0	3.0
Min, max	1, 22	1, 11

Source: Table 14.3.3.1.17 of Applicant's Study IT001-301

^[1] Worst Intensity per patient

^[2] Drug-related if at least one AE of Diarrhea is drug related

^[3] N = number of patients in the safety population

Abbreviations: uUTI, uncomplicated urinary tract infection

Of note, food did not appear to impact efficacy in the Phase 3 uUTI trial. Administration of the sulopenem etzadroxil/probenecid bilayer tablet in the fed or fasted states resulted in comparable overall response rates of 65.2% and 66.3%, respectively, at the TOC visit for the entire microbiologically-evaluable population. This was consistent with efficacy results in the MMITTR population, where efficacy rates were reported as 65.4% in the fed state and 59.4% in the fasted state.

Based on the findings that food increases bioavailability and may improve tolerability by shortening the duration of treatment-emergent diarrhea, the clinical pharmacology review team recommends that the sulopenem etzadroxil/probenecid bilayer tablet should be administered with food (b) (4)

Drug-Drug Interactions

Summary of In Vitro Studies

In vitro studies indicated that sulopenem is a substrate of OAT3, and sulopenem etzadroxil is a substrate of P-gp and inhibitor of CYP3A4/5, P-gp, BCRP, OAT1 and OAT3. No clinical evaluation of sulopenem etzadroxil as a OAT1/3, CYP3A4/5, BCRP and P-gp inhibitor was performed by the

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

Applicant. Given that sulopenem etzadroxil is rapidly hydrolyzed upon oral administration and was undetected in plasma in the mass balance study (Study A8811006), the potential for clinically relevant DDIs with OAT1/3 is considered to be low. Because sulopenem etzadroxil is administered orally, it has the potential to inhibit CYP3A4/5, BCRP and P-gp in the gut. The sulopenem etzadroxil IC_{50} for inhibition of CYP3A4/5 could not be calculated within the concentration range studied *in vitro*, and was estimated to be $>150 \mu\text{M}$. Although the IC_{50} values for BCRP ($IC_{50}=20.4 \mu\text{M}$) and P-gp ($IC_{50}=1.91 \mu\text{M}$) are likely to be exceeded by more than 10-fold in the GI tract following administration of a single 500 mg dose of sulopenem etzadroxil, the Applicant's *in vitro* stability and release studies indicated that sulopenem etzadroxil is rapidly degraded in simulated intestinal fluid. Therefore, sulopenem etzadroxil's inhibition of BCRP and P-gp is expected to be transient. Similarly, regardless of the magnitude of the *in vitro* IC_{50} for CYP3A4/5 inhibition, sulopenem etzadroxil's effect as a CYP3A4/5 inhibitor is also expected to be transient and not result in a clinically significant DDI with CYP3A4/5 substrates.

Probenecid is a known OAT3 inhibitor, and was found to be a substrate and inhibitor of BCRP *in vitro*. No clinical evaluations of probenecid as a BCRP substrate and inhibitor were performed. The *in vitro* IC_{50} of probenecid as a BCRP inhibitor was $814 \mu\text{M}$, resulting in an I_{gut} to IC_{50} ratio of 10, which is the threshold for characterizing an orally administered drug as a BCRP inhibitor in the 2020 FDA In Vitro DDI Guidance. However, because of probenecid's low aqueous solubility (0.06 mg/mL), the probability of clinically significant BCRP-mediated DDIs with probenecid is low. Furthermore, the relevance of the interaction between probenecid and BCRP substrates or inhibitors may not be clinically meaningful. For instance, coadministration of cyclosporine (an inhibitor of BCRP) with eltrombopag (a BCRP substrate) did not have clinically meaningful implications (Aslanis et al. 2018). However, clinically significant interactions with BCRP substrates have typically been reported where multiple transporter pathways are responsible for the disposition of the substrate drug (Allred et al. 2011).

Summary of Clinical DDI Studies

Effect of P-gp Inhibitors on Sulopenem Pharmacokinetics:

Because sulopenem etzadroxil was identified as a P-gp substrate *in vitro*, the Applicant conducted a clinical DDI study to evaluate the effect of P-gp inhibitors on sulopenem exposure using oral itraconazole. In Study IT001-103, administration of a clinical dose of 200 mg itraconazole (2 x 100 mg capsules) daily for 3 days in the fasted state, followed by concomitant administration of sulopenem etzadroxil/probenecid on Day 4 in the fed state did not result in a clinically significant increase in sulopenem exposure. Therefore, no dosage adjustment is required for coadministration with P-gp inhibitors.

Effect of Antacids and Proton Pump Inhibitors (PPI) on Sulopenem Pharmacokinetics:

Results of *in vitro* solubility studies indicated that sulopenem etzadroxil is a Biopharmaceutical Classification System Class IV drug (i.e., low permeability and low solubility) that does not exhibit pH-dependent solubility within a pH range of 1.2 to 6.8. Based on this information,

coadministration of gastric pH modifiers would not be expected to impact sulopenem's exposure. However, per the Applicant, in vitro stability studies indicated that sulopenem etzadroxil was unstable in simulated gastric fluid (containing pepsin) but stable in simulated enzyme-free intestinal fluid. Therefore, gastric pH modifiers were predicted to decrease sulopenem etzadroxil's vulnerability to acid degradation and thus increase the bioavailability of sulopenem. Given that the stability of sulopenem etzadroxil was evaluated in gastric fluid in the presence of pepsin, it is unclear that its degradation was precipitated exclusively by low gastric pH.

The Applicant conducted a clinical DDI study using pantoprazole, a PPI, and aluminum hydroxide, an antacid, in Study A8811018. Administration of 40 mg pantoprazole for 3 days, followed by coadministration with sulopenem etzadroxil on Day 4 under fasted conditions did not significantly impact sulopenem exposure. Therefore, no dosage adjustment is necessary for coadministration with a PPI.

Administration of a single dose of 600 mg aluminum hydroxide with sulopenem etzadroxil under fasted conditions decreased AUC_{0-last} and C_{max} by less than 20%. According to the FDA guidance on conducting DDI studies with gastric-acid reducing agents, PPIs present the worst case scenario for pH-dependent DDIs due to their long-lasting effects on gastric pH. Thus, a negative finding from a dedicated study with a PPI, as observed in this study, indicates a lack of pH-dependent DDI. Therefore, no dosage adjustment is required for coadministration with an antacid.

Effect of Sulopenem-Etzadroxil/Probenecid on Valproic Acid Pharmacokinetics:

Concomitant administration of carbapenem antibacterial drugs and valproic acid has been associated with clinically significant reductions in serum valproic acid concentrations by an unknown mechanism, resulting in a loss of seizure control. Because sulopenem (a thiopenem) is structurally similar to carbapenems, the Applicant conducted a DDI study (Study IT001-104) with valproic acid using the sulopenem-etzadroxil/probenecid bilayer tablet, a standalone sulopenem immediate release (IR) tablet and IV sulopenem. In this study, multiple dose administration of 500 mg sulopenem etzadroxil with valproic acid decreased valproic acid AUC_{0-tau} and C_{maxSS} by approximately 25% and 19%, respectively. Similarly, coadministration of 1000 mg IV sulopenem with valproic acid also resulted in reductions of valproic acid plasma AUC_{0-tau} and C_{maxSS} of 33% and 28%, respectively. However, when administered concomitantly with sulopenem etzadroxil and probenecid, less than 10% reductions in valproic acid plasma exposures were observed. These results indicate that probenecid negates the reduction in valproic acid plasma concentrations caused by sulopenem. These findings were corroborated in the Applicant's Phase 3 cUTI study, (Study IT001-302) in which one subject in the sulopenem arm was receiving concomitant valproic acid treatment. Following the IV sulopenem treatment phase of the study (i.e., Days 1-5), valproic acid plasma/serum levels decreased to 21000 ng/mL (in serum) from a baseline of 54800 ng/mL (in plasma). However, following the switch to oral step-down therapy with sulopenem etzadroxil/probenecid, valproic acid levels recovered to 50100 ng/mL (in plasma) and 50600 ng/mL (in serum) at the end of treatment visit.

(b) (4)

the net effect of
coadministering sulopenem-etzadroxil/probenecid with valproic acid is a clinically insignificant reduction in valproic acid plasma concentrations.

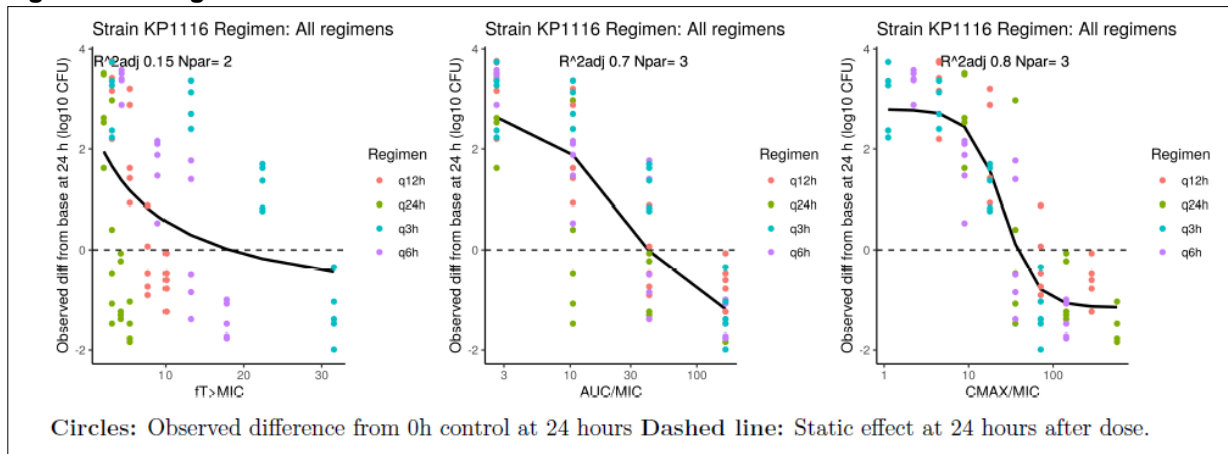
Does the clinical pharmacology information support the proposed breakpoint?

No, the clinical pharmacology information provided to support the proposed susceptibility breakpoint is insufficient.

PK/PD index and target determination for sulopenem were conducted using a murine thigh infection model. As with other β -lactams, the PK/PD driver of sulopenem's efficacy was expected to be $\%T > MIC$. However, the Applicant's dose fractionation studies failed to illustrate definitively that $T > MIC$ best correlates with sulopenem's antibacterial activity. One study report provided by the Applicant suggested AUC/MIC as the relevant efficacy determinant while another indicated that it was $T > MIC$. All the same, the Applicant assumed $T > MIC$ as the relevant index for sulopenem. On this basis, the Applicant determined $T > MIC$ target values (for various microbiological endpoints) using the dataset generated from the dose fractionation studies, which is unsupported by current practice (See Section 16.3).

A series of information requests were communicated to the Applicant to address inconsistencies in the study reports, convey expectations for the conduct and analysis of nonclinical PK/PD studies, and obtain any additional information available for review. Over the course of these communications, the Applicant provided additional insight on their approach to PK/PD index selection, revealing a flawed analysis which focused solely on select study results. The Applicant also reanalyzed the existing nonclinical PK/PD dataset in a manner more consistent with current convention. The data from the reanalysis was not definitive, but suggested that sulopenem exhibits pathogen-dependent PK/PD properties. Specifically, data for studies conducted with *K. pneumoniae* indicated that sulopenem exhibits concentration-dependent killing. This is illustrated in the 3 panels of Figure 2 for one strain of *K. pneumoniae*, where change in bacterial density is plotted as a function of $T > MIC$, AUC/MIC, and C_{max}/MIC , respectively. Based on the magnitude of the coefficient of determination (r^2), C_{max}/MIC appears to best correlate with reduction in bacterial burden, followed by AUC/MIC. Data for *E. coli* suggested that AUC_{0-24h}/MIC may be the relevant efficacy determinant against *E. coli*, followed by C_{max}/MIC . This interrelatedness of AUC/MIC and C_{max}/MIC (which are both concentration-dependent indices) in bacterial killing is not uncommon. On the other hand, for some Gram-positive pathogens, sulopenem appeared to exhibit time-dependent killing. Because the relevant PK/PD index for antibacterial drugs is typically pathogen independent, this discordance may be reflective of the complexities of sulopenem's PK/PD properties or point to experimental errors.

Figure 2. Change in Bacterial Burden vs. PK/PD Indices for a Strain of *K. Pneumoniae*



Source: Figure 6 of Applicant's Response to Clinical Pharmacology IR dated April 14th, 2021

Abbreviations: AUC area under the curve; Cmax, maximum serum concentration; MIC, minimum inhibitory concentration; PD, pharmacodynamics; PK, pharmacokinetics.

Given the lack of sufficient evidence to support the Applicant's use of $T > MIC$ as the relevant PK/PD driver of sulopenem's efficacy, the PK/PD targets and subsequent results of probability of target attainment analyses are unreliable. Therefore, target attainment analyses cannot be used to support the Applicant's proposed breakpoints.

7. Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 69. Listing of Clinical Trials Relevant to This NDA

Trial Identity	NCT no.	Study Population	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	No. of Centers and Countries
Controlled Studies To Support Efficacy and Safety								
IT001-301	NCT03354598	Adult women with uUTI	Randomized, multicenter, double-blind, double dummy	Sulopenem etzadroxil 500 mg/ probenecid 500 mg bilayer tablet BID; ciprofloxacin 500 mg tablet BID	Overall response (clinical and microbiological combined response) at test of cure (Day 12)	5 days (3 days of ciprofloxacin)/ 28 days	1802	114 study centers in 3 countries
Studies To Support Safety								
IT001-302	NCT03357614	Adults with cUTI	Randomized, multicenter, double-blind, double dummy	IV sulopenem 1 g QD followed by sulopenem etzadroxil 500 mg/ probenecid 500 mg bilayer tablet BID; IV ertapenem 1000 mg QD followed by oral ciprofloxacin 500 mg or amoxicillin/ clavulanate 875 mg BID	Overall response at test of cure (Day 21)	7-10 total days (at least 5 days IV)/ 28 days	1395	131 study centers in 13 countries

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

Trial Identity	NCT no.	Study Population	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	No. of Centers and Countries
IT001-303	NCT03358576	Adults with cIAI	Randomized, multicenter, double-blind	IV sulopenem 1 g QD followed by sulopenem etzadroxil 500 mg/ probenecid 500 mg bilayer tablet BID; IV ertapenem 1000 mg QD followed by oral ciprofloxacin 500 mg or amoxicillin/ clavulanate 875 mg BID	Clinical response at Day 28	7-10 total days (at least 5 days IV)/ 28 days	674	91 study centers in 10 countries
Other Studies Pertinent to the Review of Efficacy or Safety (e.g., Clinical Pharmacology Studies)								
IT001-101	-	Healthy adults	Randomized, double-blind, placebo-controlled, multiple-dose	Sulopenem etzadroxil or PF-04064900 500 mg; probenecid 500 mg; gallic acid	PK parameters	7 days/ 14 days	240	Single center
IT001-102	-	Healthy adults	Randomized, open-label, single dose	sulopenem etzadroxil 500 mg, probenecid 500 mg, gallic acid 400 mg, tannic acid 400 mg	PK parameters	Single dose/ 18 days	25	Single center
IT001-103	-	Healthy adults	Open-label, 2-period, 4-sequence, parallel group	IV sulopenem 1g; sulopenem etzadroxil 500 mg/ probenecid 500 mg, itraconazole 200 mg QD	PK parameters	Single dose/ 8 days	64	Single center

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

Trial Identity	NCT no.	Study Population	Trial Design	Regimen/ Schedule/ Route	Study Endpoints	Treatment Duration/ Follow Up	No. of Patients Enrolled	No. of Centers and Countries
IT001-104	-	Healthy adult males	Open-label, 2-period, 3-sequence, parallel group	IV sulopenem 1 g QD; sulopenem etzadroxil 500 mg/ probenecid 500 mg; sulopenem etzadroxil 500 mg, valproic acid 250 mg BID	PK parameters	7 days/ 10 days	30	Single center
IT001-105	-	Healthy adults	Open-label, 3-period, 4-sequence, parallel group	Sulopenem etzadroxil 500 mg/ probenecid 500 mg; sulopenem 500 mg; IV sulopenem 366 mg	Bioavailability	Single dose/ 3 days	47	Single center

Abbreviations: BID, twice daily; cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; IV, intravenous; PK, pharmacokinetics; QD, once daily; uUTI, uncomplicated urinary tract infection

7.2. Review Strategy

The clinical and statistical reviewers evaluated sulopenem's efficacy and safety for the indication of uUTI based mainly on the data generated from Study 301. Supplementary safety data were obtained from Studies 302 and 303 in cUTI and cIAI, respectively. In addition to confirming the efficacy and safety analyses conducted by the Applicant, the clinical and statistical reviewers also conducted analyses that more closely followed the original statistical analysis plan.

8. Statistical and Clinical Evaluation

8.1. Review of Relevant Individual Trials Used To Support Efficacy

8.1.1. IT001-301 for Treatment of Uncomplicated Urinary Tract Infection

Trial Design

IT001-301 (also referred to as Study 301 in this review) was a Phase 3, multi-center, double-blind, randomized trial designed to compare the efficacy, tolerability, and safety of oral sulopenem etzadroxil/probenecid with that of oral ciprofloxacin for the treatment of uUTI.

The primary objective of this study was to compare the overall response (clinical and microbiological combined response) of oral sulopenem etzadroxil/probenecid versus oral ciprofloxacin for the treatment of uncomplicated urinary tract infection (uUTI) in adult women at the primary timepoint of TOC at Day 12 (± 1 day).

Eligible women with uUTI were randomized 1:1 to receive either:

- A bilayer tablet with sulopenem etzadroxil 500 mg/probenecid 500 mg twice daily for 5 days and placebo ciprofloxacin capsules twice daily for 3 days or
- Oral ciprofloxacin 250 mg capsules twice daily for 3 days and placebo sulopenem etzadroxil/probenecid tablets twice daily for 5 days.

Randomization was conducted using a permuted block method with an Interactive Web Randomization System.

This was a double-blind, double-dummy study. Over-encapsulated ciprofloxacin capsules were used.

Study visits included screening, Days 1, 3, 5 (± 1 day) end of treatment (EOT), Day 12 (± 1 day) TOC, and Day 28 (± 2 days) final visit (FV).

Inclusion criteria were as follows:

- Female patients ≥ 18 years of age with ≥ 24 hours and ≤ 96 hours of urinary symptoms attributable to a urinary tract infection

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

- Two or more of the following signs and symptoms of uUTI: urinary frequency, urinary urgency, pain or burning on micturition, suprapubic pain
- A midstream urine specimen with:
 - A machine-read dipstick positive for nitrite
AND from the same specimen
 - Evidence of pyuria as defined as either:
 - A machine-read dipstick positive for leukocyte esterase OR
 - At least 10 white blood cells (WBCs)/mL on microscopic analysis of unspun urine
OR
 - WBC count ≥ 10 cells/HPF in the sediment of a spun urine
- Patient or the patient's legally acceptable representative able to provide a signed written informed consent prior to study enrollment

Exclusion criteria were as follows:

- Presence of signs and symptoms suggestive of acute pyelonephritis defined as: fever (temperature $>38^{\circ}$ Celsius), chills, costovertebral angle tenderness, flank pain, nausea, and/or vomiting
- Receipt of antibacterial drug therapy potentially effective as treatment of uUTI within the prior 7 days
- Patients requiring concurrent use of non-study treatments that would have a potential effect on outcome evaluations in patients with uUTI, including analgesics (e.g., non-steroidal anti-inflammatory drugs, aspirin, paracetamol, etc.), phenazopyridine, and cranberry products
- Patients with ileal loops or urinary stoma
- Patients with an indwelling urinary catheter in the previous 30 days
- Patients with paraplegia
- Patients who are likely to receive ongoing antibacterial drug prophylaxis after treatment of uUTI (e.g., patients with vesico-ureteral reflux)
- Any history of trauma to the pelvis or urinary tract
- Patient's urine culture results, if available at study entry, identify more than 2 microorganisms regardless of colony count or patient has a confirmed fungal UTI
- Patient is receiving hemodialysis, hemofiltration, peritoneal dialysis, or had a renal transplant
- Known history of creatinine clearance <50 mL/min as calculated by Cockcroft and Gault equation
- Patient known to be immunocompromised as evidenced by any of the following:
 - Human immunodeficiency virus infection, with either a recent (in the past 6 months) acquired immune deficiency syndrome-defining condition or a CD4+ T lymphocyte count $<200/\text{mm}^3$
 - Neutropenia (defined as absolute neutrophil count <1000 cells/ mm^3)

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

- Systemic or hematological malignancy requiring chemotherapeutic or radiation/immunologic interventions within 6 weeks prior to randomization or anticipated to begin prior to completion of study
- Immunosuppressive therapy, including maintenance corticosteroid therapy (>40 mg/day equivalent prednisolone for 5 days or more in the 30 days prior to randomization)
- Patients known to have a history of liver disease as defined by the following laboratory criteria:
 - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 × upper limit of normal (ULN)
 - Total bilirubin >2 × ULN
- Females of child-bearing potential who are unable to take adequate contraceptive precautions, have a positive pregnancy test result within 24 hours prior to study entry, are otherwise known to be pregnant, or are currently breastfeeding
- Patients with uncontrolled diabetes mellitus (defined as the presence of ketoacidosis, hyperosmolar hyperglycemia, or glucosuria with a random or fasting fingerstick or serum glucose ≥250 mg/dL at screening)
- History of seizures
- Patients with a history of blood dyscrasias
- Patients with a history of uric acid kidney stones
- Patients with acute gouty attack
- Patients on chronic methotrexate therapy
- Patients with a known history of myasthenia gravis
- Patients who require concomitant administration of tizanidine or valproic acid
- Patients with a history of allergy or hypersensitivity to carbapenems, β-lactams, quinolones, or probenecid, as formulated with their excipients
- Patient is considered unlikely to survive the 4-week study period or has a rapidly progressive or terminal illness, including septic shock, associated with a high risk of mortality
- The use of any other investigational drug in the 30 days prior to the first dose of study drug, or prior participation in any sulopenem clinical trial

Study Endpoints

Overall Response

The primary endpoint was overall (clinical and microbiological) success [responder] at TOC. A patient was considered to have an overall success at a given timepoint (Day 3, EOT, TOC and FV) if the following criteria were met:

- The patient was alive

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

- The patient had received no non-study antibacterial therapy for uUTI (excluding linezolid, daptomycin, vancomycin, azithromycin, metronidazole, josamycin, macrolide, nifuratel, tergyran, fluconazole, cystone and clarithromycin, as well as “antibiotics and chemotherapeutics for dermatological use” and “ophthalmologicals” since they have no activity against the pathogens in the study)
 - If an antibacterial drug active against the urinary tract pathogen was given for non-uUTI reasons, then the patient was to be considered indeterminate.
- The patient had resolution of the symptoms of uUTI present at trial entry and no new UTI symptoms (based on the PSAQ as follows). The PSAQ symptom components were reported as no symptom, mild, moderate, or severe.
 - Pain (uncomfortable pressure) in the lower abdomen/pelvic area
 - Burning (dysuria) when passing urine
 - Frequency of urination or going to the toilet very often
 - Urgency of urination or a strong and uncontrollable urge to pass urine
 - Missing PSAQ responses were to be treated as missing thus the outcome was indeterminate.
- Urine culture collected at the follow-up visit demonstrated $<10^3$ CFU/mL of the baseline uropathogen.

A patient was to be defined as a failure if at least one of the following criteria was met:

- The patient died due to uUTI
- The patient received non-study antibacterial therapy for uUTI (excluding linezolid, daptomycin, vancomycin, azithromycin, metronidazole, josamycin, macrolide, nifuratel, tergyran, fluconazole, cystone and clarithromycin, as well as “antibiotics and chemotherapeutics for dermatological use” and “ophthalmologicals” since they have no activity against the pathogens in the study)
 - Non-study antibacterial therapy for uUTI leading to failure must have been administered prior to the time of the actual study visit assessment. Antibacterial therapy for uUTI administered at the same time as a study visit would result in failure at the subsequent visit, as the patient would not have received antibacterial therapy between that visit and the prior visit. However, an investigator’s clinical assessment related to use of antibacterial drug therapy at a given visit was left to the discretion of the investigator as to a reason for failure at that visit.
- Patient had no resolution or worsening of symptoms of uUTI present at trial entry and/or had new uUTI symptoms. Missing PSAQ questions were to be treated as missing and the outcome was to be indeterminate
- Urine culture collected at the follow-up visit demonstrated $\geq 10^3$ CFU/mL of the baseline uropathogen

Patients were assigned an indeterminate outcome if any data needed to determine whether the outcome was success or failure were missing.

Microbiological Response

Per-pathogen microbiological response was assessed using the definitions listed in Table 70. It was to be analyzed at each timepoint (Day 3, EOT, TOC, and FV), and was assessed for each pathogen that a patient had at baseline. For post-baseline visits, contaminated urine cultures were considered as eradicated. A sensitivity analysis considering contaminated urine culture as not eradicated is presented below in the section “Efficacy Results – Secondary and Exploratory Endpoints.”

Table 70. Study 301: Microbiological Response Definition From Protocol

Microbiological Response	Definition
Success	The urine culture obtained at the Day 3 visit, Day 5 (± 1 day) visit, Day 12 (± 1 day) or Day 28 (± 2 days) visit demonstrates $<10^3$ CFU/mL of the baseline uropathogen; also referred to as eradication.
Persistence	A uropathogen present at baseline grew at $\geq 10^3$ CFU/mL at the time-point of analysis, i.e., Day 3, Day 5 (± 1 day), Day 12 (± 1 day) or Day 28 (± 2 days).
Persistence with increasing MIC	A urine culture taken after at least 2 full days of treatment grew $\geq 10^3$ CFU/mL of the baseline uropathogen and displayed ≥ 4 -fold higher MIC to study drug received at Day 3, Day 5 (± 1 day), Day 12 (± 1 day) or Day 28 (± 2 days), respectively.
Indeterminate	Patient was lost to follow-up or an assessment was not undertaken such that no urine culture was obtained (or culture results could not be interpreted for any reason) at either the Day 3, Day 5 (± 1 day), Day 12 (± 1 day) or Day 28 (± 2 days) visit.

Source: Protocol

Abbreviations: CFU, colony forming units; MIC, minimum inhibitory concentration

A late revision to the SAP made significant changes to the definitions of the microbiological response, which impacted the primary endpoint definition. The details of these changes are discussed below in the section on protocol amendments.

A per-pathogen microbiological success was defined as “eradication”. A pathogen microbiological failure was “persistence” or “persistence with increasing minimum inhibitory concentration (MIC)”.

A per-patient microbiological success was defined as “eradication” if all pathogens for a patient were eradicated. A per-patient microbiological failure of “persistence” or “persistence with increasing MIC” was based on the presence of one or more pathogens at that visit. Otherwise, the patient was considered “indeterminate.”

The following organisms were to be considered a uropathogen for this study:

- Monomicrobial or polymicrobial infections caused by:
 - Enterobacterales
 - *Enterococci*
 - *Pseudomonas aeruginosa*
 - *S. saprophyticus*

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

- The microbiological modified intent-to-treat (MMITT) population (discussed in further detail below) was to only include patients with uUTIs caused by Enterobacterales and/or *S. saprophyticus* (study uropathogens)

Patient-Determined Clinical Response

The patient was considered a clinical success at a given timepoint if the first three conditions in the definition of overall response were met. All other patients not meeting the success criteria were to be considered as failures unless data were unavailable to determine a success or failure. In this case, an indeterminate response was assigned. Deaths due to reasons other than the uUTI would also be considered as indeterminate responses.

Statistical Analysis Plan

Two independent primary analyses answering separate research questions in the ciprofloxacin-susceptible population and the ciprofloxacin-nonsusceptible (resistant) population were incorporated into the design and analysis of the study. In the ciprofloxacin-susceptible population, sulopenem etzadroxil/probenecid and ciprofloxacin were compared for non-inferiority, while in the ciprofloxacin-nonsusceptible population, sulopenem etzadroxil/probenecid was assessed for superiority over ciprofloxacin. The study protocol was reviewed under a special protocol assessment agreement.

Analysis Populations

The intent-to-treat (ITT) population comprised all randomized patients regardless of whether the patients received study drug.

The modified ITT (MITT) population was to include all patients in the ITT population who received at least a single dose of study medication and had the disease under study, defined as having 2 of the 4 baseline uUTI symptoms and pyuria in the baseline urinalysis.

The microbiological modified intent-to-treat (MMITT) population included all MITT patients with a positive study entry urine culture within 48 hours prior to first dose, defined as $\geq 10^5$ colony forming units (CFU)/mL of a uropathogen (Enterobacteriaceae or *Staphylococcus saprophyticus* only) and no more than 2 species of microorganisms with $\geq 10^5$ CFU/ml.

The Susceptible MMITT (MMITTS) population included all MMITT patients with a baseline uropathogen susceptible to the comparator drug, ciprofloxacin (ciprofloxacin MIC ≤ 1 mg/L), and no baseline pathogen non-susceptible to ciprofloxacin.

The Resistant MMITT (MMITTR) population included all MMITT patients with a baseline uropathogen non-susceptible (defined as MIC ≥ 2 mg/L) to the comparator drug, ciprofloxacin.

Interim Analysis

Two interim analyses for sample size re-estimation were planned when response data at TOC were available for approximately 33% and 66% of the patients (approximately 450 and 900

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

patients, respectively). For the susceptible population, the sample size re-estimation was based on the blinded overall outcome and evaluability rate (i.e., percentage of the ITT population in the MMITT population).

In the resistant population, a conditional power analysis for the superiority hypothesis in the MMITTR population was conducted when 66% of patients had been enrolled (unblinded interim analysis). If the conditional power was <40% or ≥80%, no change to the sample size would be made. If the conditional power was 40% to <80%, the sample size for MMITTR population would be calculated based on the observed overall success rates in each treatment group and increased to a maximum number. However, the maximum number was not specified. No adjustment to the overall alpha level was needed. The sample size re-estimations were conducted by an independent, unblinded statistician. A Data Monitoring Committee (DMC) would make recommendations based on the analysis results.

Statistical and Clinical Reviewers' Comment: The Applicant made changes to the planned analysis after the unblinded interim analysis was conducted. This is discussed below under protocol amendments.

Efficacy Analysis

The proportion of successes was defined using the following formula: number of successes/(number of successes + number of failures + number of indeterminates).

For the superiority test in the MMITTR population, a two-sided 95% CI for the observed treatment difference in success rates was determined using the Miettinen and Nurminen method without stratification. If the lower bound of the 95% CI was greater than 0%, the null hypothesis would be rejected and superiority of sulopenem etzadroxil/probenecid to ciprofloxacin would be concluded. According to the post-hoc tables submitted on 4/27/2021, the p-value was calculated using a Chi-squared test.

Statistical Reviewer's Comment: The method for calculating a p-value was not provided in the SAP, protocol, or study report. It appears that the Applicant reported p-values from a Chi-squared test using a 3-category outcome (success/failure/indeterminate) for some of their analyses. As the outcome is considered a binary outcome (success/combined failure and indeterminate) for the primary analysis, we report p-values calculated using a Chi-squared test with a 2-category outcome.

For the susceptible (MMITTS) population, a one-sided non-inferiority test was performed at the 2.5% level of significance using the same Miettinen and Nurminen method without stratification with a -10% non-inferiority margin.

For the overall response, patients were defined as an indeterminate if any data needed to determine whether a patient was a success or failure were missing, unless the available data showed the patient to be a failure. In the analysis, these patients were considered as not having a successful outcome.

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

Secondary and additional efficacy analyses, including per patient microbiological response, per pathogen microbiological response, investigator-determined clinical response, and patient-determined clinical response were conducted using the same methods as in the primary efficacy analyses.

Sample Size Calculation

Sample size calculations were conducted separately for the resistant population and susceptible population. For the superiority test in the MMITTR population, 105 patients per arm would provide 90% power given a two-sided alpha level of 0.05 and a 66% and 43% overall success rate in the sulopenem and ciprofloxacin groups, respectively. For the non-inferiority test in the MMITTS population, the sample size determination of 441 patients per arm was based on the method of Farrington and Manning, assuming a non-inferiority margin of 10%, a power of 90%, a one-sided alpha level of 0.025, and a 70% treatment success rate.

Assuming that 22% of the patients would have resistant pathogens and 83% of randomized subjects would meet the criteria for the MMITT population, the sample size for this study was 1364 randomized subjects.

Protocol Amendments

There were 2 protocol amendments, dated 6/7/2018 and 1/6/2020. Amendment 1 occurred prior to the start of the study. Amendment 2 occurred after the unblinded interim analysis and replaced the statement "If the conditional power is <40%, the superiority hypothesis in the MMITTR population will not be tested at the end of the study" with "If the conditional power is <40%, no change to the sample size will be made." This was to clarify that if the conditional power at the interim analysis was <40%, the superiority hypothesis in the MMITTR population would still be tested at the end of the study.

Statistical and Clinical Reviewers' Comment: Of note, the results of the unblinded interim analysis were presented to the DMC on 10/10/2019. Therefore, the Applicant already knew that the conditional power was <40% when they submitted Amendment 2 on 1/6/2020 resulting in the change to conduct superiority hypothesis testing regardless of the conditional power. This leads to concerns that the Applicant was changing the planned analysis based on the results of the unblinded interim analysis.

The first version of the SAP was finalized on 9/30/2019 prior to the unblinded interim analysis. The second version of the SAP was finalized on 3/11/2020, well after the unblinded interim analysis was conducted. This version of the SAP affected the Analysis Population and Microbiologic Response which impacted the primary endpoint of Overall Response. These changes are discussed here.

Use of polymerase chain reaction (PCR) to Determine Whether Subjects Would be Assigned to the Susceptible (MMITTS) or Nonsusceptible (MMITTR) Analysis Population

Iterum changed how discrepancies in antibacterial drug susceptibility between the local/regional laboratory and central laboratory would be addressed. This change is notable as the ciprofloxacin susceptibility status of the baseline pathogen defines whether a subject is in the MMITTS or MMITTR population. In the revised SAP, Iterum used PCR to identify mutations in the *gyrA* gene to adjudicate the ciprofloxacin susceptibility status. Although resistance to ciprofloxacin may be mediated by mutations in the bacterial *gyrA* gene, there are other gene mutations which are also associated with quinolone-resistant isolates (e.g., *parC*, *parE*) as well as plasmid-mediated resistance genes which would be missed using the testing conducted by the Applicant. In addition, bacterial mutations, if present, may not translate to functional quinolone resistance. As a result, phenotypic susceptibility results are more reliable.

Statistical, Clinical, and Clinical Microbiology Reviewers' Comment: The Division does not agree with Iterum's choice to use PCR to determine ciprofloxacin-susceptibility. Instead, the Division maintains that the phenotypic results from the central laboratory should be used in cases where there is a discrepancy between the local and central laboratory in the ciprofloxacin-susceptibility status. Subjects with a baseline ciprofloxacin nonsusceptible isolate from either a central lab culture or from a central lab confirmatory identification should be included in the MMITTR population.

Change in the Definition of Microbiological Response

In the Applicant's revised SAP, the definition of microbiological response, which is a component of the primary endpoint (overall response), was revised to determine if the isolate on the follow-up culture matched the baseline organism (Table 71). The Applicant added a footnote (delineated in red print below) to the following table defining microbiological response:

Table 71. Applicant’s Revised Definition of Microbiological Response

Microbiological response	Definition
Eradication	The urine culture obtained at the timepoint of analysis demonstrates $<10^3$ CFU/mL of the baseline uropathogen.
Persistence	A uropathogen present at baseline regardless of susceptibility grew at $\geq 10^3$ CFU/mL at the timepoint of analysis.*
Persistence with increasing MIC	A urine culture taken after at least 2 full days of treatment grew $\geq 10^3$ CFU/mL of the baseline uropathogen and displayed ≥ 4 -fold higher MIC to study drug received at the timepoint of analysis.
Indeterminate	Patient was lost to follow-up or an assessment was not undertaken such that no urine culture was obtained (or culture results could not be interpreted*) at the timepoint of analysis (contaminated results are considered a negative culture and therefore an eradication ⁷).

* The genus/species and susceptibility profiles need to match. Additional molecular testing by pulsed field gel electrophoresis (PFGE), PCR or whole genome sequencing (WGS) may be performed for confirmation; in the case of missing culture data PCR may be used to confirm the presence or absence of the baseline pathogen.

Source: Statistical Analysis Plan IT001-301, revised March 11, 2020
 Abbreviations: CFU, colony forming unit; MIC, minimum inhibitory concentration

The Applicant interpreted this footnote to mean that susceptibility profiles or molecular testing (such as WGS) could be used to differentiate between baseline and follow-up isolates of the same genus and species. As a result, a subject with a follow-up isolate at TOC that was the same genus and species as that at baseline could be considered a microbiological eradication (and eligible for assessment as an overall responder) if the two isolates had different susceptibility profiles or WGS results.

Statistical, Clinical and Clinical Microbiology Reviewers’ Comment: This is not consistent with our assessment of microbiological success/persistence, which is based on the genus and species of the organism. It is possible that there may be different (i.e., hetero-resistant) subpopulations of the same bacterial pathogen present at baseline which exhibit different antibacterial drug susceptibility profiles and have different WGS results. These subpopulations may not be identified because only a single colony was selected for analysis. As a result, the Division does not agree with the revised definition; if the post-baseline urine culture grew the same bacterial species present at baseline at $\geq 10^3$ CFU/mL, it was considered a microbiological failure. In FDA’s analyses, we use the original SAP (version 1) dated September 30, 2019, which was written before the second interim analysis.

Additionally, note that in the revised table it was not clearly stated how the Applicant would interpret the edits. The definition of persistence continues to state that persistence would be

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

determined “regardless of susceptibility” and the added footnote does not impact the definition of eradication. This could be interpreted as only changing a subject from persistence to indeterminate.

8.1.2. Study Results

Compliance With Good Clinical Practices

This study was conducted in compliance with Good Clinical Practice guidances.

Financial Disclosure

The Applicant certified that none of the investigators for Trial 301 had any disclosable financial interests or arrangements with the Applicant.

Patient Disposition

The trial was conducted between August 23, 2018 and January 20, 2020. A total of 1802 subjects from 114 study sites from three countries (USA, Ukraine, and Russia) were screened for enrollment. A total of 131 subjects failed screening. The most common reason for screening failure, occurring in 66 subjects, was failure to meet urine dipstick requirements as per inclusion criterion #3.

A total of 1671 patients from 108 study sites were randomized (835 to sulopenem, 836 to ciprofloxacin). Two sites that included 81 patients from the US (48 in the sulopenem group and 33 in the ciprofloxacin group) were excluded from the Applicant’s ITT population for the efficacy analyses (Site 202: 68 patients; Site 218: 13 patients) because the Applicant considered the data unreliable (i.e., the Applicant claimed that there were questionable microbiological results by pulse-field gel electrophoresis and concerns about PK data). These exclusions are discussed below.

The remaining 1590 patients included 787 in the sulopenem group and 803 in the ciprofloxacin group. Approximately 97% of these patients completed study drug treatment, while 3% discontinued treatment prematurely. The primary reasons for discontinuation of treatment were adverse events and “patient request.” The Applicant’s disposition of patients is reported in Table 72. Note that the only exclusions from the MITT population, other than the exclusion of patients from Sites 218 and 202 by the Applicant, were due to not receiving treatment. Approximately 18% of the patients were included in the MMITR population and approximately 50% of patients were in the MMITTS population.

Table 72. Study 301: Disposition of Patients by Treatment, ITT Population (Excluding 2 Sites)

Parameter	Sulopenem (N=787)	Ciprofloxacin (N=803)	Total (N=1590)
ITT	787 (100)	803 (100)	1590 (100)
Completed study drug	764 (97.1)	776 (96.6)	1540 (96.9)
Not received study drug	2 (0.3)	9 (1.1)	11 (0.7)
Prematurely discontinued study drug	21 (2.7)	18 (2.2)	39 (2.5)
Reasons for premature discontinuation of study drug			
Adverse event	12 (1.5)	7 (0.9)	19 (1.2)
Need for concomitant systemic antibacterial therapy	1 (0.1)	0 (0.0)	1 (0.1)
Lost to follow-up	1 (0.1)	3 (0.4)	4 (0.3)
Patient request	5 (0.6)	7 (0.9)	12 (0.8)
Investigator decision	1 (0.1)	0 (0.0)	1 (0.1)
Other	1 (0.1)	1 (0.1)	2 (0.1)
Completed the study	755 (95.9)	761 (94.8)	1516 (95.3)
Prematurely discontinued from study	32 (4.1)	42 (5.2)	74 (4.7)
Primary reason for early study termination			
Adverse event	3 (0.4)	2 (0.2)	5 (0.3)
Non-compliance with study drug	3 (0.4)	1 (0.1)	4 (0.3)
Lost to follow-up	4 (0.5)	10 (1.2)	14 (0.9)
Patient request	19 (2.4)	24 (3.0)	43 (2.7)
Investigator decision	1 (0.1)	2 (0.2)	3 (0.2)
Other	2 (0.3)	3 (0.4)	5 (0.3)
MITT Population	785 (99.7)	794 (98.9)	1579 (99.3)
Excluded from MITT Population (not receiving study drug)	2 (0.3)	9 (1.1)	11 (0.7)
Microbiological MITT (MMITT) Population	517 (65.7)	554 (69.0)	1071 (67.4)
MMITTR Population	147 (18.7)	139 (17.3)	286 (18.0)
MMITTS Population	370 (47.0)	415 (51.7)	785 (49.4)
MITT subjects excluded from MMITT			
Study uropathogen <10 ⁵ CFU/mL or no study uropathogen	268 (34.1)	240 (29.9)	508 (31.9)

Source: Adapted from Table 16 and 22, Study Report

Abbreviations: CFU, colony forming units; ITT, intent to treat; MITT, modified intent-to-treat; R, resistant; S, susceptible

As mentioned above, the Applicant excluded two sites from the efficacy analysis. Site 218 was excluded due to study misconduct (b) (7)(A)

Additionally, the decision to exclude Site 218 was made in June 2019, just one month after the site was closed and audited.

The Applicant decided to exclude Site 202 from the efficacy analysis after the trial had completed enrollment. The Applicant provided the following justification to exclude Site 202:

- High rate of contaminated urine cultures during a “certain period” of enrollment
- Four clusters of patients with closely related isolates by PFGE involving 15/68 patients
- High rate of “red/orange flags” from drug compliance artificial intelligence software
 - Dosing events were to be captured on video
- 5/31 patients in the PK component of the study had no measurable drug level

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

The timelines for activities related to Site 202 are as follows:

- The site was closed to further enrollment on April 4, 2019
- The PFGE analysis results were sent to Iterum between April 12-24, 2019
- A routine audit of the site for quality assurance purposes was done on June 5, 2019
- The investigational product was removed from the site on August 5, 2019
- An audit of the site by Iterum for quality assurance reasons was performed on October 29-30, 2019
- The decision to remove patients from Site 202 from the efficacy analyses was made in May 2020, which was after the unblinded interim analysis performed in October 2019 and after the study had completed in January 2020.

Statistical, Clinical and Clinical Microbiology Reviewers' Comment: We do not agree with Iterum's decision to exclude Site 202 from the efficacy analysis. Regarding the clusters of subjects with related pathogens, these clonal relationships may exist in UTIs in the community. In addition, most patients were not in one of these four clusters. Regarding the artificial intelligence drug compliance software, the FDA inspector found evidence that the software results were likely not interpreted correctly. Some of the subjects initially may have spit out the dose during recording because of difficulty swallowing the pills or difficulty with the phone app. However, many of these subjects confirmed that they were able to eventually take the scheduled dose which was well-documented in the source records. Regarding the finding of some subjects with no measurable drug level, it is important to note that this was a minority of subjects. The late decision to exclude this site is also questionable especially since it was after the unblinded interim analysis. Overall, the Division did not find sufficient reason to exclude Site 202.

The Applicant provided additional analyses using the original SAP and included Site 202 following a request by the FDA on 4/27/2021 (SN#0037). Table 73 shows the analysis populations using the original SAP and including Site 202 but excluding Site 218. More subjects were included in the resistant and susceptible groups based on the original SAP as compared with using the revised SAP.

Table 73. Study 301: Analysis Populations by Treatment Using the Initial SAP, ITT Population (Including Site 202)

Population	Sulopenem (N=835)	Ciprofloxacin (N=836)	Total (N=1671)
MITT	785 (94.0)	795 (95.1)	1580 (94.6)
MMITT	538 (64.4)	567 (67.8)	1105 (66.1)
MMITTR	162 (19.4)	149 (17.8)	311 (18.6)
MMITTS	376 (45.0)	418 (50.0)	794 (47.5)

Source: Reviewer's analysis

Abbreviations: ITT, intent-to-treat; MITT, modified intent-to-treat; MMITT, microbiological MITT; R, resistant; S, susceptible; SAP, statistical analysis plan

Protocol Violations/Deviations

Major protocol deviations were related to inclusion/exclusion criteria (N=8) and study medication (N=1; dosed incorrectly for all 10 doses, resulting in taking ciprofloxacin once a day instead of twice a day). Major protocol deviations were reported for three subjects in the sulopenem group and six subjects in the ciprofloxacin group (including the 1 subject taking ciprofloxacin once a day, instead of twice a day) in the MMITT population. In the MMITTR population, only 2 major deviations were reported (related with inclusion/exclusion criteria in the ciprofloxacin group).

Table of Demographic Characteristics

In the following sections, we focus on the resistant population, as the results from this population are used for the proposed indication.

Table 74 shows demographic and baseline characteristics in the resistant population, defined by the Applicant based on the initial SAP. The mean age was 55 years old. The majority of subjects (90%) were White and 59% were from the United States. The mean body mass index was 28.3 kg/m². The mean creatinine clearance rate was 74.2 mL/min.

Table 74. Study 301: Demographic and Baseline Characteristics, MMITTR Population (Including Patients From Site 202)

Parameters	Sulopenem (N=162)	Ciprofloxacin (N=149)	Total (N=311)
Age (years)			
Mean (SD)	53.6 (19.5)	55.8 (20.0)	54.7 (19.8)
Median	55.5	57.0	57.0
Range	18.0, 89.0	18.0, 87.0	18.0, 89.0
<65 years, n(%)	104 (64.2)	84 (56.4)	188 (60.5)
≥65 years, n(%)	58 (35.8)	65 (43.6)	123 (39.6)
Race, n(%)			
Asian	2 (1.2)	0	2 (0.6)
Black or African American	15 (9.3)	12 (8.1)	27 (8.7)
Other	1 (0.6)	1 (0.7)	2 (0.6)
White	144 (88.9)	136 (91.3)	280 (90.0)
Ethnicity, n(%)			
Hispanic or Latino	70 (43.2)	59 (39.6)	129 (41.5)
Not Hispanic or Latino	92 (56.8)	89 (59.7)	181 (58.2)
Not reported	0	1 (0.7)	1 (0.3)
Country			
RUS	43 (26.5)	46 (30.9)	89 (28.6)
UKR	24 (14.8)	14 (9.4)	38 (12.2)
USA	95 (58.6)	89 (59.7)	184 (59.2)
Height (cm)			
N	162	148	310
Mean (SD)	161.7 (7.7)	160.8 (7.0)	161.3 (7.4)
Median	162.5	162.0	162.0
Min, max	125.2, 178.0	143.0, 183.0	125.2, 183.0

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

Parameters	Sulopenem (N=162)	Ciprofloxacin (N=149)	Total (N=311)
Weight (kg)			
N	162	146	308
Mean (SD)	73.9 (19.0)	73.5 (17.8)	73.7 (18.5)
Median	70.2	72.4	70.8
Min, max	43.4, 156.0	42.5, 145.3	42.5, 156.0
Body mass index (kg/m ²)			
N	162	146	308
Mean (SD)	28.4 (7.2)	28.3 (6.4)	28.3 (6.8)
Median	26.3	27.2	26.9
Min, max	16.7, 53.0	15.2, 53.4	15.2, 53.4
Creatinine clearance (mL/min)			
Mean (SD)	75.8 (28.8)	72.4 (29.4)	74.2 (29.1)
Median	70.0	68.0	69.0
Min, max	17.0, 143.0	23.0, 199.0	17.0, 199.0
<30	50 (30.9)	52 (34.9)	102 (32.8)
30-60	4 (2.5)	6 (4.0)	10 (3.2)
>60	108 (66.7)	91 (61.1)	199 (64.0)
Diabetes			
Absent	132 (81.5)	122 (81.9)	254 (81.7)
Present	30 (18.5)	27 (18.1)	57 (18.3)

Source: Reviewer's analysis

Abbreviations: MMITTR; microbiological modified intent-to-treat resistant; RUS, Russia; UKR, Ukraine; USA, United States of America

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Baseline pathogens from urine are shown in Table 75. About 88% of the subjects had *E. coli*. The next most common pathogens included *K. pneumoniae* and *P. mirabilis*.

Table 75. Study 301: Pathogens from Urine at Baseline, MMITTR Population (Including Patients From Site 202)

Organism	Sulopenem (N=162)	Ciprofloxacin (N=149)	Total (N=311)
Number of Patients with at least one study uropathogen in the urine at baseline	162 (100)	149 (100)	311 (100)
<i>Escherichia coli</i>	141 (87.0)	131 (87.9)	272 (87.5)
<i>Klebsiella pneumoniae</i>	15 (9.3)	14 (9.4)	29 (9.3)
<i>Proteus mirabilis</i>	9 (5.6)	6 (4.0)	15 (4.8)
<i>Morganella morganii</i>	3 (1.9)	1 (0.7)	4 (1.3)
<i>Enterobacter cloacae</i> complex	1 (0.6)	0 (0.0)	1 (0.3)
<i>Providencia stuartii</i>	0 (0.0)	1 (0.7)	1 (0.3)

Source: Reviewer's analysis

Abbreviations: MMITTR, microbiological modified intent-to-treat resistant

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Concomitant medication use including antibacterial therapy and other categories of medications with 10 or more subjects in the resistant population are shown in Table 76. It appears that more subjects in the ciprofloxacin group took antibacterial therapy. These subjects were all considered as treatment failures in the primary efficacy analysis. Therefore, no further

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

sensitivity analyses were conducted, as reasons for use were for rescue therapy (10 subjects), an adverse event (1 subject), and dental abscess (1 subject).

Table 76. Study 301: Concomitant Medication Use in Antibacterial Therapy and Categories with 10 or More Subjects, MMITTR Population (Including Patients From Site 202)

Parameters	Sulopenem (N=162)	Ciprofloxacin (N=149)	Total (N=311)
Any concomitant medication	100 (61.7)	84 (56.4)	184 (59.2)
Antibacterial therapy	0	12 (8.1)	12 (3.9)
Beta-lactam antibacterials, penicillins	0	3 (2.0)	3 (1.0)
Other beta-lactam antibacterials	0	2 (1.3)	2 (0.6)
Other antibacterials	0	6 (4.0)	6 (1.9)
Sulfonamides and trimethoprim	0	1 (0.7)	1 (0.3)
Other concomitant medications	91 (56.2)	78 (52.3)	169 (54.3)
Blood glucose lowering drugs, excl. insulins	26 (16.0)	23 (15.4)	49 (15.8)
Lipid modifying agents	26 (16.0)	18 (12.1)	44 (14.1)
Angiotensin II antagonists	25 (15.4)	14 (9.4)	39 (12.5)
ACE inhibitors	15 (9.3)	19 (12.8)	34 (10.9)
Antithrombotic agents	21 (13.0)	11 (7.4)	32 (10.3)
Beta blocking agents	16 (9.9)	13 (8.7)	29 (9.3)
Drugs for peptic ulcer and gastro-esophageal reflux disease (GERD)	13 (8.0)	16 (10.7)	29 (9.3)
Selective calcium channel blockers with mainly vascular effects	13 (8.0)	9 (6.0)	22 (7.1)
Thyroid preparations	10 (6.2)	10 (6.7)	20 (6.4)
Low-ceiling diuretics, thiazides	10 (6.2)	6 (4.0)	16 (5.1)
Adrenergics, inhalants	8 (4.9)	5 (3.4)	13 (4.2)
Antidepressants	8 (4.9)	5 (3.4)	13 (4.2)
Insulins and analogues	4 (2.5)	9 (6.0)	13 (4.2)
Other analgesics and antipyretics	6 (3.7)	7 (4.7)	13 (4.2)
Antihistamines for systemic use	5 (3.1)	7 (4.7)	12 (3.9)
Vitamin A and D, including combinations of the two	6 (3.7)	4 (2.7)	10 (3.2)

Source: Reviewer's analysis

Abbreviations: ACE, angiotensin-converting enzyme; MMITTR, microbiological modified intent-to-treat resistant

As Table 77 shows, the most commonly reported medical history included hypertension (40.5%), type 2 diabetes mellitus (14.5%), hysterectomy (11.3%), and gastroesophageal reflux disease (10.9%). The two treatment groups were comparable regarding medical history.

Table 77. Study 301: Medical History in Conditions With 10 or More Patients, MMITTR Population (Including Patients From Site 202)

Parameters	Sulopenem (N=162)	Ciprofloxacin (N=149)	Total (N=311)
Any medical history	126 (77.8)	120 (80.5)	246 (79.1)
Cardiac disorders	35 (21.6)	22 (14.8)	57 (18.3)
Arteriosclerosis coronary artery	13 (8.0)	7 (4.7)	20 (6.4)
Cardiac failure congestive	5 (3.1)	6 (4.0)	11 (3.5)
Coronary artery disease	10 (6.2)	5 (3.4)	15 (4.8)
Myocardial ischemia	12 (7.4)	11 (7.4)	23 (7.4)
Endocrine disorders	17 (10.5)	14 (9.4)	31 (10)
Hypothyroidism	10 (6.2)	11 (7.4)	21 (6.8)

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

Parameters	Sulopenem (N=162)	Ciprofloxacin (N=149)	Total (N=311)
Gastrointestinal disorders	36 (22.2)	36 (24.2)	72 (23.2)
Chronic gastritis	8 (4.9)	9 (6.0)	17 (5.5)
Gastroesophageal reflux disease	17 (10.5)	17 (11.4)	34 (10.9)
Infections and Infestations	19 (11.7)	21 (14.1)	40 (12.9)
Cystitis	10 (6.2)	12 (8.1)	22 (7.1)
Metabolism and Nutrition Disorders	45 (27.8)	36 (24.2)	81 (26)
Hyperlipidemia	14 (8.6)	10 (6.7)	24 (7.7)
Type 2 diabetes mellitus	24 (14.8)	21 (14.1)	45 (14.5)
Musculoskeletal and connective tissue disorders	37 (22.8)	21 (14.1)	58 (18.6)
Intervertebral disc degeneration	7 (4.3)	4 (2.7)	11 (3.5)
Osteoarthritis	9 (5.6)	6 (4.0)	15 (4.8)
Osteochondrosis	6 (3.7)	8 (5.4)	14 (4.5)
Nervous system disorders	28 (17.3)	18 (12.1)	46 (14.8)
Cerebrovascular disorder	7 (4.3)	5 (3.4)	12 (3.9)
Encephalopathy	7 (4.3)	5 (3.4)	12 (3.9)
Psychiatric disorders	24 (14.8)	19 (12.8)	43 (13.8)
Anxiety	8 (4.9)	9 (6.0)	17 (5.5)
Depression	7 (4.3)	10 (6.7)	17 (5.5)
Insomnia	8 (4.9)	6 (4.0)	14 (4.5)
Respiratory, thoracic, and mediastinal disorders	23 (14.2)	17 (11.4)	40 (12.9)
Asthma	11 (6.8)	15 (10.1)	26 (8.4)
Social circumstances	26 (16.0)	14 (9.4)	40 (12.9)
Menopause	9 (5.6)	6 (4.1)	15 (4.8)
Postmenopause	17 (10.5)	8 (5.4)	25 (8.0)
Surgical and medical procedures	53 (32.7)	55 (36.9)	108 (34.7)
Appendectomy	11 (6.8)	6 (4.0)	17 (5.5)
Caesarean section	9 (5.6)	11 (7.4)	20 (6.4)
Cholecystectomy	10 (6.2)	9 (6.0)	19 (6.1)
Female sterilization	10 (6.2)	12 (8.1)	22 (7.1)
Hysterectomy	16 (9.9)	19 (12.8)	35 (11.3)
Vascular disorders	75 (46.3)	64 (43.0)	139 (44.7)
Essential hypertension	6 (3.7)	5 (3.4)	11 (3.5)
Hypertension	67 (41.4)	59 (39.6)	126 (40.5)

Source: Reviewer's analysis

Abbreviations: MMITTR, microbiological modified intent-to-treat resistant

Efficacy Results – Primary Endpoint

Table 78 shows the Applicant's results as reported in their initial study report, as well as the updated results from the Applicant using the original definition of microbiological response to determine overall response and the original definition of the MMITTR population. The major difference between these two analyses are that subjects with urine cultures that grew $\geq 10^3$ CFU/mL of the baseline uropathogen were considered as having an overall nonresponse in the second analysis (using the original SAP), regardless of susceptibility and the determination of whether the baseline and post-baseline organism were the same by whole genome sequencing. Note that the overall response rate for sulopenem decreased by an absolute difference of 11.3%. The treatment difference is smaller in the second analysis (using the original SAP) as the

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

Applicant's altered definition impacted more subjects in the sulopenem arm than the ciprofloxacin arm (26.6% vs. 18.7%).

Table 78. Study 301: Overall Response at TOC Using Revised vs. Original SAP, MMITTR Population

Outcome	Sulopenem	Ciprofloxacin	Difference (S-C) 95% CI, P-value
Applicant's results using revised SAP (with revised definitions for microbiological response and MMITTR), excluding Site 202			
Overall response	(N=147) 92 (62.6)	(N=139) 50 (36.0)	26.6 [15.1, 37.4] <0.001
Overall nonresponse	49 (33.3)	84 (60.4)	
Indeterminate	6 (4.1)	5 (3.6)	
Applicant's results using original SAP (with original definitions for microbiological response and MMITTR), excluding Site 202			
Overall response	(N=152) 78 (51.3)	(N=144) 47 (32.6)	18.7 [7.4, 29.4] 0.0011*
Overall nonresponse	68 (44.7)	92 (63.9)	
Indeterminate	6 (3.9)	5 (3.5)	

Source: Tables 52 and 83, updated Study Report

*The p-value from the updated Study Report was 0.004 with a three-category outcome (response/failure/indeterminate)

Abbreviations: CI, confidence interval; MMITTR, microbiological modified intent-to-treat resistant; SAP, statistical analysis plan; TOC, test-of-cure

Table 79 shows the Applicant's analysis using the original SAP and including Site 202. Note that as stated above, we do not agree with the removal of Site 202 from the analysis. Though there continues to be a significant treatment effect in this analysis with a p-value of 0.0062, the absolute difference was reduced to 15.3%. FDA's analysis was similar and is also reported in the table.

Table 79. Study 301: Applicant's and FDA's Analysis Overall Response Using Original SAP, Including Site 202, MMITTR Population

Outcome	Sulopenem	Ciprofloxacin	Difference (%) 95% CI	P-value
Applicant's Results				
Overall response	(N=162) 78 (48.1)	(N=149) 49 (32.9)	15.3 (4.3, 25.8)	0.0062*
FDA's Results				
Overall response	(N=160) 77 (48.1)	(N=149) 49 (32.9)	15.2 (4.4, 26.1)	0.0065

Source: Table 84, updated Study Report and reviewer's analysis

*The p-value from the updated Study Report was 0.012, from a Chi-squared test with a three-category outcome (success/failure/indeterminate)

Abbreviations: CI, confidence interval; MMITTR, microbiological modified intent-to-treat resistant; SAP, statistical analysis plan

M.O. Comment: The inclusion of Site 202 does not have a large effect on the treatment difference (15.3% vs. 18.7%) as compared to the Applicant's revised definitions of microbiological response and MMITTR (26.6% vs. 18.7%).

Data Quality and Integrity

We have found no potential issues concerning the submitted data quality that raise questions about the efficacy results. Anomalies were found with Site 218, as discussed above and below (see Sections 4.1 and 8.3 for additional details). However, the Division identified several issues with the Applicant's analysis of Study 301 which occurred after an unblinded interim analysis which call into question the reliability of the results and include the following: (1) revision to the SAP that changed the definition of the microbiological response and overall response endpoint for Study 301, (2) revision to the SAP to include use of PCR to define the patient susceptibility populations, (3) the late exclusion of clinical study Site 202 and (4) Iterum's revision to the analysis plan to allow for superiority testing in the MMITTR population after they were notified by the DMC that the conditional power was <40% at the unblinded interim analysis which, based on the original pre-specified plan, would not have resulted in testing for superiority in the MMITTR population. The Division acknowledges that there may be additional issues with the conduct of these 3 studies that we have not yet identified given the prior questionable changes to the SAP and exclusion of Site 202 after the unblinded interim analysis of Study 301.

Efficacy Results – Secondary and Other Relevant Endpoints

Clinical and Microbiological Response

Clinical and microbiological response per patient at TOC based on the original SAP as assessed by the Applicant are displayed in Table 80, where microbiological success was defined as TOC urine culture results of <10³ CFU/mL of the baseline pathogen(s) regardless of susceptibility and including Site 202 in the analysis. Clinical response was based on patient-determined clinical response defined as resolution of baseline uUTI symptoms and no new uUTI symptoms at TOC. There was a significant treatment effect in clinical success (resolution of baseline symptoms). These results using the original SAP and including Site 202 as conducted by the Applicant were similar to those conducted by the FDA. Microbiological response by pathogen: *E. coli*, *K. pneumoniae*, or *P. mirabilis* in the sulopenem group was numerically higher than in the ciprofloxacin group.

Table 80. Study 301: Clinical Response, Microbiological Response Per Patient, And Microbiological Response Per Selected Pathogen at TOC Using Original SAP, MMITTR Population

Response	Sulopenem (N=162)	Ciprofloxacin (N=149)	Difference (%) 95% CI	P-value
Clinical Response				
Clinical Success	136 (84.0)	96 (64.4)	19.5 (10.0, 29.0)	<0.0001
Clinical Failure	23 (14.2)	47 (31.5)		
Indeterminate	3 (1.9)	6 (4.0)		
Microbiological Response by Patient				
Microbiological Success	92 (56.8)	66 (44.3)	12.5 (1.4, 23.3)	0.028
Failure	62 (38.3)	76 (51.0)		
Indeterminate	8 (4.9)	7 (4.7)		
Microbiological Response by Pathogen				
<i>Escherichia coli</i>				
	N=141	N=131		
Success	85 (60.3)	64 (48.9)	11.4 (-0.4, 23.0)	0.059
Failure	56 (39.7)	67 (51.1)		
<i>Klebsiella pneumoniae</i>				
	N=15	N=14		
Success	10 (66.7)	8 (57.1)	9.5 (-25.4, 42.6)	0.597
Failure	5 (33.3)	6 (42.9)		
<i>Proteus mirabilis</i>				
	N=9	N=6		
Success	8 (88.9)	4 (66.7)	22.2 (-31.6, 67.7)	
Failure	1 (11.1)	2 (33.3)		
<i>Morganella morganii</i>				
	N=3	N=1		
Success	3 (100.0)	1 (100.0)		

Source: Reviewer's analysis based on updated data set
 CI for *P. Mirabilis* was an exact CI

Abbreviations: CI, confidence interval; MMITTR, microbiological modified intent-to-treat resistant; SAP, statistical analysis plan; TOC, test-of-cure

Persistence of Effect

The Applicant's analysis results of overall response using the original SAP are shown in Table 81. Overall, the difference between the two treatment groups was largest at the end of the treatment, and smallest at the TOC visit. The treatment effect remained statistically significant at all visits. FDA's analysis showed very similar results.

Table 81. Analysis of Overall Response by Visit Using the Original SAP, MMITTR Population (Including Patients From Site 202)

Outcome	Sulopenem (N=162)	Ciprofloxacin (N=149)	Difference (%) (95% CI)	P-value
Overall response at EOT	98 (60.5)	38 (25.5)	35.0 (24.3, 44.8)	<0.001
Overall nonresponse	58 (35.8)	108 (72.5)		
Indeterminate	6 (3.7)	3 (2.0)		
Overall response at TOC	78 (48.1)	49 (32.9)	15.3 (4.3, 25.8)	0.0062*
Overall nonresponse	76 (46.9)	95 (63.8)		
Indeterminate	8 (4.9)	5 (3.4)		
Overall response at FV	97 (59.9)	58 (38.9)	21.0 (9.9, 31.5)	<0.001
Overall nonresponse	57 (35.2)	77 (51.7)		
Indeterminate	8 (4.9)	14 (9.4)		

Source: Table 84, updated Study Report

*The p-value from the updated Study Report was 0.012, from a Chi-squared test with a three-category outcome (success/failure/indeterminate)

Abbreviations: CI, confidence interval; EOT, end of treatment; FV, final visit; MMITTR, microbiological modified intent-to-treat resistant; SAP, statistical analysis plan; TOC, test-of-cure

Efficacy Results – Secondary and Exploratory Endpoints

In the primary efficacy analysis, contaminated urine cultures were considered as successes for the microbiological outcome. As a sensitivity analysis, we identified 3 subjects on sulopenem and 1 subject on ciprofloxacin who were considered as overall responders in the primary efficacy analysis despite their cultures showing ≥ 3 organisms recovered (with no organism information). Considering them as failures, the results are shown in Table 82.

Table 82. FDA’s Analysis of Overall Response at TOC, Contaminated Urine Culture as Failure in the Definition of Microbiological Success, MMITTR Population

Outcome	Sulopenem (N=160)	Ciprofloxacin (N=149)	Difference (%) 95% CI	P-value
Overall response	74 (46.3)	48 (32.3)	14.0 (3.1, 24.6)	0.012

Source: Reviewer’s analysis

Abbreviations: CI, confidence interval; MMITTR, microbiological modified intent-to-treat resistant; TOC, test-of-cure

FDA’s analysis of overall response using complete eradication of baseline pathogens at TOC (defined as $<10^2$ CFU/mL) and the original SAP is displayed in Table 83. Compared with FDA’s primary analysis, 8 additional sulopenem subjects and 4 additional ciprofloxacin subjects were found to have their baseline pathogen between 10^2 and 10^3 CFU/mL at TOC and were considered as non-responders.

Table 83. FDA’s Analysis of Overall Response at TOC Using Complete Eradication as Definition of Microbiological Success, MMITTR Population

Outcome	Sulopenem (N=160)	Ciprofloxacin (N=149)	Difference (%) 95% CI	P-value
Overall response	69 (43.1)	44 (29.5)	13.6 (2.9, 24.1)	0.013

Source: Reviewer’s analysis

Abbreviations: CI, confidence interval; MMITTR, microbiological modified intent-to-treat resistant; TOC, test-of-cure

Additional Analyses Conducted on the Individual Trial

Interim Analyses

As noted earlier in this review, two interim analyses for sample size re-estimation were planned to be conducted in Study 301 when response data at TOC were available for approximately 33% and 66% of the patients (approximately 450 and 900 patients, respectively). Blinded sample size re-estimations for the MMITTS non-inferiority assessment were to be conducted at both interim analyses and an unblinded sample size re-estimation using conditional power for the MMITTR superiority assessment was to be conducted at the second interim analysis. However, the interim analyses were delayed such that the two interim analyses were conducted at the same time.

The results from the interim analyses for the MMITTS population and unblinded analysis for the conditional power assessment of the MMITTR population were presented to the DMC on October 10, 2019. The non-inferiority sample size re-estimation for the MMITTS population at the second interim analysis resulted in a recommendation to add up to 828 patients to the study. The Applicant chose to increase the sample by as many as 400 subjects.

The conditional power from the unblinded interim analysis for the resistant population was less than 40%. Because of this low conditional power, the sample size was not changed for the resistant population. As noted above, based on the SAP in place at the time of the interim analysis, the final analysis of the MMITTR population was not to be conducted if the conditional power was <40%. However, this text was removed from the SAP after the interim analysis. Note that though it does not appear that this requirement is needed to control the Type I error, there is concern that the SAP was changed based on the results of the unblinded interim analysis.

The original unblinded interim analysis results when approximately 66% of the subjects were enrolled showed only a minimal effect of sulopenem over ciprofloxacin for overall response (see Table 84). The Applicant was notified by the DMC that: "The conditional power with the revised sample size for MMITTR is below 40%. So there isn't a need for any sample size calculation for the superiority test."¹ After being notified of this finding, the Applicant changed the microbiological response definition. To demonstrate the large impact this change had on the study results, the second analysis in this table reports the results using this altered endpoint on the same subjects who were included in the interim analysis. The sulopenem response rate increased 20.7% while the ciprofloxacin response rate increased by 3.1%, and the difference between the sulopenem and ciprofloxacin response rates changed from 8.3% to 25.9%. Additional changes to the analyses were made after the interim analysis, including the change to the MMITTR definition and the exclusion of Site 202 from the analysis. The third row considers these changes on the group of subjects from Study 301 available at the interim analysis. These changes in the revised SAP increased the difference in the response rates between sulopenem and ciprofloxacin to 31.4%. As stated above, we did not agree with the Applicant's interpretation of the changes to the SAP and exclusion of Site 202 after the outcome of the interim analysis was known by the Applicant.

¹ Email from DMC member to Applicant dated 10/29/2019, submitted to the NDA on 2/2/2021.

Table 84. Change in Applicant’s Overall Response Results from Subjects Included in the Interim Analysis, MMITTR Population

Overall Response	Sulopenem	Ciprofloxacin	P-value
October 2019 interim results	33/87 (37.9%)	29/98 (29.6%)	0.23
Using Applicant’s new microbiological response definition	51/87 (58.6%)	32/98 (32.7%)	0.0004
Using Applicant’s new microbiological response definition, updated MMITTR definition, and excluding Site 202	48/80 (60.0%)	26/91 (28.6%)	<0.0001

Source: Reviewer’s analysis

Abbreviations: MMITTR, microbiological modified intent-to-treat resistant

Subgroup Analyses

Subgroup analysis results by age, race, and country per the original SAP are shown in Table 85. As age increased, the treatment effect increased. The vast majority of subjects were White and it is difficult to make any conclusions regarding other races due to the small sample sizes. In the US, the treatment effect was consistent with the overall effect, while in Russia and Ukraine the observed treatment effect was lower and higher than the overall effect, respectively.

Table 85. FDA’s Subgroup Analyses of the Overall Response by Age, Race, and Country, MMITTR Population, Including Patients From Site 202

Variable	Sulopenem (N=162)	Ciprofloxacin (N=149)	Difference (%) (95% CI)
Age (years)			
<30	17/25 (68.0)	12/21 (57.1)	10.9 (-17.0, 37.7)
30-60	38/67 (56.7)	26/59 (44.1)	12.7 (-4.9, 29.4)
60 or above	23/70 (32.9)	11/69 (15.9)	16.9 (2.6, 30.8)
Race			
Asian	0/2 (0)	0	
Black or African American	9/15 (60.0)	6/12 (50.0)	10.0 (-26.7, 44.7)
White	69/144 (47.9)	42/136 (30.9)	17.0 (5.6, 28.0)
Other	0/1 (0)	1/1 (100)	
Country			
RUS	17/46 (37.0)	18/43 (41.9)	-4.9 (-24.8, 15.3)
UKR	14/24 (58.3)	4/14 (28.6)	29.8 (-3.6, 56.2)
USA	46/95 (48.4)	28/89 (31.5)	17.0 (2.8, 30.5)

Source: Reviewer’s analysis

CI for UKR was an exact CI

Abbreviations: CI, confidence interval; MMITTR, microbiological modified intent-to-treat resistant; RUS, Russia; UKR, Ukraine; USA, United States of America

Table 86 shows the FDA’s analysis results from the subgroup analysis by baseline creatinine clearance using the original SAP. The number of subjects with a creatinine clearance <30 mL/min was too small to make a reliable estimation. As the following table shows, the treatment effect was similar between the last two categories of creatinine clearance, though the response rates were higher in the >60 mL/min group.

Table 86. Study 301: Subgroup Analysis of Overall Response at TOC by Creatinine Clearance, MMITTR Population (Including Patients From Site 202)

Creatinine Clearance (mL/min)	Sulopenem (N=162)	Ciprofloxacin (N=149)	Difference (%) (95% CI)
<30	2/4 (50)	0/6 (0)	
30-60	14/50 (28.0)	9/52 (17.3)	10.7 (-5.7, 27.7)
>60	62/108 (57.4)	40/91 (44.0)	13.5 (-0.5, 26.9)

Source: Reviewer's analysis

Abbreviations: CI, confidence interval; MMITTR, microbiological modified intent-to-treat resistant; TOC, test-of-cure

Results in Susceptible (MMITTS) Population

There were 794 subjects in the susceptible population (376 and 418 subjects in the sulopenem and ciprofloxacin treatment groups, respectively), including Site 202. The mean age was 50.5 years with a range of 18 to 96 years. About 27% of subjects were 65 years of age or older. The majority of subjects were of White race. Fifty-three percent of subjects were from the US. The majority of subjects had a baseline creatinine clearance $\geq$ 30 mL/min.

Table 87 shows the Applicant's results as reported in the initial study report, as well as the updated results using the original definition of microbiological response to determine overall response, the original definition of the MMITTS population, and the exclusion/inclusion of data from Site 202. Note that the results are consistent in that non-inferiority was not demonstrated within the pre-defined 10% non-inferiority margin. Additionally, sulopenem had a significantly lower overall response rate compared to ciprofloxacin.

Table 87. Study 301: Applicant's Analysis Results - Overall Response at TOC Using the Revised vs. Original SAP, MMITTS Population (Excluding/Including Site 202)

Overall response at TOC	Sulopenem	Ciprofloxacin	Difference (%) [95% CI]
Applicant's Results using revised definitions for micro response and MMITTS population, excluding Site 202			
	(N=370)	(N=415)	
Overall response	247 (66.8)	326 (78.6)	-11.8 (-18.0, -5.6)
Overall nonresponse	105 (28.4)	65 (15.7)	
Indeterminate	18 (4.9)	24 (5.8)	
Applicant's Results using original definitions of micro response and MMITTS, excluding Site 202			
	(N=365)	(N=410)	
Overall response	218 (59.7)	296 (72.2)	-12.5 (-19.1, -5.9)
Overall nonresponse	129 (35.3)	90 (22.0)	
Indeterminate	18 (4.9)	24 (5.8)	
Applicant's Results using original definitions of micro response and MMITTS, including Site 202			
	(N=376)	(N=418)	
Overall response	227 (60.4)	300 (71.8)	-11.4 (-17.9, -4.8)
Overall nonresponse	130 (34.6)	91 (21.8)	
Indeterminate	19 (5.1)	27 (6.5)	

Source: Tables 87, 121, 122, Study Report

Abbreviations: CI, confidence interval; MMITTS, microbiological modified intent-to-treat susceptible; SAP, statistical analysis plan; TOC, test-of-cure

8.1.3. Assessment of Efficacy Across Trials

Along with the results from the uUTI resistant and susceptible populations, the Applicant conducted two additional Phase 3 trials, one in complicated urinary tract infection (cUTI) and one in complicated intra-abdominal infection (cIAI). The results of these studies are discussed here.

Study 302-cUTI

Study 302 was a Phase 3, multi-center, double-blind, randomized trial designed to compare the efficacy, tolerability, and safety of IV sulopenem followed by oral sulopenem with that of IV ertapenem followed by oral ciprofloxacin or amoxicillin/clavulanate for the treatment of cUTI.

Subjects were randomized 1:1 to receive either IV sulopenem 1000 mg once daily for at least 5 days (5 doses) followed by sulopenem etzadroxil 500 mg co-administrated with oral probenecid 500 mg twice daily to complete 7-10 total days of treatment or ertapenem IV 1000 mg once daily for at least 5 days (5 doses) followed by oral ciprofloxacin 500 mg or amoxicillin-clavulanate 875 mg twice daily to complete 7-10 total days of therapy. Duration of treatment could be extended up to a total duration of 14 days for patients with bacteremia at baseline.

The primary efficacy endpoint was overall response (resolution of symptoms and clearance of the baseline uropathogen) at Day 21 (TOC). The primary analysis population was the microbiological modified Intent-to-Treat population (MMITT), defined as subjects who received at least a single dose of study medication, had the disease under study (having 2 of the 5 baseline cUTI symptoms), and had a positive study entry urine culture within 48 hours prior to the first dose and no more than 2 species of microorganisms identified in the study entry urine culture with $\geq 10^5$ CFU/mL, except in the situation where 1 of the organisms cultured from the urine was also isolated from blood cultures drawn at baseline. A positive urine culture was defined as $\geq 10^5$ CFU/mL of a uropathogen (Enterobacteriales only, susceptible to sulopenem [MIC ≤ 1] and ertapenem [MIC ≤ 0.5]). Patients with a study pathogen isolated from baseline blood cultures were included in the MMITT population regardless of the patient's baseline urine culture result.

As in Study 301, the Applicant's efficacy results were based on definitions of microbiological responses using the same footnote for "Persistence" (See the section of "Protocol Amendments" in Study 301). We requested the reanalysis of the data based on the definitions without using PCR data. The results from the two analyses from the initial report and from the updated report were consistent.

The two treatment groups were comparable with respect to demographic characteristics. The majority of subjects were females (about 55%). The mean age was about 59 years (range: 18 to 94 years). The majority of subjects had acute pyelonephritis (57.1% sulopenem; 56.9% ertapenem); *E. coli* was the most common organism isolated (76.1% on sulopenem; 78.6% on ertapenem).

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

As noted in Table 88, this study failed to show noninferiority using a 10% NI margin. Sulopenem was significantly worse than the active comparator, ertapenem.

Table 88. Study 302: Overall Response at TOC, MMITT Population

	Sulopenem (N=444)	Ertapenem (N=440)	Difference (%) [95% CI]
Overall Response	265 (59.7)	296 (67.3)	-7.6 (-13.9, -1.3)
Overall nonresponse	162 (36.5)	122 (27.7)	
Indeterminate	17 (3.8)	22 (5.0)	

Source: Table 62, Study Report

Abbreviations: CI, confidence interval; MMITT, microbiological modified intent-to-treat; TOC, test-of-cure

Study 303-clAI

Study 303 was a Phase 3, multi-center, double-blind, randomized trial designed to compare the efficacy, tolerability, and safety of IV sulopenem followed by oral sulopenem with that of IV ertapenem followed by oral ciprofloxacin and metronidazole or amoxicillin/clavulanate for the treatment of clAI.

A total of 674 subjects were randomized (1:1) to receive either IV sulopenem 1000 mg once daily for at least 5 days (5 doses) followed by sulopenem etzadroxil 500 mg coadministered with oral probenecid 500 mg twice daily to complete 7-10 total days of treatment or ertapenem IV 1000 mg once daily for at least 5 days (5 doses) followed by oral ciprofloxacin 500 mg and metronidazole or amoxicillin-clavulanate 875 mg twice daily to complete 7-10 total days of therapy. Duration of treatment could be extended up to a total duration of 14 days for patients with bacteremia at baseline. The primary efficacy endpoint was clinical response at the TOC visit (Day 28).

The two treatment groups were comparable with respect to demographic characteristics. The majority of subjects were male (about 53.5%). The mean age was about 54 years (range: 18 to 90 years). The number of subjects with clAI caused by appendicitis with perforation or periappendiceal abscess was similar (47.5%); *E. coli* was the most common organism isolated (75.9% on sulopenem; 77.4% on ertapenem).

The primary efficacy endpoint was clinical response at the TOC visit. The analysis population was the MMITT population (MMITT), which included all randomized patients who received at least a single dose of study medication, had the disease under study, had at least 1 Gram-negative study pathogen (aerobic or anaerobic organisms) identified at study entry within 48 hours prior to the first dose of study drug and up to 24 hours after the first dose, regardless of isolate susceptibility and regardless of other organisms identified in the culture.

The results are shown in Table 89. After initial unblinding of the study, imbalances in outcome by treatment were identified by the Applicant, such as lower efficacy with sulopenem compared to the active comparator in subjects with *Pseudomonas aeruginosa*, more failures due to surgical interventions in the sulopenem arm, lower success rates in subjects receiving only IV sulopenem compared to only receiving IV ertapenem. Therefore, the Applicant conducted a post-hoc analysis by re-examining and re-analyzing the data. We do not agree with

the Applicant's post-hoc analysis after the study data were unblinded. This study failed to show noninferiority using a 10% margin, either based on the primary analysis or the post-hoc analysis.

Table 89. Study 303: Applicant's Analysis Primary and Post-Hoc Results - Clinical Response at TOC, MMITT Population

Clinical Response	Sulopenem (N=249)	Ertapenem (N=266)	Difference (%) [95% CI]
Primary: Success	204 (81.9)	233 (87.9)	-6.0 (-12.2, 0.2)
Post-hoc: Success	213 (85.5)	240 (90.2)	-4.7 (-10.3, 1.0)
Failure	27 (10.8)	17 (6.4)	
Indeterminate	9 (3.6)	9 (3.4)	

Abbreviations: CI, confidence interval; MMITT, microbiological modified intent-to-treat; TOC, test-of-cure

8.1.4. Integrated Assessment of Effectiveness

Study 301 demonstrated that in patients with ciprofloxacin-nonsusceptible uUTI, sulopenem was superior to ciprofloxacin in overall response (combined microbiological response and clinical response) at the TOC visit with a difference of 15.3% (95% CI: 4.3%, 25.8%) and a p-value of 0.0062, according to the original statistical analysis plan and including data from clinical Site 202.

Of note, sulopenem failed to demonstrate noninferiority to ciprofloxacin in the ciprofloxacin-susceptible population of this trial. As the cUTI (Study 302) and cIAI (Study 303) trials did not meet the pre-specified noninferiority margins, there is a lack of other evidence of efficacy to support the single successful trial in uUTI. In fact, sulopenem was statistically inferior to the comparator in the ciprofloxacin-susceptible population of Study 301 and in the cUTI Study 302.

Additionally, the Division identified several issues with the Applicant's analysis of Study 301 which occurred after an unblinded interim analysis which call into question the reliability of the results and include the following: (1) revision to the SAP that changed the definition of the microbiological response and overall response endpoint for Study 301, (2) revision to the SAP to include use of PCR to define the patient susceptibility populations, (3) the late exclusion of clinical study Site 202 and (4) Iterum's revision to the analysis plan to allow for superiority testing in the MMITTR population after they were notified by the DMC that the conditional power was <40% at the unblinded interim analysis which, based on the original pre-specified analysis plan, would not have resulted in testing for superiority in the MMITTR population. The Division acknowledges that there may be additional issues with the conduct of these 3 studies that we have not yet identified given the prior questionable changes to the SAP and exclusion of Site 202 after the unblinded interim analysis of Study 301.

8.2. Review of Safety

8.2.1. Safety Review Approach

The primary safety analysis was conducted on the data derived from the Phase 3 uUTI Study 301 as this is the indication sought by the Applicant in this NDA. Additional analyses were

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

conducted on the combined Phase 3 study population which includes safety data from Studies 301, 302 (cUTI), and 303 (cIAI). The Phase 1 studies conducted by the Applicant and Pfizer as well as the Phase 2 studies conducted by Pfizer did not provide significant additional safety data; data from these studies are summarized at the end of Section 8.2.4.

8.2.2. Review of the Safety Database

Overall Exposure

The safety database for sulopenem (Table 90) includes 825 subjects who received sulopenem for the treatment of uUTI and an additional 1030 subjects in controlled Phase 3 studies who received sulopenem for other indications. In Study 301, subjects were randomized to receive oral sulopenem etzadroxil/probenecid for 5 days or oral ciprofloxacin for 3 days which matched the actual median duration of treatment in each arm. In Study 302, the median total duration of treatment (IV and oral) was 10 days in each arm of which the median duration of oral treatment was 4 days. In Study 303, the median total duration of treatment (IV and oral) was 9 days in each arm of which the median duration of oral treatment was 3 days.

M.O. Comment: 13 subjects from Site 218 in Study 301 (8 from the sulopenem arm and 5 from the ciprofloxacin arm) were removed from the safety database (b) (7)(A)

Table 90. Safety Database for Sulopenem

Clinical Trial Groups	N=5789	
	Sulopenem Etzadroxil + Probenecid / Sulopenem (n=3861)	Active Control (n=1928)
Controlled trials conducted for this indication		
Study 301 (uUTI)	825	822 (ciprofloxacin)
Controlled trials conducted for other indications		
Study 302 (cUTI)	695	697*
Study 303 (cIAI)	335	333*
5 Applicant-conducted Phase 1 studies (IV/oral)	276	-
14 Pfizer-conducted Phase 1 studies (IV/oral)	298	-
5 Pfizer-conducted, Phase 2 studies (IV)	1432	76

Source: Reviewer Table

* Active comparator was IV ertapenem followed by oral ciprofloxacin or amoxicillin/clavulanate

Abbreviations: cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; IV, intravenous; uUTI, uncomplicated urinary tract infection

The demographic and other baseline patient characteristics of Study 301 were balanced between the study arms; these data are summarized in Table 91. All subjects were female as uUTI can by definition only occur in women and girls. There was sufficient representation of ages, ethnicities, and body mass indices (BMIs). Most subjects were White, but there were

some subjects of other races. Most subjects were in the United States, but the safety of the drug is unlikely to differ greatly in the two other countries represented in the study (Ukraine and Russia).

Table 91. Demographic and Other Baseline Patient Characteristics of the Study 301 Safety Population

Characteristic	Sulopenem Etzadroxil + Probenecid N=825	Ciprofloxacin N=822
Age (years), mean	49.8	50.2
Age (years), median	50	51
Categorical age (years), n (%)		
18 - 29	159 (19.3)	165 (20.1)
30-60	387 (46.9)	352 (42.8)
≥60	279 (33.8)	305 (37.1)
≥65	218 (26.4)	233 (28.3)
Sex, n (%)		
Female	825 (100)	822 (100)
Race, n (%)		
American Indian or Alaska Native	10 (1.2)	3 (0.4)
Asian	11 (1.3)	7 (0.9)
Black or African American	74 (9.0)	66 (8.0)
Native Hawaiian or Other Pacific Islander	0	1 (0.1)
Other	4 (0.5)	3 (0.4)
White	726 (88.0)	742 (90.3)
Ethnicity, n (%)		
Hispanic or Latino	291 (35.3)	255 (31.0)
Not Hispanic or Latino	529 (64.1)	566 (68.9)
Not Reported/Unknown	5 (0.6)	1 (0.1)
Country, n (%)		
Russia	195 (23.6)	224 (27.3)
Ukraine	144 (17.5)	137 (16.7)
United States	486 (58.9)	461 (56.1)
BMI by category (kg/m ²), n (%)		
<25	319 (38.7)	345 (42.0)
25 - 30	248 (30.1)	224 (27.3)
>30	255 (30.9)	241 (29.3)
Missing	3 (0.4)	12 (1.5)
Creatinine clearance by category (mL/min), n (%)		
<30	15 (1.8)	10 (1.2)
30 - 60	206 (25.0)	206 (25.1)
>60	604 (73.2)	605 (73.6)
Missing	0	1 (0.1)

Source: Reviewer Table

The demographic and other baseline patient characteristics of the integrated Phase 3 safety population (Studies 301, 302, and 303) were balanced between the study arms; these data are summarized in Table 92. The integrated safety population was mostly female and White which may limit the generalizability of the safety findings. However, subjects exposed to sulopenem in

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

the 5 Applicant-conducted Phase 1 studies were mostly Black or African-American (194/276, 70%) which increases the diversity of the overall safety population.

Table 92. Demographic and Other Baseline Patient Characteristics of Integrated Phase 3 Safety Population

Characteristic	Sulopenem Etzadroxil + Probenecid / Sulopenem N=1855	Comparator N=1852
Age (years), mean	53.5	54.5
Age (years), median	56	58
Categorical age (years), n (%)		
<65	1215 (65.5)	1163 (62.8)
65 - 74	384 (20.7)	416 (22.5)
75 - 84	218 (11.8)	233 (12.6)
>85	38 (2.0)	40 (2.2)
Sex, n (%)		
Female	1371 (73.9)	1353 (73.1)
Male	484 (26.1)	499 (26.9)
Race, n (%)		
American Indian or Alaska Native	10 (0.5)	3 (0.2)
Asian	12 (0.6)	11 (0.6)
Black or African American	75 (4.0)	72 (3.9)
Native Hawaiian or Other Pacific Islander	1 (0.1)	1 (0.1)
Other	5 (0.3)	3 (0.2)
White	1752 (94.4)	1762 (95.1)
Ethnicity, n (%)		
Hispanic or Latino	321 (17.3)	283 (15.3)
Not Hispanic or Latino	1526 (82.3)	1565 (84.5)
Not Reported/Unknown	8 (0.4)	4 (0.2)
Country, n (%)		
Bulgaria	247 (13.3)	235 (12.7)
Czech Republic	18 (1.0)	17 (0.9)
Estonia	52 (2.8)	55 (3.0)
Georgia	118 (6.4)	137 (7.4)
Croatia	8 (0.4)	6 (0.3)
Hungary	95 (5.1)	67 (3.6)
Latvia	57 (3.1)	72 (3.9)
Poland	2 (0.1)	3 (0.2)
Russia	394 (21.2)	439 (23.7)
Serbia	6 (0.3)	16 (0.9)
Slovakia	10 (0.5)	8 (0.4)
Ukraine	317 (17.1)	289 (15.6)
United States	531 (28.6)	508 (27.4)
BMI by category (kg/m ²), n (%)		
<25	702 (37.8)	724 (39.1)
25 - 30	606 (32.7)	584 (31.5)
>30	544 (29.3)	529 (28.6)
Missing	3 (0.2)	15 (0.8)

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

Characteristic	Sulopenem Etzadroxil + Probenecid / Sulopenem N=1855	Comparator N=1852
Creatinine clearance by category (mL/min), n (%)		
<30	54 (2.9)	64 (3.5)
30 - 60	503 (27.1)	501 (27.1)
>60	1288 (69.4)	1272 (68.7)
Missing	10 (0.5)	15 (0.8)

Source: Reviewer Table

Abbreviations: BMI, body mass index

Adequacy of the safety database:

The safety database is acceptable. There were over 800 patients exposed to sulopenem for the treatment of uUTI in Study 301 who received the indicated dose and duration. The subjects in Studies 302 and 303 provide additional safety information.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

The Applicant's safety database includes subjects from Study 301 who were enrolled at Sites 202 (68 subjects) and 218 (13 subjects). These two sites were closed by the Applicant because of concerns of misconduct. (b) (7)(A)

The Applicant excluded subjects from both sites from the efficacy database but included them in the safety database. In addition, the incidence of TEAEs reported from sites in Ukraine was much lower compared to sites in the United States and Russia (Section 8.2.7).

M.O. Comment: The Applicant's rationale for excluding Site 202 from the efficacy analysis was that there were four clusters of patients with closely related isolates by PFGE and there was concern for intentional medication nonadherence based on artificial intelligence compliance software and no measurable drug levels in several of the subjects with available PK data. We did not agree that these issues justified removing all subjects from Site 202 from the efficacy analyses and decided to include these subjects in our analyses. Of note, the adverse event profile among subjects from Site 202 did not differ from the overall study population. Regarding Site 218, there were no TEAEs reported from this site, but as there were only 13 subjects enrolled at this site, the impact on the safety findings is limited. However, these 13 subjects from Site 218 were removed from the Agency's safety database. The lower rate of TEAEs from Ukraine is likely a result of differing patient attitudes and investigator reporting behaviors.

Categorization of Adverse Events

AEs were accurately classified as treatment-emergent if they occurred at or after the first dose of study drug. The Applicant used the Medical Dictionary for Regulatory Activities, version 21.0 for all Phase 3 studies. Coding of verbatim terms to the Medical Dictionary for Regulatory Activities preferred terms was generally acceptable.

Routine Clinical Tests

In Study 301, complete blood count with differential and serum chemistries, including liver enzymes, were checked at baseline and at TOC (Day 12). Urinalysis and urine culture were obtained at baseline, Day 3, EOT (Day 5), TOC, and Day 28. Vital signs were checked at baseline, EOT, and TOC.

M.O. Comment: The routine clinical tests were acceptable.

8.2.4. Safety Results

Deaths

There was one death in Study 301. Subject (b) (6) was a 71-year-old Hispanic/Latina woman in the United States who received sulopenem from (b) (6) to (b) (6), was diagnosed with lung adenocarcinoma on (b) (6) and died on (b) (6).

M.O. Comment: This death was not related to the study drug as it was due to cancer which could not have developed so soon after exposure to the study drug.

In the integrated Phase 3 safety population, there were 11 deaths, 7 (0.4%) in the sulopenem arm and 4 (0.2%) in the comparator arm (Table 93). However, 3 sulopenem subjects and 1 comparator subject died related to a diagnosis of cancer. Excluding the deaths related to cancer, there were 4 (0.2%) deaths in the sulopenem arm and 3 (0.2%) in the comparator arm.

Table 93. Deaths in the Integrated Phase 3 Safety Population

Treatment Arm	AE Associated With Death (Preferred Term)	Study Day of Start of AE	Day of Death
Sulopenem			
IT001-301 (b) (6)	Lung adenocarcinoma	15	171
IT001-302	Renal cell carcinoma	5	25
IT001-302	Salivary gland neoplasm	6	6
IT001-303	Cardiac arrest	11	11
IT001-303	Multiple organ dysfunction syndrome	5	5
IT001-303	Cerebrovascular accident	4	4
IT001-303	Sudden death	28	28

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

Treatment Arm	Subject ID	AE Associated With Death (Preferred Term)	Study Day of Start of AE	Day of Death
Comparator	(b) (6)			
	IT001-303	Acute respiratory failure	2	4
		Cardiac failure acute	4	
	IT001-303	Colon cancer	6	7
	IT001-303	Renal failure	4	5
	IT001-303	Multiple organ dysfunction syndrome	2	2

Source: Reviewer Table

Abbreviations: AE, adverse event

M.O. Comment: Review of these subjects' narratives revealed the following:

- *Given the short duration of treatment, the deaths related to cancer are not related to the study drug.*
- *Subject IT001-303, (b) (6) was a 76-year-old woman with a history of left bundle branch block and ischemic heart disease who was treated with IV and PO sulopenem following surgery for cholecystitis and intraabdominal abscess. On Day 11, she was found pulseless. Cardiopulmonary resuscitation was unsuccessful, and she died. This death is unlikely to be related to the study drug given the patient's age and history of heart disease.*
- *Subject IT001-303, (b) (6) was an 88-year-old woman who was treated with IV sulopenem following surgery for gangrenous appendicitis with peritonitis. On Day 3, she developed hepatic, renal, cardiovascular, respiratory, and cerebral failure and was started on mechanical ventilation. She died on Day 5. The autopsy showed hypertrophic cardiomyopathy. The direct cause of death was reported as cardiovascular failure. This death is unlikely to be related to the study drug as the patient had preexisting cardiac disease based on the hypertrophic myocardium found at autopsy.*
- *Subject IT001-303, (b) (6) was a 77-year-old woman with a history of cardiovascular disease and diabetes mellitus who was treated with IV sulopenem following surgery for complicated cholecystitis. On Day 4, the subject experienced a sudden loss of consciousness with hypotension and was diagnosed with a stroke (CVA). She quickly worsened and died the same day. The autopsy showed ischemic stroke. This death is unlikely to be related to the study drug given the prior risk factors of cardiovascular disease and diabetes mellitus.*
- *Subject IT001-303, (b) (6) was a 74-year-old woman with a history of hypertension who was treated with IV and PO sulopenem following surgery for gastric ulcer perforation and peritonitis. She completed her course of sulopenem on Day 11 and was deemed a clinical success at EOT and at Day 21. She died at home on Day 28 and no further information was available. The cause of death is unknown, but could have been due to cardiac arrest, stroke, or pulmonary embolism. This death is unlikely to be related to the study drug as it occurred several days after the last dose.*
- *Subject IT001-303, (b) (6) was a 64-year-old man with history of hypertension who was treated with IV ertapenem following surgery for gangrenous cholecystitis with perforation, local peritonitis, and subhepatic abscesses. On Day 3, he developed acute respiratory dysfunction and heart failure and died the next day. No autopsy was performed. This death*

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

is unlikely to be related to the study drug as it appears more likely to be related to the underlying abdominal infection and sepsis. However, this could be a case of treatment failure.

- *Subject IT001-303, (b) (6) was an 87-year-old woman with a history of metastatic colon cancer who was treated with IV ertapenem for large intestine perforation with secondary peritonitis that was found during surgery. Over the several days following the surgery she developed hypotension, anuric renal failure, and elevated liver enzymes. She died on Day 5 with the reported cause of death of renal insufficiency. This death and the elevated liver enzymes are likely to be unrelated to the study drug and more likely related to metastatic colon cancer.*
- *Subject IT001-303, (b) (6) was a 55-year-old man with a history of oral cancer who was treated with IV ertapenem following surgery for perforated ulcer and peritonitis. He died on Day 2 after developing hypotension and cerebral edema. The autopsy showed metastatic cancer. This death is unlikely to be related to the study drug and more likely to be related to the metastatic cancer.*

Serious Adverse Events

In Study 301, there were 11 unique SAEs reported in 8 subjects, 6 (0.7%) in the sulopenem arm and 2 (0.2%) in the ciprofloxacin arm (Table 94).

Table 94. SAEs Occurring in Study 301

Treatment Arm Subject ID	SAE (Preferred Term)	Study Day of Start of SAE
Sulopenem Etzadroxil + Probenecid		
(b) (6)	Lung adenocarcinoma	15
	Presyncope	21
	Angioedema	1
	Small intestinal obstruction	22
	Abdominal pain upper	24
	Chest pain	24
	Pyelonephritis acute	17
	Urosepsis	17
Ciprofloxacin		
(b) (6)	Diarrhea	16
	Pneumonia	9
	Bile duct stone	5

Source: Reviewer Table

Abbreviations: SAE, serious adverse event

M.O. Comment: It is important to note that study drug was given for 5 days. AEs starting later in the study are less likely to be related to the study drug. After review of the subject narratives, the following SAEs are notable:

- *Angioedema: Subject (b) (6) was a 54-year-old woman who developed swelling of the face 20 minutes after taking the first dose of sulopenem. Dyspnea started 10 minutes later.*

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

The subject did not seek medical attention, but instead went to a pharmacy and took an over-the-counter antihistamine on the advice of a pharmacist. The symptoms resolved within 3 hours. It appears likely that the SAE of angioedema was related to the sulopenem.

- *Pyelonephritis and urosepsis: Subject (b) (6) was a 46-year-old woman who was treated with sulopenem x 5 days for a P. mirabilis uUTI. At the TOC visit (Day 12) she had no uUTI symptoms and the urine culture was negative. However, on Day 17 she presented with fever, flank pain, and dysuria. She was found to have an obstructing kidney stone with hydronephrosis and acute kidney injury. A repeat urine culture grew P. mirabilis. She was treated with non-study antibacterial drugs and percutaneous nephrostomy. At the Day 28 visit she had no further symptoms. The kidney stone was the likely cause for the recurrent infection; the study drug was unlikely to be related.*
- *Diarrhea and pneumonia: Subject (b) (6) was an 81-year-old woman who was treated with ciprofloxacin x 5 days for uUTI. On Day 9 she presented with altered mental status and cough; she was diagnosed with a pneumonia and was hospitalized. She was treated with non-study antibacterial drugs (cefepime, vancomycin, azithromycin, and cefdinir). The pneumonia was considered resolved by Day 13. She developed diarrhea on Day 14 and was hospitalized on Day 16 with volume loss and pre-renal acute kidney injury likely secondary to the diarrhea. The diarrhea and acute kidney injury later resolved. The pneumonia was unlikely to be related to the study drug. It is possible the antibacterial drugs for the pneumonia as well as the ciprofloxacin for the uUTI led to the diarrhea.*

In the integrated Phase 3 safety population, there were 78 unique SAEs reported from 65 subjects, 45 (2.4%) in the sulopenem arm and 20 (1.1%) in the comparator arm. SAEs by system organ class (SOC) are shown in Table 95.

Table 95. SAEs in the Integrated Phase 3 Safety Population by SOC

System Organ Class	Sulopenem Etzadroxil + Probenecid / Sulopenem	Comparator
	n (%) N=1855	n (%) N=1852
Infections and infestations	21 (1.1)	6 (0.3)
Gastrointestinal disorders	8 (0.4)	6 (0.3)
Cardiac disorders	4 (0.2)	3 (0.2)
General disorders and administration site conditions	4 (0.2)	2 (0.1)
Neoplasms benign, malignant, and unspecified	3 (0.2)	1 (0.1)
Renal and urinary disorders	2 (0.1)	2 (0.1)
Respiratory, thoracic, and mediastinal disorders	2 (0.1)	2 (0.1)
Nervous system disorders	2 (0.1)	1 (0.1)
Injury, poisoning and procedural complications	1 (0.1)	1 (0.1)
Skin and subcutaneous tissue disorders	1 (0.1)	0
Vascular disorders	1 (0.1)	0
Hepatobiliary disorders	0	1 (0.1)

Source: Reviewer Table

Abbreviations: SAE, serious adverse event; SOC, system organ class

Table 96. SAEs in the SOC of Infections and Infestations in the Integrated Phase 3 Safety Population

Preferred Term	Sulopenem Etzadroxil + Probenecid / Sulopenem	Comparator
	n (%) N=1855	n (%) N=1852
Abdominal abscess	6 (0.3)	0
Urinary tract infection	5 (0.3)	0
Pyelonephritis ¹	4 (0.2)	3 (0.2)
Liver abscess	2 (0.1)	1 (0.1)
Pneumonia	1 (0.1)	2 (0.1)
Appendiceal abscess	1 (0.1)	0
Colon gangrene	1 (0.1)	0
Peritonitis	1 (0.1)	0
Urosepsis	1 (0.1)	0
Abscess neck	0	1 (0.1)
Cystitis	0	1 (0.1)

Source: Reviewer Table

¹ Pyelonephritis includes the preferred terms of pyelonephritis, pyelonephritis acute, and pyelonephritis chronic.
 Abbreviations: SAE, serious adverse event; SOC, system organ class

M.O. Comment: Regarding subjects who experienced an SAE in the integrated Phase 3 safety population:

- *The imbalance between the treatment arms is mostly accounted for by the imbalance in the SOC of infections and infestations (Table 96). Within this SOC, the PTs of abdominal abscess and urinary tract infections account for much of the imbalance.*
- *Review of the narratives for abdominal abscess, appendiceal abscess, and liver abscess (all from Study 303 in cIAI) revealed that most occurred after treatment was completed.*
- *Review of the narratives for urinary tract infections, pyelonephritis, and cystitis (almost all from Study 302 in cUTI) revealed that all occurred after treatment was completed.*
- *Regarding these SAEs due to infections, these events are not directly attributable to the study drug, but likely rather reflect either treatment failure or a complication of the primary infection. However, it is difficult to make that determination with the available data.*

Dropouts and/or Discontinuations Due to Adverse Effects

In Study 301, there were 21 unique TEAEs that led to study drug discontinuation reported in 21 subjects, 13 (1.6%) in the sulopenem arm and 8 (1.0%) in the ciprofloxacin arm (Table 97).

Table 97. TEAEs Leading to Study Drug Discontinuation in Study 301

Preferred Term	Sulopenem Etzadroxil +	
	Probenecid n (%) N=825	Ciprofloxacin n (%) N=822
Vomiting	3 (0.4)	1 (0.1)
Abdominal pain*	2 (0.2)	2 (0.2)
Diarrhea	2 (0.2)	1 (0.1)
Dizziness	2 (0.2)	0
Nausea	1 (0.1)	4 (0.5)
Angioedema	1 (0.1)	0
Dyspnea	1 (0.1)	0
Hypertension	1 (0.1)	0

Source: Reviewer Table

* Abdominal pain includes the preferred terms of abdominal pain and dyspepsia.

Abbreviations: TEAE, treatment-emergent adverse event

M.O. Comment:

- *Angioedema was likely related to sulopenem; Subject (b) (6) was discussed above in the SAE subsection.*
- *There were several discontinuations due to GI adverse events (diarrhea, nausea, vomiting, abdominal pain, and dyspepsia). These discontinuations were all possibly related to the study drug. However, there were only a few subjects who discontinued study treatment due to diarrhea despite it being a fairly common adverse event (AE), especially in the sulopenem arm. Overall, there was not an imbalance between the arms related to discontinuations due to GI-related AEs.*
- *Regarding the two sulopenem subjects with dizziness, both were possibly related to sulopenem as the events occurred after starting the drug.*
- *Regarding the sulopenem subject with hypertension and another with dyspnea, it is unclear whether these discontinuations were related to the study drug. For the subject with hypertension, no BP values were provided.*

There was also one patient in the ciprofloxacin arm who dropped out of Study 301 due to pneumonia (Subject (b) (6) described above in the SAE subsection).

In the integrated Phase 3 safety population, there were 41 subjects who discontinued the study drug or discontinued from the study, 21 (1.1%) in the sulopenem arm and 20 (1.1%) in the comparator arm. Excluding the AEs from Study 301 which are discussed above and the SAEs which are discussed in the SAE subsection, Table 98 summarizes the remaining discontinuations due to AEs.

Table 98. Discontinuations Due to Nonserious AEs in Studies 302 and 303

Treatment Arm		Preferred Term	M.O. Comments
Subject ID			
Sulopenem	(b) (6)		
IT001-302	(b) (6)	Pruritus	<i>Possibly related to IV sulopenem</i>
IT001-302	(b) (6)	Cerebrovascular accident	<i>Unclear if actual stroke occurred. Subject had a history of chronic osteochondrosis. After one dose of study drug, subject had back pain with left arm and leg weakness but refused hospitalization.</i>
IT001-302	(b) (6)	Hepatitis toxic	<i>Elevated AST of 131 U/L and ALT of 143 U/L with normal bilirubin. Both were normal at TOC. Possibly related to IV sulopenem. Subject also took acetaminophen and metamizole which could have caused the elevated liver enzymes.</i>
IT001-303	(b) (6)	Diarrhea	<i>Likely related to study drug. Diarrhea started on second day of oral sulopenem. Resolved the same day.</i>
IT001-303	(b) (6)	Rash	<i>Likely related to study drug. Rash developed on the third day of oral sulopenem. Resolved 10 days later.</i>
Comparator	(b) (6)		
IT001-302	(b) (6)	Hypersensitivity	<i>Narrative did not provide details on the "allergic reaction" which occurred on Day 4 of IV ertapenem and resolved 3 days later.</i>
IT001-302	(b) (6)	Urticaria	<i>Likely related to IV ertapenem; occurred on Day 5 of study drug and resolved the next day</i>
IT001-302	(b) (6)	Vomiting	<i>Possibly related to oral study drug</i>
IT001-302	(b) (6)	Hypertension	<i>Temporally related to IV ertapenem, but no blood pressure values were reported</i>
IT001-303	(b) (6)	Diarrhea	<i>Possibly related to IV ertapenem</i>
IT001-303	(b) (6)	Syncope	<i>Possibly related to oral ciprofloxacin as syncope is noted on its label</i>
IT001-303	(b) (6)	Pneumonia	<i>Unrelated to study drug, but notable that pneumonia was diagnosed while on an antibacterial drug</i>
IT001-303	(b) (6)	Pneumonia	<i>Unrelated to study drug, but notable that pneumonia was diagnosed while on an antibacterial drug</i>

Source: Reviewer Table

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IV, intravenous; M.O., medical officer; TOC, test-of-cure

M.O. Comment: Safety findings for sulopenem noted from the discontinuations due to AEs in Studies 302 and 303 include rash, pruritus, diarrhea, and elevated liver enzymes.

Significant Adverse Events

In Study 301, there were 15 unique TEAEs which were rated as severe from 8 subjects, 7 (0.8%) in the sulopenem arm and 1 (0.1%) in the ciprofloxacin arm. Excluding SAEs, there were 8 TEAEs rated as severe from 4 subjects, all in the sulopenem arm. (1) Subject (b) (6) was discussed in the SAE subsection. In addition to having the SAEs of pyelonephritis and urosepsis, she also experienced acute kidney injury, hydronephrosis, ureterolithiasis, and vomiting which all appear to be related to the obstructing kidney stone and pyelonephritis. (2) Subject (b) (6) was a 34 year-old woman who experienced dizziness on Day 2 which led to study drug discontinuation. (3) Subject (b) (6) was a 45 year-old woman who experienced hypertension

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

on Day 15. (4) Subject (b) (6) was a 41 year-old woman who experienced abdominal and flank pain on Day 2 which did not result in study drug discontinuation.

M.O. Comment: The case of hypertension is unlikely to be related to sulopenem given its late onset. The abdominal and flank pain experienced by Subject (b) (6) could be related to the underlying UTI. Overall, the TEAEs rated as severe, but not deemed as SAEs, did not reveal additional safety signals.

In the integrated Phase 3 safety population, there were 57 TEAEs which were rated as severe from 43 subjects, 27 (1.5%) in the sulopenem arm and 16 (0.9%) in the comparator arm. Excluding SAEs, there were 19 TEAEs rated as severe from 14 subjects, 7 (0.4%) in the sulopenem arm and 7 (0.4%) in the comparator arm. Four of the sulopenem subjects are discussed above, the remaining 3 experienced the following severe TEAEs: urinary fistula, gastrointestinal carcinoma, anemia, and white blood cell count increased.

M.O. Comment: Given the short duration of therapy, urinary fistula and carcinoma are unlikely to be related to the study drug. Subject IT001-303/(b) (6) experienced anemia on Day 2. The baseline hemoglobin value was 9.6 g/dL and on Day 5 it was 12.1 g/dL. No value from Day 2 is provided. The reported AE of anemia is unlikely to be related to the study drug as the hemoglobin value was in the normal range by Day 5 and the subject did not stop the study drug. Subject IT001-303/(b) (6) experienced an increased WBC count on Day 20 which was after the end of therapy. The increased WBC count is unlikely to be related to the study drug.

Treatment Emergent Adverse Events and Adverse Reactions

In Study 301, subjects with at least one TEAE numbered 207 in the sulopenem arm (25.1%) and 115 in the ciprofloxacin arm (14.0%). TEAEs by primary system organ class are listed in Table 99. TEAEs occurring in at least 0.5% of either treatment arm are listed in Table 100 with the remaining TEAEs listed in Table 153 in the appendix.

Table 99. TEAEs by System Organ Class in Study 301

System Organ Class	Sulopenem Etzadroxil + Probenecid	Ciprofloxacin
	n (%) N=825	n (%) N=822
Gastrointestinal disorders*	140 (17.0)	65 (7.9)
Infections and infestations	38 (4.6)	21 (2.6)
Nervous system disorders	31 (3.8)	23 (2.8)
Renal and urinary disorders	12 (1.5)	1 (0.1)
General disorders and administration site conditions	10 (1.2)	4 (0.5)
Musculoskeletal and connective tissue disorders	8 (1.0)	5 (0.6)
Respiratory, thoracic and mediastinal disorders	6 (0.7)	4 (0.5)
Skin and subcutaneous tissue disorders	6 (0.7)	3 (0.4)
Vascular disorders	6 (0.7)	1 (0.1)
Investigations	4 (0.5)	4 (0.5)
Reproductive system and breast disorders	4 (0.5)	2 (0.2)
Metabolism and nutrition disorders	3 (0.4)	1 (0.1)
Injury, poisoning and procedural complications	3 (0.4)	0

System Organ Class	Sulopenem Etzadroxil + Probenecid	Ciprofloxacin
	n (%) N=825	n (%) N=822
Hepatobiliary disorders	2 (0.2)	1 (0.1)
Eye disorders	1 (0.1)	1 (0.1)
Psychiatric disorders	1 (0.1)	1 (0.1)
Cardiac disorders	1 (0.1)	0
Neoplasms benign, malignant, and unspecified	1 (0.1)	0
Immune system disorders	0	2 (0.2)
Ear and labyrinth disorders	0	1 (0.1)

Source: Reviewer Table

* Includes non-serious nausea reported from Subject IT001-301, (b) (6) which was erroneously not categorized as treatment-emergent.

Table 100. TEAEs Occurring in $\geq 0.5\%$ of Subjects in Either Treatment Arm in Study 301

Preferred Term	Sulopenem Etzadroxil + Probenecid	Ciprofloxacin
	n (%) N=825	n (%) N=822
Diarrhea	103 (12.5)	21 (2.6)
Nausea*	32 (3.9)	30 (3.6)
Headache	18 (2.2)	18 (2.2)
Abdominal pain ¹	18 (2.2)	12 (1.5)
Vomiting	13 (1.6)	11 (1.3)
Vulvovaginal mycotic infection ²	11 (1.3)	5 (0.6)
Dizziness	9 (1.1)	5 (0.6)
Urine odor abnormal	8 (1.0)	1 (0.1)
Hypertension ³	6 (0.7)	4 (0.5)
Back pain	4 (0.5)	2 (0.2)

Source: Reviewer Table

* Includes non-serious nausea reported from Subject IT001-301, (b) (6) which was erroneously not categorized as treatment-emergent

¹ Abdominal pain includes the PTs of abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, and dyspepsia

² Vulvovaginal mycotic infection includes the PTs of vulvovaginal mycotic infection and vulvovaginal candidiasis and the lowest level term of yeast infection

³ Hypertension includes the PTs of hypertension and blood pressure increased

Abbreviations: PT, preferred term; TEAE, treatment-emergent adverse event

M.O. Comment: There is an imbalance in the number of subjects with at least one TEAE with more subjects in the sulopenem arm having a TEAE.

- The SOC of gastrointestinal disorders and specifically the PT of diarrhea accounts for much of the difference between the arms. Additional analyses of the diarrhea TEAEs are summarized in Section 8.2.5.1. To a lesser extent, there was also an imbalance in the incidence of abdominal pain with more subjects in the sulopenem arm reporting that AE.*
- Within the infections and infestations SOC, PTs indicating vaginal yeast infection accounted for much of the imbalance between the treatment arms.*
- The gastrointestinal AEs and vaginal yeast infection AEs in the sulopenem arm may be due to the broad spectrum coverage of sulopenem that includes coverage of anaerobic bacteria.*

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

- *Within the nervous system disorders SOC, the PT of dizziness accounted for much of the imbalance between the treatment arms. There was also a subject in the sulopenem arm with the PT of presyncope which may also relate to dizziness.*
- *The imbalance in the renal and urinary disorders is mostly accounted for by the PT of urine odor abnormal. The Sponsor notes that sulfur-containing metabolites of sulopenem are the likely cause of this TEAE.*
- *Review of the general disorders and administration site conditions SOC did not reveal a single PT that accounted for the imbalance between the treatment arms. However, the PTs of pyrexia, chills, and fatigue were noted in at least 2 sulopenem subjects. These PTs are likely to be related to the underlying UTI and not related to the study drug.*
- *Within the vascular disorders SOC, there were more sulopenem subjects compared to ciprofloxacin subjects with the PTs of hypertension (3 vs. 1) and hypotension (2 vs. 1). However, it is likely that these differences resulted by chance.*

In the integrated Phase 3 safety population, there were 397 (21.4%) subjects in the sulopenem arm and 305 (16.5%) subjects in the comparator arm with at least one TEAE. TEAEs by primary system organ class are listed in Table 101. TEAEs occurring in at least 0.5% of either treatment arm are listed in Table 102 with the remaining TEAEs listed in Table 154 in the appendix.

Table 101. TEAEs by System Organ Class in the Integrated Phase 3 Safety Population

System Organ Class	Sulopenem Etzadroxil + Probenecid / Sulopenem	Comparator
	n (%) N=1855	n (%) N=1852
Gastrointestinal disorders	215 (11.6)	141 (7.6)
Infections and infestations	82 (4.4)	66 (3.6)
Nervous system disorders	63 (3.4)	51 (2.8)
General disorders and administration site conditions	27 (1.5)	14 (0.8)
Respiratory, thoracic, and mediastinal disorders	18 (1.0)	18 (1.0)
Renal and urinary disorders	18 (1.0)	6 (0.3)
Skin and subcutaneous tissue disorders	14 (0.8)	12 (0.6)
Vascular disorders	14 (0.8)	9 (0.5)
Musculoskeletal and connective tissue disorders	13 (0.7)	7 (0.4)
Investigations	12 (0.6)	14 (0.8)
Injury, poisoning and procedural complications	12 (0.6)	11 (0.6)
Metabolism and nutrition disorders	11 (0.6)	11 (0.6)
Cardiac disorders	11 (0.6)	9 (0.5)
Reproductive system and breast disorders	11 (0.6)	5 (0.3)
Psychiatric disorders	9 (0.5)	9 (0.5)
Blood and lymphatic system disorders	5 (0.3)	6 (0.3)
Neoplasms benign, malignant, and unspecified (incl. cysts and polyps)	4 (0.2)	1 (0.1)
Hepatobiliary disorders	3 (0.2)	5 (0.3)
Ear and labyrinth disorders	1 (0.1)	2 (0.1)
Eye disorders	1 (0.1)	2 (0.1)
Immune system disorders	0	4 (0.2)

Source: Reviewer Table

Abbreviations: TEAE, treatment-emergent adverse event

Table 102. TEAEs Occurring in $\geq 0.5\%$ of Subjects in Either Treatment Arm in the Integrated Phase 3 Safety Population

Preferred Term	Sulopenem Etzadroxil + Probenecid / Sulopenem	Comparator
	n (%) N=1855	n (%) N=1852
Diarrhea	137 (7.4)	50 (2.7)
Nausea*	53 (2.9)	49 (2.6)
Headache*	41 (2.2)	35 (1.9)
Abdominal pain ¹	28 (1.5)	18 (1.0)
Vomiting	22 (1.2)	22 (1.2)
Dizziness	15 (0.8)	10 (0.5)
Vulvovaginal mycotic infection ²	14 (0.8)	12 (0.6)
Hypertension ³	13 (0.7)	15 (0.8)
Wound infection ⁴	5 (0.3)	12 (0.6)

Source: Reviewer Table

* Includes AEs which were erroneously not categorized as treatment-emergent

¹ Abdominal pain includes the PTs of abdominal pain, abdominal pain upper, abdominal pain lower, abdominal discomfort, and dyspepsia

² Vulvovaginal mycotic infection includes the PTs of vulvovaginal mycotic infection and vulvovaginal candidiasis and the lowest level term of yeast infection

³ Hypertension includes the PTs of hypertension, hypertensive crisis, and blood pressure increased

⁴ Wound infection includes the PTs of wound infection and postoperative wound infection

Abbreviations: AE, adverse event; PT, preferred term; TEAE, treatment-emergent adverse event

M.O. Comment:

- *Similar to Study 301, PTs in the gastrointestinal SOC, specifically diarrhea and abdominal pain account for much of the imbalance in TEAEs.*
- *In the general disorders and administration site conditions SOC, the PTs related to fever (pyrexia, feeling hot) and infusion site reactions (infusion site pain, infusion site extravasation, infusion site phlebitis) accounted for much of the imbalance between the treatment arms. As the current NDA is for an oral formulation, infusion site reactions will not be an issue.*
- *In the renal and urinary disorders SOC, abnormal urine odor accounted for much of the imbalance. As noted above, the odor is a result of sulfur-containing metabolites.*
- *In the musculoskeletal and connective tissue disorders SOC, back pain (3 vs. 6) accounted for much of the imbalance. However, it is possible some of these cases were related to UTI rather than a musculoskeletal source.*
- *In the reproductive system and breast disorders SOC, PTs related to vulvovaginal symptoms (vaginal discharge, vulvovaginal pruritus, vaginal hemorrhage, vulvovaginal dryness) accounted for the imbalance.*

Laboratory Findings

Regarding analysis of laboratory data, the Applicant attempted to normalize results which were obtained from local laboratories instead of the central laboratory by multiplying them by the

ratio of the upper reference ranges from the two different laboratories. In this review, the original laboratory values were used without any normalization.

For Study 301, review of the average chemistry and hematology laboratory values at baseline and TOC (Day 12) did not reveal significant differences between the treatment arms. From baseline to TOC, there was a small decrease in the average neutrophil count (absolute and percentage) in both treatment arms. For example, at baseline the average neutrophil measurement was 63% in both arms but dropped to 60% at TOC.

M.O. Comment: The slight decrease in neutrophil counts is likely due to reduced inflammation as a result of treatment of the uUTI.

Peak postbaseline elevations of ALT and AST among subjects in Study 301 are shown in Table 103 and Table 105, respectively. Among subjects with an ALT value available after Day 1, there were more sulopenem subjects with an elevated ALT compared to the ciprofloxacin arm (Table 103). More details on the ALT elevations is provided in Table 104. There was not a notable imbalance in AST elevations between the treatment arms (Table 105). There was one possible case of Hy's Law; Subject (b) (6) in the ciprofloxacin arm had choledocholithiasis with obstruction of the terminal portion of the bile duct and obstructive jaundice. On Day 13, the subject's ALT =149 U/L, AST =205 U/L, total bilirubin =8.03 mg/dL, and alkaline phosphatase =552 U/L. Given the biliary obstruction and elevation in alkaline phosphatase, this is not a true Hy's Law case.

Table 103. Peak ALT Elevations in Study 301

ALT Post-Baseline Elevation	Sulopenem Etzadroxil + Probenecid	Ciprofloxacin
	n (%) N=808	n (%) N=797
ULN < ALT <2x ULN	28 (3.5)	27 (3.4)
2x ULN < ALT <3x ULN	5 (0.6)	0
3x ULN < ALT <5x ULN	4 (0.5)	1 (0.1)
5x ULN < ALT <10x ULN	1 (0.1) ^a	0

Source: Reviewer Table

a Subject (b) (6) had a peak ALT of 208 U/L (5.07x ULN) on Day 11 which improved to 46 U/L on Day 16.

Abbreviations: ALT, alanine aminotransferase; ULN, upper limit of normal

Table 104. ALT Values for Subjects in 301 With Any Postbaseline ALT Elevation >2x ULN

Treatment Arm Subject ID	Baseline ALT (U/L)	TOC ALT (U/L)	Additional ALT Values (U/L)	Notes
Sulopenem (b) (6)	108	128		Fatty liver disease
	16	85	21 (Day 27)	
	34	95		
	102	52	90 (Day 32)	
	11	148		
	216	21	137 (Day 3)	
	20	208	46 (Day 16)	Obesity
	85	125		Hemolyzed specimen
	54	105		
112	97			
Ciprofloxacin (b) (6)	110	149	29 (Day 28)	

Source: Reviewer Table

Abbreviations: ALT, alanine aminotransferase; TOC, test-of-cure; ULN, upper limit of normal

M.O. Comment: Several of the subjects with elevated ALT values had elevations at baseline which were likely to due to underlying conditions such as fatty liver disease. However, there were 4 subjects, all in the sulopenem arm, who started with a normal ALT value at baseline, but were found to have an elevated ALT at the TOC visit. For two of these subjects, a laboratory check after the TOC visit showed improvement in the elevation, but for the other two subjects there is no information provided. These data suggest that sulopenem may cause elevation of ALT.

Table 105. Peak AST Elevations in Study 301

AST Post-Baseline Elevation	Sulopenem Etzadroxil + Probenecid		Ciprofloxacin
	n (%)	N=808	n (%)
ULN < AST <2x ULN	28 (3.5)		22 (2.8)
2x ULN < AST <3x ULN	2 (0.2)		1 (0.1)
3x ULN < AST <5x ULN	1 (0.1)		1 (0.1)
5x ULN < AST <10x ULN	1 (0.1) ^a		1 (0.1) ^b

Source: Reviewer Table

^a Subject (b) (6) had a screening AST of 21 U/L which peaked at 173 U/L (5.09x ULN) on Day 13 then improved to 22 U/L on Day 27.

^b Subject (b) (6) had a screening AST of 124 U/L which peaked at 205 U/L (6.03x ULN) on Day 13 then improved to 30 U/L on Day 28.

Abbreviations: AST, aspartate aminotransferase; ULN, upper limit of normal

In the integrated Phase 3 safety population, review of the average chemistry and hematology laboratory values did not reveal significant differences between the treatment arms. There was a slight decrease in the average leukocyte count from baseline to TOC which likely reflects resolving infection. Peak postbaseline elevations of ALT and AST among subjects in the integrated Phase 3 safety population are shown in Table 106 and Table 107, respectively.

Table 106. Peak ALT Elevations in the Integrated Phase 3 Safety Population

ALT Post-Baseline Elevation	Sulopenem Etzadroxil + Probenecid / Sulopenem	Comparator
	n (%) N=1831	n (%) N=1814
ULN < ALT <3x ULN	215 (11.7)	237 (13.1)
3x ULN < ALT <5x ULN	20 (1.1)	10 (0.6)
5x ULN < ALT <10x ULN	8 (0.4)	4 (0.2)
10x ULN < ALT <20x ULN	1 (0.1) ^a	1 (0.1) ^b

Source: Reviewer Table

^a Subject IT001-303/ (b) (6) had a screening ALT of 11 U/L, a Day 11 value of 8 U/L, and a Day 27 value of 692 U/L (16.9x ULN). No additional laboratory data from later timepoints are available.

^b Subject IT001-302/ (b) (6) had a screening ALT of 11 U/L which increased to 54 U/L on Day 5 and peaked at 411 U/L (10x ULN) on Day 11 then improved to 222 U/L on Day 20.

Abbreviations: ALT, alanine aminotransferase; ULN, upper limit of normal

Table 107. Peak AST Elevations in the Integrated Phase 3 Safety Population

AST Post-Baseline Elevation	Sulopenem Etzadroxil + Probenecid / Sulopenem	Comparator
	n (%) N=1830	n (%) N=1814
ULN < AST <3x ULN	186 (10.2)	190 (10.5)
3x ULN < AST <5x ULN	13 (0.7)	9 (0.5)
5x ULN < AST <10x ULN	5 (0.3)	4 (0.2)
10x ULN < AST <20x ULN	0	2 (0.1)
20x ULN < AST <35x ULN	1 (0.1) ^a	1 (0.1) ^b

Source: Reviewer Table

^a Subject IT001-303/ (b) (6) had a screening AST of 14 U/L, a Day 11 value of 13 U/L, and a Day 27 value of 788 U/L (23.2x ULN). No additional laboratory data from later timepoints are available.

^b Subject IT001-303/ (b) (6) had a screening AST of 33 U/L and a Day 5 value of 1186 U/L (34.9x ULN).

Abbreviations: AST, aspartate aminotransferase; ULN, upper limit of normal

M.O. Comment: Similar to the results from Study 301, there were more sulopenem subjects with elevations in ALT >3x ULN compared to the comparator arm in the integrated Phase 3 safety database. There was not a notable imbalance in elevations in AST. Regarding subject IT001-303/ (b) (6) in the sulopenem arm, the elevations in ALT and AST occurred after the completion of study drug. As a result, these elevations are less likely to be related to sulopenem. However, review of the narrative for this subject did not reveal an alternative cause for the elevations in transaminases.

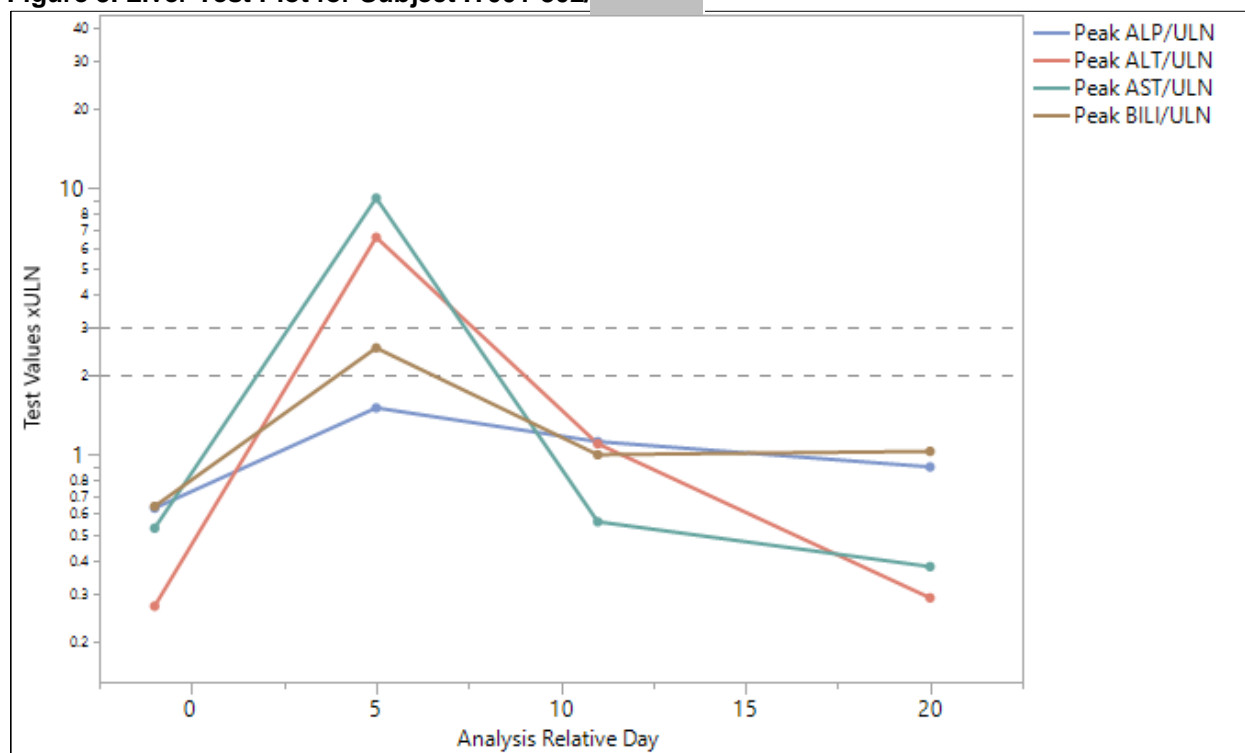
There was a total of 9 possible Hy's Law cases in the integrated Phase 3 safety population, 5 in the sulopenem arm and 4 in the comparator arm. Of these subjects, 6 had the elevations at baseline and all had improved values in AST, ALT, and total bilirubin during the course of the study. As a result, these cases are unlikely to be related to the study drug. One subject (IT001-303/ (b) (6)), as noted above, had elevations which started after the study drug was completed. The liver test plots of the remaining two subjects are shown below.

Subject IT001-302/ (b) (6) (Figure 3) in the sulopenem arm had normal values for ALT, AST, and bilirubin at baseline, which all increased by Day 5 before returning to the normal range for the rest of the study. The peak values on Day 5 were ALT 269 U/L, AST 313 U/L, and total bilirubin 2.77 mg/dL. IV sulopenem was given through Day 5 and the oral tablet given on Days 6 and 7; study drug was not prematurely discontinued. This subject had a history of

schizoaffective disorder for which he was taking valproic acid. The Sponsor reports the cause of the liver test elevations was a drug-drug interaction between valproic acid and sulopenem. Of note, the valproic acid level was 54800 ng/mL at baseline, 21000 ng/mL on Day 5, and 50600 ng/mL on Day 11.

M.O. Comment: Penem antibacterial drugs are associated with decreased valproic acid levels through interference with conversion of valproic acid glucuronide back to active valproic acid due to a decreased enteric bacterial population and through activation of UDP-glucuronosyltransferase enzymes which promote glucuronidation of valproic acid. This drug-drug interaction between penem antibacterial drugs and valproic acid has also been reported to be associated with liver injury (Li et al. 2021). However, it is notable that the liver enzymes in this case quickly returned to normal and the study drug was not discontinued.

Figure 3. Liver Test Plot for Subject IT001-302/ (b) (6)



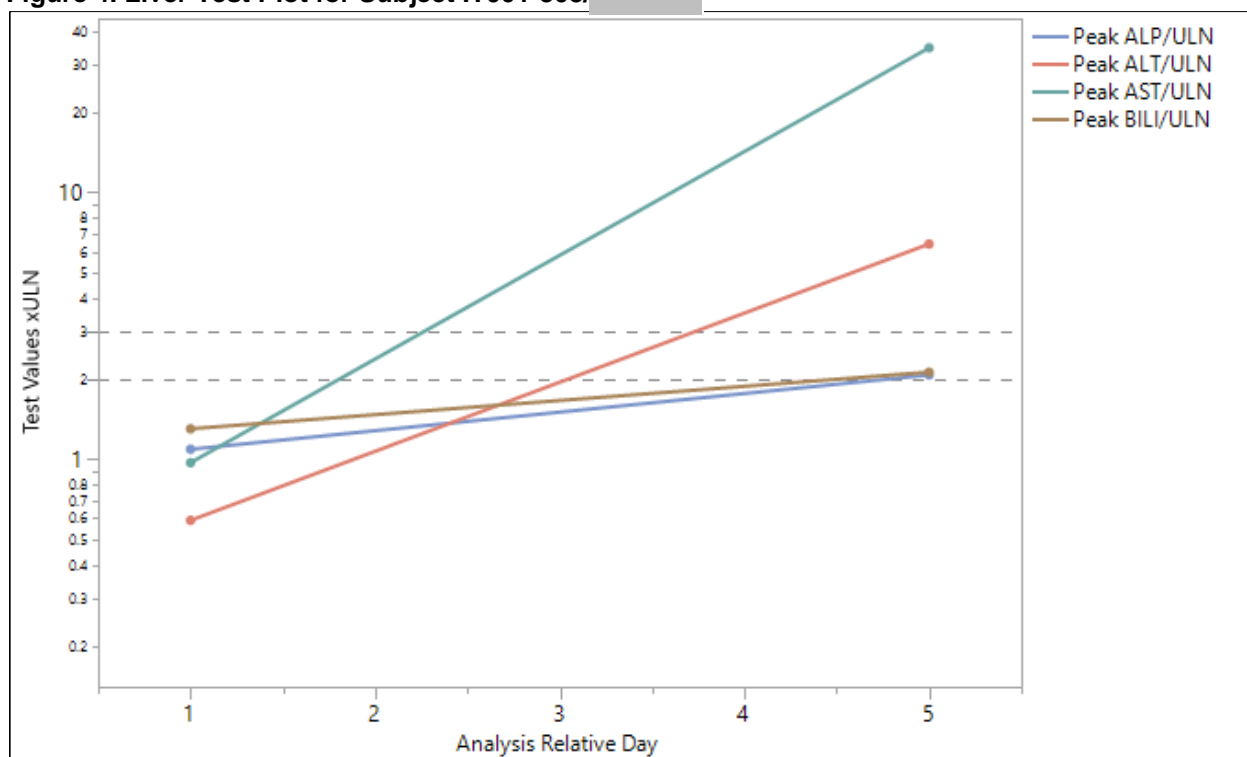
Source: Reviewer/JMP Clinical

Abbreviations: ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; BILLI, bilirubin; ULN, upper limit of normal

Subject IT001-303/ (b) (6) (Figure 4) in the comparator arm had colon cancer with liver metastases who was enrolled in Study 303 for peritonitis secondary to bowel perforation. She died on Day 5 after the development of anuria and hypotension.

M.O. Comment: These elevations in liver tests are likely related to metastatic cancer and possible shock liver and less likely related to the study drug.

Figure 4. Liver Test Plot for Subject IT001-303/ (b) (6)



Source: Reviewer/JMP Clinical

Abbreviations: ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; BILI, bilirubin; ULN, upper limit of normal

Vital Signs

Review of the vital sign data from Studies 301, 302, and 303 did not reveal any significant differences between the treatment arms.

Electrocardiograms

Electrocardiograms were not collected in Studies 301, 302, or 303 as there was adequate data regarding sulopenem and cardiac conduction from the Phase 1 program. See the QT subsection below for further information.

QT

On 06 Sept 2017, FDA notified Iterum that data from the Phase 1 Study A7371007 were adequate to serve as a substitute for a thorough QT study and therefore Iterum did not need to conduct a dedicated thorough QT study. The following is a summary of the QT Interdisciplinary Review Team review from 2017.

Study A7371007 was a randomized, investigator- and subject-blinded, sponsor-unblinded, placebo-substitution, sequential cohort, crossover design, single escalating dose study of IV sulopenem. A total of 26 healthy subjects were randomized to treatment in 2 cohorts. Each

NDA Multi-disciplinary Review and Evaluation {NDA 213972} {sulopenem etzadroxil/probenecid}

cohort had 3 crossover periods and consisted of 12 subjects each. Each subject received a single IV dose of either placebo or sulopenem (400 mg, 800 mg, 1600 mg, 2400 mg, and 2800 mg IV infusion over 1 h) in each dosing period. The 2800 mg IV infusion over 1 hour resulted in a mean C_{max} of 109.7 $\mu\text{g/mL}$ and a $\Delta\Delta\text{QTcF}$ of 0.07 ms with 90% CI of -4.20 to 4.34 ms. The QT Interdisciplinary Review Team concluded sulopenem does not prolong the QTc interval. Of note, the C_{max} for the oral 500 mg sulopenem etzadroxil and 500 mg probenecid tablet is in the range of 1.6-1.9 $\mu\text{g/mL}$ which much lower than the 2800 mg IV dose which did not prolong the QT interval.

Analysis of the heart rate, PR interval, and QRS interval data from Study A7371007 did not reveal any notable findings.

Immunogenicity

Not applicable for this NDA.

Summary of Phase 1/2 Clinical Studies

The Applicant and Pfizer conducted 24 Phase 1 and Phase 2 studies of sulopenem with both IV and oral formulations that exposed a total of 2006 subjects to sulopenem (Table 90). Review of the Phase 1 studies revealed the following safety signals: diarrhea, nausea, abdominal pain, headache, dizziness, rash, and abnormal urine odor. One subject receiving oral sulopenem/probenecid experienced mild angioedema of the face and lip and discontinued study drug. All these safety signals were also identified in the Phase 3 program. In the Pfizer-conducted Phase 2 studies, there were 4 subjects with fatal SAEs; 3 received sulopenem and 1 received comparator. Review of the narratives for these subjects revealed that 2 of the 3 deaths among the sulopenem-treated subjects were related to underlying malignancy. The other death in the sulopenem arm was related to a myocardial infarction and pneumonia which were unlikely to be related to the study drug.

M.O. Comment: The Phase 1 and Phase 2 studies do not reveal additional safety signals related to sulopenem.

8.2.5. Analysis of Submission-Specific Safety Issues

No specific safety issues were identified prior to review of this NDA. However, as diarrhea was noted to be a common TEAE for which there was a notable imbalance between the treatment arms, further analyses of diarrhea events were conducted and are summarized in this subsection. In addition, a discussion of liver enzyme elevations is provided above in the subsection labeled "Laboratory Findings."

8.2.5.1. Diarrhea

As noted in Section 8.2.4, diarrhea occurred as a TEAE in 103 (12.5%) subjects in the sulopenem arm and 21 (2.6%) in the ciprofloxacin arm in Study 301. The severity of the diarrhea events is

summarized in Table 108. Most diarrhea events were mild, and none were noted as severe among the sulopenem subjects.

Table 108. Maximum Diarrhea Severity Among Subjects in Study 301

Maximum Severity	Sulopenem Etzadroxil + Probenecid	Ciprofloxacin
	n (%) N=825	n (%) N=822
Mild	84 (10.2)	18 (2.2)
Moderate	19 (2.3)	2 (0.2)
Severe	0	1 (0.1)

Source: Reviewer Table

The Applicant determined the total duration of diarrhea for each affected subject by pooling separately reported AEs. These data by treatment arm are summarized in the first two columns of Table 109. The protocol for Study 301 recommended that study drug be taken with food but allowed subjects to take it with or without food. If a subject took all their doses of study drug with food (between 2 hours before to 30 minutes after the dose) they were noted as “fed.” The duration of diarrhea by fed/fasted status is shown in Table 109.

Table 109. Duration of Diarrhea Among Subjects in Study 301

Duration (Days)	Overall		Fasted		Fed	
	Sulopenem N=103	Ciprofloxacin N=21	Sulopenem N=51	Ciprofloxacin N=13	Sulopenem N=51	Ciprofloxacin N=8
Mean	3.9	2.5	4.7	2.8	3.08	2
Median	3	2	4	3	2	2
Minimum	1	1	1	1	1	1
Maximum	22	6	22	6	12	3

Source: Reviewer Table

M.O. Comment: The average duration of diarrhea was longer by about one day in sulopenem subjects compared to ciprofloxacin subjects. However, there were 29 subjects with a duration of diarrhea longer than 5 days; all but 2 were in the sulopenem arm. Subjects who took the study drug with food and developed a TEAE of diarrhea had a shorter duration of diarrhea, a difference of 2 days on average, compared to the sulopenem subjects who did not take all their doses with food. The review team will consider whether the labeling should recommend taking the drug with food to reduce the duration of diarrhea. In summary, diarrhea is a common, but not serious, safety finding for oral sulopenem.

8.2.6. Clinical Outcome Assessment Analyses Informing Safety/Tolerability

Not applicable to this NDA

8.2.7. Safety Analyses by Demographic Subgroups

The incidence of TEAEs in Study 301 by demographic and other baseline characteristic subgroups are summarized in Table 110. A similar analysis of the incidence of diarrhea as a TEAE is summarized in Table 111.

Table 110. Subjects With At Least One TEAE by Demographic and Other Baseline Patient Characteristics in Study 301

Characteristic	Sulopenem Etzadroxil + Probenecid	Ciprofloxacin
Categorical age (years), n (%)		
18 - 29	39/159 (24.5)	21/165 (12.7)
30-60	107/387 (27.6)	47/352 (13.4)
≥60	61/279 (21.9)	47/305 (15.4)
≥65	53/218 (24.3)	37/233 (15.9)
Race, n (%)		
American Indian or Alaska Native	4/10 (40.0)	1/3 (33.3)
Asian	3/11 (27.3)	1/7 (14.3)
Black or African American	20/74 (27.0)	8/66 (12.1)
Native Hawaiian or Other Pacific Islander	-	1/1 (100.0)
Other	2/4 (50.0)	0/3 (0)
White	178/726 (24.5)	104/742 (14.0)
Ethnicity, n (%)		
Hispanic or Latino	84/291 (28.9)	44/255 (17.3)
Not Hispanic or Latino	120/529 (22.7)	71/566 (12.5)
Not Reported/Unknown	3/5 (60.0)	0/1 (0.0)
Country, n (%)		
Russia	42/195 (21.5)	37/224 (16.5)
Ukraine	7/144 (4.9)	2/137 (1.5)
United States	158/486 (32.5)	76/461 (16.5)
BMI by category (kg/m²), n (%)		
<25	66/319 (20.7)	46/245 (18.8)
25 - 30	63/248 (25.4)	26/224 (11.6)
>30	78/255 (30.6)	42/241 (17.4)
Missing	0/3 (0.0)	1/12 (8.3)
Creatinine clearance by category (mL/min), n (%)		
<30	1/15 (6.7)	2/10 (20.0)
30 - 60	56/206 (27.2)	32/206 (15.5)
>60	150/604 (24.8)	81/605 (13.4)
Missing	-	0/1 (0.0)

Source: Reviewer Table

Abbreviations: BMI, body mass index; TEAE, treatment-emergent adverse event

Table 111. Subjects With the TEAE of Diarrhea by Demographic and Other Baseline Patient Characteristics in Study 301

Characteristic	Sulopenem Etzadroxil + Probenecid	Ciprofloxacin
Categorical age (years), n (%)		
18 - 29	17/159 (10.7)	2/165 (1.2)
30-60	55/387 (14.2)	5/352 (1.4)
≥60	31/279 (11.1)	14/305 (4.6)
≥65	26/218 (11.9)	13/233 (5.6)
Race, n (%)		
American Indian or Alaska Native	1/10 (10.0)	0/3 (0.0)
Asian	2/11 (18.2)	0/7 (0.0)
Black or African American	14/74 (18.9)	0/66 (0.0)
Native Hawaiian or Other Pacific Islander	-	0/1 (0.0)
Other	1/4 (25.0)	0/3 (0.0)
White	85/726 (11.7)	21/742 (2.8)

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

Characteristic	Sulopenem Etzadroxil + Probenecid	Ciprofloxacin
Ethnicity, n (%)		
Hispanic or Latino	45/291 (15.5)	9/255 (3.5)
Not Hispanic or Latino	57/529 (10.8)	12/566 (2.1)
Not Reported/Unknown	1/5 (20.0)	0/1 (0.0)
Country, n (%)		
Russia	14/195 (7.2)	5/224 (2.2)
Ukraine	0/144 (0)	0/137 (0)
United States	89/486 (18.3)	16/461 (3.5)
BMI by category (kg/m ²), n (%)		
<25	37/319 (11.6)	5/245 (2.0)
25 - 30	25/248 (10.1)	6/224 (2.7)
>30	41/255 (16.1)	9/241 (3.7)
Missing	0/3 (0.0)	1/12 (8.3)
Creatinine clearance by category (mL/min), n (%)		
<30	0/15 (0)	0/10 (0)
30 - 60	23/206 (11.2)	10/206 (4.9)
>60	80/604 (13.2)	11/605 (1.8)
Missing	-	0/1 (0)

Source: Reviewer Table

Abbreviations: BMI, body mass index; TEAE, treatment-emergent adverse event

M.O. Comment: The incidence of TEAEs in the overall population was 24.8% in the sulopenem arm and 13.9% in the ciprofloxacin arm while the incidence of diarrhea was 12.4% in the sulopenem arm and 2.5% in the ciprofloxacin arm. Subjects with Hispanic/Latino ethnicity, those with BMI >30, and those in the United States were more likely to have a TEAE compared to the overall population. Among these groups, the difference in the incidence of TEAEs between the arms was mostly accounted for by diarrhea as it was in the general population. Review of the demographic data shows that most subjects with Hispanic/Latino ethnicity and BMI >30 were enrolled in the United States. The higher rates of TEAEs and diarrhea in these subjects may be due to different physiological responses based on ethnicity or obesity or could be related to differences in AE reporting by country/site. An example of likely reporting differences is that the rate of TEAEs in Ukraine was notably lower than in Russia or the United States and there were no TEAEs of diarrhea reported from Ukraine.

8.2.8. Specific Safety Studies/Clinical Trials

There were no dedicated safety studies for this NDA.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

In the Phase 3 integrated safety population, there were 5 subjects with a TEAE in the neoplasms SOC, 4 in the sulopenem arm and 1 in the comparator arm. These cases were discussed in the deaths and significant adverse events subsections above. Review of these subjects found that most cases were related to preexisting cancer.

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

M.O. Comment: Given the short duration of treatment, it does not appear that any of the cases of cancer were related to the study drug. Overall, there is no clinical evidence that sulopenem is carcinogenic.

Human Reproduction and Pregnancy

Pregnant women were excluded from all clinical studies of sulopenem. However, there was one pregnancy reported in a patient who received sulopenem in the integrated Phase 3 safety population. The subject had a negative local urine pregnancy test at screening, but the central laboratory test was reported positive 3 days later. The study drug (oral sulopenem/probenecid for uUTI) was stopped at that time. The subject had an uneventful pregnancy and delivered a healthy infant 8 months later.

M.O. Comment: There are insufficient data to draw any conclusions regarding the effects of sulopenem on human reproduction and pregnancy.

Pediatrics and Assessment of Effects on Growth

There are no data on the safety of sulopenem in pediatric patients less than 18 years of age. The Sponsor submitted an agreed initial pediatric study plan (iPSP) on 21 February 2018. The label for probenecid includes a contraindication for children under the age of 2 years. After consultation with the pediatric team in the Division of Pediatric and Maternal Health, no apparent scientific basis for this pediatric contraindication was found. As a result, no pediatric contraindication will be added to the sulopenem/probenecid label.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Sulopenem does not have known drug abuse potential.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Sulopenem is not approved for use in any country.

Expectations on Safety in the Postmarket Setting

If approved, the oral tablet formulation of sulopenem may be used off-label to treat uUTI caused by quinolone-susceptible pathogens and for stepdown therapy for other infections such as cUTI and cIAI. There are no distinct safety concerns regarding this possible off-label use, but the Phase 3 studies for cUTI and cIAI did not meet their primary efficacy endpoints.

8.2.11. Integrated Assessment of Safety

The safety data for sulopenem in the treatment of uUTI were derived from Study 301 which evaluated 5 days of oral sulopenem compared to 3 days of oral ciprofloxacin. The subjects in

Study 301 were all adult women. Additional safety data were reviewed from Study 302 in cUTI and Study 303 in cIAI which included use of both the IV and oral formulations of sulopenem. The Phase 1 and Phase 2 studies confirmed the safety findings of the Phase 3 studies. The collective safety issues identified from these sources will be summarized in this section.

Two subjects taking oral sulopenem/probenecid experienced angioedema involving the face and one also had associated dyspnea. One subject was enrolled in Study 301 and another in one of the Phase 1 studies. Both subjects stopped the study drug due to the angioedema events. Both subjects took antihistamine drugs and neither experienced any sequelae from these events. Regardless, angioedema associated with dyspnea suggests involvement of the airway which could be life-threatening. Hypersensitivity is included as a warning in the proposed labeling.

Gastrointestinal adverse events, including diarrhea, nausea, and abdominal pain, were common among subjects taking oral sulopenem/probenecid. In Study 301, 17% of sulopenem subjects experienced a GI adverse event compared to 8% of ciprofloxacin subjects. In particular, diarrhea was a prominent adverse event associated with sulopenem with 12% experiencing at least one event of diarrhea. However, the diarrhea and other GI adverse events were generally mild and not treatment-limiting. The duration of diarrhea appeared to be reduced when sulopenem was taken with food. GI adverse events and diarrhea will be noted in section 6 of the labeling and the review team will consider recommending that sulopenem be taken with food to reduce the incidence and/or duration of diarrhea.

Elevations in ALT were more common among sulopenem subjects compared to ciprofloxacin subjects in Study 301. This was also noted in the integrated Phase 3 population which included Studies 302 and 303. In Study 301, the elevations in ALT were generally less than 5x the upper limit of normal. There were no cases of Hy's Law in Study 301. However, there was a subject in Study 302 who met Hy's Law criteria on Day 5, but subsequently had normal liver enzyme tests. The Sponsor reports the cause of the liver test elevations was a drug-drug interaction between valproic acid and sulopenem. (b) (4)

. Elevated transaminases will be noted in section 6 of the labeling.

Other nonserious adverse events that occurred uncommonly, but more frequently among sulopenem subjects compared to the comparator subjects include dizziness, rash, abnormal urine odor, and vulvovaginal yeast infection. All these adverse reactions will be included in section 6 of the labeling.

Overall, the safety issues with oral sulopenem/probenecid do not preclude approval; the known risks of sulopenem can be managed by appropriate labeling.

8.3. Statistical Issues

One Phase 3 study is included in this NDA for the indication of treatment of uUTI. We have identified the following statistical issues related to this study.

Late Change of SAP

After the unblinded interim analysis in October 2019, the conditional power was noted to be less than 40% in the MMITTR (ciprofloxacin-nonsusceptible) population. On March 11, 2020, the SAP was changed to revise the definitions of the MMITT populations and microbiological response based on PCR and antibacterial susceptibility data. The Division did not agree with these changes. Instead, the Division analyzed efficacy based on the original SAP. Although the study results remained significant, they were not as significant as initially reported.

Late Decision of Removing Study Site 202

Sites 202 and 218 were removed from the efficacy analyses by the Applicant. Site 202 was removed due to unreliable laboratory results. Site 218 was removed due to the concern of study misconduct. For Site 218, the Division agreed with the removal. However, for Site 202, the Division did not find sufficient justifications for its removal. Therefore, Site 202 was included in the Division's efficacy analysis.

As noted, these changes were made after the unblinded interim analysis for the resistant population and led to a larger treatment effect with a more significant p-value as compared to the Division's analysis using the original SAP.

8.4. Conclusions and Recommendations

This NDA contains one Phase 3 clinical trial in uUTI (Study 301) for the proposed indication. The Applicant also submitted the data from one Phase 3 study in cUTI (Study 302) and one Phase 3 study in cIAI (Study 303) as supportive information. The Division has the following conclusions:

When using the original, agreed-upon SAP and including Site 202 we found there was a lower level of statistical significance for the difference in overall response rate by treatment arm in the ciprofloxacin-resistant (MMITTR) population than was initially reported ($p > 0.001$ vs. $p < 0.00001$) in Study 301.

Regarding the lack of other evidence of efficacy, we note that in Study 301, significantly inferior results were observed in the overall response rate for sulopenem compared to ciprofloxacin in the ciprofloxacin susceptible (MMITTS) population. In addition, significantly inferior results for sulopenem were observed in the complicated urinary tract infections trial (Study 302) and there was a lack of noninferiority of sulopenem in the complicated intra-abdominal infections trial (Study 303).

From a safety perspective, there is an adequate safety database for oral sulopenem/probenecid. Identified safety issues include hypersensitivity reactions, elevated liver enzymes, and GI adverse reactions. Overall, the safety issues with oral sulopenem/probenecid do not preclude approval; the known risks of sulopenem can be managed by appropriate labeling.

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

The Division recommends that the NDA receive a Complete Response given the lack of substantial evidence of effectiveness and that the Applicant consider the following future steps:

1. Re-evaluate the proposed dose/dosing regimen given the issues associated with PK-PD/target attainment.
2. Conduct a second Phase 3 uUTI study to provide additional evidence of effectiveness.
3. Use a more relevant comparator given the current standard of care, such as nitrofurantoin.

9. Advisory Committee Meeting and Other External Consultations

No advisory committee meeting was held, and no external consultations were obtained as there were no issues that needed input from external experts.

10. Pediatrics

There are currently no clinical data available on the safety and efficacy of sulopenem in children and adolescents <18 years old. Iterum submitted their initial pediatric study plan (iPSP) for sulopenem for the treatment of uUTI, (b) (4) on 19 Sep 2017. (b) (4)

(b) (4). The Division (b) (4) recommended that Iterum study uUTI in children 2 years and older and consider requesting a partial waiver from studying uUTI in children less than 2 years old. The iPSP was discussed with PeRC on 8 Nov 2017. PeRC agreed with the Division's recommendation for a partial waiver in pediatric patients less than 2 years of age for uUTI (treated using the oral formulation) and with granting a deferral (b) (4). After Division feedback, Iterum resubmitted their pediatric study plan on 21 Feb 2018 including revisions based on Agency feedback. The Division confirmed agreement of the iPSP on 26 Feb 2018. Of note, PeRC also reviewed the revised iPSP in February 2018 and reiterated their agreement with the partial waiver in pediatric patients less than 2 years of age for uUTI and with granting the deferral of all pediatric studies as presented in the Agreed iPSP.

11. Labeling Recommendations

11.1. Prescription Drug Labeling

Table 112. Significant High-Level Labeling Changes (Not Direct Quotations)

Section	Proposed Labeling	Tentative Labeling
1 INDICATIONS AND USAGE	• uUTI caused by microorganisms proven or strongly suspected to be nonsusceptible to a quinolone • Limitation of use: [TRADENAME] is not indicated for (b) (4)	• Deleted limitation of use statement as it is unnecessary
M.O. Comment: The indication statement that includes organisms that are “nonsusceptible to a quinolone” remains under discussion as it is unclear whether this is a clinically meaningful population given there are other antibacterials drugs available to treat such infections. This statement is likely to be revised based on future studies.		
2 DOSAGE AND ADMINISTRATION	• (b) (4) • No dosage adjustment is required in patients with reduce renal function	• Recommends dosing with food (b) (4) • Not recommended in patients with CrCl <15 mL/min and patients on hemodialysis
M.O. Comment: Because food increases bioavailability and may shorten the duration of diarrhea, FDA recommends taking sulopenem with food. Sulopenem has not been studied in subjects with CrCl <15 mL/min.		
4 CONTRAINDICATIONS	• TRADENAME is not recommended for use in persons with known uric acid kidney stones	• Risk of uric acid kidney stones changed to a warning rather than a contraindication
5 WARNINGS AND PRECAUTIONS		• Added warnings for uric acid kidney stones and exacerbation of gout
M.O. Comment: (b) (4)		
6 ADVERSE REACTIONS	• Table 1 listed adverse reactions occurring $\geq 2\%$.	• Adjusted number of subjects to exclude data from Site 218 • Added adverse reactions $\geq 1\%$ to Table 1 • Added “elevated transaminases” to list of “Other Adverse Reactions” (ARs experienced in patients at a rate of <1%) • Combined (b) (4) with “rash” • (b) (4) were removed from the list of adverse reactions.

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

Section	Proposed Labeling	Tentative Labeling
M.O. Comment: Subjects from Site 218 were removed from the safety database (b) (7)(A) Elevations in liver transaminases were noted in the laboratory data. In addition to (b) (4) in Study 301, rash was noted as an adverse reaction from a subject taking oral sulopenem in Study 303.		
7 DRUG INTERACTIONS		Added a table to summarize the effect on drug concentration and recommendations regarding concomitant use of several drugs/drug classes.
8 USE IN SPECIFIC POPULATIONS	No dosage adjustment for renal function	- The pregnancy and lactation subsections were rewritten to succinctly summarize the data - Added recommendation to avoid with CrCl <15 mL/min (b) (4)
M.O. Comment: Sulopenem has not been studied in subjects with CrCl <15 mL/min.		
12 CLINICAL PHARMACOLOGY	The Applicant provided data on pharmacokinetics and microbiology	- This section was rewritten to align the content and format with the current labeling guidance - The second list of bacterial pathogens was revised to remove (b) (4)
13 NONCLINICAL TOXICOLOGY	The Applicant provided data on mutagenesis and fertility	These sections were rewritten to provide more details on the data
14 CLINICAL STUDIES	The Applicant summarized their analysis of Study 301	This subsection was not revised given the lack of substantial evidence of efficacy

12. Risk Evaluation and Mitigation Strategies

Not applicable given the proposed Complete Response action.

13. Postmarketing Requirements and Commitment

Not applicable given the proposed Complete Response action.

14. Deputy Division Director (DAI) Comments

I concur with the conclusions of the multi-disciplinary review team.

15. Office Director (OID) Comments

I concur with the conclusions of the multi-disciplinary review team.

16. Appendices

16.1. References

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NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

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16.2. Financial Disclosure

Table 113. Covered Clinical Study (Name and/or Number): IT001-301

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>135</u>		

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
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: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
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) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Table 114. Covered Clinical Study (Name and/or Number): IT001-302

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>132</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
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: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
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) <u>0</u>		

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Table 115. Covered Clinical Study (Name and/or Number): IT001-303

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>91</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
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: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
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) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

16.3. OCP Appendices (Technical Documents Supporting OCP Recommendations)

Table 116. Summary of Bioanalytical Method Validation Reports

Method Type	LC-MS/MS
Validation Report#	A7379006
Studies Analyzed	A8811006, A8811009 and A8811018
Biological Matrix	Plasma
Anticoagulant	Heparin
Calibration curve	25 to 5000 ng/mL
Analyte of Interest	Sulopenem
Internal Standard	[¹³ C ₃]-Sulopenem
Method Validation Summary	
Intra-run accuracy (for all QC concentrations)	≤5%
	Acceptability Yes

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

Intra-run precision (for all QC concentrations)	≤-4.6%	Yes
Inter-run accuracy (for all QC concentrations)	1.9% to ≤7.9%	Yes
Inter-run precision (for all QC concentrations)	-3.6% to ≤0.4%	Yes
Selectivity	No response ≥5% Internal Standard	Yes
Short-term or bench-top temperature stability	6 h on ice bath 45 h at 1 to 8°C	Yes
Freeze-Thaw stability	3 free-thaw cycles	Yes
Long-term storage	685 days at -70 °C	Yes
Incurred Sample Reanalysis	ISR was not required during the sample analysis period ^a	N/A
Method Type	LC-MS/MS	
Validation Report #	A8819003 A8811009 and A8811018	
Studies Analyzed		
Biological Matrix	Urine	
Calibration curve	1.00 to 500 µg/mL	
Analyte of Interest	Sulopenem	
Internal Standard	(b) (4)	
	Method Validation Summary	Acceptability
Intra-run accuracy (for all QC concentrations)	-9.3% to 14%	Yes
Intra-run precision (for all QC concentrations)	≤12%	Yes
Inter-run accuracy (for all QC concentrations)	-6.7% to 12%	Yes
Inter-run precision (for all QC concentrations)	≤8.6%	Yes
Selectivity	No response ≥5% Internal Standard	Yes
Short-term or bench-top temperature stability	6 h at 25 °C	Yes
Freeze-Thaw stability	8 free-thaw cycles	Yes
Long-term storage	62 Days at -70 °C	Yes

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

Method Type	LC-MS/MS	
Validation Report #	AV16-CP70,429-03	
Studies Analyzed	IT001-101, IT001-102, IT001-104, IT001-105 and IT001-301	
Biological Matrix	Plasma	
Anticoagulant	Potassium Oxalate/Sodium Fluoride	
Calibration curve	10 to 1500 ng/mL	
Analyte of Interest	Sulopenem	
Internal Standard	¹³ C ₃ -70429	
	Method Validation Summary	Acceptability
Intra-run accuracy (for all QC concentrations)	-14.7 to 12.8%	Yes
Intra-run precision (for all QC concentrations)	6.9% to <15% (≤16.3% at LLOQ)	Yes
Inter-run accuracy (for all QC concentrations)	-5.8% to 4.8%	Yes
Inter-run precision (for all QC concentrations)	7.3% to 14.5%	Yes
Selectivity	No response ≥5% Internal Standard	Yes
Short-term or bench-top temperature stability	4.5 h at 25 °C	Yes
Freeze-Thaw stability	4 free-thaw cycles	Yes
Long-term storage	621 Days at -70 °C	Yes
Incurred Sample Reanalysis	>67% ±20% of mean	Yes
Method Type	LC-MS/MS	
Validation Report#	A8819001	
Studies Analyzed	A8811001	
Biological Matrix	Whole Blood	
Anticoagulant	Potassium oxalate/Sodium Fluoride	
Calibration curve	1.00 to 50.0 ng/mL	
Analyte of Interest	Sulopenem Etzadroxil	
Internal Standard	PF-00450316	
	Method Validation Summary	Acceptability
Intra-run accuracy (for all QC concentrations)	≤-9.0 to 5.3%	Yes
Intra-run precision (for all QC concentrations)	≤2.8 to <15% (≤19.8% at LLOQ)	Yes
Inter-run accuracy (for all QC concentrations)	-5.1% to 2.3%	Yes
Inter-run precision (for all QC concentrations)	≤-9.0 to 5.3%	Yes
Selectivity	No response ≥5% Internal Standard	Yes

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

Short-term or bench-top temperature stability	3 h on wet ice	Yes
Freeze-Thaw stability	2 free-thaw cycles	Yes
Long-term storage	101 Days at -70 °C	Yes
Incurred Sample Reanalysis	ISR was not required during the sample analysis period ^a	N/A
Method Type/Validation Report Number	GC/MS; A8819004 (Used for Analysis of 2-Ethylbutyric Acid in Study A8811009)	
Biological Matrix	Whole Blood	
Anticoagulant (if applicable)	Potassium Oxalate/Sodium Fluoride	
Calibration curve	50 to 5017 ng/mL	
Analyte of Interest	2-Ethylbutyric Acid	
Internal Standard	2-Methylbutyric d9 acid	
	Method Validation Summary	Acceptability
Intra-run accuracy (for all QC concentrations)	-9.69% to 17.36%	Yes
Intra-run precision (for all QC concentrations)	<15% for all QCs except LLOQ (≤19.6% at LLOQ)	Yes
Inter-run accuracy (for all QC concentrations)	-9.69% to <15% (≤17.36% at LLOQ)	Yes
Inter-run precision (for all QC concentrations)	<-15% for all QCs except LLOQ (≤-19.6%)	Yes
Selectivity	No response ≥5% Internal Standard	Yes
Short-term or bench-top temperature stability	72 h at 2-6 °C in 80:20 Hexane: Ethyl Acetate	Yes
Freeze-Thaw stability	3 cycles	Yes
Long-term storage	127 Days at -20°C and -80°C	Yes
Incurred Sample Reanalysis	ISR was not required during the sample analysis period ^a	N/A
Method Type	LC-MS/MS	
Validation Report#	AV18-Probenecid-01	
Studies Analyzed	IT001-105	
Biological Matrix	Plasma	
Anticoagulant (if applicable)	Potassium Oxalate	
Calibration curve	10 to 1500 µg/mL	
Analyte of Interest	Probenecid	
Internal Standard	Probenecid-D14	
	Method Validation Summary	Acceptability
Intra-run accuracy (for all QC concentrations)	10.3% to -4.0%	Yes

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

Intra-run precision (for all QC concentrations)	2.5% to 5.3%	Yes
Inter-run accuracy (for all QC concentrations)	4.7% to -2.0%	Yes
Inter-run precision (for all QC concentrations)	2.1% to 10.1%	Yes
Selectivity	No response $\geq$ 5% Internal Standard	Yes
Short-term or bench-top temperature stability	6.0 h at 25 °C	Yes
Freeze-Thaw stability	5 cycles	Yes
Long-term storage	227 Days at -70 °C	Yes
Incurred Sample Reanalysis	>67% $\pm$ 20% of mean	Yes
Method Type	LC-MS/MS	
Validation Report #	AV18-Valproic Acid-01 IT001-104	
Studies Analyzed		
Biological Matrix	Plasma	
Anticoagulant	EDTA K2Plasma	
Calibration curve	3.00 to 150 μ g/mL	
Analyte of Interest	Valproic Acid	
Internal Standard	Valproic Acid-D6	
	Method Validation Summary	Acceptability
Intra-run accuracy (for all QC concentrations)	-6.0% to 1.3%	Yes
Intra-run precision (for all QC concentrations)	2.1% to 2.5%	Yes
Inter-run accuracy (for all QC concentrations)	5.0% to $\leq$ -3.0%	Yes
Inter-run precision (for all QC concentrations)	2.2 to 7.2%	Yes
Selectivity	No response $\geq$ 5% Internal Standard	Yes
Short-term or bench-top temperature stability	6.3 h at 25 °C	Yes
Freeze-Thaw stability	4 cycles	Yes
Long-term storage	39 days at -70 °C	Yes
Incurred Sample Reanalysis	ISR was not performed during sample analysis period	N/A

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

^a Bioanalytical Sample Analysis preceded the 2013 version of the FDA BMV Guidance, which recommended ISR as part of method validation

Abbreviations: ISR, incurred sample reanalysis; LC-MS/MS, liquid chromatography with tandem mass spectrometry; QC, quality control

Table 117. Individual Clinical Pharmacology Reports Reviewed

Study Number	Description
<i>Human Pharmacokinetic Studies in Healthy Volunteers</i>	
Study A8811001	Single Ascending Dose Study of Two Oral Sulopenem Prodrugs
Study A8811003	Single and Multiple Ascending Dose Study of Sulopenem Etzadroxil
Study IT001-105	Absolute Bioavailability and Food Effect Study of To-Be-Marketed Oral Bilayer Tablet
<i>ADME</i>	
Study A8811006	Phase 1 Study to Evaluate the Metabolism and Excretion of [¹⁴ C]PF-03709270 in Healthy Adult Volunteers
<i>Intrinsic Factor Studies</i>	
Study A8811009	Open-label 2-Way Crossover Study to Investigate the PK, Safety and Tolerability of IV Sulopenem and Oral Sulopenem Etzadroxil in Subjects with Varying Degrees of Renal Impairment and Normal Renal Function
<i>Clinical Drug-Drug Interactions</i>	
Study IT001-102	Phase 1, Randomized, Open-label, Single-dose, 4-way Crossover Study to Determine PK of Sulopenem following Single Dose Administration of Sulopenem Etzadroxil with either Probenecid, Gallic Acid or Tannic Acid
Study IT001-101	Phase 1 Study to Evaluate the Safety, Tolerability and PK of Sulopenem Prodrugs in Healthy Volunteers in Fed and Fasted Conditions and with or without Probenecid
Study IT001-103	Phase 1, Open-label, 2-Period, 4-Sequence, Parallel Study to Estimate Effects of Multiple-Dose Administration of Itraconazole on the PK of Sulopenem in Healthy Adult Subjects
Study IT001-104	Phase 1, Open-label, 2-Period, 3-Sequence, Parallel Study to Evaluate Effects of Sulopenem Multiple-Dose Administration on the PK of Valproic Acid in Healthy Adult Male Subjects
Study A8811018	Exploratory Phase 1 Study to Evaluate the Safety, Tolerability and PK of Sulopenem Etzadroxil with Gastric pH Modifiers
<i>In Vitro Pharmacokinetic Studies</i>	
Studies 17IT001-2017_03_14_Iterum Therapeutics_(b)(4) and 17IT002-2017_06_30_Iterum Therapeutics_(b)(4)-00	Permeability of Sulopenem and Sulopenem Prodrugs across Caco-2 Cell Monolayers
Study DM2004-070429-013	Sulopenem Protein Binding Study
Study Iterum-03-09Aug2019	Characterization of Sulopenem In Vitro Metabolism Using Recombinant UGT and CYP enzymes
<i>In Vitro Drug-Drug Interaction Studies</i>	
Studies DM2006-070429-029 and 17081086ITX	Evaluation of Sulopenem and Sulopenem Etzadroxil's Inhibitory and Induction Potential on CYP Enzymes
Studies 17081088ITX and Iterum-02-08-Mar2019-A1	Evaluation of Sulopenem and Sulopenem Etzadroxil as Substrates and Inhibitors of Human Transporters
Study Iterum-02-08-Mar2019-A1	Evaluation of Probenecid as Substrate and Inhibitor of Human Transporters

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

Study Number	Description
<i>Nonclinical PK/PD Studies</i>	
Study 810-00081	Murine Model Studies to Determine PK/PD Target

Abbreviations: ADME, absorption, distribution, metabolism, and excretion; IV, intravenous; PD, pharmacodynamics; PK, pharmacokinetics

Human PK Studies in Healthy Volunteers

Single Ascending Dose

Study A8811001 was a single ascending dose study to characterize the PK, safety, and tolerability of two sulopenem oral prodrugs, PF-03678685 and PF-03709270 (i.e., sulopenem etzadroxil) in healthy adult volunteers. Eighteen male subjects aged 21 to 52 years with a mean body mass index (BMI) of 24.0 kg/m² were enrolled and randomized to 2 cohorts to receive one of the two sulopenem oral prodrugs or placebo according to the schematic in Table 118.

Table 118. Treatments Received in Cohorts 1 and 2

Sequence	N	Period 1	Period 2	Period 3	Period 4
Cohort 1					
1	3	Placebo	1000 mg	2000 mg	600 mg
2	3	400 mg	Placebo	2000 mg	600 mg
3	3	400 mg	1000 mg	Placebo	Placebo
Cohort 2					
1	3	Placebo	1000 mg	2000 mg	
2	3	400 mg	Placebo	2000 mg	
3	3	400 mg	1000 mg	Placebo	

Source: Tables S2 and S3 of Applicant's ISR A8811001

All doses were administered following an 8 h fast; subjects were required to refrain from eating or drinking anything except water for another 4 h post-dosing. Sulopenem prodrugs were administered as oral powders (supplied as 100 mg, 300 mg, and 500 mg dose strengths) for reconstitution. Dose escalations within each cohort were based upon available preliminary safety, tolerability, and PK from previous dosing periods. Whole blood and plasma PK samples were collected pre-dose and at pre-specified times post-dose for measurement of sulopenem, sulopenem prodrugs and formate (a by-product of prodrug hydrolysis) using validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) methods. Pharmacokinetic assessments included: C_{max}, T_{max}, area under the curve (AUC) and t_{1/2}.

Per the Applicant, this study was expected to inform the selection of an appropriate sulopenem prodrug for future studies. Both prodrugs were well-tolerated and there were no study discontinuations due to adverse events (AEs). One subject in the sulopenem etzadroxil cohort was no longer willing to participate and withdrew from the study after receiving single doses of 400 and 1000 mg in Periods 1 and 2, respectively. Following Period 1, all subjects from the PF-03678685 cohort were discontinued from the study because exposures of sulopenem from the 400 mg dose were considered too low to warrant further study. Because PF-03678685, sulopenem etzadroxil and formate were not detected in whole blood or plasma samples at any dose level, PK parameters are only summarized for sulopenem (Table 119).

Table 119. Mean ($\pm$ SD) PK Parameters for Sulopenem Following Dosing With PF-03678685 or PF-03709270 (Sulopenem Etzadroxil)

Treatment	Dose (mg)	C _{max} (ng/mL)	T _{max} ^a (hr)	AUC _{last} (hr ng/mL)	T _{1/2} (hr)
PF-03678685	400	859 $\pm$ 150	1.00 (0.50,1.50)	1763 $\pm$ 302	0.98 $\pm$ 0.30
PF-03709270	400	1464 $\pm$ 442	1.00 (0.50,3.00)	3455 $\pm$ 670	0.84 $\pm$ 0.16
	600	1508 $\pm$ 340	1.00 (1.00,3.00)	3914 $\pm$ 514	0.76 $\pm$ 0.10
	1000	2860 $\pm$ 570	0.75 (0.50,1.50)	6421 $\pm$ 1208	1.00 $\pm$ 0.17
	2000	4667 $\pm$ 1181	1.00 (1.00,3.00)	13131 $\pm$ 2101	1.10 $\pm$ 0.62

Source: Tables 13.5.2.1 and 13.5.2.2

TC=target concentration

^a Median (range) provided for T_{max}.

Abbreviations: AUC, area under the curve; C_{max}, maximum serum concentration; PK, pharmacokinetics; T_{max}, time to maximum concentration

Based on power model analysis, the AUC of sulopenem increased in a nearly dose proportional manner while C_{max} increased less than dose proportionally over the dose range of 400 mg to 2000 mg, as summarized in Table 120.

Table 120. Analysis of Dose Proportionality for Dose Range of 400 to 2000 mg

Parameter	Estimated Slope for ln(Dose)	90% CI for Slope	Equivalence Bounds
AUC _{last}	0.88	0.81, 0.95	0.86, 1.14
C _{max}	0.78	0.67, 0.89	

Source: Reviewer's analysis

Abbreviations: AUC, area under the curve; CI, confidence interval; C_{max}, maximum serum concentration.

Single and Multiple Ascending Dose

Study A8811003 was a PK, safety, and tolerability study of single and multiple ascending doses of sulopenem etzadroxil that also evaluated the effect of probenecid on sulopenem exposure. Seventy-two healthy male adult subjects were planned for enrollment into 6 cohorts (N=12/cohort). Dose escalation was contingent upon the absence of serious AEs and dose-limiting intolerance. The planned dosing schemes for Cohorts 1 through 6 are summarized in Table 121 and Table 122. Subjects in the multiple dose cohorts were dosed for 10 days using a sulopenem etzadroxil powder in bottle formulation at dose strengths of 600 mg and 2000 mg.

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

Table 121. Dosing in Cohort 1 (Single Ascending Dose)

Sequences	Number of Subjects Planned	Period 1	Period 2	Period 3	Period 4
1	3	Placebo QD	4000 mg QD PF-03709270	8000 mg QD PF-03709270	TBD ^a
2	3	2000 mg QD PF-03709270	Placebo QD	8000 mg QD PF-03709270	TBD
3	3	2000 mg QD PF-03709270	4000 mg QD PF-03709270	Placebo QD	TBD
4	3	2000 mg QD PF-03709270	4000 mg QD PF-03709270	8000 mg QD PF-03709270	Placebo

Abbreviations: TBD = to be determined, MTD = maximum tolerated dose, QD = once daily

^a The dose administered during Period 4 was planned to be 12,000 mg PF-03709270 if MTD was not reached or 6000 mg PF-03709270 if the 8000 mg dose was not well tolerated.

Source: Table S2 of Applicant's ISR A8811003

Table 122. Dosing Scheme in Cohorts 2 to 6 (Multiple Ascending Dose)

Number of Subjects	Cohort 2	Cohort 3	Cohort 4 ^a	Cohort 5 ^a	Cohort 6 ^a
9	2000 mg PF-03709270 BID	1200 mg PF-03709270 + 1000 mg probenecid BID	2000 mg PF-03709270 TID	4000 mg PF-03709270 BID	4000 mg PF-03709270 TID
3	Placebo BID	Placebo + 1000 mg probenecid BID	Placebo TID	Placebo BID	Placebo TID

Abbreviations: BID = twice daily, TID = 3 times daily

^a Cohorts 4 through 6 were not enrolled in this study.

Source: Table S3 of Applicant's ISR A8811003

All doses were administered under fasted conditions. Blood samples were collected pre-dose and at pre-specified times post-dosing for measurement of sulopenem, formate and 2-ethylbutyric acid. Pharmacokinetic assessments included: C_{max} , T_{max} , AUC_{0-inf} , AUC_{0-last} , AUC_{0-tau} , R_{ac} and $t_{1/2}$. A 24 h urine collection was also performed for subjects in the multiple dose cohorts on Day 6. Blood and urine samples were assayed using validated LC-MS/MS methods.

Reviewer's Comment: In addition to the release of sulopenem, hydrolysis of the sulopenem etzadroxil prodrug ester bond yields formate and 2-ethylbutyric acid as by-products.

Ultimately, 11 male healthy volunteers aged 22-48 years (mean = 30.6 years) were enrolled in Cohort 1, where 2 of 5 study discontinuations were due to treatment-emergent adverse event (TEAEs). Each subject in this cohort reported at least 1 TEAE, with diarrhea being most frequently reported. Single doses of 2000 mg and 4000 mg were considered well-tolerated while doses of 6000 mg and 8000 mg were poorly tolerated due to a greater frequency and severity of AEs. Twenty-four healthy volunteers aged 23-51 years (twenty-three males and one female), were enrolled in Cohorts 2 and 3, three of whom discontinued the study due to AEs. Overall, 12 of the 24 subjects in Cohorts 2 and 3 reported at least 1 adverse event. As with the single ascending dose portion of this study, diarrhea was the most frequently observed AE, occurring in 18 (75%) of subjects. Due to the prevalence and severity of treatment-related gastrointestinal AEs observed in Cohort 2 (where sulopenem etzadroxil 2000 mg twice daily [BID] was administered), Cohorts 4 through 6 of this study were not enrolled. Multiple dose administration of 1200 mg sulopenem etzadroxil with 1000 mg probenecid (Cohort 3) was better tolerated than multiple doses of 2000 mg sulopenem etzadroxil.

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

Following oral administration of single doses of 2000 mg to 8000 mg, AUC increased in an approximately dose proportional manner while C_{max} increased less than dose proportionally (Table 123). Mean sulopenem exposures in Cohort 3, where subjects received 1200 mg sulopenem etzadroxil with 1000 mg probenecid BID were moderately higher than exposures observed in Cohort 2 following administration of 2000 mg sulopenem etzadroxil BID (Table 62). The terminal half-life of sulopenem was ~1.44 h with probenecid and 1.27h in the absence of probenecid. Interindividual variability was moderate (18 to 26%) for both AUC and C_{max} on Days 1 and 10 with and without probenecid. Mean accumulation ratios were below 1 for both Cohorts 2 and 3 due to an inexplicable reduction in both AUC and C_{max} on Day 10 compared to Day 1. This reduction was less pronounced when sulopenem etzadroxil was administered with probenecid (6%) versus without (30%).

The 24-hour urinary excretion accounted for approximately 16 to 17% of the total parent dose (i.e. active sulopenem component) in both Cohort 2 and 3. In the presence of probenecid, CL_r decreased by ~65% compared to administration of sulopenem etzadroxil alone. Formate was unquantifiable at any dose levels evaluated in this study and concentrations of 2-EBA were below the lower limit of quantification (LLOQ) at most time points.

Table 123. Summary of Sulopenem Plasma PK Parameter Values Following Single Oral Dose Administration of Sulopenem Etzadroxil

Parameter ^a	PF-03709270 2000 mg QD	PF-03709270 4000 mg QD	PF-03709270 6000 mg QD	PF-03709270 8000 mg QD
N, n	9, 9	8, 8	4, 2	8, 8
AUC _{inf} (ng.hr/mL)	12200 (29)	26900 (35)	NC	76500 (53)
AUC _{last} (ng.hr/mL)	12100 (29)	25800(31)	NC	56700 (16)
C_{max} (ng/mL)	4650 (27)	6750 (24)	NC	8880 (18)
T_{max} (hr)	1.00 (1.00-2.00)	1.00 (1.00-2.00)	NC	1.30 (1.00–5.00)
T_{last} (hr)	8.00 (8.00–12.00)	12.00 (8.00–12.00)	NC	12.00 (12.00–24.00)
$t_{1/2}$ (hr)	1.36 (30)	1.94 (64)	NC	7.26 (71)
TAMIC1	4.79 (4.32–8.25)	9.01 (5.33–18.70)	NC	20.63 (12.40–24.00)
TAMIC2	4.15 (2.67-5.58)	7.21 (4.24–13.40)	NC	15.58 (11.40-23.30)

Source: Table 13.5.2.1

Abbreviations: AUC_{inf} = area under the concentration-time curve from time 0 to infinite time, AUC_{tau} = area under the concentration-time curve from time 0 to time_τ (the dosing interval), C_{max} = maximum (peak) observed drug concentration after single dose administration, C_{trough} = minimum (trough) observed drug concentration, hr = hour, MIC_{0.5} = time above the duration of plasma concentrations exceeding 0.5 μg/mL, MIC_{1.0} = time above the duration of plasma concentrations exceeding 1.0 μg/mL, N = number of subjects; n = number of subjects contributing to the mean, NC = summary statistics not calculated, QD = once daily, R = accumulation ratio, ssTc = time steady state concentration was above MIC_{0.5}/MIC_{1.0}, $t_{1/2}$ = elimination half-life, TAMIC1 = time above minimum inhibitory concentration, when minimum concentration is 0.5 μg/mL, TAMIC2 = time above minimum inhibitory concentration, when minimum concentration is 1.0 μg/mL, T_{max} = time to reach peak or maximum concentration following drug administration

^a Geometric mean (%CV) for AUC_{inf}, AUC_{last}, AUC_{tau}, and C_{max} ; arithmetic mean (%CV) for $t_{1/2}$; median (range) for T_{max} , T_{last} , TAMIC1, and TAMIC2.

Table 124. Summary of Sulopenem Plasma PK Parameter Values Following Multiple Dose Administration With and Without Probenecid

Parameter ^a	PF-03709270 1200 mg/ Probenecid 1000 mg BID	PF-03709270 2000 mg BID
<i>Study Day 1; Plasma</i>		
N, n	9, 8	9, 9
AUC _{inf} (ng.hr/mL)	20400 (24)	18100 (26)
AUC _{tau} (ng.hr/mL)	20000 (21)	17500 (24)
C _{max} (ng/mL)	6520 (25)	6090 (19)
T _{max} (hr)	1.00 (1.00–3.00)	1.00 (1.00–2.00)
T _{last} (hr)	8.00 (6.00–12.00)	8.00 (8.00–12.00)
t _{1/2} (hr)	2.09 (63)	1.66 (50)
TAMIC1	7.01 (30)	6.93 (34)
TAMIC2	5.48 (32)	5.57 (28)
<i>Study Day 10; Plasma</i>		
N, n	9, 6	9, 8
AUC _{inf} (ng.hr/mL)	NC	NC
AUC _{tau} (ng.hr/mL)	18800 (18)	12200 (21)
C _{max} (ng/mL)	6660 (23)	5480 (18)
T _{max} (hr)	1.30 (1.00–2.00)	1.00 (1.00)
C _{trough} (ng/mL)	13.44 (83)	0.00 (283)
T _{last} (hr)	8.00 (8.00–12.00)	8.00 (6.00–12.00)
t _{1/2} (hr)	1.44 (14)	1.27 (26)
TAMIC1	6.35 (11)	4.70 (24)
TAMIC2	4.74 (11)	3.61 (24)
Rac	0.892 (9)	0.685 (18)
<i>Study Day 6; Urine</i>		
Ae ₂₄ (ug)	139000 (30) (N=9, n=8)	253000 (26) (N=9, n=9)
Ae% (%)	16.2 (29) (N=9, n=8)	17.3 (26) (N=9, n=9)
CL/R (mL/hr)	7.77 (21) (N=9, n=6)	22.0 (25) (N=9, n=8)

Source: Tables 13.5.2.1.2 and 13.5.2.2.2; Appendix B5.2.1.2

Abbreviations: AE₂₄ = amount of CP-70,429 excreted in urine over 24 hours post dose administration, AE% = percent of CP-70,429 dose excreted in urine, AUC_{inf} = area under the concentration-time curve from time 0 to infinite time, AUC_{tau} = area under the concentration-time curve from time 0 to time_t (the dosing interval), BID = twice daily, CL/R = renal clearance, C_{max} = maximum (peak) observed drug concentration after single dose administration, C_{trough} = minimum (trough) observed drug concentration, MIC_{0.5} = time above the duration of plasma concentrations exceeding 0.5 µg/mL, MIC_{1.0} = time above the duration of plasma concentrations exceeding 1.0 µg/mL, N = number of subjects; n = number of subjects contributing to the mean, NC = summary statistics not calculated, Rac = accumulation ratio, t_{1/2} = elimination half-life, TAMIC1 = time above minimum inhibitory concentration, when minimum concentration is 0.5 µg/mL, TAMIC2 = time above minimum inhibitory concentration, when minimum concentration is 1.0 µg/mL, T_{max} = time to reach peak or maximum concentration following drug administration

^a Geometric mean (%CV) for AUC_{inf}, AUC_{last}, AUC_{tau}, C_{max}, and CL/R; arithmetic mean (%CV) for t_{1/2}, AE%; median (range) for T_{max}, T_{last}, TAMIC1, and TAMIC2

Absolute Bioavailability and Food Effect

Study IT001-105 was an open label, single-center, four sequence, three period study to assess the safety, tolerability, and absolute bioavailability of the to-be-marketed sulopenem etzadroxil and probenecid bilayer tablet in the fed and fasted state. This study also evaluated the PK, safety, and tolerability of two other sulopenem formulations: an oral powder-in-bottle (PIB) sulopenem etzadroxil formulation and intravenous (IV) sulopenem. Additionally, this study was used to bridge the probenecid layer of the bilayer tablet and commercial probenecid by comparing the PK of probenecid following administration of the bilayer tablet to that of

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

probenecid, USP tablet (an FDA-approved generic drug version of Benemid). Shown in Table 125 are the details of drug administration in each cohort of the study.

Table 125. Treatment Sequence of the Four Cohorts in Study IT001-105

Cohort	n	Study Period 1 (Fasted)	Study Period 2 (Fed)*	Study Period 3 (Fasted)
1	14	PF-03709270 500 mg + Probenecid 500 mg fixed-dose tablet	PF-03709270 500 mg + Probenecid 500 mg fixed-dose tablet	Sulopenem 366 mg IV infused over 1 h
2	8	PF-03709270 500 mg Powder-in-Bottle	PF-03709270 500 mg Powder-in-Bottle*	Sulopenem 366 mg IV infused over 1 h
3	12	PF-03709270 500 mg Powder-in-Bottle	PF-03709270 500 mg Powder-in-Bottle	Sulopenem 366 mg IV infused over 1 h
4	12	Sulopenem 1000 mg IV infused over 3 h	Sulopenem 1000 mg IV infused over 3 h	Sulopenem 1000 mg IV infused over 3 h + Probenecid 500 mg PO

*Subjects in Cohort 2 received all assigned treatment in a fasted state.
 IV = intravenous; n = number of subjects per Cohort; PO = oral.
 Source: Study Protocol (Appendix 16.1.1)

Reviewer's Comment: Per the Applicant, the objective of including Cohort 2 was to investigate the effect of a single 500 mg dose of sulopenem etzadroxil on the PK of sulopenem when separated by a 7-day washout period. Given the decrease in sulopenem exposure following multiple dose administration of sulopenem etzadroxil (in Study A8811003), this evaluation was deemed necessary to determine whether a period effect may explain this observation. However, it is the reviewer's opinion that given sulopenem's short half-life, the dosing regimen indicated for Cohort 2 is insufficient to address the stated question.

Per the Applicant, the proposed dosing regimen for Study Period 2 of Cohort 4 was intended to evaluate any potential food effect on the PK of IV sulopenem. Given that food does not impact the absorption of parenteral administration, no food effect is expected.

Both oral sulopenem etzadroxil formulations contain 366 mg of the sulopenem active component. For this reason, 366 mg IV sulopenem was used to assess the absolute bioavailability of the oral formulations. Drug administration across cohorts proceeded as described below:

- Period 1 - After an overnight fast of at least 10 h, subjects received their assigned single dose treatments and continued fasting for at least 4 h post-dosing.
- Period 2 - Following a 7-day washout, subjects were readmitted into their assigned cohorts to receive the same treatments as indicated for Period 1. With the exception of Cohort 2, all other cohorts were provided a standard high-fat breakfast (~800-1000 kCal total, 50% fat) 30 min before dosing. Subjects in Cohort 2 received their assigned treatment under the same fasted conditions outlined for Period 1.
- Period 3 - Following another 7-day washout period, subjects were readmitted into their assigned cohorts. Cohorts 1-3 received 366 mg sulopenem IV infused over 1 h while Cohort 4 received 1000 mg sulopenem IV infused over 3 h in combination with a 500 mg oral probenecid tablet.

PK Sampling and Assessments

Plasma PK samples were collected on Day 1 at pre-dose and at pre-specified times through 12 h post-dosing. The following plasma PK parameters of sulopenem were calculated: C_{max} , T_{max} , AUC_{0-last} , AUC_{0-inf} , AUC_{extrap} , V_z , V_z/F , clearance (CL), and $t_{1/2}$. Plasma samples were assayed for sulopenem and formate using validated LC/MS/MS methods. Whole blood samples were also assayed for PF-03678685 and PF-03709270 (sulopenem etzadroxil) using a validated LC-MS/MS method.

The PK population was comprised of subjects who received any study drug and had sufficient data to calculate at least 1 pre-planned PK parameter. Absolute bioavailability was calculated for both the bilayer tablet and PIB under fasting conditions using 366 mg IV as reference. The effect of food on the PK of sulopenem was also determined using a paired t-test on the natural-log transformed C_{max} and AUCs of the fed versus fasted state. Similarly, for Cohorts 2 and 4, paired t-test on the log transformed C_{max} and AUCs was used for comparison of Periods 1 and 2.

Demographics

Forty-six healthy male and female subjects with mean age 35.8 years and BMI of 25.76 kg/m² were enrolled in this study. The majority of the subjects (87%) were male and Black (67.4%). No previous or concomitant medications were recorded for any subjects in this study. Although the study's inclusion criteria indicated that subjects with estimated glomerular filtration rate (eGFR) ≥ 85 mL/min/1.73m² were to be enrolled in the study, three subjects in Cohort 1, one subject in Cohort 2 and one subject in Cohort 3 with eGFR values in the range of 75 mL/min/1.73m² to 83 mL/min/1.73 m² participated in the study.

Reviewer's Comment: Of the five subjects indicated as having an eGFR in the range of 75 mL/min/1.73m² to 83 mL/min/1.73 m² under protocol deviations, individualized eGFR values ranged from 94 mL/min to 113 mL/min. Individualization of eGFRs for all other subjects enrolled in this study identified only two subjects (both in Cohort 1) whose eGFR fell within the range of 83 to 88 mL/min and would thus be categorized as having mild renal impairment according to the FDA's guidance on pharmacokinetics in patients with impaired renal function. Sulopenem exposures for these 2 subjects were generally within the range of exposures observed in subjects with eGFR ≥ 90 mL/min and are summarized below (Table 126):

Table 126. Comparison of Sulopenem Exposures for Subjects With eGFR <90 mL/min to Those With eGFR ≥ 90 mL/min in Cohort 1

Subject	eGFR	Bilayer Tablet (Fasted)		Bilayer Tablet (Fed)		Sulopenem 366 mg IV	
		C_{max} (ng/mL)	AUC_{0-inf} (ng·h/mL)	C_{max} (ng/mL)	AUC_{0-inf} (ng·h/mL)	C_{max} (ng/mL)	AUC_{0-inf} (ng·h/mL)
(b) (6)	83 mL/min	1800	5418	4950	8736	11000	13236
(b) (6)	88 mL/min	4060	6216	2430	7410	10000	11950
Rest of Cohort 1	≥ 90 mL/min	979-2410	2633-7057	1170-4160	5264-9952	6520-9880	9614-14566

Source: Reviewer's analysis

Abbreviations: AUC area under the curve; C_{max} , maximum serum concentration; eGFR, estimated glomerular filtration rate.

Results

All formulations of sulopenem were well-tolerated. Of the 46 subjects enrolled in the study, 2 subjects discontinued the study (for reasons unrelated to AEs). In the fasted state, 2 subjects (14.3%) in the bilayer tablet cohort and 7 (35.0%) in the PIB cohort experienced TEAEs. Only 1 of these AEs were gastrointestinal (GI) in nature; all others were characterized as abnormal urine odor. In the fed state, only 1 subject receiving sulopenem etzadroxil reported TEAE, which again was abnormal urine odor.

The absolute bioavailability of sulopenem for the PIB formulation was 31% in the fasted state and 38% in the fed state. Absolute bioavailability for the bilayer tablet (i.e., sulopenem etzadroxil in combination with probenecid) was 40%, as shown in Table 127. During Period 2, a subject in Cohort 1 registered unusually low plasma concentrations of sulopenem and probenecid in the fed state in spite of having adequate concentrations of both drugs in the fasted state. No definitive explanation for this observation could be provided, except for potential subject non-compliance. Therefore, this subject was re-dosed in the fed state. When PK data from redosing this subject in the fed state was included in analyses, it was determined that a high fat meal increased the mean absolute bioavailability of sulopenem for the bilayer tablet to 64.4% (Table 128). Sensitivity analysis conducted by exclusion of data from this subject resulted in a similar estimated bioavailability (i.e. 64.6%) in the fed state.

Table 127. Absolute Bioavailability Analysis and Comparison of Plasma Sulopenem PK Parameters for Cohort 1 – Bilayer Tablet (Fasted)

PK Parameter (Unit)	Fasted 366 mg IV (A)		Fasted Bilayer Tab (B)		Ratio of Geom. Mean (B/A) (%)	90% CI for Ratio (%) [2]
	n	Geom Mean [1]	n	Geom. Mean [1]		
AUC _{0-last} (h*ng/mL)	14	11527.42	14	4616.01	40.0	34.72, 46.19
AUC _{0-inf} (h*ng/mL)	14	11561.06	14	4646.89	40.2	34.89, 46.30

Note: Data from Subject (b) (6) are included in the analyses.
 A paired 2-sample t-test was performed on the log-transformed PK parameters.
 A subject must have had a calculable PK parameter in both treatments (test and reference) in order to be included in the analysis for that parameter.
 Bilayer tab = PF-03709270 500 mg + probenecid 500 mg fixed-dose PO tablet; 366 mg IV = sulopenem 366 mg IV infused over 1 h.
 [1] Geometric means were presented after back transformation to the original scale.
 [2] The 90% CIs were presented after back transformation to the original scale.
 AUC_{0-inf} = area under the concentration-time curve from time 0 extrapolated to infinity; AUC_{0-last} = area under the concentration-time curve from time 0 to the last quantifiable time; CI = confidence interval; Geom = geometric;
 IV = intravenous(ly); PK = pharmacokinetic(s); PO = oral; tab = tablet.
 Source: Post-text Table 14.2.3.1

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

Table 128. Absolute Bioavailability Analysis and Comparison of Plasma Sulopenem PK Parameters With Redosing for Cohort 1 – PK Parameter Population – Bilayer Tablet (Fed State)

PK Parameter (Unit)	Fasted 366 mg IV (A)		Fed Bilayer Tab (B)		Ratio of Geom. Mean (B/A) (%)	90% CI for Ratio (%) [2]
	n	Geom. Mean [1]	n	Geom. Mean [1]		
AUC _{0-last} (h*ng/mL)	14	11527.42	14	7308.43	63.4	57.54, 69.85
AUC _{0-inf} (h*ng/mL)	13	11521.39	13	7423.51	64.4	58.23, 71.30

Subject (b) (6) data, as redosing Study Period 2 data for Subject (b) (6), was used to replace Study Period 2 data for Subject (b) (6) in the analysis.
 Bilayer tab = PF-03709270 500 mg + probenecid 500 mg fixed-dose PO tablet; 366 mg IV = sulopenem 366 mg IV infused over 1 h.
 A paired 2-sample t-test was performed on the log-transformed PK parameters.
 A subject must have had a calculable PK parameter in both treatments (test and reference) in order to be included in the analysis for that parameter.
 [1] Geometric means were presented after back transformation to the original scale.
 [2] The 90% CIs were presented after back transformation to the original scale.
 AUC_{0-inf} = area under the concentration-time curve from time 0 extrapolated to infinity; AUC_{0-last} = area under the concentration-time curve from time 0 to the last quantifiable time; CI = confidence interval; Geom. = geometric;
 IV = intravenous(ly); PK = pharmacokinetic(s); PO = oral; tab = tablet.
 Source: Post-text Table 14.2.3.2.2

For Cohort 2, comparison of sulopenem PK parameters following administration of a single 500 mg oral dose of sulopenem etzadroxil in Study Periods 1 and 2 did not show a significant difference (Table 129).

Table 129. Period Effect Analysis of Plasma Sulopenem PK Parameters for Cohort 2

PK Parameter (Unit)	Fasted PIB Period 1 (A)		Fasted PIB Period 2 (B)		Ratio of Geom. Mean (B/A) (%)	90% CI for Ratio (%) [2]
	n	Geom. Mean [1]	n	Geom. Mean [1]		
AUC _{0-last} (h*ng/mL)	8	3440.41	8	3396.21	98.7	94.24, 103.40
AUC _{0-inf} (h*ng/mL)	6	3483.83	6	3385.43	97.2	91.98, 102.67
C _{max} (ng/mL)	8	1633.99	8	1688.77	103.4	85.51, 124.92

PIB = PF-03709270 500 mg PO Powder-in-Bottle.
 A paired 2-sample t-test was performed on the log-transformed PK parameters.
 A subject must have had a calculable PK parameter in both treatments (test and reference) in order to be included in the analysis for that parameter.
 [1] Geometric means were presented after back transformation to the original scale.
 [2] The 90% CIs were presented after back transformation to the original scale.
 AUC_{0-inf} = area under the plasma concentration-time curve from time 0 extrapolated to infinity; AUC_{0-last} = area under the plasma concentration-time curve from time 0 to the last quantifiable concentration; CI = confidence interval; C_{max} = maximum observed plasma concentration; Geom. = geometric; PIB = Powder-in-Bottle; PO = oral; PK = pharmacokinetic.
 Source: Post-text Table 14.2.3.4

As would be anticipated, food intake did not yield a statistically significant effect on the PK of sulopenem following IV administration (Table 130).

Table 130. Effect of Food on Plasma Sulopenem PK Parameters for IV Sulopenem

PK Parameter (Unit)	Fasted 1000 mg IV (A)		Fed 1000 mg IV (B)		Ratio of Geom. Mean (B/A) (%)	90% CI for Ratio (%) [2]
	n	Geom. Mean [1]	n	Geom. Mean [1]		
AUC _{0-last} (h*ng/mL)	12	28443.79	12	24939.51	87.7	83.76, 91.78
AUC _{0-inf} (h*ng/mL)	12	28515.02	12	25015.75	87.7	83.82, 91.82
C _{max} (ng/mL)	12	9154.94	12	8735.74	95.4	91.99, 98.97

1000 mg IV = sulopenem 1000 mg IV infused over 3 h
 A paired 2-sample t-test was performed on the log-transformed PK parameters.
 A subject must have had a calculable PK parameter in both treatments (test and reference) in order to be included in the analysis for that parameter.
 [1] Geometric means were presented after back transformation to the original scale.
 [2] The 90% CIs were presented after back transformation to the original scale.
 AUC_{0-inf} = area under the plasma concentration-time curve from time 0 extrapolated to infinity; AUC_{0-last} = area under the plasma concentration-time curve from time 0 to the last quantifiable concentration; CI = confidence interval; C_{max} = maximum observed plasma concentration; Geom. = geometric; IV = intravenous(ly); PK = pharmacokinetic(s).
 Source: [Post-text Table 14.2.3.10](#)

The PK of oral probenecid following administration of the bilayer tablet (under fed and fasted conditions) and in combination with IV sulopenem are summarized in Table 131. The AUC and C_{max} of probenecid in the fasted state were comparable following administration of the bilayer and commercial tablets to Cohorts 1 and 4, respectively. Administration of the bilayer tablet with a high fat meal decreased probenecid AUC_{0-inf} by 8% and C_{max} by 36%.

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

Table 131. Individual Values and Descriptive Statistics of Plasma Probenecid PK Parameters by Cohort

PK Parameter (Unit)	Statistic	Cohort 1/Period 1 (Fasted Bilayer Tab)	Cohort 1/Period 2 (Fed Bilayer Tab)	Cohort 4/Period 3 (Fasted IV + Prob)
C _{max} (ng/mL)	n	13	13	11
	Mean (SD)	43700.0 (14494.83)	31738.5 (9827.64)	41390.9 (10678.90)
	Geom. Mean (Geom. CV%)	41229.1 (38.2)	30411.5 (30.9)	40198.4 (25.6)
T _{max} (h)	n	13	13	11
	Median (Min, Max)	3.000 (1.00, 10.00)	2.000 (1.50, 6.00)	3.520 (1.02, 6.02)
AUC _{0-∞} (h*ng/mL)	n	13	13	11
	Mean (SD)	257849.6 (89346.61)	213170.0 (53249.13)	209606.1 (33631.88)
	Geom. Mean (Geom. CV%)	244274.3 (35.4)	206793.7 (26.6)	207213.7 (15.9)
AUC _{0-inf} (h*ng/mL)	n	10	7	9
	Mean (SD)	270094.9 (101531.82)	249022.7 (83584.12)	243212.3 (38306.44)
	Geom. Mean (Geom. CV%)	255441.6 (35.6)	237041.1 (35.2)	240525.3 (16.0)
t _{1/2} (h)	n	10	7	9
	Mean (SD)	2.923 (0.828)	3.828 (0.504)	3.779 (0.531)
Lambda z (1/h)	n	10	7	9
	Mean (SD)	0.256 (0.074)	0.184 (0.024)	0.187 (0.029)
CL/F (L/h)	n	10	7	9
	Mean (SD)	2.062 (0.700)	2.218 (0.763)	2.102 (0.335)
V _d /F (L)	n	10	7	9
	Mean (SD)	8.814 (3.912)	11.936 (3.455)	11.354 (1.848)

Subject (b) (6) and Subject (b) (6) shared the same USUBJID IT001-105. (b) (6) Data for Subject (b) (6) referred to the subject with 3 study periods and Subject (b) (6) referred to the same subject in the redosing Study Period 2 in a fed state. Data from all study periods for Subject (b) (6) are excluded from the analyses.

Cohort 1 = Bilayer tab (fasted) + bilayer tab (fed) + 366 mg IV (fasted).
 Cohort 4 = 1000 mg IV (fasted) + 1000 mg IV (fed) + (IV + prob) (fasted).
 Bilayer tab = PF-03709270 500 mg + probenecid 500 mg fixed-dose PO tablet; 366 mg IV = sulopenem 366 mg IV infused over 1 h, 1000 mg IV = sulopenem 1000 mg IV infused over 3 h; IV + prob = sulopenem 1000 mg IV infused over 3 h + probenecid 500 mg PO tablet.
 Geom. CV% = 100*(exp (SD²-1))^{0.5}, where SD was the standard deviation of the log-transformed data.
 AUC_{0-∞} = area under the plasma concentration-time curve from time 0 extrapolated to infinity; AUC_{0-inf} = area under the plasma concentration-time curve from time 0 to the last quantifiable concentration; CL/F = apparent total body clearance following extravascular administration; C_{max} = maximum observed plasma concentration; CV = coefficient of variance; Geom. = geometric; IV = intravenous(iy); lambda z = apparent first-order terminal elimination rate constant; min = minimum; PK = pharmacokinetic; PO = oral; prob = probenecid; SD = standard deviation; tab = tablet; t_{1/2} = terminal elimination half-life; t_{max} = time to C_{max}; V_d/F = apparent volume of distribution following extravascular administration.

Source: Post-text Table 14.2.2.6

ADME

Study A8811006

Study A8811006 evaluated the metabolic profile, safety, tolerability, and routes of excretion of sulopenem in 4 healthy adult male subjects following administration of a single 2000 mg oral dose of [¹⁴C]sulopenem etzadroxil containing ~200 μCi of radiocarbon under fasted conditions. Blood samples were collected pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 5, 8, 12, 24, 48, 72 and 96 h post-dosing into heparin-coated tubes for determination of plasma CP-70429 (sulopenem) concentrations. At these same timepoints, blood samples were also obtained for measurement of total plasma radioactivity. For profiling and identification of [¹⁴C]sulopenem etzadroxil metabolites in plasma, blood samples were obtained pre-dose and at the 0.5, 1, 3, 6 and 12 h post-dosing.

Urine samples were collected pre-dose and pooled (per subject) at intervals of 0-8, 24-48, 48-72, 72-96, 96-120, 120-144 and 144-168 h post-dosing for analysis of total radioactivity and identification of metabolites. The daily urine collections were considered complete if the 24 h urinary excretion of creatinine was 20 to 25 mg/kg. A pre-dose fecal sample was obtained on Day 0 and post-dosing feces were collected (and pooled by subject at 24 h intervals) until up to

168 h. All toilet papers that came into contact with feces was also collected. Subjects were discharged before Day 7 if either ~90% of the administered radioactivity was recovered from urine and feces, or 24 h urine and fecal samples from 2 consecutive collections each had radioactivity levels amounting to ~1% of the total administered radioactivity.

Analytical Methods

Quantitation of sulopenem in plasma was performed using a validated LC-MS/MS method with an LLOQ of 25.0 ng/mL and upper limit of quantification of 5,000 ng/mL. Radioanalysis of plasma and urine sample was conducted using liquid scintillation counting (LSC) for at least 5 min or 100,000 counts. For radioanalysis of feces, samples were combusted and analyzed by LSC. Oxidation efficiency was evaluated daily by analyzing a commercial radiolabeled standard both directly in scintillation cocktail and by oxidation. Acceptance criteria were combustion recoveries of 95 to 105%. The sensitivity of detection of radioactivity was 100 dpm.

For metabolite profiling, plasma samples were pooled per the Hamilton method (i.e. across timepoints for each subject). For urine, samples were pooled from 0-48 h for each subject and for feces, fecal homogenates containing the highest levels of excreted radioactivity (i.e. samples obtained between 0-120 h) were pooled per subject for analysis. Metabolite quantification was performed by measuring the areas of individually separated high-performance liquid chromatography (HPLC) peaks by HPLC with radio-detection. Identification of the metabolites from HPLC column eluent was performed by mass spectrometry.

Results

PK parameters for sulopenem and total radioactivity were determined from plasma concentration-time data. Quantitation of metabolites in biological matrices was expressed as percentage of dose in urine and feces, and percentage of sample for plasma. The mean of total recovered radioactivity was 85.1% (range 80.2 to 95.0%), most of which was recovered within the first 72 h (Table 70). Although the mean total recovered radioactivity was <90%, both urine and fecal samples from 2 consecutive collections had radioactivity levels approximately less than 1% of the total administered dose for all subjects. The percentages of radioactivity recovered in urine and feces were similar, i.e., 44.3% vs. 40.8%, respectively (Table 132).

Table 132. Mean Cumulative Amount ($\pm$ SD) of Total Radioactivity Excreted in Urine and Feces Independently, as Well as Combined, Following a Single Oral Dose of [^{14} C] PF-03709270 in Healthy Male Subjects

Collection Interval (h)	Cumulative Urine Ae (%)	Cumulative Feces Ae (%)	Cumulative Total Ae (%)
0-24	39.3 (7.6)	10.4 (11.3)	49.7
0-48	43.1 (5.6)	17.2 (18.8)	60.3
0-72	44.0 (5.1)	37.7 (6.1)	81.7
0-96	44.2 (5.1)	37.7 (6.1)	81.9
0-120	44.3 (5.0)	40.5 (2.1)	84.8
0-144	44.3 (5.0)	40.7 (1.9)	85.0
0-168	44.3 (5.0)	40.8 (1.8)	85.1

Source: Table 2 of Appendix A14 in Applicant's ISR A8811006
Abbreviations: Ae, amount excreted

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

Reviewer's Comment: By 48 h, 43% of total radioactivity was recovered in urine. Within the first 48 h, fecal recoveries were highly variable; 2 subjects had unusually low fecal recoveries (mean = 3.13%) compared to the other 2 (mean = 31.2%). No dosing or sampling issues were reported that could explain these observations.

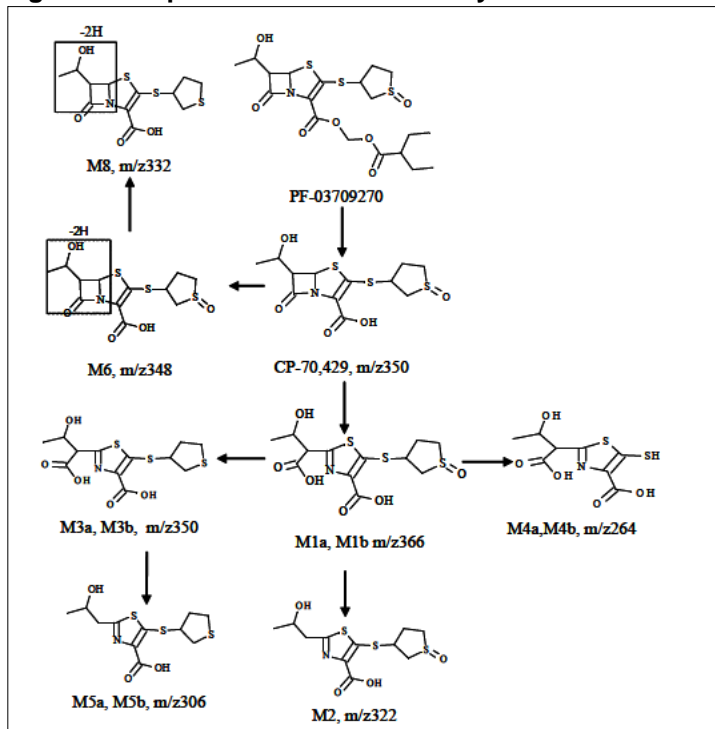
The prodrug, sulopenem etzadroxil, was undetected at any timepoint. The proposed biotransformation pathway of the prodrug is provided in Figure 5. Based on AUC_{0-last} , sulopenem accounted for 32% of circulating plasma total radioactivity (Figure 6) and the mean observed terminal half-life of sulopenem in plasma was 1.1 h. Quantifiable levels of radioactivity were observed in plasma through 96 h post-dose. However, this collection interval was insufficient to estimate the terminal half-life of total radioactivity in plasma. Aside from sulopenem, major circulating metabolites were the 2 diastereomers, M1a and M1b, accounting for 21.8% and 43.6%, respectively. These inactive metabolites are formed by hydrolysis of the sulopenem β -lactam ring (Figure 5). Sulopenem was the major metabolite recovered in urine, accounting for 26.9% of the administered dose (based on 0-48 h pooled urine). In feces, sulopenem only accounted for 3.1% of administered dose (based on 0-120 h pooled feces). In feces, the majority of metabolites are proposed to be derived from sulfoxide reduction by gut microbial activity. In urine, M1a and M1b accounted for 7.4% and 2.5%, respectively, of the administered dose.

Reviewer's Comment: In vitro studies evaluating the stability and release of sulopenem in human blood, and simulated gastric and intestinal fluids provided the following key observations:

- *In human blood, sulopenem concentrations did not exceed ~30% of sulopenem etzadroxil input, indicating possible biotransformation in blood.*
- *Sulopenem etzadroxil was slowly degraded in simulated gastric fluid containing pepsin; however, this did not produce detectable concentrations of sulopenem, suggesting the formation of other degradants.*
- *In enzyme-free simulated intestinal fluid, sulopenem etzadroxil was stable. However, in simulated intestinal fluid containing porcine pancreatin, sulopenem etzadroxil was rapidly degraded.*
- *It was observed that in porcine small intestinal fluid, sulopenem etzadroxil was rapidly degraded, and sulopenem was undetectable.*

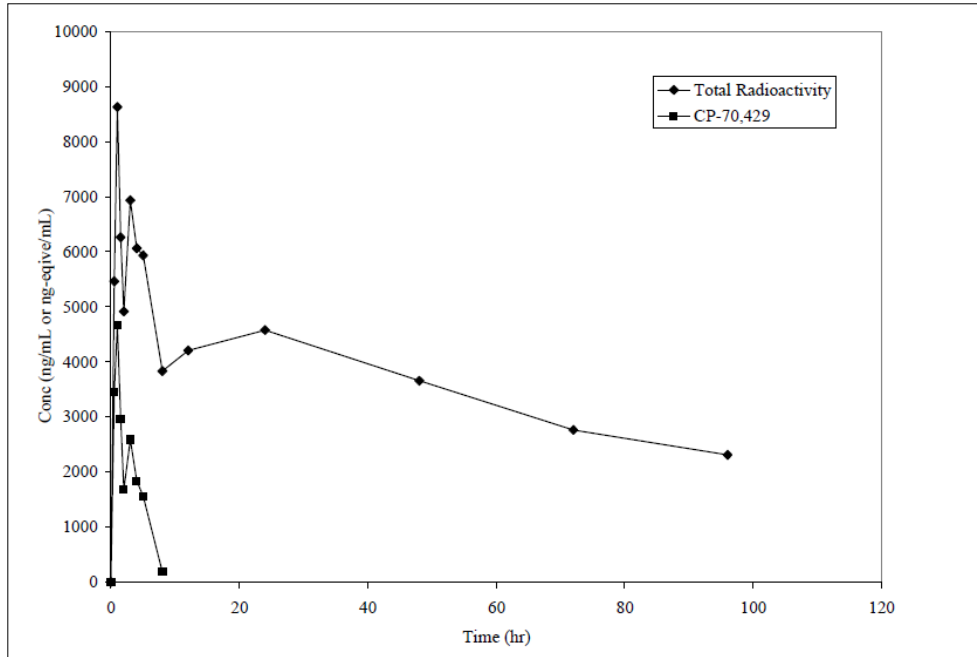
Although these studies did not elucidate the structural identity of the other degradants from the prodrug, the observations lend some additional insight on the fate of sulopenem etzadroxil and sulopenem. The low percentage of plasma radioactivity attributable to sulopenem may be explained in part by substantial and rapid degradation of the prodrug both by gastric enzymes and in blood.

Figure 5. Proposed Metabolic Pathways of PF-03709270 (Sulopenem Etzadroxil) in Humans



Source: Figure 1 of Applicant's ISR A8811006

Figure 6. Mean Plasma Concentration-Time Profiles for [¹⁴C]Sulopenem Etzadroxil and Sulopenem



Source: Figure 3 of Applicant's ISR A8811006

Renal Impairment

Study A8811009 was an open-label, 2-way crossover study which evaluated the PK, safety, and tolerability of IV sulopenem and oral sulopenem etzadroxil in subjects with varying degrees of renal function. Mass balance studies indicated that renal clearance accounted for ~50% of total sulopenem excretion. Because of the apparent importance of renal clearance and the likelihood that sulopenem will be administered in patients with renal impairment, this study was necessary to determine the impact of renal impairment on the PK of sulopenem.

The study was designed to enroll 8 subjects per renal function group (except for the severe renal impairment cohort, where N=5). Subjects were selected based on their estimated CL_{Cr} based on the Cockcroft Gault equation and were classified as follows:

- Group 1: Normal Renal Function (CL_{Cr} >80 mL/min)
- Group 2: Mild Renal Impairment (CL_{Cr} >50 and ≤80 mL/min)
- Group 3: Moderate Renal Impairment (CL_{Cr} ≥30 and ≤50 mL/min)
- Group 4: Severe Renal Impairment (CL_{Cr} <30 mL/min)

Reviewer's Comments: The Applicant's classification of renal function groups was based on the 1998 FDA Guidance on Pharmacokinetics in Patients with Impaired Renal Function – Study Design, Data Analysis, and Impact on Dosing and Labeling. Reclassification of renal function groups according to the 2020 version of the guidance displaces 4 subjects from the mild to the moderate impairment group. Notably, subjects with kidney failure, classified as having CL_{Cr} <15 mL/min were omitted from this study.

Subjects were required to have stable renal function, defined as having 2 serum creatinine values obtained within 7-14 days which differed by ≤20% (for subjects with renal impairment) and ≤25% for subjects with normal renal function. Subjects in Groups 1 through 4 participated in 2 treatment periods with dosing in these periods separated by a washout period of 14 days. Subjects fasted for 8 h before and 3 h after dosing. On Day 1 of each treatment period, subjects received a single dose of study drug as follows:

- Period 1: 800 mg sulopenem 1.5h IV infusion, except in Group 4, where only 1 subject was administered 800 mg and all others received 200 mg sulopenem 1.5 h IV infusion.
- Period 2: 1000 mg (2 X 500 mg) sulopenem etzadroxil immediate release (IR) tablets.

Reviewer's Comment: An interim analysis of PK data from 1 subject in the severe impairment group during the IV dosing period indicated higher sulopenem exposures than predicted. To maintain IV exposures within the Applicant's observed maximally tolerated dose (MTD) for IV dosing, the protocol was amended to administer 200 mg sulopenem for the remaining severely renally impaired subjects.

Subjects with normal renal function who received any prescription drugs, vitamins, and dietary supplements within 7 days or 5 half-lives (whichever was longer) prior to the first dose of study drug were excluded. Renally impaired subjects on any immunosuppressive drugs (including cyclosporine, tacrolimus and sirolimus) and drugs known to affect estimation of CL_{Cr} (including cimetidine, trimethoprim and cibenzoline) were also excluded.

PK Sampling and Assessments

Plasma samples for assessment of sulopenem PK and metabolites were collected pre-dose and at pre-specified times post-dosing. Urine samples were also obtained pre-dose and at intervals of 0-6, 6-12 and 12-24 h post-dose. The following PK parameters were calculated: AUC_{0-24} , AUC_{0-last} , AUC_{0-inf} , C_{max} , T_{max} , V_z , V_z/F , CL/F , CL , CL_r , CL_{nr} , $t_{1/2}$, and Ae_{24} . Plasma protein-binding was not determined in this study. A one-way ANOVA model with group as a fixed effect was used to compare log-transformed AUC_{inf} , AUC_{last} and C_{max} for mild, moderate, and severe renal impairment groups to the normal renal function group.

Reviewer's Comment: Because the plasma protein binding of sulopenem is 11%, changes in protein binding resulting from impaired renal function are expected to be low. Therefore, use of total concentrations is appropriate.

Results

Study Population

With the exception of race and renal status, overall mean demographic characteristics were similar across renal function groups. Seventeen male and twelve female subjects aged 38 to 78 years with a mean BMI of 27.7 kg/m² were enrolled in this study and a majority of the subjects (86.2%) were White. One subject in the severe impairment group discontinued the study after Period 1 (i.e., following administration of IV sulopenem) due to AEs, leaving twenty-eight PK evaluable subjects.

Protocol Deviations

Twelve subjects did not have metabolite assays performed and three subjects (two in the normal renal function group and one in the severe impairment group) did not save all urine for processing.

Reviewer's Comment: Overall, the implications of these protocol deviations are considered to be minor. Consistent with the observations from the single ascending doses (SAD) and multiple ascending doses (MAD) studies, concentrations of 2-EBA and formate were below LLOQ at most timepoints in subjects for whom metabolites were evaluated.

The Applicant did not specify which intervals of urine collection may have been impacted by the lapses in urine collection and analysis. The reviewer's analysis of raw urine PK data for the 2 subjects from the normal renal function group with incomplete urine collection yielded no indication of which (or how many) urine samples were impacted by the protocol deviation. Exclusion of urine PK data from these subjects had only a modest effect, which was an increase in the estimated mean urine concentration for the 0-6 h collection interval from 177.45 µg/mL to 201.2 µg/mL.

Pharmacokinetics

Following administration of a single 1000 mg oral dose of sulopenem etzadroxil, AUC of sulopenem increased 7.4-fold in subjects with severe renal impairment compared to those with normal renal function, and C_{max} increased 2.9-fold (Table 133). Sulopenem half-life increased with worsening renal function, but remained short (i.e. 2.8 h) in subjects with severe renal impairment. Sulopenem etzadroxil was well-tolerated and the incidence of AEs was comparable across renal function groups.

Reviewer's Comment: The bioavailability of sulopenem in this study increased progressively from 22% with normal renal function to 35% in subjects with severe renal impairment. The mechanism underlying this increase is unknown, but may be due to gastroparesis (delayed gastric emptying) observed in severe renal impairment and more commonly, in end-stage renal disease (Kumar 2021). Because sulopenem is poorly soluble (Biopharmaceutical Classification System Class IV), slowed gastric emptying may provide additional time and opportunity for drug dissolution and thus result in absorption of a larger proportion of the administered dose.

It has been reported that renal impairment results in downregulation of renal OAT transporter expression and function (VanWert et al. 2010) and the probenecid USPI notes that probenecid may not be effective when $GFR \leq 30$ mL/min. Because probenecid requires functional OAT transporters to exert its effect, chronic renal impairment diminishes probenecid's effectiveness as an OAT3 inhibitor. Therefore, concomitant administration of probenecid with sulopenem etzadroxil is not expected to further increase sulopenem exposures in subjects with severe renal impairment. The single 1000 mg dose of sulopenem etzadroxil used in the renal impairment study is intended to be the total daily dose for the treatment of uUTI administered 500 mg BID for a total duration of 5 days. Given that sulopenem exposures increase approximately dose proportionally (within the dose range of 400 mg to 2000 mg), administration of a 500 mg dose of sulopenem etzadroxil in subjects with severe renal impairment is anticipated to yield a sulopenem AUC_{0-inf} of ~23995 ng·h/mL. The AUC_{0-inf} at the MTD of 4000 mg from SAD studies is 26900 ng/mL. In MAD studies, dose escalation beyond the starting 2000 mg BID dose of sulopenem etzadroxil was infeasible due to the occurrence of severe adverse events at higher doses. 1200 mg sulopenem etzadroxil in combination with 1000 mg BID probenecid appeared to be well tolerated and yielded moderately higher exposures than the 2000 mg BID sulopenem etzadroxil regimen. Day 10 AUC_{tau} for 1200 mg sulopenem etzadroxil plus 1000 mg was 18800 ng·h/mL, which is 28% lower than the exposure anticipated for 500 mg in subjects with severe renal impairment. Given sulopenem's short half-life even in the setting of severe renal impairment (i.e., 2.75 h) and the short treatment duration of 5 days, the proposed dose is expected to be safe in subjects with severe renal impairment. However, because sulopenem PK has not been evaluated in subjects with $CLcr < 15$ mL/min or subjects on dialysis, the sulopenem etzadroxil/probenecid bilayer tablet cannot be used in this population.

Table 133. PK Parameters Following Oral Administration of 1000 mg Sulopenem Etzadroxil in Renal Function Groups

Parameter	Normal Function N=8	Mild Impairment N=4	Moderate Impairment N=12	Severe Impairment N=4
AUC _{inf} (ng·h/mL)	6523 (20)	13130 (35)	19622 (38)	47990 (32)
AUC ₂₄ (ng·h/mL)	6538 (20)	13222 (37)	19958 (39)	47810 (31)
AUC _{last} (ng·h/mL)	6403 (21)	12903 (35)	19231 (31)	47560 (32)
CL/F (L/h)	153.5 (20)	76.3 (31)	50.9 (42)	20.9 (32)
C _{max} (ng/mL)	2747 (15)	3913 (27)	5136 (29)	7830 (9)
T _{max} (h)	1.5 (0.5-2.0)	1.75 (1.0-3.0)	1.5 (1.0-3.0)	2.5 (1.5 – 4.0)
t _{1/2} (h)	0.84 (14)	1.4 (28)	1.6 (30)	2.75 (30)
CL _r (L/h)	15.47 (12)	7.78 (41)	5.25 (50)	3.29 (99)
Ae ₂₄ (µg)	102700 (20)	103143 (34)	105117 (41)	186400 (68)

Source: Reviewer's analysis

Data presented as Geometric mean (%CV) for all except, median (range) for T_{max}; arithmetic mean (%CV) for t_{1/2}.

Abbreviations: Ae, amount excreted; AUC, area under the curve; CL, clearance; C_{max}, maximum serum concentration; PK, pharmacokinetics; T_{max}, time to maximum concentration

Successful treatment of urinary tract infections is expected to be contingent upon the achievement of adequate concentrations of study drug in urine (Gilbert 2006). Thus, in patients with renal insufficiency, sufficiently high urine concentrations may be difficult to achieve. Where sulopenem is concerned, the cumulative amount excreted in urine following a single oral dose was generally comparable across the renal function groups studied (Table 133).

Reviewer's Comment: CL_r decreases with decreasing renal function, thus the rate of sulopenem elimination is expected to be fastest with normal renal function and slowest with severe renal impairment. This may result in variable sulopenem concentrations across urine collection intervals, which may have implications for efficacy. However, for a short half-life drug like sulopenem, regardless of the differences in sulopenem concentrations at the various urine collection intervals, the resulting amount of sulopenem recovered is similar across renal function groups. Of note, the higher 24 h urine recovery of sulopenem in the severe impairment was driven by a single outlier whose urine recovery was 365000 µg; exclusion of this subjects brings the Ae₂₄ to 126877 µg, which is in closer agreement with the values observed in other renal function groups.

Clinical Drug-Drug Interactions

Study IT001-102 was a Phase 1, randomized, open-label single-dose, 4-way crossover study to evaluate the effect of gallic acid, tannic acid, and probenecid on the plasma PK of sulopenem. Sulopenem was administered as the etzadroxil prodrug in a PIB formulation. Probenecid is an OAT3 inhibitor commonly used in this capacity to increase the plasma exposures of β-lactam antibiotics. Gallic acid and tannic acid are phenolic compounds that are structurally similar to probenecid and suggested to also inhibit OAT3.

Thirteen healthy male and female subjects were enrolled in this study. The 4 treatment periods were as follows:

- Period 1 – 500 mg sulopenem etzadroxil alone
- Period 2 – Sulopenem etzadroxil 500 mg + probenecid 500 mg

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{sulopenem etzadroxil/probenecid}

- Period 3 - Sulopenem etzadroxil 500 mg + gallic acid 400 mg
- Period 4 - Sulopenem etzadroxil 500 mg + tannic acid 400 mg

A 3-period probenecid sub-study was also conducted in 12 additional male and female subjects in which a single 500 mg dose of sulopenem etzadroxil PIB was administered with probenecid. The treatment periods were as follows:

- Period 1 – Concurrent administration with a single 500 mg dose of probenecid
- Period 2 – Staggered with administration of probenecid occurring 1 h after sulopenem etzadroxil dosing
- Period 3 – Concurrent administration of sulopenem etzadroxil with 250 mg probenecid, followed by a second 250 mg dose of probenecid 1 h later.

All doses were administered in the fasted state, and a washout period of 6 days was used between treatment periods. Blood samples for PK analysis were obtained pre-dose and at pre-specified times post-dosing for 12 h. PK parameters estimated included AUC_{0-last} , AUC_{0-inf} , C_{max} , T_{max} , CL/F and $t_{1/2}$. The mean difference between test and reference treatments, geometric mean ratios and their 90% CIs were determined.

Results

No prior medications were reported and concomitant medications were limited to administration of over-the-counter Tylenol severe cold and flu to treat a viral syndrome in one subject. All treatments were well tolerated and of the 3 discontinuations from the primary study, none were due to AEs. An approximately 33% increase in sulopenem AUC was observed when administered with 500 mg probenecid, which exceeds the 5% increase observed with gallic acid (Table 134). Inexplicably, sulopenem exposure with coadministration of tannic acid (a precursor to gallic acid) resulted in a ~12% reduction in sulopenem AUC. Results of the probenecid sub-study indicate that the maximum benefit of probenecid is observed with simultaneous administration of sulopenem etzadroxil (Table 135).

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

Table 134. Statistical Analysis of Sulopenem PK Parameters for Primary Study

Comparison	Parameter (unit)	N	GM		%Ratio (Test/Reference)	90% Confidence Interval of Ratio
			Test	Reference		
Sulopenem etzadroxil + probenecid (Test) versus sulopenem etzadroxil Alone (Reference)	C _{max} (ng/mL)	10	1980	1880	105.55	[95.97; 116.07]
	AUC _{last} (h*ng/mL)	10	5060	3790	133.34	[126.03; 141.07]
	AUC _{inf} (h*ng/mL)	10	5110	3820	133.62	[126.14; 141.54]
	t _{1/2}	10	1.05	0.94	111.34	[98.38; 126.00]
	TAMIC _{0.5}	10	3.70	2.79	132.48	[120.19; 146.04]
	TAMIC _{1.0}	10	2.06	1.45	142.25	[125.03; 161.84]
Sulopenem etzadroxil + gallic acid (Test) versus sulopenem etzadroxil Alone (Reference)	C _{max} (ng/mL)	10	2130	1880	113.50	[103.21; 124.82]
	AUC _{last} (h*ng/mL)	10	3990	3790	105.25	[99.49; 111.36]
	AUC _{inf} (h*ng/mL)	10	4020	3820	105.02	[99.15; 111.25]
	t _{1/2}	10	1.00	0.94	106.36	[93.99; 120.37]
	TAMIC _{0.5}	10	2.72	2.79	97.31	[88.28; 107.26]
	TAMIC _{1.0}	10	1.49	1.45	102.74	[90.31; 116.90]
Sulopenem etzadroxil + tannic acid (Test) versus sulopenem etzadroxil Alone (Reference)	C _{max} (ng/mL)	10	1780	1880	94.71	[86.08; 104.21]
	AUC _{last} (h*ng/mL)	10	3360	3790	88.59	[83.71; 93.76]
	AUC _{inf} (h*ng/mL)	10	3390	3820	88.73	[83.74; 94.02]
	t _{1/2}	10	0.99	0.94	104.88	[92.62; 118.77]
	TAMIC _{0.5}	10	2.63	2.79	94.03	[85.26; 103.70]
	TAMIC _{1.0}	10	1.16	1.45	79.68	[69.99; 90.72]

Source: Table 11-6 of Applicant's ISR IT001-102
 Abbreviations: AUC, area under the curve; C_{max}, maximum serum concentration; GM, geometric mean; PK, pharmacokinetics; TAMIC, time above minimum inhibitory concentration

Table 135. Statistical Analysis of Sulopenem PK for Probenecid Sub-Study

Comparison	Parameter (unit)	N	GM		%Ratio (Test/Reference)	90% Confidence Interval of Ratio
			Test	Reference		
sulopenem etzadroxil + probenecid 500 mg 1 hour later (Test) versus sulopenem etzadroxil + probenecid 500 mg (Reference)	C _{max} (ng/mL)	12	1940	2260	86.19	[72.08; 103.06]
	AUC _{last} (h*ng/mL)	12	4200	4880	86.13	[78.04; 95.07]
	AUC _{inf} (h*ng/mL)	12	4240	4930	86.05	[77.95; 94.99]
	t _{1/2}	12	1.13	1.06	105.83	[97.78; 114.54]
	TAMIC _{0.5}	12	2.89	3.07	94.06	[82.26; 107.55]
	TAMIC _{1.0}	12	1.66	2.04	81.48	[67.58; 98.24]
sulopenem etzadroxil + probenecid 250 mg + probenecid 250 mg 1 hour later (Test) versus sulopenem etzadroxil + probenecid 500 mg (Reference)	C _{max} (ng/mL)	12	1880	2260	83.27	[69.64; 99.57]
	AUC _{last} (h*ng/mL)	12	4460	4880	91.52	[82.92; 101.01]
	AUC _{inf} (h*ng/mL)	12	4510	4930	91.47	[82.86; 100.97]
	t _{1/2}	12	1.13	1.06	105.73	[97.69; 114.43]
	TAMIC _{0.5}	12	3.22	3.07	104.79	[91.65; 119.82]
	TAMIC _{1.0}	12	1.60	2.04	78.71	[65.28; 94.90]

Source: Table 11-10 of Applicant's ISR IT001-102
 Abbreviations: AUC, area under the curve; C_{max}, maximum serum concentration; GM, geometric mean; PK, pharmacokinetics; TAMIC, time above minimum inhibitory concentration

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

Study IT001-101

Study IT001-101 was a Phase 1, randomized, double-blinded, placebo-controlled, multiple dose study of two sulopenem prodrugs (PF-04064900 and PF-03709270) with and without probenecid (under fed and fasted conditions) or gallic acid (under fasted conditions). The study objectives included:

- To evaluate the safety and tolerability of sulopenem prodrugs following multiple dose administration
- To evaluate the effect of food on PK, safety, and tolerability of the sulopenem prodrugs
- To characterize the PK of sulopenem and its prodrugs when coadministered with probenecid
- To estimate the relative oral bioavailability of the sulopenem prodrugs
- To evaluate the effect of different doses of probenecid when co-administered with a single dose of sulopenem etzadroxil
- To evaluate the effect of gallic acid on the PK of sulopenem when coadministered with sulopenem etzadroxil

Two hundred and forty healthy adult male and female subjects aged 20-60 years with CLcr ranging from 91 to 156 mL/min were randomized to 5 treatment groups as indicated in Table 74. Of these, 192 subjects were enrolled in Treatment Groups 1-4 and 48 subjects were enrolled in Treatment Group 5. For both prodrugs, an oral powder in bottle formulation was used.

Blood samples were obtained pre-dosing and at pre-specified times post-dosing to assess sulopenem and sulopenem prodrug PK parameters. Urine samples were also obtained pre-dose and post-dosing on Days 2 and 7 of treatment for assessment of sulopenem urine PK. On Day 1, urine was collected at 2 h intervals through 12 h post-dosing, and at 6 h intervals on Day 7 through 24 h post-dosing. For plasma, parameters of interest included: C_{max} , T_{max} , AUC_{last} , AUC_{tau} on Days 1 and Day 7, $t_{1/2}$ and R_{ac} . For urine, Ae_{24} and CLr were calculated.

Reviewer's Comment: Given that sulopenem etzadroxil (PF-03709270) was the prodrug selected for marketing, and probenecid was the OAT3 inhibitor of choice for the to-be-marketed formulation, the study results will focus on observations made following administration of this prodrug in the presence and absence of probenecid. Additionally, because food effect and bioavailability were determined under IT001-105 for the to-be-marketed formulation, the effect of food on sulopenem exposure will not be covered under the review of this study.

Table 136. Summary of Treatment Groups for Study IT001-101

Treatment Group	Treatment	n	Dose	Dosing frequency	Fed/Fasted	Duration of dosing (days)	For PK
1	A	16	500 mg PF-04064900	BID	Fasted	7	8
	B	16	500 mg PF-03709270	BID	Fasted	7	8
	C	16	PIB placebo	BID	Fasted	7	–
2	A	16	500 mg PF-04064900	BID	Fed	7	8
	B	16	500 mg PF-03709270	BID	Fed	7	8
	C	16	PIB placebo	BID	Fed	7	–
3	D	16	500 mg PF-04064900 + 500 mg probenecid	BID	Fasted	7	8
	E	16	500 mg PF-03709270 + 500 mg probenecid	BID	Fasted	7	8
	F	16	PIB placebo + probenecid	BID	Fasted	7	–
4	D	16	500 mg PF-04064900 + 500 mg probenecid	BID	Fed	7	8
	E	16	500 mg PF-03709270 + 500 mg probenecid	BID	Fed	7	8
	F	16	PIB placebo + probenecid	BID	Fed	7	–
5	G	8	500 mg PF-03709270 + 500 mg probenecid +500 mg probenecid (1 hr postdose)	QD	Fasted	1	8
	H	8	500 mg PF-03709270 + 250 mg probenecid +250 mg probenecid (1 hr postdose)	QD	Fasted	1	8
	I	8	500 mg PF-03709270 + 250 mg probenecid	QD	Fasted	1	8
	J	8	500 mg PF-03709270 + 1000 mg probenecid	QD	Fasted	1	8
	K	8	1000 mg PF-03709270 + 1000 mg probenecid	QD	Fasted	1	8
	L	8	500 mg PF-03709270 + 200 mg gallic acid (if feasible)	QD	Fasted	1	8

BID = twice daily; PIB = powder in bottle; PK = pharmacokinetics
 Source: Study protocol); [Table 14.1.1.1](#), [Table 14.1.1.2](#) and [Table 14.1.1.3](#)

Results

Five subjects were reported as having major protocol deviations, one of which belonged to the sulopenem etzadroxil treatment groups. One subject did not receive study drug on Days 5 through 7 due to the development of angioedema and pruritis, and was subsequently withdrawn from the study. With the exception of this subject, treatments were generally well tolerated. Most TEAEs were graded as mild (97.3%) for Treatment Groups 1-4. In Treatment Group 5, all TEAEs were regarded as mild. No subjects were excluded from either the safety or PK populations for Treatment Groups 1-5.

As observed in Study A8811003, there was an unexplained decline in sulopenem exposure following multiple dose administration of sulopenem etzadroxil that was mitigated by coadministration of probenecid (PK summary under fed conditions provided in Table 137). Consistent with sulopenem's short half-life, accumulation was minimal (based on AUC, $R_{ac} = 1.06$) following multiple dose administration of sulopenem etzadroxil (even in combination

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

with probenecid). The reduction in renal clearance of sulopenem observed with concomitant administration of probenecid was more pronounced following multiple dose administration, and paralleled a greater increase in sulopenem plasma exposure. The cumulative amount of sulopenem recovered over a 24 h period is similar in the presence and absence of probenecid (Table 138).

Table 137. Effect of 500 mg Probenecid on Sulopenem PK Parameters Under Fed Conditions

Day	Sulopenem Etzadroxil	Sulopenem Etzadroxil With Probenecid	
	Geometric Mean	Geometric Mean	GMR
Day 1 (N=8)			
C _{max} (ng/mL)	1731 (39.6)	1616 (34.11)	0.93
AUC _{tau} (ng·h/mL)	4414 (24.9)	6255 (22.14)	1.42
Day 7 (N=8)			
C _{max} (ng/mL)	1179 (22.6)	1587 (21.75)	1.35
AUC _{tau} (ng·h/mL)	3706 (23.8)	6631 (27.70)	1.79

Source: Table 14.2.3.2 and of Applicant's ISR IT001-101

Abbreviations: AUC area under the curve; C_{max}, maximum serum concentration; GMR, geometric mean ratio; PK, pharmacokinetics.

Consistent with observations from Study A8811018, AUC of sulopenem increased an additional ~1.3-fold with coadministration of 1000 mg probenecid compared with 500 mg probenecid (i.e. 5533.9 ng·h/mL vs. 4276 ng·h/mL at Day 7 in the fasted state). Exposures were comparable following coadministration of 250 mg or 500 mg probenecid with sulopenem etzadroxil (4128 vs. 4276 ng·h/mL in the fasted state). Following coadministration of 1000 mg sulopenem etzadroxil and 1000 mg probenecid, C_{max} and AUC exposures were approximately doubled compared with sulopenem exposures observed after coadministration of 500 mg sulopenem etzadroxil and 500 mg probenecid. At a dose of 200 mg, gallic acid yielded a 1.5-fold increase in Day 7 sulopenem exposures (i.e. 3892.1 ng·h/mL vs. 2647 ng·h/mL), which is comparable to the 1.6-fold increase observed with 250 mg of probenecid at Day 7.

Reviewer's Comment: Of note, 250 mg and 1000 mg doses of probenecid were administered under fasted conditions. Hence, comparisons of fold-change in sulopenem exposures at the different probenecid dose levels are only described for fasted conditions. As observed in Study A8811003, there were unexplained reductions in sulopenem exposures following multiple dose administration of sulopenem etzadroxil that were mitigated by concomitant administration of probenecid.

The rationale underlying the greater effect of probenecid on renal clearance at Day 7 compared to Day 1 is unclear given its estimated half-life of 3-4 h.

Table 138. Summary of Sulopenem Cumulative Urine PK Parameters Following Administration of Sulopenem Etzadroxil With and Without Probenecid Day 1 (Left) and Day 7 (Right) under Fed Conditions

	CLr (L/h)	Percent Recovered (%)	Cumulative Amount Recovered (ng)	CLr (L/h)	Percent Recovered (%)	Cumulative Amount Recovered (ng)
PF-03709270						
N	8	8	8	7	8	8
Mean	17.668	15.608	78.038	18.980	13.646	68.230
SD	3.4424	3.2295	16.148	3.0492	3.5211	17.606
%CV	19.48	20.69	20.69	16.07	25.80	25.80
gCV%	19.66	19.68	19.68	16.09	27.02	27.02
Minimum	12.91	12.61	63.06	15.43	9.341	46.70
Median	17.687	14.810	74.050	19.359	13.628	68.142
Maximum	23.60	21.82	109.1	23.26	18.11	90.53
Geometric Mean	17.378	15.340	76.701	18.772	13.239	66.196
PF-03709270 + 500 mg Probenecid						
N	8	8	8	8	8	8
Mean	13.017	16.222	81.112	9.9143	12.952	64.760
SD	3.6194	4.8331	24.166	2.5272	2.0827	10.414
%CV	27.80	29.79	29.79	25.49	16.08	16.08
gCV%	29.45	26.04	26.04	24.58	16.32	16.32
Minimum	8.125	12.70	63.50	7.468	10.35	51.77
Median	12.960	14.836	74.178	9.6520	13.452	67.262
Maximum	17.93	27.22	136.1	14.81	16.33	81.64
Geometric Mean	12.563	15.717	78.584	9.6550	12.805	64.025

gCV% is geometric CV% = $100 \times \sqrt{\frac{s^2}{\bar{x}^2} - 1}$, where s is the standard deviation of the log transformed values.
 Source: Table 14.2.4.1 and Table 14.2.4.2

Abbreviations: CL, clearance; CV, coefficient of variation; PK, pharmacokinetics

Study IT001-103

Study IT001-103 was a Phase 1, 2-period, 4-sequence, parallel study to evaluate the effects of multiple dose administration of itraconazole (a P-gp inhibitor) on the PK of sulopenem in healthy adult subjects. The rationale for this study is that in vitro, sulopenem etzadroxil was identified as a P-gp substrate. This review focuses on the two study cohorts wherein the to-be-marketed bilayer tablet was used.

Thirty-two adult male and female subjects were enrolled in the cohorts of interest. Drug administration was as follows:

- Period 1 - Single 500 mg sulopenem etzadroxil/500 mg probenecid bilayer tablet under fed (Cohort 2) and fasted (Cohort 3) conditions
- Period 2 – Following a washout period of 3 days, 200 mg of itraconazole (2 X 100 mg oral capsules) was administered once daily for 4 days in the fasted state for both Cohorts 2 and 3. On Day 4, itraconazole was coadministered with a single oral dose of the bilayer tablet under fed (Cohort 2) and fasted (Cohort 3) conditions.

Blood samples for PK assessment were obtained pre-dosing and at pre-specified times through 12 h post-dosing. Plasma PK parameters such as AUC_{0-t} , AUC_{extrap} , AUC_{0-inf} , C_{max} and $t_{1/2}$ were summarized descriptively. The C_{max} and AUCs of sulopenem in the bilayer tablet administered alone in the fasted and fed states, respectively, were compared to the exposures achieved in

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

the presence of itraconazole using a paired t-test for the natural-log transformed C_{max} and AUCs.

Reviewer's Comment: The itraconazole dose (200 mg) used in this study provides adequate exposure for P-gp inhibition. Because sulopenem etzadroxil is rapidly hydrolyzed to sulopenem after oral administration, a clinically significant drug-drug interaction (DDI) with P-gp inhibitors such as itraconazole is unlikely.

Results

Sulopenem was generally well tolerated. One subject in Cohort 3 (where the bilayer tablet was administered in the fasted state) discontinued from the study after Period 1 due to AEs.

In both the fed and fasted states, coadministration of itraconazole did not significantly impact the AUC of sulopenem (Table 139 and Table 140). However, in the fed state, the 90% CI for the geometric mean ratio for C_{max} exceeded the 80-125% bioequivalence range.

Table 139. Effect of Itraconazole on Plasma Sulopenem PK Parameters for Cohort 2

PK Parameter (unit)	Study Period 1 Bilayer Tab Fed		Study Period 2 Itraconazole + Bilayer Tab Fed		Ratio GM (Itraconazole + Bilayer Tab Fed)/Fed Bilayer Tab (%)	90% CI for Ratio (%)[2]
	n	GM[1]	n	GM[1]		
C_{max} (ng/mL)	16	2253.77	16	2815.85	124.9	(105.58, 147.85)
AUC _{0-t} (h·ng/mL)	16	6117.37	16	6813.44	111.4	(105.19, 117.93)
AUC _{0-∞} (h·ng/mL)	16	6145.91	16	6843.79	111.4	(105.21, 117.86)
T _{free>MIC0.5} (h)	16	3.89	16	3.90	100.4	(94.32, 106.82)

Note: A paired t-test was performed on logarithm-transformed PK parameters. A subject must have a calculable PK parameter in both treatments (test and reference) in order to be included in the analysis of that parameter.

- Geometric means were the means after back transformation to the original scale.
- The 90% CIs were presented after back transformation to the original scale. Note the study was not powered for statistical inferences, but these ranges are a useful tool for comparison.

AUC = area under the plasma concentration-time curve; AUC_{0-∞} = AUC from time 0 extrapolated to infinity; AUC_{0-t} = AUC from time 0 to time of the last quantifiable concentration; bilayer tab = sulopenem etzadroxil 500 mg + probenecid 500 mg film-coated, fixed-dose combination, bilayer tablet; CI = confidence interval; C_{max} = maximum observed plasma concentration; GM = geometric mean; PK = pharmacokinetic(s); T_{free>MIC0.5} = time above minimum inhibitory concentration.

Source: [Post-text Table 14.2.3.2](#)

Table 140. Effect of Itraconazole on Plasma Sulopenem PK Parameters for Cohort 3

PK Parameter (unit)	Study Period 1 Bilayer Tab Fasted		Study Period 2 Itraconazole + Bilayer Tab Fasted		Ratio GM (Itraconazole + Bilayer Tab Fasted)/Fasted Bilayer Tab (%)	90% CI for Ratio (%)[2]
	n	GM[1]	n	GM[1]		
C_{max} (ng/mL)	15	1770.59	15	1602.33	90.5	(77.47, 105.72)
AUC_{0-t} (h·ng/mL)	15	4141.40	15	4261.86	102.9	(93.51, 113.25)
$AUC_{0-\infty}$ (h·ng/mL)	15	4166.84	15	4296.45	103.1	(93.80, 113.34)
$T_{free>MIC_{0.5}}$ (h)	15	3.03	15	3.23	106.4	(97.02, 116.59)

Note: A paired t-test was performed on logarithm-transformed PK parameters. A subject must have a calculable PK parameter in both treatments (test and reference) in order to be included in the analysis of that parameter.

1. Geometric means were the means after back transformation to the original scale.
2. The 90% CIs were presented after back transformation to the original scale. Note the study was not powered for statistical inferences, but these ranges are a useful tool for comparison.

AUC = area under the plasma concentration-time curve; $AUC_{0-\infty}$ = AUC from time 0 extrapolated to infinity; AUC_{0-t} = AUC from time 0 to time of the last quantifiable concentration; bilayer tab = sulopenem etzadroxil 500 mg + probenecid 500 mg film-coated, fixed-dose combination, bilayer tablet; CI = confidence interval; C_{max} = maximum observed plasma concentration; GM = geometric mean; PK = pharmacokinetic(s); $T_{free>MIC_{0.5}}$ = time above minimum inhibitory concentration.

Source: Post-text Table 14.2.3.3

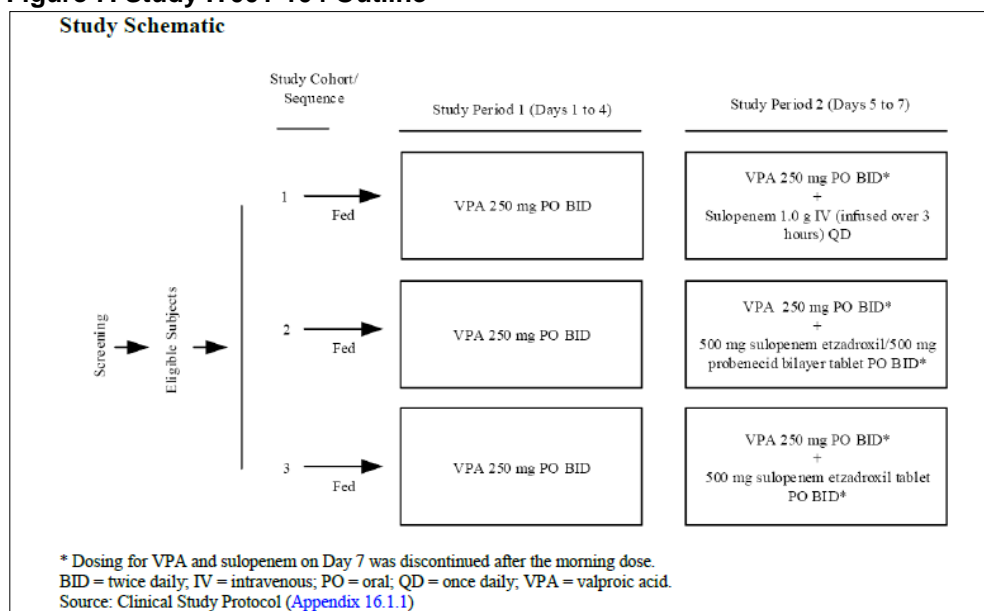
Reviewer's Comment: Because food increases the bioavailability of itraconazole capsules, observations under the fed state are considered the worse-case scenario of P-gp inhibition. Interestingly, the 90% CI of the geometric mean ratio for C_{max} exceeded the upper bounds of the 80-125% bioequivalence range when itraconazole was coadministered with the bilayer tablet in the fed state but fell below the lower bounds of the bioequivalence range in the fasted state. The reasons underlying these observations for C_{max} in the fed and fasted states for the bilayer tablet are unknown. When itraconazole was administered with a single dose of IR sulopenem etzadroxil under fed conditions in Cohort 4 (data not shown), the 90% CI for C_{max} , AUC_{0-t} and AUC_{0-inf} were all within the 80-125% bioequivalence range. The increase in C_{max} for the bilayer tablet under fed conditions is not considered to be clinically significant (from a safety perspective) given that sulopenem etzadroxil doses up to 4000 mg (C_{max} = 6750 µg/mL) were well tolerated in SAD studies.

Study IT001-104

Study IT001-104 was a Phase 1, open-label, 2-period, 3-sequence, parallel study designed to evaluate the effects of multiple-dose administration of IV sulopenem, sulopenem etzadroxil/probenecid bilayer oral tablet or sulopenem etzadroxil oral tablet on the steady-state PK profile of valproic acid in healthy adult subjects. The rationale underpinning this study is the observation that carbapenems may decrease the plasma concentrations of valproic acid.

Each of the 3 cohorts enrolled 10 healthy adult male volunteers. The study schematic is illustrated in Figure 7 below.

Figure 7. Study IT001-104 Outline



Source: Figure 1 of Applicant's ISR IT001-104

Valproic acid, 250 mg, was administered orally 12 h apart for 7 days. Sulopenem was administered BID for 3 days as IV, etzadroxil bilayer tablet and etzadroxil IR tablet from Days 5 through 7 of the study. All oral doses were administered in the fed state.

Reviewer's Comment: The valproic acid dose in this study is clinically relevant (consistent with the initial dose for patients weighing 55 to 87.9 lbs). Because high fat food increases the oral bioavailability of sulopenem, food intake allows assessment of the effect of highest possible sulopenem exposures for oral administration on valproic acid PK.

Blood samples for valproic acid PK assessment were obtained as follows:

- Day 1: pre-dosing
- Day 4: 72, 73, 74, 75, 76, 77, 78, 80, and 84 h post-Day 1 dosing
- Day 7: 144, 145, 146, 147, 148, 149, 150, 152, and 156 h post-Day 1 dosing

Plasma PK parameters determined for valproic acid included AUC_{0-tau} , AUC_{0-last} , C_{maxss} , C_{minss} , C_{avg} , T_{max} and $t_{1/2}$. For sulopenem, PK samples were obtained pre-dose and through 12 h post-dosing on Days 5 (Cohorts 2 and 3 only) and 7. Sulopenem plasma PK parameters such as AUC_{0-t} , AUC_{extrap} , AUC_{0-inf} , C_{max} , T_{max} and $t_{1/2}$ were also summarized descriptively. A paired t-test was performed on natural log-transformed values for valproic acid PK parameters (in the presence and absence of valproic acid). The geometric mean ratio and accompanying 90% CI for valproic acid PK parameters with and without sulopenem were also determined.

Results

Valproic acid administered alone or in combination with the various sulopenem formulations was well tolerated. The incidence of TEAEs was low across all 3 cohorts; diarrhea was only observed when valproic acid was administered with the sulopenem etzadroxil IR tablet in

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

Cohort 3. The severity of all TEAEs was considered mild. There was only 1 subject discontinuation from the study and it was unrelated to the occurrence of AEs.

Consistent with observations involving carbapenems, administration of multiple doses of 500 mg sulopenem etzadroxil with valproic acid decreased valproic acid plasma AUC_{0-tau} and C_{maxss} (Table 141) by approximately 25% and 19%, respectively. Similarly, coadministration of 1 g IV sulopenem with valproic acid resulted in reductions of valproic acid plasma AUC_{0-tau} and C_{maxss} of 33% and 28%, respectively. However, when the bilayer tablet containing 500 mg probenecid was administered, the reductions in AUC_{0-tau} and C_{maxss} were 9% and 7%, respectively, and the 90% CI of the geometric mean ratio fell within the bioequivalence bounds of 80 to 125% (Table 142).

Reviewer's Comment: The exact mechanism by which carbapenems decrease valproic acid plasma concentrations is unknown, but is thought to involve interference with the conversion of valproic acid glucuronide back to active valproic acid and/or activation of UGT to promote glucuronidation. The mechanism by which probenecid counters the effect of sulopenem on valproic acid may be due to probenecid's inhibition of UGTs and thus glucuronidation.

Table 141. Effect of Sulopenem Etzadroxil Alone on Valproic Acid Plasma PK Parameters

PK Parameter (Unit)	Study Period 1 VPA		Study Period 2 VPA + Etzadroxil Tablet		Ratio Geometric LS Mean ((VPA + Etzadroxil Tablet)/VPA) (%)	90% CI for Ratio (%) [2]
	n	GM [1]	n	GM [1]		
AUC_{0-t} (h·µg/mL)	10	559.30	10	442.41	79.1	(74.13, 84.41)
AUC_{0-tau} (h·µg/mL)	6	540.77	6	405.87	75.1	(69.00, 81.64)
C_{maxss} (µg/mL)	10	57.74	10	46.69	80.9	(75.24, 86.89)
Swing	10	0.48	10	0.56	115.4	(103.92, 128.10)
DOF	6	0.42	6	0.48	113.9	(98.36, 131.91)

Note: Cohort 3 = VPA versus VPA + etzadroxil tablet. Valproic acid alone is the reference group and VPA + etzadroxil tablet is the test group.
 Note: A paired t-test was performed on logarithm-transformed PK parameters. A subject must have had a calculable PK parameter in both treatments (test and reference) in order to be included in the analysis of that parameter.
 1. Geometric means are the means after back transformation to the original scale.
 2. The CIs are presented after back transformation to the original scale.
 AUC_{0-t} = area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration;
 AUC_{0-tau} = area under the plasma concentration-time curve from time 0 extrapolated to the dosing interval, Tau;
 C_{maxss} = maximum observed plasma concentration during a dosing interval; CI = confidence interval; DOF = degree of fluctuation; etzadroxil tablet = sulopenem etzadroxil 500 mg tablet; GM = geometric mean; LS = least squares;
 PK = pharmacokinetic; VPA = valproic acid.
 Source: Post-text Table 14.2.3.3

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

Table 142. Effect of Sulopenem Etzadroxil/Probenecid Combination on Valproic Acid Plasma PK Parameters

PK Parameter (Unit)	Study Period 1 VPA		Study Period 2 VPA + Bilayer Tablet		Ratio Geometric LS Mean ([VPA + Bilayer Tablet]/VPA) (%)	90% CI for Ratio (%) [2]
	n	GM [1]	n	GM [1]		
AUC _{0-t} (h·µg/mL)	9	525.19	9	480.97	91.6	(86.71, 96.72)
AUC _{0-∞} (h·µg/mL)	6	530.51	6	483.25	91.1	(83.65, 99.19)
C _{maxSS} (µg/mL)	9	54.18	9	50.41	93.0	(88.78, 97.50)
Swing	9	0.49	9	0.56	114.1	(88.37, 147.34)
DOF	6	0.38	6	0.43	111.2	(86.74, 142.64)

Note: Cohort 2 = VPA versus VPA + bilayer tablet. Valproic acid alone is the reference group and VPA + bilayer tablet is the test group.
 Note: A paired t-test was performed on logarithm-transformed PK parameters. A subject must have had a calculable PK parameter in both treatments (test and reference) in order to be included in the analysis of that parameter.
 1. Geometric means are the means after back transformation to the original scale.
 2. The CIs are presented after back transformation to the original scale.
 AUC_{0-t} = area under the plasma concentration-time curve from time 0 to time of the last quantifiable concentration;
 AUC_{0-∞} = AUC from time 0 extrapolated to the dosing interval, Tau; bilayer tablet = sulopenem etzadroxil
 500 mg + probenecid 500 mg film-coated, fixed-dose combination, bilayer tablet; CI = confidence interval;
 C_{maxSS} = maximum observed plasma concentration during a dosing interval; DOF = degree of fluctuation; GM = geometric mean; LS = least squares; PK = pharmacokinetic; VPA = valproic acid.
 Source: Post-text Table 14.2.3.2

Study A8811018

Study A8811018 was a Phase 1 Study with two objectives: 1) to evaluate the safety, tolerability, and PK of sulopenem etzadroxil with gastric pH modifiers and b) to evaluate the effect of probenecid doses of 500 and 1000 mg on sulopenem exposure when coadministered with sulopenem etzadroxil.

Study participants were divided into 2 Cohorts. Eight healthy male and female volunteers were enrolled in Cohort 1 and nine male subjects were enrolled in Cohort 2 for the probenecid study. The drug administration schedule for the 2 cohorts is summarized in Table 143. All treatments were administered in the fasted state. Cohort 1 was administered a 600 mg IR tablet formulation while Cohort 2 received a 500 mg IR tablet formulation.

Table 143. Drug Administration Schedule for Study Cohorts

Cohort	Period 1	Period 2	Period 3
1	1200 mg PF-03709270 + 600 mg aluminum hydroxide	1200 mg PF-03709270	40 mg pantoprazole once daily for 4 days (Days -2, -1 0, 1), on Day 1 1200 mg PF-03709270
2	1000 mg PF-03709270 + 500 mg probenecid	1000 mg PF-03709270 + 1000 mg probenecid	

Source: Table S1 of Applicant's ISR A8811018

Blood samples for the assessment of sulopenem PK in plasma were collected pre-dose and at pre-specified times after administration of sulopenem etzadroxil. Urine was collected for the analysis of urine sulopenem and creatinine over a 12 h period for Cohort 2 only. PK parameters estimated included AUC_{0-inf}, AUC_{0-last}, C_{max}, T_{max}, t_{1/2}, Ae₁₂ and CL_r.

For Cohort 1, natural log transformed sulopenem AUC_{0-last} and C_{max} were analyzed using a mixed effect model with treatment as a fixed effect and subject as a random effect.

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

A single dose of 1200 mg sulopenem etzadroxil was the reference treatment and a single dose of 600 mg aluminum hydroxide +1200 mg sulopenem etzadroxil or a single dose of 40 mg pantoprazole +1200 mg sulopenem etzadroxil were the test treatments. A similar model was used for Cohort 2, where a single dose of 1000 mg sulopenem +500 mg probenecid was the reference and a single dose of 1000 mg sulopenem +1000 mg probenecid was the test treatment.

Results

All subjects in both cohorts completed the study and all drug treatments were well tolerated. Following administration of aluminum hydroxide with sulopenem etzadroxil, sulopenem plasma AUC and C_{max} decreased by 14% and 19%, respectively, and the resulting 90% CI of the geometric mean ratio fell outside the bioequivalence range of 80 – 125% (Table 144). However, when coadministered with pantoprazole, the 90% CI of the geometric mean ratio for both AUC and C_{max} fell within the bioequivalence range.

Table 144. Summary of Statistical Analysis for Administration of Sulopenem Etzadroxil With Gastric pH Modifiers

Parameter (units)	Ratio	Ratio
Aluminum Hydroxide		
AUC _{0-last} (ng·h/mL)	85.67	78.59, 120.07
C_{max} (ng/mL)	80.85	66.04, 98.98
Pantoprazole		
AUC _{0-last} (ng·h/mL)	97.24	82.99, 124.38
C_{max} (ng/mL)	101.60	82.99, 124.38

Source: Table S6 of Applicant's ISR A8811018

Abbreviations: AUC, area under the curve; C_{max} , maximum serum concentration.

Reviewer's Comment: The significant reduction in sulopenem AUC and C_{max} observed with the administration of aluminum hydroxide appears to be driven by lower sulopenem exposures with concomitant administration of the antacid for 1 subject. The Applicant does not offer an explanation for the lower exposures observed for sulopenem etzadroxil + aluminum hydroxide in this subject. When data from the subject are excluded from the analysis, the reduction in AUC and C_{max} improve to 7% and 14%, respectively. According to the FDA guidance on evaluating gastric pH-dependent drug interactions, results of an interaction study with a proton-pump inhibitor (PPI) present the worst-case scenario for pH-dependent DDIs due to the long-lasting effect of this class on gastric pH. Therefore, a negative result with a PPI, as is the case here, is indicative of a lack of pH-dependent DDI.

The main goal of the probenecid portion of the study was to inform probenecid dose selection for use in combination in a fixed-dose tablet. The doses evaluated (500 mg and 1000 mg) are consistent with the standard doses of probenecid generally recommended for coadministration with β -lactams to improve their plasma exposures. Both sulopenem AUC and C_{max} increased approximately 1.4-fold with a 2-fold increase in the dose of probenecid (Table 145). The amount of sulopenem recovered in urine over 12 h decreased by 9% with a 2-fold increase in the dose of probenecid.

Table 145. Sulopenem PK Parameters Following Coadministration of Sulopenem Etzadroxil With Probenecid Doses of 500 mg and 1000 mg

Pharmacokinetic Parameters (units)	PF-03709270 1000 mg + Probenecid 500 mg	PF-03709270 1000 mg + Probenecid 1000 mg
N	9	9
n	9	9
AUC _{inf} ^a (ng•hr/mL)	6060 (24)	8450 (21)
AUC _{last} ^a (ng•hr/mL)	5950 (24)	8340 (22)
C _{max} ^a (ng/mL)	1890 (32)	2690 (20)
T _{max} ^b (hr)	2.00 [1.00-3.00]	1.50 [1.00-4.05]
t _½ ^c (hr)	1.02 (0.152)	1.25 (0.136)
TAMIC _{0.5} ^c (hr)	4.35 (0.826)	4.86 (0.766)
TAMIC _{1.0} ^c (hr)	3.00 (0.734)	3.53 (0.615)
Ae ₁₂ ^c (ug)	69900 (21500)	63700 (22800)
CL _r ^c (L/hr)	11.6 (3.14)	7.57 (2.42)

N = Number of subjects; n = Number of subjects contributing to the mean for AUC_{inf} and t_½

^a geometric mean (CV%); ^b median (range); ^c arithmetic mean (standard deviation)

Source: Table S7 of Applicant's ISR A8811018

Abbreviations: Ae, total amount excreted; AUC, area under the curve; CL, clearance; C_{max}, maximum serum concentration; T_{max}, time to maximum concentration

Summary of In Vitro ADME

Absorption

Studies 17IT001-2017_03_14_Iterum Therapeutics_{(b) (4)} and 17IT002-2017_06_30_Iterum Therapeutics_{(b) (4)}-00 evaluated the permeability of sulopenem, PF-03709270 (sulopenem etzadroxil) and PF-04064900 across Caco-2 cell monolayers in the presence and absence of probenecid. Sulopenem's permeability was 0.08 to 0.09 x 10⁻⁶ cm/s at concentrations of 20 μM to 1mM. The permeability of sulopenem etzadroxil was also low in the A-B direction (0.07 to 0.31 x 10⁻⁶ cm/s) and moderate in the opposite direction (3.59 to 8.73 x 10⁻⁶ cm/s) at concentrations of 20 μM to 1mM. Therefore, the efflux ratio for sulopenem etzadroxil was >2. The addition of probenecid had no effect on P_{app} or efflux ratio of sulopenem or sulopenem etzadroxil.

Distribution

Study DM2004-070429-013 evaluated the extent of sulopenem binding to human plasma proteins at concentrations of 1, 10, 50 and 100 μg/mL using ultrafiltration. Sulopenem plasma protein binding was low, with bound (unbound) fraction of 10.7 (0.893±0.200) and was concentration-independent over the range of 1 to 100 μg/mL.

Metabolism

CYP450 and UGT Reaction Phenotyping

The metabolic stability of sulopenem in the presence of human recombinant UGTs (UGT1A1, 1A3, 1A4, 1A6, 1A9, 2B7 and 2B15) and CYPs (1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 3A4 and 3A5) at concentrations of 1 and 10 μM in Study Iterum-03-09Aug2019. No metabolism was observed when sulopenem was incubated with recombinant UGT or CYP enzymes. For unspecified reasons, the Applicant states that in vitro metabolism of sulopenem could not be characterized sufficiently using human liver microsomes or hepatocytes. No in vitro metabolism studies were conducted for sulopenem etzadroxil because it is expected to be rapidly hydrolyzed to the active sulopenem moiety.

Reviewer's Comment: The review team postulates that the inability to illustrate in vitro metabolism of sulopenem using human liver microsomes or hepatocytes is because sulopenem may be susceptible to non-CYP and UGT-mediated biotransformations in these in vitro test systems. Thus, the Applicant's use of recombinant CYP and UGT enzymes elucidates the involvement (or lack thereof) of these enzymes in the disposition of sulopenem.

In Vitro Drug-Drug Interaction Studies

CYP Inhibitory and Induction Potential

Studies DM2006-070429-029 and 17081086ITX evaluated the inhibitory potential of sulopenem and sulopenem etzadroxil on pooled human liver microsomal activity of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP3A4/5. Sulopenem was found to not be a direct or time-dependent inhibitor of CYP isoforms tested up to 150 μM . Sulopenem etzadroxil was found to be a time-dependent inhibitor of CYP3A4/5, but an IC_{50} could not be calculated within the concentration range studied, and was estimated to be $>150 \mu\text{M}$. The potential of sulopenem to induce the activities of CYPs 1A2, 2B6 and 3A4 were evaluated in Study 17081087ITX using pooled human hepatocytes. No induction of enzyme activity was observed using sulopenem concentrations of 0.07 to 150 μM . The induction potential of sulopenem etzadroxil was not evaluated.

Transporter Studies

Studies 17081088ITX and Iterum-02-08-Mar2019-A1 evaluated sulopenem and sulopenem etzadroxil both as substrates and inhibitors of human BSEP, P-gp, MRP2, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1 and OCT2 transporters. Bidirectional permeability was evaluated using MDCKII or HEK293 cells expressing the respective uptake transporters. Sulopenem was a substrate of OAT3 with over 34-fold accumulation in cells expressing OAT3 and inhibitor of OAT1 with $\text{IC}_{50}>150 \mu\text{M}$. Sulopenem was neither a substrate or inhibitor of BCRP, P-gp, BSEP, MRP2, MATE1, MATE2-K, OAT1B1B1, OAT1P1B3, OCT1 or OCT2. Sulopenem etzadroxil was a substrate and inhibitor of P-gp ($\text{IC}_{50}=1.91 \mu\text{M}$) and BCRP ($\text{IC}_{50}=20.4 \mu\text{M}$), and an inhibitor of OAT1 ($\text{IC}_{50}=93.6 \mu\text{M}$) and OAT3 ($\text{IC}_{50}=34.8 \mu\text{M}$). However, inhibition of OAT1 and

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

OAT3 by sulopenem etzadroxil is not expected to be clinically relevant given that it is rapidly hydrolyzed following oral administration and not detected systemically.

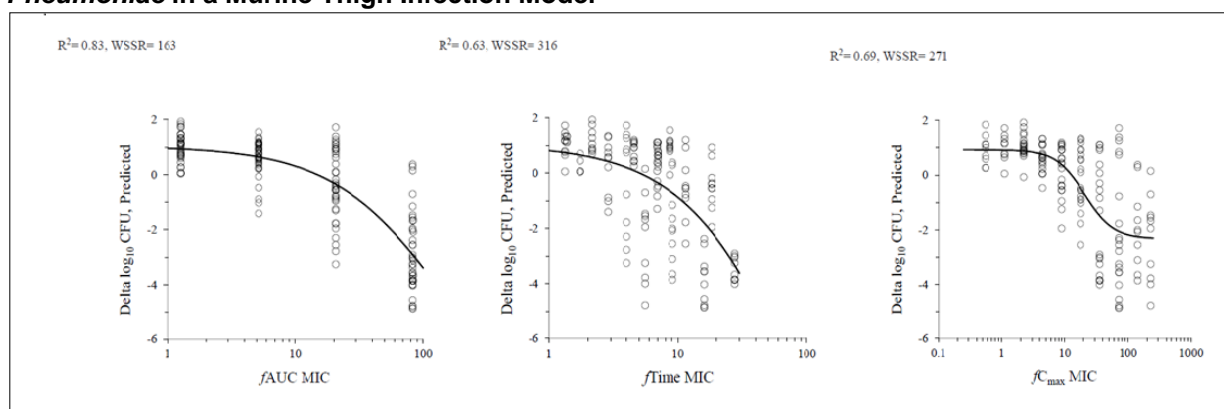
Reviewer's Comment: At 150 μM (i.e. 52.4 $\mu\text{g}/\text{mL}$), only 34% OAT1 inhibition was observed in vitro for sulopenem. Given the sulopenem C_{max} (for the bilayer tablet) in fed state = 2.66 $\mu\text{g}/\text{mL}$ and $\text{IC}_{50} > 52.4 \mu\text{g}/\text{mL}$, $I_{\text{max,u}}/\text{IC}_{50} \ll 0.1$. Therefore, sulopenem is not likely to be an OAT1 inhibitor at clinically relevant concentrations.

In Study Iterum-02-08-Mar2019-A1, probenecid was evaluated for interaction with efflux transporters, BCRP, BSEP, P-gp and MRP2. Probenecid was a substrate of BCRP and inhibitor of BSEP (only 28% inhibition observed at 250 μM) and BCRP ($\text{IC}_{50} = 814 \mu\text{M}$).

Identification of PK/PD Index of Sulopenem

The pharmacokinetics/pharmacodynamics (PK/PD) index of sulopenem was evaluated with dose-fractionation in a murine thigh infection model using 2 strains each of *E. coli*, *K. pneumoniae*, *S. pneumoniae* and *S. pyogenes* with sulopenem minimum inhibitor concentration (MIC) in the range of 0.0078 – 1 $\mu\text{g}/\text{mL}$. Immunosuppressed mice were used in studies involving *E. coli* while all other dose-fractionation studies were conducted in immunocompetent mice. Sulopenem total daily doses in the range of 3.125 – 200 mg/kg/day were administered according to q3h, q6h, q12h and q24h dosing regimens 24h post-inoculation of murine thigh muscles to delineate the PK/PD driver of sulopenem's antibacterial activity. Accompanying PK studies were conducted for sulopenem single doses of 4.69, 18.75, 75 and 300 mg/kg. Because protein binding of sulopenem in mouse plasma was determined to be 0.01 and concentration independent, adjustment of PK parameters for protein binding was negligible. The correlation of AUC/MIC , $C_{\text{max}}/\text{MIC}$, and $T > \text{MIC}$ to the PD data (i.e., change in $\log_{10}$ CFU) was determined by non-linear least-squares regression analysis using a Hill-type model. Based on the coefficient of determination (r^2), results presented for *S. pneumoniae* in Figure 8 suggest that AUC/MIC is the PK/PD index that best correlated with sulopenem's antibacterial activity.

Figure 8. Determination of PK/PD Index of Sulopenem From Dose Fractionation Studies Using *S. Pneumoniae* in a Murine Thigh Infection Model



Source: Figure 2 of Applicant's Response to Clinical Pharmacology IR dated February 11th 2021
Abbreviations: MIC, minimum inhibitory concentration; PD, pharmacodynamic; PK, pharmacokinetics

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

Reviewer's Comment: Although the Applicant's Summary of Clinical Pharmacology described 2 sets of nonclinical PK/PD studies, the original NDA submission provided only an abbreviated nonclinical PK/PD study report (for Study 810-00081) which offered limited information on PK/PD index and target determination in a murine thigh infection model. Therefore, an IR (dated 02/11/2021) was issued to the Applicant, seeking clarification on which of the studies described in the Summary of Clinical Pharmacology was used to inform PK/PD targets for probability of target attainment (PTA) analysis. In response to this IR, the Applicant provided an unpublished manuscript, an abstract presented at 2 scientific conferences and laboratory notebook pages. Per the Applicant, information contained in the report for Study 810-00081, abstract and laboratory notebook pages were integrated into the unpublished manuscript. Therefore, the manuscript served as the Applicant's primary source of information for the identification of a PK/PD index and target for sulopenem.

*Per the reviewer's assessment, the integrity of PK and PD information provided by the Applicant is questionable due to discrepancies in the data and results summarized in the Study 810-00081 report, abstract and unpublished manuscript. Key issues identified by the reviewer include: a) incongruity of the best PK/PD index for sulopenem suggested by Study 810-00081 and the unpublished manuscript, b) differences in values of PK parameters reported in the abstract compared to the unpublished manuscript, and c) inconsistencies in the methodology described within the unpublished manuscript. Study report 810-00081 briefly outlined dose-fractionation studies conducted with a single isolate each of *K. pneumoniae* and *S. pneumoniae* in a murine thigh infection model. In this report, $T > MIC$ was identified as the relevant PK/PD driver for sulopenem's activity, which is consistent with the known PK/PD driver for other penem (i.e. β -lactam) antibacterial drugs. Although data from Study 810-00081 were purportedly integrated into the unpublished manuscript, results presented in the manuscript conclude that AUC/MIC (and not $T > MIC$) is the relevant PK/PD driver. The Applicant's explanation for these contradicting observations is that both concentration and $T > MIC$ are relevant to sulopenem's activity. Additionally, inconsistencies in the values of PK parameters summarized in the abstract compared to the manuscript render the PK data unreliable. Ultimately, a dearth of details, questionable data and ambiguities regarding study methodology and PK/PD analyses render the results of the nonclinical PK/PD studies uninterpretable. Because raw data from these studies were not available, the reviewer was unable to conduct independent analyses to confirm $T > MIC$ as the PK/PD driver of sulopenem's antibacterial activity.*

Determination of PK/PD Target of Sulopenem

In an unconventional approach, the previously described dose-fractionation studies were also used by the Applicant to suggest PK/PD targets for the pathogens evaluated. Individual estimates of $T > MIC$ values for each isolate by dosing frequency are summarized in Table 84. For PTA analyses, the Applicant computed mean $T > MIC$ values of 17% and 20% as the targets required for net stasis and 1-log_{10} CFU reduction, respectively across Gram negative species (Table 146).

Table 146. Sulopenem PK/PD Endpoint Summary of TAMIC Estimates Using q3h, q6h, q12h and q24h Dosage Regimens in Immunocompetent (IC) or Immunosuppressed (IS) Thigh Infection Model

Strain (MIC)	IC/IS	Regimen	Stasis	1-log ₁₀ Reduction
<i>K. pneumoniae</i> 1116 (0.5 µg/mL)	IC	q3h	27.0	30.9
		q6h	13.7	16.8
		q12h	8.00	12.0
		q24h	3.56	4.50
<i>K. pneumoniae</i> 1108 (0.0312 µg/mL)	IC	q3h	32.1	38.4
		q6h	17.3	21.2
		q12h	8.10	10.4
		q24h	4.88	6.15
<i>E. coli</i> 1122 (0.078 µg/mL)	IS	q3h	31.3	43.7
		q6h	18.7	25.1
		q12h	9.21	12.7
		q24h	NC	NC
<i>E. coli</i> 0266 (0.039 µg/mL)	IS	q3h	40.4	44.6
		q6h	24.1	26.5
		q12h	13.7	15.6
		q24h	8.12	9.45
Mean (gram-negative pathogens)			16.6	20.3

Source: Table 2 of Applicant's Response to Clinical Pharmacology IR dated February 11th 2021

Abbreviations: PD, pharmacodynamics, PK, pharmacokinetics; TAMIC, time above minimum inhibitory concentration

Reviewer's Comment: Although the Applicant failed to show definitively that $T > MIC$ best predicted sulopenem's antibacterial activity, the unpublished manuscript summarized the magnitude of $T > MIC$ required for various PD endpoints. Of note, the Applicant's results indicate that larger magnitudes of $T > MIC$ were required with increased dosing frequency, which is inconsistent with $T > MIC$ being the driver of antibacterial activity. Additionally, $T > MIC$ values were inappropriately averaged across different experimental conditions (i.e., immunocompetent vs. immunosuppressed murine models) and pathogens. Interestingly, the values suggested for net stasis and 1-log₁₀ CFU reduction approached those described for other carbapenems (i.e., 20-30% $T > MIC$). Nonetheless, because these data (and ensuing results) are questionable, the PK/PD targets from these studies cannot be used for PTA analyses.

Nonclinical PK/PD studies were also conducted using a single strain each of *K. pneumoniae* and *S. pneumoniae* to compare the magnitude of $T > MIC$ for sulopenem and meropenem required to achieve net stasis, 1-log₁₀, 2-log₁₀ CFU reduction and EC₈₀ in an immunosuppressed thigh infection model. Using a q6h dosing frequency and doses of 3.125 – 200 mg/kg/day for both meropenem and sulopenem against *K. pneumoniae*, similar $T > MIC$ values were required to achieve the stated PD endpoints for meropenem and sulopenem as shown in Table 147.

Table 147. PK/PD Summary – TAMIC Estimates for q6h Regimens of Sulopenem or Meropenem vs. *K. Pneumoniae* 1116 in an Immunosuppressed Thigh Infection Model

Compound (MIC)	Regimen	PK/PD endpoints			
		Stasis	1-log kill	2-log kill	EC ₈₀
Sulopenem (0.5 µg/mL)	q6h	21.7 (2.28)	23.3 (1.74)	25.2 (1.70)	30.2 (14.4)
Meropenem (0.125 µg/mL)	q6h	28.2 (1.11)	29.6 (1.05)	31.0 (2.89)	46.0 (45.2)

Source: Table 4 of Applicant's Response to Clinical Pharmacology IR dated February 11th 2021
Abbreviations: EC80m 80% effectiveness concentration; PD, pharmacodynamics, PK, pharmacokinetics; TAMIC, time above the minimum inhibitory concentration

Reviewer's Comment: The method described in the manuscript for this study indicated that comparisons of $T > MIC$ estimates for meropenem and sulopenem were conducted in both immunocompetent and immunosuppressed murine thigh infection models, yet results were described solely for studies in immunosuppressed mice. While the $T > MIC$ targets identified for meropenem (and sulopenem) are consistent with the literature values for carbapenems, the validity of these values cannot be ascertained due to concerns surrounding the reliability of the data and uncertainties regarding the PK/PD analyses used to inform these values.

Population PK Analysis

Review Summary

The Applicant's population PK (PopPK) analysis reasonably describes the time-concentration profiles of sulopenem in healthy subjects and subjects with uUTI. Parameters for clearance were estimated with acceptable relative standard errors (RSE) less than 20%. There was no notable bias in goodness-of-fit (GOF) plots and the visual predictive check (VPC). The ETA shrinkages for PK parameters for clearance and volumes of distributions are modest (25% to 57%). The PopPK model is acceptable to be used to derive the summary exposure parameters (AUC_{τ} , C_{max}) for healthy and uUTI infected patients. Limitations of the popPK model were noted in describing covariate effects (such as renal function, food status, and formulations). These should be carefully considered when interpreting the model derived covariate effects and using the model for simulations for target attainment analysis.

Applicant's Population PK Analysis

The primary objectives of Applicant's analysis were to

- Characterize the PK of sulopenem following both IV and oral pro-drug administration of sulopenem
 - Develop a PopPK model describing the plasma concentrations of sulopenem
 - Assess the impact of clinically relevant covariates on the PK of sulopenem

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

- Be used for target attainment simulations to predict the proportion of subjects achieving specified target exposures

Model Development

Data: Nine Phase 1 healthy volunteer studies and three Phase 3 patient studies were included in the analysis. Sulopenem etzadroxil administration included monolayer tablets, bilayer tablets and PIB formulation and was administered with and without food and with and without probenecid (tablet) treatment. The study designs, dose, and formulations are summarized following:

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

Table 148. Trials Included in the Population PK Analysis

Study number	Study Design	Number of subjects with PK samples	Formulation	Dose	Probenecid
A1091001	Phase 1 Multiple Dose	40	IV	800 mg, 1200 mg, 1600 mg, 2000 mg	No
A7371007	Phase 1 Single Dose	24	IV	400 mg, 800 mg, 1600 mg, 2400 mg, 2800 mg	No
A8811001	Phase 1 Single Dose	9	PIB	400 mg, 600 mg, 1000 mg, 2000 mg	No
A8811008	Phase 1 Single Dose	24	Tablet*	1200 mg	Yes
A8811009	Phase 1 Renal Impairment	29	IV and Tablet	IV: 200mg, 800 mg, Tablet: 1000 mg	No
A8811015	Phase 1 Multiple Dose	48	Tablet	500 mg, 1000 mg, 1500 mg BID for 7 days	Yes
IT001-101	Phase 1 Multiple Dose	64	PIB	500 mg BID	Yes
IT001-102	Phase 1 Single Dose Four-Way Crossover	13	PIB	500 mg	Yes
IT001-105	Phase 1 Single Dose Three Period	46	IV/Bilayer Tablet/PIB	IV: 366 mg and 1000 mg, Bilayer Tablet, PIB: 500 mg	Yes
IT001-301	Phase 3 uUTI PK Substudy	125	Bilayer Tablet	500 mg BID	Yes
IT001-302	Phase 3 uUTI PK Substudy	125	IV/Bilayer Tablet	IV: 1000 mg Oral: 500 mg BID	Yes
IT001-303	Phase 3 cIAI PK Substudy	125	IV/Bilayer Tablet	IV: 1000 mg Oral: 500 mg BID	Yes

BID: twice a day; IV: intravenous; PIB: Powder in bottle; PK: pharmacokinetics; Tablet: monolayer tablet; *Only standard release formulation to be included. [Study A8811008](#), [A8811015](#), [IT001-101](#) and [IT001-105](#) investigated food effect.

Source: Applicant's PopPK report, Table 1, page 26

The dose regimen in study IT001-302 and IT001-303 was sulopenem IV 1000 mg for at least 5 days followed by the oral bilayer tablet with 500 mg of sulopenem etzadroxil and 500 mg of probenecid BID up to 5 days to complete 10 days treatment. In study IT001-301, patients were

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

dosed with the 500 mg sulopenem etzadroxil and 500 mg probenecid bilayer tablet BID for 5 days.

In total, 5269 PK observations from 287 healthy volunteers were included in the initial model development. In addition, 1850 PK observations from 377 patients were included in the model development when the Phase 3 data was added to the analysis. Phase 1 studies included rich PK sampling. In the Phase 3 studies IT001-302 and IT001-303, 5 blood samples for PK analysis were collected for each patient with nominal time points at 2 and 4 hours after the first IV dose and at 2, 4 and 6 hours after the first oral dose. In study IT001-301, 3 PK samples were collected at 2, 4 and 6 hours. For the oral dosing, patients were recommended to take the dose with food. Whether the dose was taken with food (meal or snack) or not was registered and this information was used in the modeling. If no information was available, the patient was treated as following the recommendations to take sulopenem etzadroxil with food. A summary of the demographics of the healthy subjects and patients included in the PopPK analysis by study is provided in Table 149 and Table 150.

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

Table 149. Summary of Baseline Demographic Covariates for Analysis- Phase 1 Studies

Study	IT001-105	A1091001	A7371007	A8811009	
	(N = 46)	(N = 40)	(N = 24)	(N = 29)	
Age (yr)					
Mean (SD)	35.8 (9.0)	35.4 (10)	36.2 (12)	62.5 (9.9)	
Median (range)	37.0 (21.0 - 54.0)	35.0 (20.0 - 55.0)	37.5 (20.0 - 54.0)	61.0 (38.0 - 78.0)	
Weight (kg)					
Mean (SD)	79.2 (11)	77.8 (8.9)	82.7 (10)	80.5 (9.8)	
Median (range)	77.9 (58.9 - 104)	78.0 (57.0 - 97.0)	82.0 (65.0 - 100)	80.0 (57.7 - 96.8)	
Gender					
Female	6 (13.0%)	0 (0.0%)	1 (4.2%)	12 (41.4%)	
Male	40 (87.0%)	40 (100.0%)	23 (95.8%)	17 (58.6%)	
Race					
Asian	2 (4.3%)	0 (0.0%)	1 (4.2%)	0 (0.0%)	
Black	31 (67.4%)	3 (7.5%)	12 (50.0%)	3 (10.3%)	
Other	2 (4.3%)	2 (5.0%)	0 (0.0%)	1 (3.4%)	
White	11 (23.9%)	35 (87.5%)	11 (45.8%)	25 (86.2%)	
Creatinine clearance (ml/min)					
Mean (SD)	115 (19)	131 (16)	120 (22)	62.0 (32)	
Median (range)	113 (81.5 - 160)	132 (90.0 - 159)	118 (82.9 - 171)	52.6 (21.4 - 123)	
Study	IT001-101	A8811008	IT001-102	A8811015	A8811001
	(N = 56)	(N = 12)	(N = 23)	(N = 48)	(N = 9)
Age (yr)					
Mean (SD)	37.7 (11)	37.1 (10)	38.7 (12)	33.5 (11)	32.4 (10)
Median (range)	35.5 (18.0 - 59.0)	32.5 (24.0 - 54.0)	38.0 (20.0 - 59.0)	28.5 (18.0 - 55.0)	34.0 (21.0 - 52.0)
Weight (kg)					
Mean (SD)	82.1 (12)	85.8 (9.8)	81.3 (11)	81.6 (12)	75.0 (8.0)
Median (range)	82.6 (55.4 - 118)	85.0 (69.0 - 104)	80.3 (61.3 - 105)	82.5 (61.0 - 111)	77.0 (64.0 - 89.0)
Gender					
Female	3 (5.4%)	0 (0.0%)	4 (17.4%)	2 (4.2%)	0 (0.0%)
Male	53 (94.6%)	12 (100.0%)	19 (82.6%)	46 (95.8%)	9 (100.0%)
Race					
Asian	0 (0.0%)	1 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Black	40 (71.4%)	4 (33.3%)	17 (73.9%)	23 (47.9%)	4 (44.4%)
Other	0 (0.0%)	3 (25.0%)	0 (0.0%)	8 (16.7%)	0 (0.0%)
White	16 (28.6%)	4 (33.3%)	6 (26.1%)	17 (35.4%)	5 (55.6%)
Creatinine clearance (ml/min)					
Mean (SD)	120 (24)	108 (21)	124 (23)	114 (21)	115 (15)
Median (range)	118 (83.1 - 183)	110 (68.7 - 135)	122 (93.1 - 163)	111 (79.1 - 160)	116 (93.3 - 144)

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

Source: Applicant's PopPK report. Table 2 and Table 3. Page 28-29.

Table 150. Summary of Baseline Demographic Covariates for Analysis- Phase 3 Studies

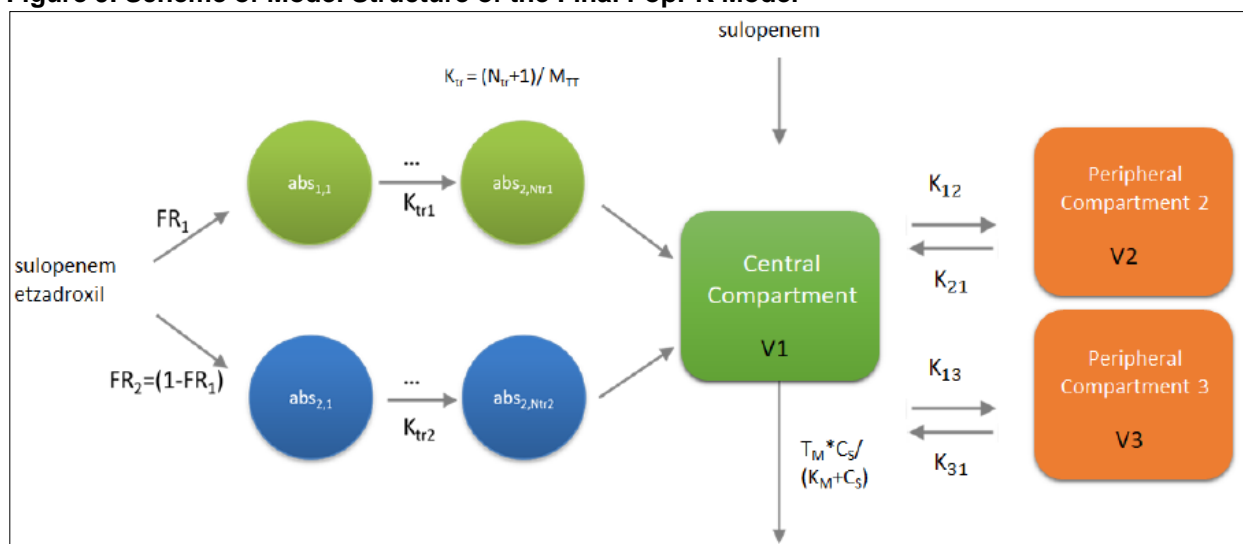
Study	IT001-301	IT001-302	IT001-303	All
	(N = 118)	(N = 122)	(N = 125)	(N = 365)
Age (yr)				
Mean (SD)	48.6 (17)	59.6 (17)	56.3 (17)	54.9 (18)
Median (range)	49.0 (18.0 - 84.0)	63.0 (18.0 - 91.0)	56.0 (18.0 - 90.0)	56.0 (18.0 - 91.0)
Weight (kg)				
Mean (SD)	75.4 (19)	77.3 (17)	83.3 (20)	78.8 (19)
Median (range)	72.6 (44.5 - 133)	76.0 (38.8 - 129)	80.0 (50.0 - 140)	76.3 (38.8 - 140)
Gender				
Female	118 (100.0%)	58 (47.5%)	55 (44.0%)	231 (63.3%)
Male	0 (0.0%)	64 (52.5%)	70 (56.0%)	134 (36.7%)
Race				
Asian	1 (0.8%)	1 (0.8%)	0 (0.0%)	2 (0.5%)
Black	13 (11.0%)	0 (0.0%)	0 (0.0%)	13 (3.6%)
Other	4 (3.4%)	0 (0.0%)	0 (0.0%)	4 (1.1%)
White	100 (84.7%)	121 (99.2%)	125 (100.0%)	346 (94.8%)
Creatinine clearance (ml/min) IV dose				
Mean (SD)	na	89.3 (37)	104 (40)	96.5 (39)
Median (range)	na	86.1 (16.9 - 243)	98.1 (21.2 - 219)	92.1 (16.9 - 243)
Creatinine clearance (ml/min) PO dose				
Mean (SD)	117 (47)	92.2 (37)	123 (42)	111 (44)
Median (range)	109 (25.5 - 292)	92.3 (19.1 - 243)	117 (35.0 - 251)	103 (19.1 - 292)
Food status, oral				
Fasted	8 (6.8%)	18 (16.4%)	5 (4.8%)	31 (9.3%)
Food, meal	55 (46.6%)	79 (71.8%)	81 (77.1%)	215 (64.6%)
Food, snack	15 (12.7%)	10 (9.1%)	12 (11.4%)	37 (11.1%)
Missing	5 (4.2%)	0 (0.0%)	0 (0.0%)	5 (1.5%)
Planned meal	22 (18.6%)	3 (2.7%)	6 (5.7%)	31 (9.3%)
Planned Snack	13 (11.0%)	0 (0.0%)	1 (1.0%)	14 (4.2%)

Source: Applicant's PopPK report. Table 4. Page 30.

Software: The PopPK analysis was carried out using Non-linear Mixed Effects Modeling (Version 7.4.3) and post-processing of Non-linear Mixed Effects Modeling analysis results was carried out in R version 3.5.2. Model development was carried out using first order conditional estimation with interaction.

Phase 1 PopPK model: Initial PopPK model was developed based on Phase 1 data which included oral and IV PK data of sulopenem. The structural model developed was a 3-compartment model with non-linear elimination. The schematic model structure is shown below (Figure 9).

Figure 9. Scheme of Model Structure of the Final PopPK Model



Source: Applicant's PopPK report. Figure 9. Page 50.

Abbreviations: K_M : concentration for half maximum rate of elimination; V1: central volume of distribution; V2: peripheral compartment 2 volume of distribution; V3: peripheral compartment 3 volume of distribution; Q1: first intercompartment clearance; Q2: Second intercompartment clearance; NTR1: number of transit compartments for first transit chain; MTT1: mean transit time for first transit chain; PK, pharmacokinetics.

Following oral administration, there were a second peak in the observed concentrations after some oral doses. This was described using an absorption model with two parallel chains of transit compartments. T_M and concentration for half maximum rate of elimination (K_M) were estimated to 2540 $\mu\text{g}/\text{h}$ and 77.9 $\mu\text{g}/\text{mL}$. V1, V2, and V3 were estimated to 12.6 L, 7.40 L and 4.49 L, respectively.

Inter individual variability (IIV) for T_M , V1, V2 and V3 were 16.1%, 20.2%, 25.3% and 21.2%, respectively. The IIV for the parameters related to absorption were 23.0%, 71.1% and 189% for mean transit time for first transit chain (MTT1), number of transit compartments for first transit chain (NTR1) and the fraction of dose going into the fast or slow absorption chain, respectively. The inter occasion variability estimated for MTT1 was 26.0%.

The bioavailability (F) of sulopenem etzadroxil was estimated to 21.2%. Food increased F by 32.6% for the PIB and monolayer tablet formulation, and 47.2% for the bilayer tablet. Food prolonged absorption and MTT1 by 63.0% for the monolayer tablet and PIB formulation. PIB formulation also showed a faster overall absorption as compared to mono- and bilayer tablet, 20.1%. There was also a statistically significant effect on F following multiple oral dosing without probenecid, predicting a 24.7% lower F on day 7.

Administering IV sulopenem and oral sulopenem etzadroxil with probenecid reduced T_M by 32.4% at probenecid dose ranging from 250-500 mg and with 52.0% at the higher probenecid dose (1000 mg). Probenecid was also found to be a covariate on the volumes of distributions (reducing the volumes by 12.2%). Creatinine clearance (CLcr) had an impact on T_M , resulting in 8.35% decrease in T_M for every 10 ml/min change in CLcr. Refer to Applicant's PopPK report, Table 9 and 10 (parameter estimates of the Phase 1 popPK model), Figures 10, 11, 12, 13 (GOF plots), and Figure 14 and Figure 15 (prediction corrected VPC plots).

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

Reviewer's Comment: The Phase 1 PopPK model adequately describes the observed PK data for healthy subjects. The GOF plots do not show any notable bias and the VPC plots by dose groups showed a good agreement between the predicted and the observed data, as well as capturing the variability of the observed data. For further model building, the Applicant fixed the transit compartment parameters (i.e., MTT1, NTR1, NTR2) and the effect of probenecid, and food with the estimates from the Phase 1 model and re-estimated the rest parameters with pooled data including Phase 3 data.

Final PopPK model: The structural model of the final model is the same as Phase 1 PopPK model. Phase 3 patient data were added to the model development and additional covariate relationships were examined in a stepwise procedure. In addition to the structural covariates included in Phase 1 model, the final model includes body weight as a covariate on V1, V2, and V3 with allometric scaling with exponent of 1, and sex was included for T_M. Separate residual variability for the Phase 3 studies was included and a Phase 3 study effect was estimated for MTT1. The parameter estimates for the final covariate model are listed in Table 151.

Table 151. Parameter Estimates (RSE) and Median (95% CI) for the Final Model

	Alias	Estimate	Relative SE (%)	Transformed Estimate	95% CI	Transformation
	TM (μg/h)	7.77	0.7	2.37e+03	(2.12e+03 - 2.65e+03)	log
	KM (μg/mL)	4.27	1.4	71.5	(63.7 - 80.3)	log
	V1 (L)	2.53	1.2	12.6	(11.8 - 13.3)	log
	V2 (L)	2.05	2.9	7.77	(6.91 - 8.73)	log
	Q1 (L/h)	2.58	2.8	13.2	(11.5 - 15.2)	log
	MTT1 (h)*	0.430		1.54		log
	NTR1*	0.158		1.17		log
	Bioavailability oral %	-1.40	2.7	0.198	(0.186 - 0.210)	logit
	MTT2 (h)*	2.71		15.0		log
	NTR2*	2.85		17.3		log
	Q2 (L/h)	0.702	14.2	2.02	(1.66 - 2.45)	log
	V3 (L)	1.52	3.4	4.57	(4.13 - 5.07)	log
	Fraction of dose to first absorption chain	4.17		0.985		logit
	Proportional error Phase 1 oral	0.356	0.7		(0.351 - 0.361)	none
	Proportional error Phase 1 IV	0.192	0.7		(0.189 - 0.195)	none
	Probenecid on TM*	-0.324				none
	High dose preobenecid on TM*	-0.520				none
	Creatinine clearance on TM	0.00737	2.3		(0.00704 - 0.00770)	none
	Food on bioavailability, bi-layer*	-0.399				none
	Food on MTT1, monolayer tablet and PIB*	0.630				none
	Time dependency on bioavailability*	0.266				none
	PIB on MTT1*	-0.201				none
	Probenecid on V1, V2 and V3*	-0.122				none
	Food on bioavailability, PIB and monolayer*	-0.286				none
	Proportional error Phase 3 oral	0.506	3		(0.476 - 0.536)	none
	Proportional error Phase 3 IV	0.675	2.8		(0.638 - 0.712)	none
	Study 301 and 302 on MTT1	0.387	10.2		(0.309 - 0.465)	none
	Sex (female) on TM	-0.145	14.4		(-0.186 - -0.104)	none
	Body weight on V1, V2 and V3	1.00				none
	Study 303 on MTT1	0.655	8.5		(0.545 - 0.765)	none

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

Parameter	Alias	Estimate	Relative SE (%)	Transformed Estimate	95% CI	Transformation
$\omega_{1.1}$	ω_{TM}^2	0.0643	10.4		(0.0513 - 0.0773)	none
$\omega_{2.1}$	$\omega_{V1, TM}^2$	0.0127	66.3		(-0.00376 - 0.0292)	none
$\omega_{2.2}$	ω_{V1}^2	0.0308	21		(0.0181 - 0.0435)	none
$\omega_{3.1}$	$\omega_{V2, TM}^2$	0.0306	30.8		(0.0121 - 0.0491)	none
$\omega_{3.2}$	$\omega_{V2, V1}^2$	0.0301	23.1		(0.0165 - 0.0437)	none
$\omega_{3.3}$	ω_{V2}^2	0.0612	24.2		(0.0322 - 0.0902)	none
$\omega_{4.1}$	$\omega_{V3, TM}^2$	0.0310	27.5		(0.0143 - 0.0477)	none
$\omega_{4.2}$	$\omega_{V3, V1}^2$	0.0143	43.1		(0.00223 - 0.0264)	none
$\omega_{4.3}$	$\omega_{V3, V2}^2$	0.0458	20.8		(0.0271 - 0.0645)	none
$\omega_{4.4}$	ω_{V3}^2	0.0505	21.4		(0.0293 - 0.0717)	none
$\omega_{6.6}$	ω_{MTT1}^2 *	0.0528				none
$\omega_{7.7}$	ω_{NTR1}^2 *	0.506				none
$\omega_{8.8}$	ω_F^2	0.104	9		(0.0857 - 0.122)	none
$\omega_{11.11}$	ω_{FRAC}^2 *	3.59				none
$\omega_{13.13}$	$\omega_{IOV_M T T 1}^2$ *	0.0637				none

Source: Applicant's PopPK report. Table 12 and Table 13. Pages 69-70.

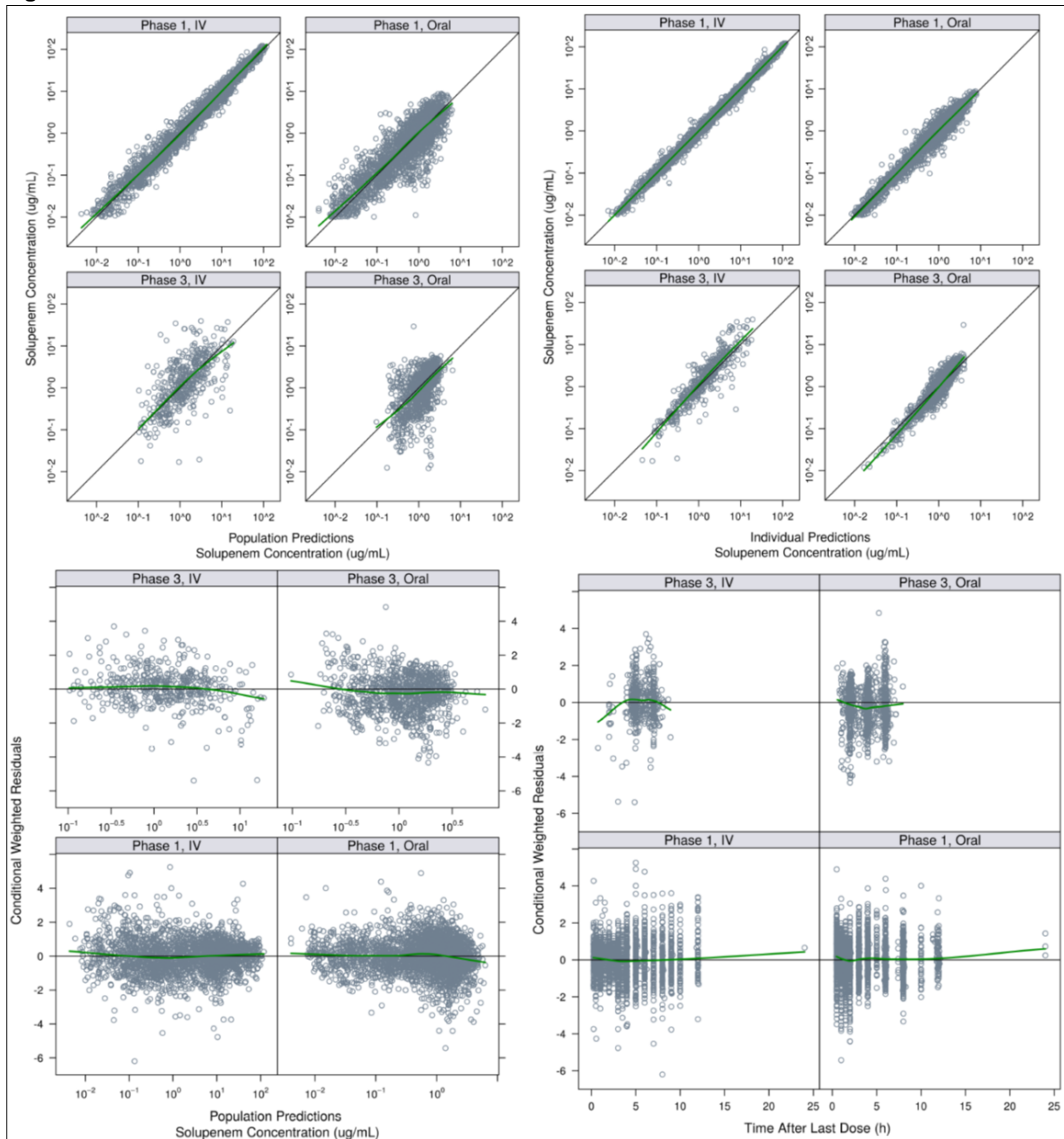
Relative SE (%) are given for the normal parameters. Transformed 95% CI are given for the transformed parameters.

*Fixed parameters based on Phase 1 model.

Abbreviations: CI, confidence interval; RSE, relative standard error

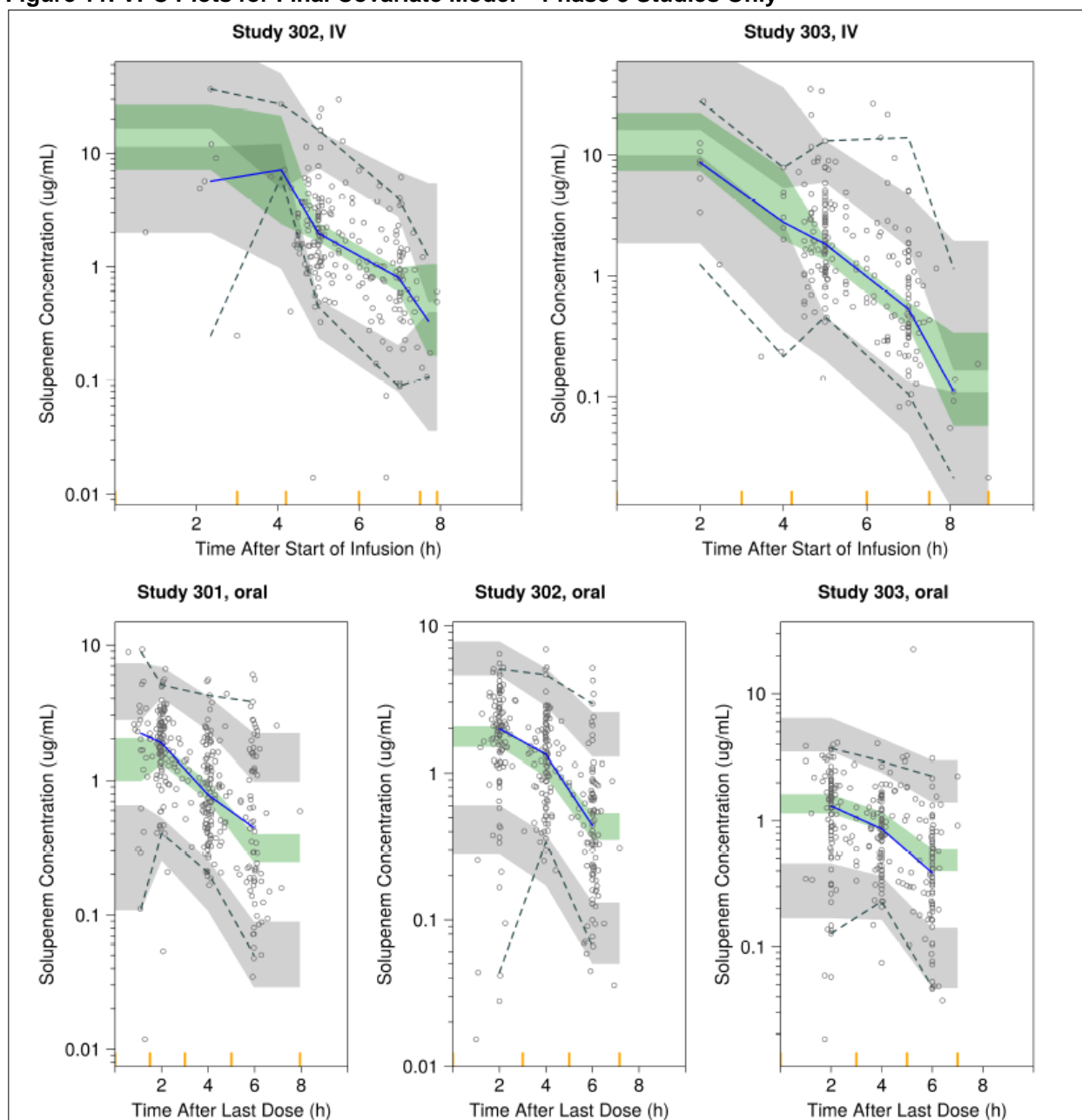
The GOF plots and VPC plots for the final covariate model are shown in Figure 10 and Figure 11. Only phase 3 study VPCs are presented.

Figure 10. Goodness-of-Fit Plots for Final Covariate Model



Source: Applicant's PopPK report. Figures 20, 21, 22. Pages 71-74.

Figure 11. VPC Plots for Final Covariate Model – Phase 3 Studies Only



Source: Applicant's PopPK report. Figure 24. Page 76.

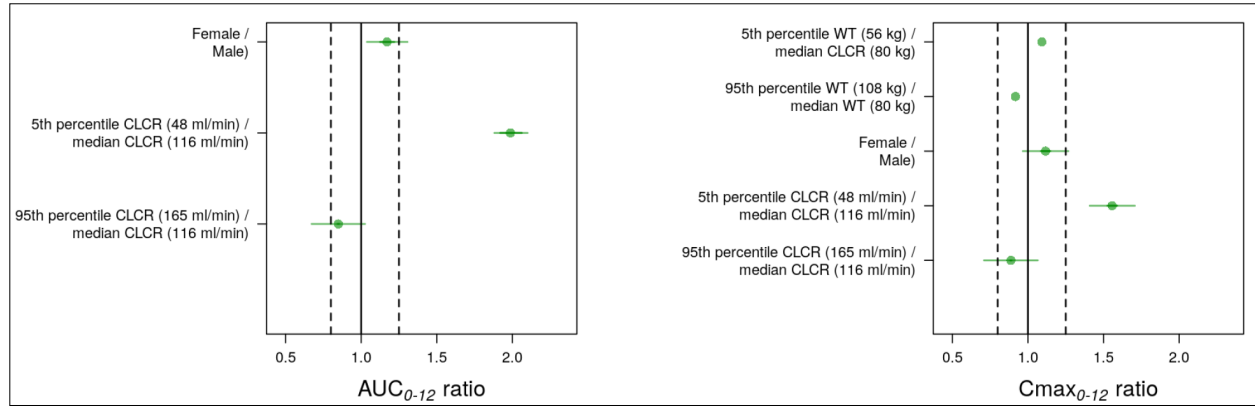
Solid Blue Line: Median of the observed sulopenem concentrations; Dashed Lines: 2:5th and 97:5th percentiles of the observed sulopenem concentrations, Shaded Area: The shaded areas indicate the 95% CI around the prediction-corrected median (green area); 2.5th and 97.5th percentiles of the simulated concentrations (grey areas).

Abbreviations: VPC, visual predictive check

Females were estimated to have 14.5% lower T_M as compared to males. The age range included in PK dataset was 18 to 78 years and graphical examination of ETA-age plot did not show a notable trend. Race was not a significant covariate on the PK parameters. The PopPK analysis dataset included the renal impairment study (Study A8811009) and the PopPK model estimated that CL_{cr} has an impact on the T_M , resulting in 7.37% decrease in T_M for every 10 mL/min

change in CL_{cr}. The impact of the statistically significant intrinsic covariates on exposure is presented in Figure 12. The effects of body weight, age, CL_{cr}, and sex on ETA of T_M are presented in Figure 13.

Figure 12. Effect of Covariates Included in the Final PK Model on Sulopenem Exposure

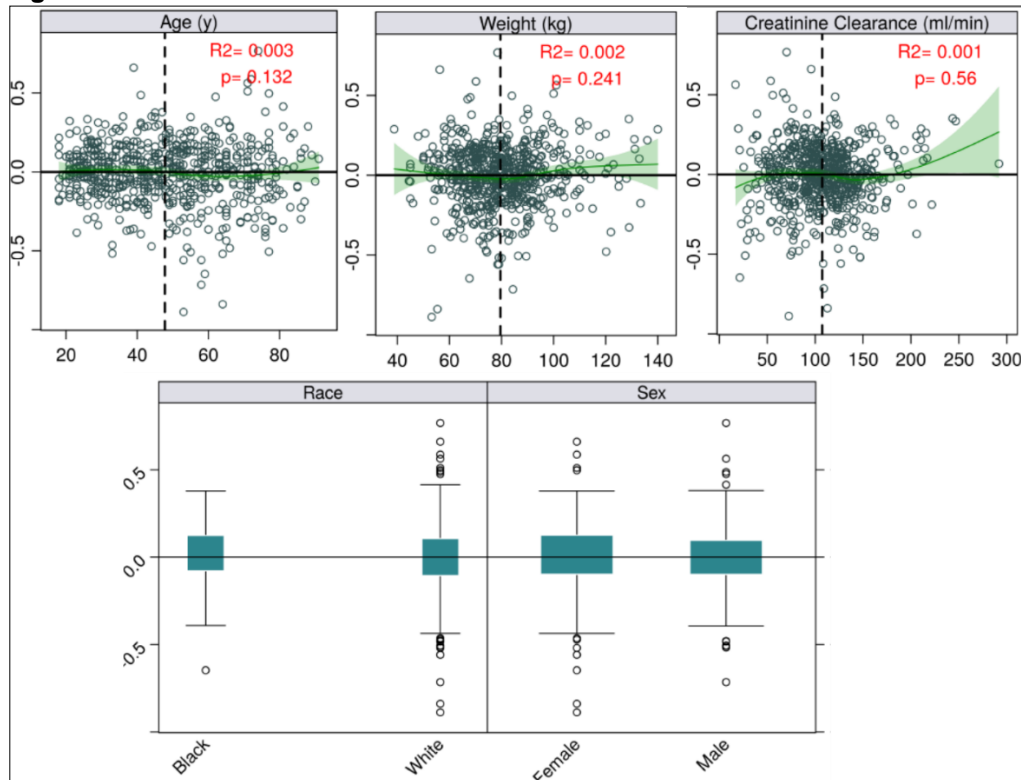


Source: Applicant's PopPK report. Figure 25. Page 79.

The reference patient is an 80 kg male with CL_{cr} of 116 ml/min, receiving a 500 mg bilayer tablet. The independent effect of each covariate is investigated, keeping all other characteristics similar to the reference population. Lower and higher covariate values for WT and CL_{cr} are based on the observed 5th and 95th percentiles of the subjects included in the analysis.

Abbreviations: AUC, area under the curve; CL_{cr}, creatinine clearance; C_{max}, maximum serum concentration; PK, pharmacokinetics.

Figure 13. ETA of T_M -Covariate Plots



Source: Applicant's PopPK report. Figure A.6.2 and Figure A.6.3. pages 127-130.

Patients were estimated to have slower absorption as compared to healthy volunteers, with 38.7% higher MTT₁ for uncomplicated and complicated urinary tract infection (uUTI and cUTI)

patients and 65.5% higher MTT1 for complicated intraabdominal infection (cIAI) patients as compared to the healthy subjects. The model predicted exposure in terms of AUC_{0-12h} and $C_{max, 0-12h}$ following IV and oral single dosing is summarized below (Table 152). The simulations are based on the individual dosing and individual predicted PK parameters.

Table 152. Summary of AUC_{0-12h} and C_{max} by Study and Route

Study	Route	AUC ($\mu\text{g}\cdot\text{h}/\text{mL}$)		C_{max} ($\mu\text{g}/\text{mL}$)		n
		Mean	(SD)	Mean	(SD)	
301	IV	NaN	NA	NaN	NA	0
	Oral	4.87	1.65	1.39	0.425	118
302	IV	36.9	9.92	11.8	3.00	116
	Oral	4.43	1.34	1.68	2.14	110
303	IV	36.8	14.3	11.6	4.28	113
	Oral	4.06	1.46	1.16	1.10	105

Source: Applicant's PopPK report. Table 14. Page 77.

Abbreviations: AUC area under the curve; C_{max} , maximum serum concentration; IV, intravenous

Reviewer's Comment: In general, the Applicant's final PopPK model acceptably describes the observed PK data collected from Phase 1 and Phase 3 studies. Most PK parameters were estimated with acceptable precision (%RSE <20%) and IIVs were estimated with %RSE <50%. ETA shrinkages for T_M , V1, V2, and V3 were modest (25%, 57%, 48%, and 49%). The GOF plots by route of administration did not show any obvious bias. The VPC plots showed that the model predictions are in agreement with the observed concentrations for both Phase 1 and Phase 3 studies. Therefore, the reviewer agrees that this model can be used to derive the summary exposure metrics such as AUC and C_{max} for the study populations.

Body weight, and sex minimally impact sulopenem exposure and these impacts are not considered clinically meaningful. With decreasing CLcr from 116 to 48 mL/min, there is a 2- fold increase in sulopenem AUC0-12h following a 500 mg bilayer tablet. The model predicted magnitude of CLcr impact is somewhat smaller than those observed in the dedicated RI study. In the RI study, sulopenem AUCinf increased in subjects with mild, moderate, and severe renal function by 210%, 350% and 740% after a single oral dose of 1000 mg sulopenem etzadroxil, and 170% (mild RI) and 250% (moderate RI) after an 800 mg IV dose. Note that a different formulation (tablet without probenecid) was used in the RI study from the proposed formulation (bilayer tablet with probenecid). The impacts of renal impairment on probenecid and the associated impact on sulopenem exposures were not incorporated in the Applicant's PopPK model.

The complexity of the structural model and the potential interactions between intrinsic/extrinsic factors that are correlated to each other (i.e., renal function, food effects, and formulations (with or without probenecid) make it difficult to interpret the model-estimated covariate effects. Therefore, this limitation should be carefully considered when this model is used for simulations for target attainment analysis. One example is food effect. The model-derived food effect on bilayer tablets is mainly driven by the data from the food effect study (IT001-105) which showed

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

a significant food effect (approx. 50% higher exposure vs. fasted). While most subjects (90.7%) from Phase 3 studies were recorded as in a fed status during dosing, the model predicted exposures for Phase 3 subjects are generally lower than those observed in healthy subjects with fed status and more close to those observed in fasted status. It is not clear whether the lower exposures observed in the Phase 3 studies are due to the inherent PK difference between patients (uUTI, cUTI) vs. healthy subjects, or the way food status was recorded in the Phase 3 studies (i.e., inaccurate record of food status, or the consumed food ([planned] meal/snack) different from those (high-fat meal) consumed in Study IT001-105.

Because of the deficiencies in the determination of PK/PD targets noted by the Clinical Pharmacology reviewer (See Appendix 16.3), the Applicant's target attainment analysis could not be evaluated by the reviewer. In the Phase 3 efficacy trial (IT001-301) supporting the proposed indication, PK samples were collected in a subset (n=118) of intent-to-treat (ITT) population (n=787). Therefore, the exposure-response for clinical efficacy/safety was not further evaluated by the reviewer.

16.4. Additional Safety Analyses

Table 153. TEAEs Occurring in <0.5% of Subjects in Study 301

Preferred Term	Sulopenem Etzadroxil	
	+ Probenecid n (%) N=825	Ciprofloxacin n (%) N=822
Bacterial vaginosis	3 (0.4)	2 (0.2)
Feces soft	3 (0.4)	3 (0.4)
Pruritus	3 (0.4)	0
Pyrexia	3 (0.4)	1 (0.1)
Rhinitis	3 (0.4)	3 (0.4)
Upper respiratory tract infection	3 (0.4)	0
Vaginal discharge	3 (0.4)	0
Arthropod bite	2 (0.2)	0
Candida infection	2 (0.2)	1 (0.1)
Candiduria	2 (0.2)	0
Chills	2 (0.2)	1 (0.1)
Cholelithiasis	2 (0.2)	0
Constipation	2 (0.2)	1 (0.1)
Cough	2 (0.2)	2 (0.2)
Dry mouth	2 (0.2)	1 (0.1)
Dysgeusia	2 (0.2)	0
Fatigue	2 (0.2)	1 (0.1)
Gastroesophageal reflux disease	2 (0.2)	0
Hypotension	2 (0.2)	0
Influenza	2 (0.2)	0
Nasopharyngitis	2 (0.2)	1 (0.1)
Pain in extremity	2 (0.2)	1 (0.1)
Pharyngitis streptococcal	2 (0.2)	0
Vitamin D deficiency	2 (0.2)	0
Abnormal feces	1 (0.1)	0
Acute kidney injury	1 (0.1)	0

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

Preferred Term	Sulopenem Etzadroxil	Ciprofloxacin
	+ Probenecid n (%) N=825	n (%) N=822
Angioedema	1 (0.1)	0
Arthralgia	1 (0.1)	1 (0.1)
Asthenia	1 (0.1)	2 (0.2)
Cardiac murmur	1 (0.1)	0
Chest pain	1 (0.1)	0
Conjunctival hemorrhage	1 (0.1)	0
Conjunctivitis	1 (0.1)	0
Cyst	1 (0.1)	0
Dehydration	1 (0.1)	0
Dermatitis allergic	1 (0.1)	0
Dyspnea	1 (0.1)	0
Eructation	1 (0.1)	0
Flank pain	1 (0.1)	0
Flatulence	1 (0.1)	0
Gastroenteritis	1 (0.1)	1 (0.1)
Gastroenteritis viral	1 (0.1)	0
Hematuria	1 (0.1)	0
Hemorrhoids	1 (0.1)	1 (0.1)
Hepatomegaly	1 (0.1)	0
Hydronephrosis	1 (0.1)	0
Hypoesthesia	1 (0.1)	0
Infectious mononucleosis	1 (0.1)	0
Ligament sprain	1 (0.1)	0
Lung adenocarcinoma	1 (0.1)	0
Malaise	1 (0.1)	0
Migraine	1 (0.1)	0
Nephrolithiasis	1 (0.1)	0
Edema peripheral	1 (0.1)	0
Oral herpes	1 (0.1)	0
Oropharyngeal pain	1 (0.1)	0
Pain	1 (0.1)	0
Paresthesia	1 (0.1)	0
Phlebolith	1 (0.1)	0
Pleural effusion	1 (0.1)	0
Presyncope	1 (0.1)	0
Psychotic disorder	1 (0.1)	0
Pyelonephritis acute	1 (0.1)	0
Renal pain	1 (0.1)	0
Respiratory disorder	1 (0.1)	0
Respiratory tract infection	1 (0.1)	0
Respiratory tract infection viral	1 (0.1)	0
Sinus congestion	1 (0.1)	1 (0.1)
Skin lesion	1 (0.1)	0
Small intestinal obstruction	1 (0.1)	0
Tachycardia	1 (0.1)	0
Ureterolithiasis	1 (0.1)	0
Urosepsis	1 (0.1)	0
Vaginal infection	1 (0.1)	2 (0.2)

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

Preferred Term	Sulopenem Etzadroxil + Probenecid	Ciprofloxacin
	n (%) N=825	n (%) N=822
Vulvovaginal pruritus	1 (0.1)	0
Abscess limb	0	1 (0.1)
Altered visual depth perception	0	1 (0.1)
Anxiety	0	1 (0.1)
Bile duct stone	0	1 (0.1)
Decreased appetite	0	1 (0.1)
Dermal cyst	0	1 (0.1)
Drug hypersensitivity	0	2 (0.2)
Epistaxis	0	1 (0.1)
Erythema	0	1 (0.1)
Glycosylated hemoglobin increased	0	1 (0.1)
Gonorrhea	0	1 (0.1)
Impetigo	0	1 (0.1)
Lumbosacral radiculopathy	0	1 (0.1)
Musculoskeletal pain	0	1 (0.1)
Pelvic pain	0	1 (0.1)
Pharyngitis	0	1 (0.1)
Pneumonia	0	1 (0.1)
Rash	0	1 (0.1)
Toothache	0	1 (0.1)
Vertigo	0	1 (0.1)
Viral upper respiratory tract infection	0	2 (0.2)
Vulvovaginal burning sensation	0	1 (0.1)

Source: Reviewer Table

Abbreviations: TEAE, treatment emergent adverse events.

Table 154. TEAEs Occurring in <0.5% of Subjects in the Integrated Phase 3 Safety Population

Preferred Term	Sulopenem Etzadroxil + Probenecid / Sulopenem	Comparator
	n (%) N=1855	n (%) N=1852
Constipation	8 (0.4)	7 (0.4)
Pyrexia	8 (0.4)	2 (0.1)
Urine odor abnormal	8 (0.4)	1 (0.1)
Back pain	6 (0.3)	3 (0.2)
Urinary tract infection	6 (0.3)	1 (0.1)
Abdominal abscess	6 (0.3)	0
Wound infection	5 (0.3)	12 (0.6)
Nasopharyngitis	5 (0.3)	5 (0.3)
Upper respiratory tract infection	5 (0.3)	2 (0.1)
Vaginal discharge	5 (0.3)	1 (0.1)
Hypophosphatemia	5 (0.3)	0
Pruritus	5 (0.3)	0
Hypokalemia	4 (0.2)	7 (0.4)
Pneumonia	4 (0.2)	6 (0.3)
Cough	4 (0.2)	4 (0.2)
Dry mouth	4 (0.2)	3 (0.2)

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Preferred Term	Sulopenem Etzadroxil + Probenecid / Sulopenem n (%) N=1855	Comparator n (%) N=1852
Rhinitis	4 (0.2)	3 (0.2)
Chest pain	3 (0.2)	3 (0.2)
Feces soft	3 (0.2)	3 (0.2)
Urinary retention	3 (0.2)	3 (0.2)
Anxiety	3 (0.2)	2 (0.1)
Bacterial vaginosis	3 (0.2)	2 (0.1)
Dysgeusia	3 (0.2)	2 (0.1)
Pleural effusion	3 (0.2)	2 (0.1)
Dyspnea	3 (0.2)	1 (0.1)
Hypomagnesaemia	3 (0.2)	1 (0.1)
Pain in extremity	3 (0.2)	1 (0.1)
Influenza	3 (0.2)	0
Pyelonephritis acute	3 (0.2)	0
Tachycardia	3 (0.2)	0
Rash ¹	2 (0.1)	7 (0.4)
Anemia	2 (0.1)	6 (0.3)
Asthenia	2 (0.1)	2 (0.1)
Chills	2 (0.1)	2 (0.1)
Fatigue	2 (0.1)	2 (0.1)
Candida infection	2 (0.1)	1 (0.1)
Gastroesophageal reflux disease	2 (0.1)	1 (0.1)
Infusion site pain ²	2 (0.1)	1 (0.1)
Liver abscess	2 (0.1)	1 (0.1)
Somnolence	2 (0.1)	1 (0.1)
Vulvovaginal pruritus	2 (0.1)	1 (0.1)
Arthropod bite	2 (0.1)	0
Candiduria	2 (0.1)	0
Cardiac failure	2 (0.1)	0
Cardiac failure congestive	2 (0.1)	0
Cerebrovascular accident	2 (0.1)	0
Cholelithiasis	2 (0.1)	0
Hiccups	2 (0.1)	0
Hyperhidrosis	2 (0.1)	0
Hypotension	2 (0.1)	0
Leukocytosis	2 (0.1)	0
Pharyngitis streptococcal	2 (0.1)	0
Vitamin D deficiency	2 (0.1)	0
Wound secretion	2 (0.1)	0
Atrial fibrillation	1 (0.1)	4 (0.2)
Delirium	1 (0.1)	3 (0.2)
Respiratory tract infection viral	1 (0.1)	3 (0.2)
Alanine aminotransferase increased	1 (0.1)	2 (0.1)
Aspartate aminotransferase increased	1 (0.1)	2 (0.1)
Decreased appetite	1 (0.1)	2 (0.1)
Oral herpes	1 (0.1)	2 (0.1)
Oropharyngeal pain	1 (0.1)	2 (0.1)
Pleurisy	1 (0.1)	2 (0.1)
Vaginal infection	1 (0.1)	2 (0.1)

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Preferred Term	Sulopenem Etzadroxil + Probenecid / Sulopenem n (%) N=1855	Comparator n (%) N=1852
Abdominal distension	1 (0.1)	1 (0.1)
Acute respiratory failure	1 (0.1)	1 (0.1)
Arthralgia	1 (0.1)	1 (0.1)
Atrial flutter	1 (0.1)	1 (0.1)
Blood creatinine increased	1 (0.1)	1 (0.1)
Conjunctivitis	1 (0.1)	1 (0.1)
Epistaxis	1 (0.1)	1 (0.1)
Flatulence	1 (0.1)	1 (0.1)
Gastroenteritis	1 (0.1)	1 (0.1)
Gastrointestinal hypomotility	1 (0.1)	1 (0.1)
Hemorrhoids	1 (0.1)	1 (0.1)
Hepatic enzyme increased	1 (0.1)	1 (0.1)
Hypoxia	1 (0.1)	1 (0.1)
Ileus	1 (0.1)	1 (0.1)
Multiple organ dysfunction syndrome	1 (0.1)	1 (0.1)
Procedural pain	1 (0.1)	1 (0.1)
Pyelonephritis chronic	1 (0.1)	1 (0.1)
Sinus congestion	1 (0.1)	1 (0.1)
Small intestinal obstruction	1 (0.1)	1 (0.1)
Ureterolithiasis	1 (0.1)	1 (0.1)
Abnormal feces	1 (0.1)	0
Acute kidney injury	1 (0.1)	0
Alopecia	1 (0.1)	0
Anal fissure	1 (0.1)	0
Angioedema	1 (0.1)	0
Appendiceal abscess	1 (0.1)	0
Arthritis reactive	1 (0.1)	0
Cardiac arrest	1 (0.1)	0
Cardiac murmur	1 (0.1)	0
Chest discomfort	1 (0.1)	0
Colon gangrene	1 (0.1)	0
Conjunctival hemorrhage	1 (0.1)	0
Cyst	1 (0.1)	0
Dehydration	1 (0.1)	0
Depression	1 (0.1)	0
Dermatitis allergic	1 (0.1)	0
Disturbance in attention	1 (0.1)	0
Dry skin	1 (0.1)	0
Enterocutaneous fistula	1 (0.1)	0
Epididymitis	1 (0.1)	0
Eructation	1 (0.1)	0
Feeling hot	1 (0.1)	0
Femoral neck fracture	1 (0.1)	0
Flank pain	1 (0.1)	0
Fungal skin infection	1 (0.1)	0
Gastroenteritis viral	1 (0.1)	0
Gastrointestinal anastomotic leak	1 (0.1)	0
Gastrointestinal carcinoma	1 (0.1)	0

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Preferred Term	Sulopenem Etzadroxil + Probenecid / Sulopenem n (%) N=1855	Comparator n (%) N=1852
Hematuria	1 (0.1)	0
Hepatitis toxic	1 (0.1)	0
Hepatomegaly	1 (0.1)	0
Herpes virus infection	1 (0.1)	0
Hydronephrosis	1 (0.1)	0
Hypoesthesia	1 (0.1)	0
Ileus paralytic	1 (0.1)	0
Incision site pain	1 (0.1)	0
Infectious mononucleosis	1 (0.1)	0
Infusion site extravasation	1 (0.1)	0
Infusion site phlebitis	1 (0.1)	0
Initial insomnia	1 (0.1)	0
Insomnia	1 (0.1)	0
Internal hemorrhage	1 (0.1)	0
International normalized ratio increased	1 (0.1)	0
Intestinal perforation	1 (0.1)	0
Ligament sprain	1 (0.1)	0
Liver function test abnormal	1 (0.1)	0
Liver function test increased	1 (0.1)	0
Lung adenocarcinoma	1 (0.1)	0
Malaise	1 (0.1)	0
Mesenteric artery thrombosis	1 (0.1)	0
Migraine	1 (0.1)	0
Nephrolithiasis	1 (0.1)	0
Nipple pain	1 (0.1)	0
Edema peripheral	1 (0.1)	0
Orchitis	1 (0.1)	0
Orchitis noninfective	1 (0.1)	0
Osteochondrosis	1 (0.1)	0
Pain	1 (0.1)	0
Palpitations	1 (0.1)	0
Paresthesia	1 (0.1)	0
Peritonitis	1 (0.1)	0
Phlebitis	1 (0.1)	0
Phlebolith	1 (0.1)	0
Post procedural bile leak	1 (0.1)	0
Post procedural persistent drain fluid	1 (0.1)	0
Post-traumatic amnesic disorder	1 (0.1)	0
Presyncope	1 (0.1)	0
Psychotic disorder	1 (0.1)	0
Pulmonary congestion	1 (0.1)	0
Pulmonary embolism	1 (0.1)	0
Renal cell carcinoma	1 (0.1)	0
Renal impairment	1 (0.1)	0
Renal pain	1 (0.1)	0
Respiratory disorder	1 (0.1)	0
Respiratory tract infection	1 (0.1)	0

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{sulopenem etzadroxil/probenecid}

Preferred Term	Sulopenem Etzadroxil + Probenecid / Sulopenem n (%) N=1855	Comparator n (%) N=1852
Salivary gland neoplasm	1 (0.1)	0
Sepsis	1 (0.1)	0
Skin lesion	1 (0.1)	0
Stoma site abscess	1 (0.1)	0
Sudden death	1 (0.1)	0
Swelling	1 (0.1)	0
Tachypnoea	1 (0.1)	0
Thrombocytosis	1 (0.1)	0
Tinnitus	1 (0.1)	0
Tonsillitis	1 (0.1)	0
Urethral stenosis	1 (0.1)	0
Urinary fistula	1 (0.1)	0
Urosepsis	1 (0.1)	0
Vaginal hemorrhage	1 (0.1)	0
Ventricular fibrillation	1 (0.1)	0
Volvulus of small bowel	1 (0.1)	0
Vulvovaginal dryness	1 (0.1)	0
White blood cell count increased	1 (0.1)	0
Wound abscess	1 (0.1)	0
Wound hematoma	1 (0.1)	0
Viral upper respiratory tract infection	0	3 (0.2)
Drug hypersensitivity	0	2 (0.1)
Hepatitis	0	2 (0.1)
Hypoglycemia	0	2 (0.1)
Intestinal obstruction	0	2 (0.1)
Post procedural hematoma	0	2 (0.1)
Pyelonephritis	0	2 (0.1)
Stomatitis	0	2 (0.1)
Syncope	0	2 (0.1)
Abscess limb	0	1 (0.1)
Abscess neck	0	1 (0.1)
Allergy to arthropod sting	0	1 (0.1)
Altered visual depth perception	0	1 (0.1)
Angina unstable	0	1 (0.1)
Aphthous ulcer	0	1 (0.1)
Ascites	0	1 (0.1)
Atrioventricular block complete	0	1 (0.1)
Bile duct obstruction	0	1 (0.1)
Bile duct stone	0	1 (0.1)
Blood alkaline phosphatase increased	0	1 (0.1)
Blood urea increased	0	1 (0.1)
Bradycardia	0	1 (0.1)
Bundle branch block left	0	1 (0.1)
Bundle branch block right	0	1 (0.1)
Cardiac failure acute	0	1 (0.1)
Chest injury	0	1 (0.1)
Colon cancer	0	1 (0.1)
Confusional state	0	1 (0.1)

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Preferred Term	Sulopenem Etzadroxil + Probenecid / Sulopenem n (%) N=1855	Comparator n (%) N=1852
Conjunctivitis allergic	0	1 (0.1)
Coordination abnormal	0	1 (0.1)
Cystitis	0	1 (0.1)
Delirium tremens	0	1 (0.1)
Dermal cyst	0	1 (0.1)
Dermatitis exfoliative	0	1 (0.1)
Ear pain	0	1 (0.1)
Erythema	0	1 (0.1)
Eye abscess	0	1 (0.1)
Gamma-glutamyltransferase increased	0	1 (0.1)
Gastric ulcer	0	1 (0.1)
Gastritis	0	1 (0.1)
Gingival pain	0	1 (0.1)
Glycosylated hemoglobin increased	0	1 (0.1)
Gonorrhea	0	1 (0.1)
Hematoma	0	1 (0.1)
Hepatic hematoma	0	1 (0.1)
Herpes simplex	0	1 (0.1)
Hydrothorax	0	1 (0.1)
Hyperglycemia	0	1 (0.1)
Hypersensitivity	0	1 (0.1)
Impetigo	0	1 (0.1)
Infusion related reaction	0	1 (0.1)
Infusion site coldness	0	1 (0.1)
Intervertebral disc degeneration	0	1 (0.1)
Intestinal anastomosis complication	0	1 (0.1)
Intra-abdominal fluid collection	0	1 (0.1)
Intra-abdominal hematoma	0	1 (0.1)
Intra-abdominal hemorrhage	0	1 (0.1)
Irritability	0	1 (0.1)
Irritable bowel syndrome	0	1 (0.1)
Laryngitis	0	1 (0.1)
Limb injury	0	1 (0.1)
Lumbosacral radiculopathy	0	1 (0.1)
Mental status changes	0	1 (0.1)
Micturition disorder	0	1 (0.1)
Musculoskeletal pain	0	1 (0.1)
Myocardial ischemia	0	1 (0.1)
Oral candidiasis	0	1 (0.1)
Pancreatitis acute	0	1 (0.1)
Pelvic pain	0	1 (0.1)
Peripheral swelling	0	1 (0.1)
Pharyngeal edema	0	1 (0.1)
Pharyngitis	0	1 (0.1)
Phlebitis superficial	0	1 (0.1)
Pneumothorax	0	1 (0.1)
Postoperative wound complication	0	1 (0.1)

Preferred Term	Sulopenem Etzadroxil + Probenecid / Sulopenem n (%) N=1855	Comparator n (%) N=1852
Pulmonary artery thrombosis	0	1 (0.1)
Pulmonary edema	0	1 (0.1)
Radius fracture	0	1 (0.1)
Renal failure	0	1 (0.1)
Respiratory failure	0	1 (0.1)
Seizure	0	1 (0.1)
Sinus node dysfunction	0	1 (0.1)
Stenosis of vesicourethral anastomosis	0	1 (0.1)
Systemic inflammatory response syndrome	0	1 (0.1)
Tachyarrhythmia	0	1 (0.1)
Testicular swelling	0	1 (0.1)
Thrombophlebitis	0	1 (0.1)
Tongue fungal infection	0	1 (0.1)
Toothache	0	1 (0.1)
Toxic skin eruption	0	1 (0.1)
Tracheitis	0	1 (0.1)
Transfusion-associated dyspnea	0	1 (0.1)
Tremor	0	1 (0.1)
Urticaria	0	1 (0.1)
Varices esophageal	0	1 (0.1)
Vascular encephalopathy	0	1 (0.1)
Vertigo	0	1 (0.1)
Vulvovaginal burning sensation	0	1 (0.1)

Source: Reviewer Table

¹ Rash includes the PTs of rash and rash erythematous

² Includes AEs which were erroneously not categorized as treatment-emergent

Abbreviations: TEAE, treatment emergent adverse events.

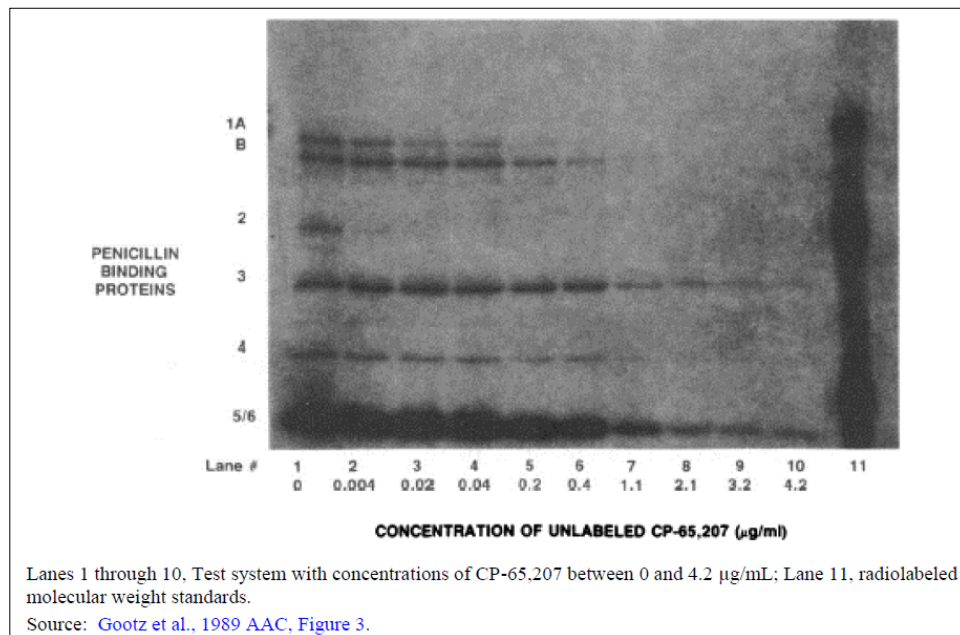
16.5. Clinical Microbiology

16.5.1. In Vitro Information

16.5.1.1. Mechanism of Action

Sulopenem is a penem antibacterial drug that inhibits bacterial cell wall synthesis by binding to penicillin-binding proteins (PBPs). A competitive binding assay was conducted with ³H-penicillin in *E. coli* strain W-7 that showed sulopenem (CP-65,207) had the highest affinity for PBP2, with concentrations as low as 0.004 µg/mL (Figure 14) (Gootz 1989). It has also shown that the relative order of affinity towards PBPs of sulopenem in *E. coli* was PBP2>PBP1A > PBP1B > PBP4>PBP3>PBP5/6. Additionally, it was determined through a hydrolysis study that CP-65207 was highly stable to some cephalosporinases, including plasmid-encoded enzymes TEM-1, SHV-1, and PSE-2.

Figure 14. Autoradiograph of Competitive Binding of Unlabeled CP-65,207 Versus 3HPenicillin G for *E. coli* W-7 PBPs



16.5.1.2. Bactericidal Activity

The bactericidal activity of sulopenem was demonstrated in several time-kill studies. Sulopenem exhibited bactericidal killing in one study (Uppsala 2018-10-11), at concentrations $\geq 4X$ the MIC against *E. coli* and *K. pneumoniae* isolates (Table 155).

Table 155. Strains Used in Uppsala Time-Kill Study and Sulopenem MIC Values

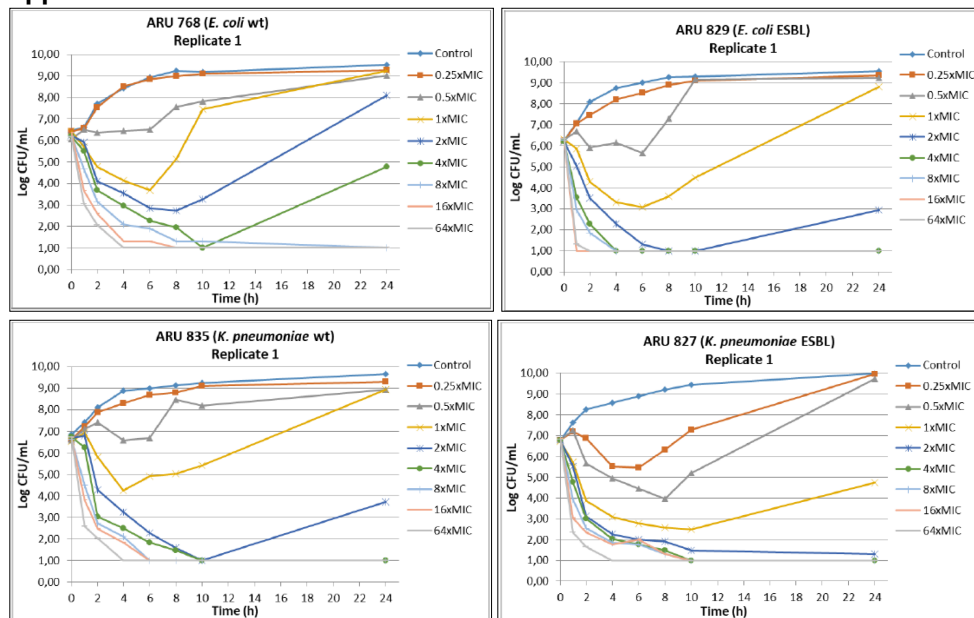
Strain	Isolate	Sulopenem Median MIC (µg/mL)
ARU 768	<i>E. coli</i> ATCC 25922 wild type QC	0.032
ARU 829	<i>E. coli</i> clinical isolate, from urine, ESBL ⁺	0.064
ARU 835	<i>K. pneumoniae</i> ATCC 43816 wild type	0.064
ARU 827	<i>K. pneumoniae</i> clinical isolate, from urine, ESBL ⁺	0.25

Source: Project Report Uppsala 2018-10-11, page 8

Abbreviations: MIC, minimum inhibitory concentration

Bactericidal activity was seen at $\geq 4X$ the MIC against ARU 829 (*E. coli* ESBL⁺) and ARU 835 (*K. pneumoniae* ATCC 43816) and at $\geq 8X$ the MIC against ARU 768 (*E. coli* ATCC 25922) and ARU 827 (*K. pneumoniae* ESBL⁺) (Figure 15).

Figure 15. Time-Kill Kinetic Activity for Sulopenem Against *E. Coli* and *K. Pneumoniae* Isolates – Uppsala



Source: Project Report Uppsala 2018-10-11, page 14

A second in vitro time-kill kinetic study was conducted by comparing sulopenem to ertapenem using *E. coli* and *K. pneumoniae* isolates (JMI Study; 17-ITR-01 Part 2). The MIC values of the isolates are presented in Table 156.

Table 156. Broth Microdilution MIC Values of Sulopenem and Ertapenem Against Organisms Used in the JMI Time-Kill Study

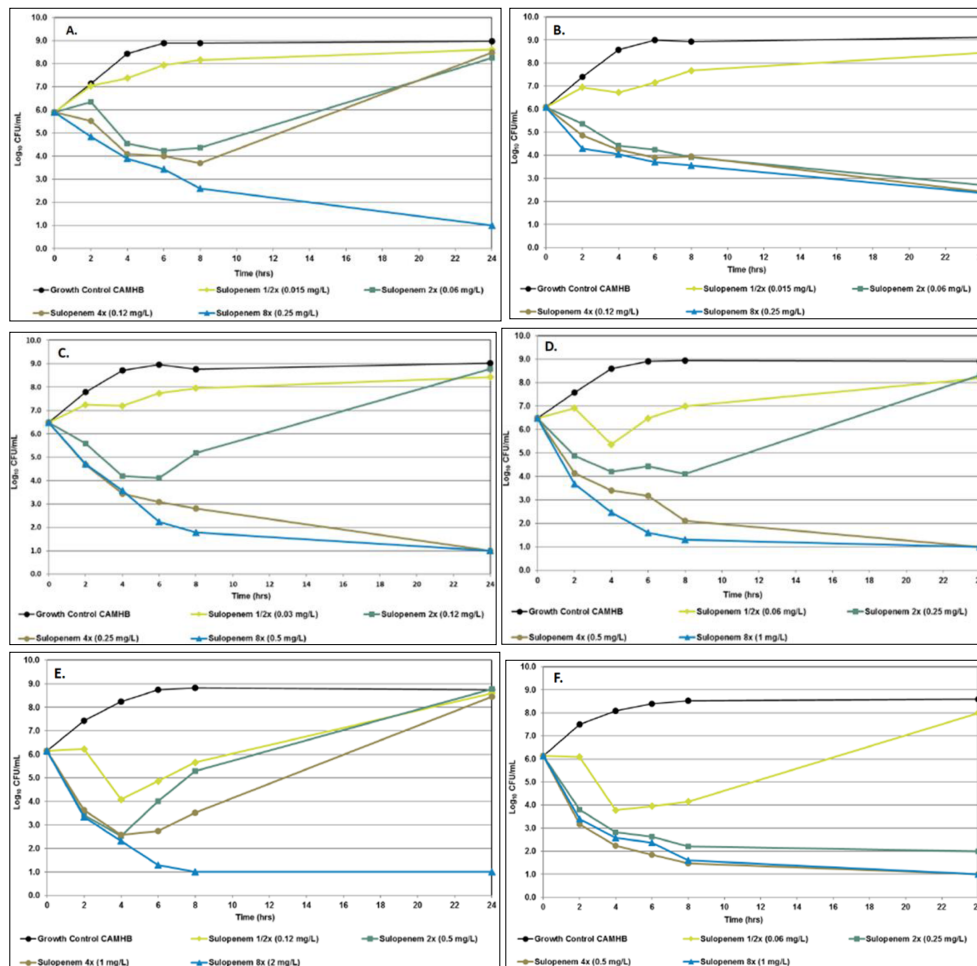
Organism	Phenotype	Modal MIC (µg/mL)	
		Sulopenem	Ertapenem
<i>E. coli</i> ATCC 25922	QC strain	0.03	0.015
<i>E. coli</i> ATCC 35218	TEM-1	0.03	0.015
<i>E. coli</i> NCTC 13353	CTX-M-15; ESBL	0.06	0.25
<i>E. coli</i> #937054	CTX-M-15; ESBL	0.12	0.25
<i>K. pneumoniae</i> ATCC 700603	SHV-18; ESBL	0.25	0.12
<i>K. pneumoniae</i> #396798	CTX-M-15; ESBL	0.12	0.25

ESBL, Extended-spectrum β-lactamase-producing strain.

Source: 17-ITR-01 Part 2, adapted from Table 2
 Abbreviations: MIC, minimum inhibitory concentration.

Bactericidal activity was observed for sulopenem at ≥4X the MIC for all isolates with the exception of *E. coli* ATCC 25922 and *K. pneumoniae* ATCC 700603 where regrowth was observed at 24 hr at 4X the MIC (Figure 16 A through Figure 16 F).

Figure 16. Time-Kill Curves for Sulopenem and Ertapenem Against *E. Coli* and *K. Pneumoniae* Isolates – JMI



Source: 17-ITR-01 Part 2, Figures 1, 5, 9, 13, 17, 21.

Sulopenem time-kill curves; A, *E. coli* ATCC 25922; B, *E. coli* ATCC 35218; C, *E. coli* NCTC 13353; D, *E. coli* #937054; E, *K. pneumoniae* ATCC 700603; F, *K. pneumoniae* #396798.

In summary, sulopenem showed bactericidal activity against *E. coli* and *K. pneumoniae* isolates at $\geq 4X$ the MIC and was also bactericidal against pneumococci at $\geq 2X$ the MIC.

16.5.1.3. Mechanisms of Resistance

The development of resistance to sulopenem was evaluated in spontaneous mutation frequency studies using two *E. cloacae* isolates and in serial passage studies using clinical isolates of *E. coli* and *K. pneumoniae*.

In a spontaneous mutation frequency study, colonies were isolated at a frequency of 1×10^{-8} with a ≤ 2 -fold increase in MIC from the parent strain. In the serial passage mutation studies, MIC values increased 16-fold during 15 serial passages in two out of the three tested *E. coli* isolates and were unchanged for the third isolate. MIC values increased 8-fold during serial passage for one of the two *K. pneumoniae* isolates tested, and MIC values increased from 0.5 to 256 $\mu\text{g}/\text{mL}$ for the other isolate.

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Similar to other carbapenems, resistance to sulopenem occurs primarily due to enzymatic inactivation by carbapenemases, but also can be caused by β -lactamase production, efflux pump expression, and changes in porins and/or PBPs (Papp-Wallace et al. 2011; Papp-Wallace 2019).

16.5.1.4. Interaction With Other Antimicrobials

Interactions of sulopenem with nine other antimicrobial agents were evaluated in a checkerboard assay using four *E. coli* and two *K. pneumoniae* isolates (JMI final report 17-ITR-01 Part 3). The antimicrobial drugs that were tested in combination with sulopenem were amoxicillin, aztreonam, ceftriaxone, doxycycline, gentamicin, levofloxacin, nitrofurantoin, trimethoprim-sulfamethoxazole, and vancomycin (Table 157). No instance of antagonism was observed in vitro between sulopenem and other antibacterial drugs against tested *E. coli* and *K. pneumoniae* isolates. Only, two instances of synergy were observed, both with trimethoprim-sulfamethoxazole, against *E. coli* ATCC 35218 (TEM-1) and *E. coli* 937054 (ESBL, CTX-M-15).

Table 157. Summary of the Minimum and Maximum FICI Values Observed During Checkerboard Testing of Sulopenem With a Variety of Agents Against *E. Coli* and *K. Pneumoniae*

	AMX		ATM		CFT		DOX		GEN		LEV		NIT		VAN		TMP	
	Min ¹	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
<i>E. coli</i> NCTC 13353	-	-	-	-	-	-	1.02	1.50	0.63	1.25	0.75	1.25	1.03	1.50	-	-	-	-
<i>E. coli</i> ATCC 35218	-	-	0.63	1.25	0.56	0.75	0.75	1.25	0.52	1.01	0.56	1.25	0.56	1.25	0.75	≥ 1.25	0.38	0.56
<i>E. coli</i> ATCC 25922	0.63	1.25	0.75	1.25	0.63	1.06	0.63	1.50	0.51	0.75	0.75	1.25	0.56	1.25	-	-	0.75	1.25
<i>E. coli</i> 937054	-	-	-	-	-	-	0.56	0.75	0.52	1.06	0.504	1.25	0.52	1.25	0.52	≥ 1.13	0.50	1.13
<i>K. pneumoniae</i> ATCC 700603	-	-	-	-	0.52	1.113	1.004	2.5	1.06	2.13	1.06	1.5	0.504	1.25	-	-	0.63	1.25
<i>K. pneumoniae</i> 396798	-	-	-	-	-	-	0.51	0.75	0.50	0.63	0.502	1.25	-	-	-	-	0.51	1.13

AMX, amoxicillin; ATM, aztreonam; CFT, ceftriaxone; DOX, doxycycline; GEN, gentamicin; LEV, levofloxacin; NIT, nitrofurantoin; VAN, vancomycin; TMP, trimethoprim-sulfamethoxazole. Synergy values shaded and in bold. ¹Min/Max refer to FICI values based on minimum and maximum replicate MIC values.

Source: JMI final report 17-ITR-01 Part 3, Table 2.

Abbreviations: FICI, fractional inhibitory concentration index.

16.5.1.5. In Vitro Spectrum and Activity

In vitro susceptibility testing was performed to determine the MIC by following the Clinical Laboratory Standard Institute guidelines (CLSI M07, M11, and M100). Sulopenem demonstrated in vitro activity against aerobic and anaerobic gram-positive and gram-negative bacteria in profiling, surveillance, and clinical studies. The in vitro MIC_{50/90} values (inhibits the growth of $\geq 50\%$ and $\geq 90\%$ of the isolates) were determined for sulopenem in all studies but this review only focuses on relevant uUTI pathogens from 3 recent surveillance studies and a single uUTI clinical study (IT001-301).

The activity of sulopenem was evaluated in a large collection of clinical isolates (UTI and IAI infection sources) from the US, Europe, and Canada. The first study was conducted by testing 873 aerobic clinical isolates collected from 2013-2015 (International Health Management Associates [IHMA]; Study IHMA_2757); the second study was conducted by testing 1,918 aerobic clinical isolates collected from 2016-2017 (JMI; Study 17-ITR-05); and a third

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surveillance study was conducted by testing 3,126 aerobic clinical isolates collected from 2016 in Canada (the Health Sciences Centre; CANWARD 2016).

In Vitro Activity Against Aerobic Gram-negative Bacteria

Sulopenem exhibited in vitro activity against Enterobacterales including uUTI-relevant pathogens and *H. influenzae* but had poor or no activity against *P. aeruginosa* and *A. baumannii*. A summary of the MIC_{50/90} values for sulopenem against gram-negative aerobic bacteria has been presented in Table 158.

Against *E. coli* isolates, sulopenem had MIC_{50/90} values of 0.03/0.06, 0.03/0.03, 0.03/0.06, 0.03/0.03 µg/mL against US-European isolates from 2013-2015, 2016-2017, Canadian (2016) and US (2019) isolates, respectively. The MIC_{50/90} value was 0.03/0.06 µg/mL against uUTI clinical study isolates (N=900).

Against *K. pneumoniae* isolates, sulopenem had MIC_{50/90} values of 0.06/0.12, 0.03/0.12, 0.06/0.12, and 0.03/0.06 µg/mL against US-European isolates from 2013-2015, 2016-2017, Canadian (2016) and US (2019) isolates, respectively. The MIC_{50/90} value was 0.06/0.12 µg/mL against uUTI clinical study isolates (N=96).

Against 33 *K. aerogenes* isolates from 2019, sulopenem had MIC_{50/90} value of 0.12/0.25 µg/mL. The MIC_{50/90} value was 0.06/0.12 µg/mL against uUTI clinical isolates (N=10).

Against *K. oxytoca* isolates, sulopenem had MIC_{50/90} values of 0.06/0.06, 0.03/0.06, 0.06/0.12 and 0.03/0.06 µg/mL against US-European isolates from 2013-2015, 2016-2017.

Against *P. mirabilis* isolates, sulopenem had MIC_{50/90} values of 0.25/0.5, 0.12/0.25, 0.25/0.5, and 0.25/0.25 µg/mL against US-European isolates from 2013-2015, 2016-2017, Canadian (2016) and US (2019) isolates, respectively. The MIC_{50/90} value was 0.25/0.25 µg/mL against uUTI clinical study isolates (N=32). Sulopenem showed similar activity against *P. vulgaris* isolates in profiling studies.

Against *E. cloacae* species complex isolates, sulopenem had MIC_{50/90} values of 0.12/0.5, 0.06/1.0, 0.12/0.5, and 0.12/0.5 µg/mL against US-European isolates from 2013-2015, 2016-2017, Canadian, and US isolates, respectively. The MIC_{50/90} value was 0.12/0.5 µg/mL against clinical study isolates.

Against 60 US-European *E. aerogenes* isolates from 2013-2015, sulopenem had an overall MIC_{50/90} value of 0.12/0.25 µg/mL.

Against *C. freundii* complex isolates, sulopenem had MIC_{50/90} values of 0.06/0.25, 0.06/0.25, and 0.06/0.12 µg/mL against US-European isolates from 2013-2015 and 2016-2017, and US isolates, respectively.

Against *C. koseri* isolates, sulopenem had MIC_{50/90} values of 0.03/0.03 and 0.03/0.06 µg/mL against US-European isolates from 2013-2015 and 2016-2017, respectively.

Against *S. marcescens* isolates, sulopenem had MIC_{50/90} values of 0.25/2.0, 0.5/4.0 and 0.5/2.0 µg/mL against US-European isolates from 2013-2015, Canadian and US isolates, respectively.

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

Against *Providencia* spp., sulopenem had overall MIC_{50/90} values of 0.12/0.25 and 0.12/0.5 µg/mL against US-European isolates from 2013-2015 (N=17) and US isolates from 2019 (N=14), respectively.

Against *Providencia alcalifaciens* isolates from profiling study (N=20), sulopenem had MIC_{50/90} value of 0.12/0.25 µg/mL.

Against *Providencia stuartii* isolates from profiling study (N=32), sulopenem had MIC_{50/90} values of 0.25/0.25 µg/mL.

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Table 158. MIC_{50/90} Values (µg/mL) of Sulopenem Against Aerobic Gram-Negative Bacteria – Surveillance

Organism	Region	Year	N	MIC ₅₀	MIC ₉₀
Enterobacterales	US-Europe	2013-2015	682	0.06	0.5
	US-Europe	2016-2017	1515	0.03	0.25
	Canada	2016	1055	0.03	0.25
	US	2019	1,647	0.03	0.25
<i>E. coli</i>	US-Europe	2013-2015	189	0.03	0.06
	US-Europe	2016-2017	753	0.03	0.03
	Canada	2016	612	0.03	0.06
	US	2019	983	0.03	0.03
<i>K. pneumoniae</i>	US-Europe	2013-2015	65	0.06	0.12
	US-Europe	2016-2017	303	0.03	0.12
	Canada	2016	184	0.06	0.12
	US	2019	273	0.03	0.06
<i>K. oxytoca</i>	US-Europe	2013-2015	61	0.06	0.06
	US-Europe	2016-2017	75	0.03	0.06
	Canada	2016	67	0.06	0.12
	US	2019	41	0.03	0.06
<i>K. aerogenes</i>	US	2019	33	0.12	0.25
<i>P. mirabilis</i>	US-Europe	2013-2015	19	0.25	0.5
	US-Europe	2016-2017	150	0.12	0.25
	Canada	2016	40	0.25	0.5
	US	2019	91	0.25	0.25
<i>E. cloacae</i> complex	US-Europe	2013-2015	66	0.12	0.5
	US-Europe	2016-2017	75	0.06	1.0
	Canada	2016	92	0.12	0.5
	US	2019	110	0.12	0.5

Organism	Region	Year	N	MIC ₅₀	MIC ₉₀
<i>E. aerogenes</i>	US-Europe	2013-2015	60	0.12	0.25
<i>C. freundii</i> complex	US-Europe	2013-2015	61	0.06	0.25
	US-Europe	2016-2017	46	0.06	0.25
	US	2019	29	0.06	0.12
<i>C. koseri</i>	US-Europe	2013-2015	29	0.03	0.03
	US-Europe	2016-2017	60	0.03	0.06
	US	2019	9	0.03	-
<i>S. marcescens</i>	US-Europe	2013-2015	60	0.25	2
	Canada	2016	60	0.5	4
	US	2019	36	0.5	2
<i>M. morgannii</i>	US-Europe	2013-2015	22	0.5	1
	US-Europe	2016-2017	79	0.5	1
	US	2019	20	1	1
<i>P. aeruginosa</i>	US-Europe	2013-2015	66	>16	>16
	Canada	2016	324	>8	>8
<i>A. baumannii</i>	US-Europe	2013-2015	63	16	>64
<i>H. influenzae</i>	Canada	2016	133	0.12	0.5

US, United States; MIC, minimum inhibitory concentration; MIC₅₀, MIC against 50% of the isolates; MIC₉₀, MIC against 90% of the isolates.

Source: IHMA_2757, 17-ITR-05, CANWARD 2016, 18-ITR-03.

In Vitro Activity Against Aerobic Gram-positive Bacteria

Among gram-positive aerobic bacteria, sulopenem demonstrated in vitro activity against certain bacterial species including uUTI relevant pathogens *Staphylococcus saprophyticus* and *Streptococcus agalactiae*. A summary of the MIC_{50/90} values for sulopenem against gram-positive aerobic bacteria has been presented in Table 159.

Table 159. MIC_{50/90} Values (µg/mL) of Sulopenem Against Aerobic Gram-Positive Bacteria – Surveillance

Organism	Region	Year	N	MIC ₅₀	MIC ₉₀
S. aureus	US-Europe	2016-2017	101	0.12	>16
	Canada	2016	662	0.06	8
MSSA	US-Europe	2016-2017	61	0.06	0.12
	Canada	2016	550	0.06	0.12
MRSA	US-Europe	2016-2017	40	16	>16
	Canada	2016	112	>8	>8
S. saprophyticus	US-Europe	2013-2015	31	0.25	0.25
	US-Europe	2016-2017	61	0.25	0.25
E. faecalis	US-Europe	2013-2015	30	4	8
	US-Europe	2016-2017	101	4	8
	Canada	2016	101	≥8	≥8
E. faecium	US-Europe	2016-2017	100	>16	>16
	Canada	2016	38	>8	>8
S. pneumoniae	Canada	2016	117	≤0.008	0.03
S. pyogenes	Canada	2016	44	0.015	0.03
S. agalactiae	US-Europe	2016-2017	40	0.03	0.06
	Canada	2016	38	0.03	0.06

US, United States; MIC, minimum inhibitory concentration; MIC₅₀, MIC against 50% of the isolates; MIC₉₀, MIC against 90% of the isolates.

Source: [IHMA_2757](#), [17-ITR-05](#), [CANWARD 2016](#)

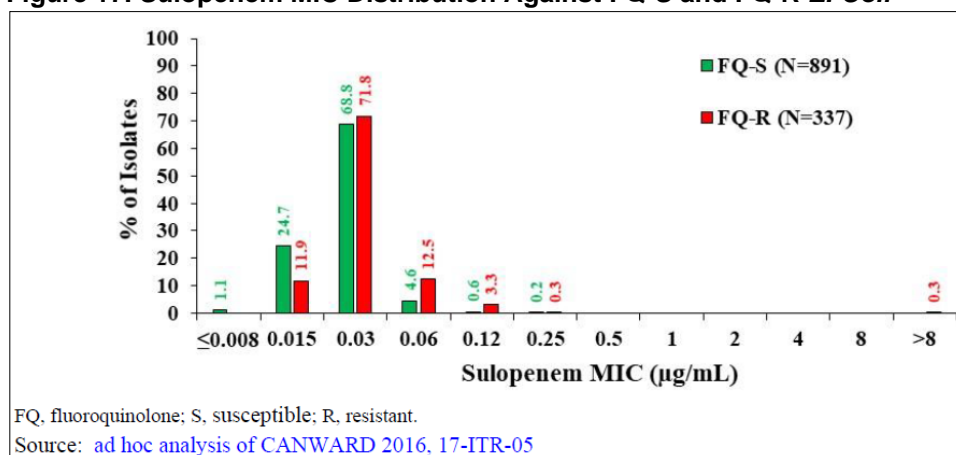
Abbreviation: MRSA, methicillin-resistant Staphylococcus aureus, MSSA, methicillin susceptible Staphylococcus aureus

Sulopenem Activity Against Organisms With Key Resistance Phenotypes

Escherichia Coli (FQ-R, ESBL)

Against surveillance isolates, sulopenem had an MIC_{50/90} value of 0.03/0.03 µg/mL against fluoroquinolone-susceptible (FQ-S) *E. coli* isolates (N=891) compared to 0.03/0.06 µg/mL against fluoroquinolone resistance (FQ-R) *E. coli* isolates (N=337). The MIC₉₀ values are only one doubling dilution higher for FQ-R isolates. The sulopenem MIC distribution is shown in Figure 17.

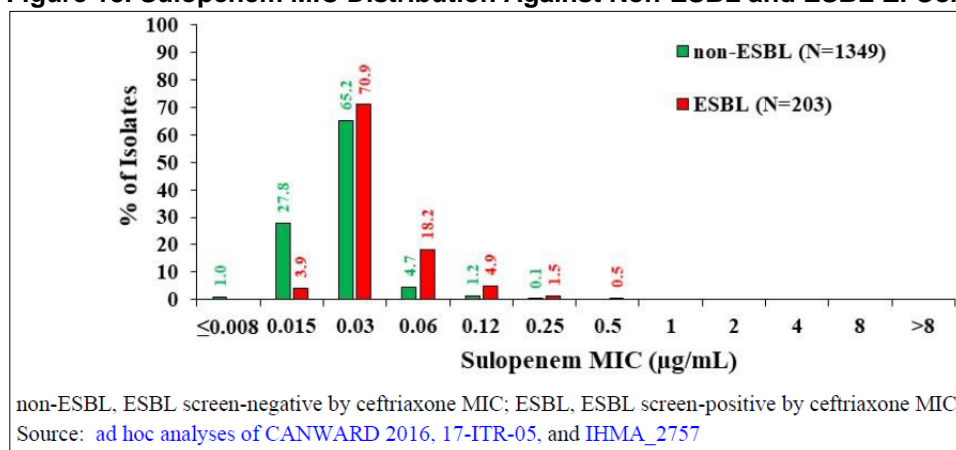
Figure 17. Sulopenem MIC Distribution Against FQ-S and FQ-R *E. Coli*



Abbreviations: MIC, minimum inhibitory concentration

Based on phenotypic ESBL screening (ceftriaxone MIC values ≥ 2 µg/mL), sulopenem MIC distribution against non-ESBL (N=1349) and ESBL isolates (N=203) of *E. coli* is shown in Figure 18. Against non-ESBL isolates, sulopenem had an MIC_{50/90} value of 0.03/0.03 µg/mL compared to 0.03/0.06 µg/mL for ESBL isolates.

Figure 18. Sulopenem MIC Distribution Against Non-ESBL and ESBL *E. Coli*

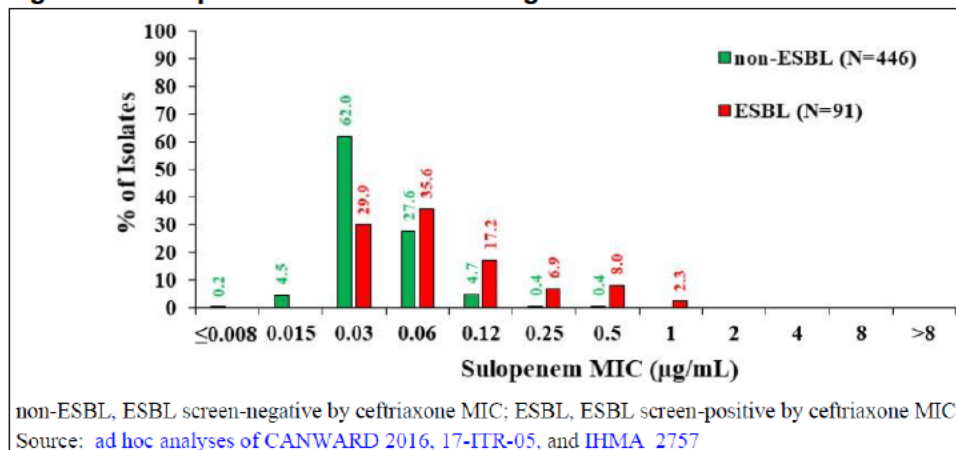


Abbreviations: ESBL, extended spectrum beta-lactamases; MIC, minimum inhibitory concentration

Klebsiella Pneumoniae (ESBL, Carbapenem-Resistant Enterobacterales)

Sulopenem MIC distribution against non-ESBL and ESBL isolates is shown in Figure 19. Against non-ESBL *K. pneumoniae* isolates (N=446), sulopenem had MIC_{50/90} values of 0.03/0.06 µg/mL compared to 0.06/0.5 µg/mL for ESBL isolates (N=91).

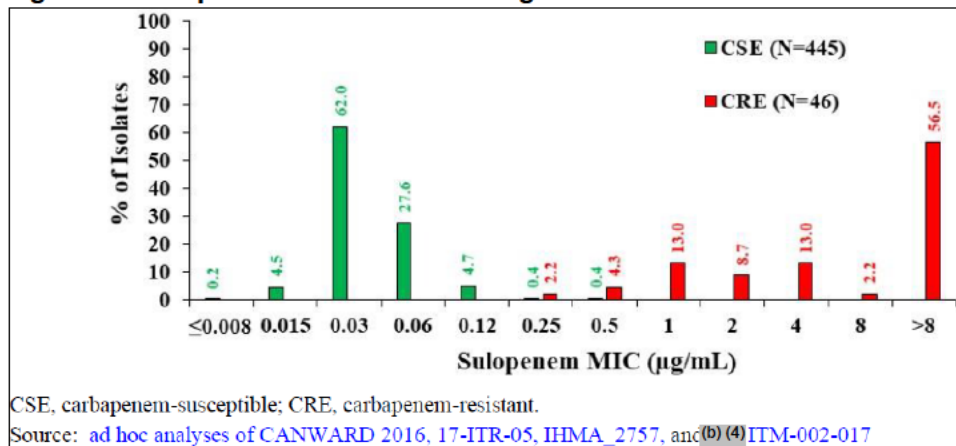
Figure 19. Sulopenem MIC Distribution Against Non-ESBL and ESBL *K. Pneumoniae*



Abbreviations: ESBL, extended spectrum beta-lactamases; MIC, minimum inhibitory concentration

Sulopenem MIC distribution against carbapenem-susceptible Enterobacterales (CSE) and carbapenem-resistant Enterobacterales (CRE) isolates of *K. pneumoniae* is shown in Figure 20. Against carbapenem-susceptible Enterobacterales isolates (N=445), sulopenem had MIC_{50/90} values of 0.03/0.06 µg/mL compared to >8/>8 µg/mL for CRE isolates (N=46).

Figure 20. Sulopenem MIC Distribution against CSE and CRE *K. Pneumoniae*



Abbreviations: MIC, minimum inhibitory concentration

Carbapenem-Resistant Enterobacterales

Sulopenem had very little to no activity against CRE isolates with known carbapenemases (study IHMA_3234). Sulopenem MIC_{50/90} value of ≥16/>16 µg/mL was observed for CRE expressing isolates such as IMP (N=50), KPC (N=50), NDM (N=50), VIM (N=50), and OXA (N=50) carbapenemases, compared to 1.0/4.0 µg/mL for CRE isolates (N=50) that were negative for known carbapenemases. A breakdown of isolates by species and resistance mechanism is shown in Table 160 and the sulopenem MIC distribution against these isolates is shown in Figure 21.

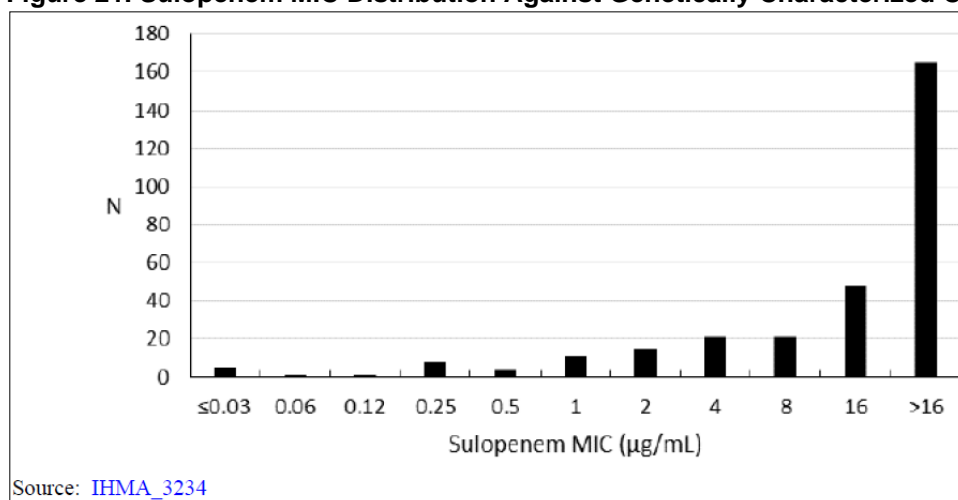
Table 160. Types of Carbapenemases Evaluated by Enterobacteriales Species

Organism	Genotype (n)						Species Total
	IMP	KPC	NDM	OXA	VIM	Cpnase neg	
<i>Citrobacter freundii</i>	15			1	4		20
<i>Enterobacter cloacae</i>	12	1	11	1	21	8	54
<i>Enterobacter kobei</i>	1						1
<i>Escherichia coli</i>	2	4	7	3		14	30
<i>Klebsiella aerogenes</i>	2			1			3
<i>Klebsiella oxytoca</i>	4	2		1	3		10
<i>Klebsiella pneumoniae</i>	10	43	29	37	14	28	161
<i>Providencia rettgeri</i>			3				3
<i>Providencia stuartii</i>					6		6
<i>Raoultella ornithinolytica</i>				2			2
<i>Raoultella planticola</i>				3			3
<i>Serratia marcescens</i>	4			1	2		7
Genotype Total	50	50	50	50	50	50	300

Cpnase, carbapenemase

Source: [IHMA_3234](#)

Figure 21. Sulopenem MIC Distribution Against Genetically Characterized CRE (N=300)



Source: [IHMA_3234](#)

Abbreviations: CRE, carbapenem-resistant Enterobacteriales; MIC, minimum inhibitory concentration

16.5.1.6. Assessment of Cross-resistance

Besides the beta-lactam class of antimicrobial, sulopenem is not expected to demonstrate cross-resistance.

16.5.1.7. Susceptibility Testing Methods

Studies were conducted to determine the in vitro susceptibility testing methods for sulopenem by following the CLSI guidelines (CLSI M23; CLSI M07) (Study (b) (4) 615). These include the following:

- Evaluating the impact of potential variation of test parameters in standard broth microdilution MIC testing;
- Development of a disk diffusion susceptibility testing;

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

- Evaluating the correlation between broth microdilution relative to disk diffusion and agar dilution methods; and
- Establishing quality control (QC) parameters.

Effect of Test Parameters on MIC Values

The effect of different test parameters on the activity of sulopenem was evaluated using QC isolates from American Type Culture Collections (ATCC). The evaluated parameters included: test medium cation content, test medium pH, inoculum density, inclusion of lysed horse blood in test medium, and incubation atmosphere (ambient vs. 5% CO₂).

Effect of Divalent Cations on the Activity of Sulopenem

The in vitro activity of sulopenem was tested using cation-adjusted Mueller-Hinton broth (CAMHB) containing varying concentrations of calcium and magnesium cations against the four QC strains, *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, *E. faecalis* ATCC 29212, and *S. aureus* ATCC 29213. Sulopenem did not appear to show significant variation in the in vitro MIC values. (Table 161).

Table 161. Effect of Divalent Cation Concentration on Sulopenem Activity

Organism	Geometric Mean MIC (µg/mL) from 6 Replicates							
	Ca ⁺⁺ 5 µg/mL mg ⁺⁺ 5 µg/mL	Ca ⁺⁺ 25 µg/mL mg ⁺⁺ 5 µg/mL	Ca ⁺⁺ 5 µg/mL mg ⁺⁺ 10 µg/mL	Ca ⁺⁺ 25 µg/mL mg ⁺⁺ 10 µg/mL	Ca ⁺⁺ 10 µg/mL mg ⁺⁺ 10 µg/mL	Ca ⁺⁺ 50 µg/mL mg ⁺⁺ 12.5 µg/mL	Ca ⁺⁺ 20 µg/mL mg ⁺⁺ 10 µg/mL	Ca ⁺⁺ 25 µg/mL mg ⁺⁺ 15 µg/mL
<i>Escherichia coli</i> ATCC 25922	0.03	0.03	0.03	0.03	0.03	0.03	0.03	0.03
<i>Pseudomonas aeruginosa</i> ATCC 27853	16	16	16	>8	16	16	16	16
<i>Enterococcus faecalis</i> ATCC 29212	4.0	4.0	4.0	4.0	4.0	2.8	4.0	3.2
<i>Staphylococcus aureus</i> ATCC 29213	0.05	0.05	0.05	0.06	0.06	0.08	0.06	0.06

Grey shaded cells represent results under standard conditions.

Source: Study (b) (4) 515, adapted from Table 4

Abbreviations: MIC, minimum inhibition concentration

Effect of Medium pH on the Activity of Sulopenem

Sulopenem activity was maintained against the four QC strains over the pH range from 6.0 to 8.0 with little variation compared to the standard MIC testing at pH 7.2 – 7.4 (Table 162).

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

Table 162. Effect of Test Medium pH on Sulopenem Activity

Organism	Geometric Mean MIC (µg/mL) from 5 Replicates at pH:						
	6.0	6.5	7.0	7.2	7.4	7.6	8.0
<i>Escherichia coli</i> ATCC 25922	0.06	0.05	0.03	0.03	0.04	0.05	0.05
<i>Pseudomonas aeruginosa</i> ATCC 27853	>16	>16	>16	16	16	16	16
<i>Enterococcus faecalis</i> ATCC 29212	2.0	2.3	3.5	4.0	4.0	4.0	4.0
<i>Staphylococcus aureus</i> ATCC 29213	0.03	0.05	0.05	0.07	0.09	0.09	0.10

Grey shaded cells represent results under standard conditions.

Source: adapted from Study (b) (4) 615, Table 5

Abbreviations: MIC, minimum inhibition concentration

Effect of Inoculum Density on the Activity of Sulopenem

Sulopenem activity was evaluated using an inoculum range of 10^3 through 10^7 CFU/mL. Sulopenem geometric mean MIC values were increased at the higher inoculum densities compared to the standard inoculum density of approximately 5×10^5 CFU/mL against the QC organisms (Table 163).

Table 163. Effect of Inoculum Density on Sulopenem Activity

Organism	Geometric Mean MIC (µg/mL) and Inoculum Density (CFU/mL) from 5 Replicates:									
	Sulo MIC	CFU/mL	Sulo MIC	CFU/mL	Sulo MIC	CFU/mL	Sulo MIC	CFU/mL	Sulo MIC	CFU/mL
<i>Escherichia coli</i> ATCC 25922	0.013	5.1E+03	0.023	4.6E+04	0.030	5.1E+05	0.083	5.7E+06	1.024	2.0E+07
<i>Pseudomonas aeruginosa</i> ATCC 27853	24.0	6.4E+03	24.0	4.6E+04	24.0	5.2E+05	23.44	5.1E+06	26.93	1.6E+07
<i>Enterococcus faecalis</i> ATCC 29212	2.0	5.0E+03	2.0	2.5E+04	2.77	2.8E+05	3.18	6.2E+06	5.10	8.9E+06
<i>Staphylococcus aureus</i> ATCC 29213	0.03	5.0E+03	0.033	4.3E+04	0.052	6.2E+05	0.152	6.5E+06	0.185	1.2E+07

Grey shaded cells represent results under standard conditions. Sulo, sulopenem; CFU, colony-forming unit;

Source: adapted from Study (b) (4) 615, Table 6

Abbreviations: CFU, colony-forming unit; MIC, minimum inhibition concentration

Effect of Testing in Medium With Lysed Horse Blood and Varied Incubation

The effects of supplementing test medium with 3 – 5% lysed horse blood compared to the standard CAMHB and the impact of incubating at 5% CO₂ as opposed to the standard ambient atmosphere on the activity of sulopenem were evaluated against the QC strains (Table 164). The sulopenem geometric mean MIC values increased slightly in the presence of lysed horse blood compared to CAMHB. Against all four QC strains, sulopenem geometric mean MIC values in the presence and absence of CO₂ were within ± one log₂ dilution.

Table 164. Effect of Supplementation of Test Medium With Lysed Horse Blood and Incubation in CO₂ on Sulopenem Activity

Organism	Geometric Mean MIC (µg/mL) from 5 Replicates at pH:			
	CAMHB	Lysed horse blood broth	Ambient Incubation	Incubation in 5% CO ₂
<i>Escherichia coli</i> ATCC 25922	0.030	0.049	0.019	0.031
<i>Pseudomonas aeruginosa</i> ATCC 27853	24.0	26.93	24.0	30.21
<i>Enterococcus faecalis</i> ATCC 29212	2.77	2.77	2.77	2.22
<i>Staphylococcus aureus</i> ATCC 29213	0.05	0.054	0.053	0.026

Grey shaded cells represent results under standard conditions.

Source: adapted from Study (b) (4) 615, Table 7, 8

Abbreviations: CAMHB, cation-adjusted Mueller-Hinton broth; MIC, minimum inhibitory concentration

Disk Content Studies

The Applicant submitted data from disk diffusion susceptibility testing with sulopenem disk masses of 5, 10, and 20 µg verses broth microdilution MIC testing by using concurrent inoculum of the following pathogens: 110 *S. aureus* (including methicillin-resistant *staphylococcus aureus*), 63 CoNS, 81 *S. pneumoniae*, 26 GAS, 27 GBS, 27 VGS, 105 enterococci, 116 Enterobacterales (including extended spectrum beta-lactamase), 31 lactose non-fermenting gram-negative bacilli and 91 *H. influenzae* (Study (b) (4) 615). The disk zone diameters and MIC values of the tested isolates were correlated in scatterplots to develop provisional interpretive criteria for the disk diffusion testing of sulopenem. QC ranges have been established using the 2 µg sulopenem disk.

Correlation of Broth Microdilution vs. Agar Dilution MIC Values

Susceptibility testing was conducted in parallel by broth microdilution and agar dilution using concurrent inoculum of 398 isolates (106 staphylococci, 102 Enterobacterales, 102 *S. pneumoniae* and 88 *H. influenzae* isolates) by following the CLSI guidelines (CLSI M07).

Essential agreement between broth microdilution and agar dilution MIC values did not exceed 95% for any of these tested groups of organisms, however, the maximum agreements of 93.8%, and 94.1% were achieved for methicillin-susceptible *staphylococcus aureus* (n=64) and Enterobacterales (n=102), respectively.

Quality Control Studies

Quality control (QC) studies for sulopenem have been conducted using CLSI M23 guidelines for the establishment of QC ranges for broth microdilution susceptibility testing of aerobes (Study (b) (4) 631), and disk diffusion susceptibility testing of Enterobacterales (Study (b) (4) ITM-004-18).

QC ranges for the Broth Microdilution Testing of Sulopenem Against Aerobes

Studies were performed to establish the QC ranges for broth microdilution susceptibility testing of sulopenem against aerobes (Study (b) (4) 631) in accordance with the CLSI M23 guidelines. A summary of the QC ranges for sulopenem approved by the CLSI are shown in Table 165.

Table 165. Summary of QC Ranges for the Broth Microdilution Testing of Sulopenem Against Aerobes

Organism	QC Range (µg/mL)	No. of dilutions in Range	Total N	N (%) in Range
<i>E. coli</i> ATCC 25922	0.015 to 0.06	3	240	240/240 (100)
<i>S. aureus</i> ATCC 29213	0.015 to 0.12	3	240	240/240 (100)
<i>E. faecalis</i> ATCC 29212	2 to 8	3	240	236/240 (98.3)
<i>S. pneumoniae</i> ATCC 49619	0.03 to 0.12	3	240	240/240 (100)
<i>H. influenzae</i> ATCC 49766	0.06 to 0.25	3	249	249/249 (100)

Source: Study (b) (4) 631 and CLSI M100

Abbreviations: QC, quality control

QC Ranges for the Disk Diffusion Testing of Sulopenem Against Enterobacterales

A Tier 2 study was performed to establish the QC range for *E. coli* ATCC 25922 for sulopenem using 2 µg disks by following the M23 guidelines ((b) (4) ITM-004-18). Two lots of sulopenem 2 µg disks were used in this study, both manufactured by Liofilchem (Roseto degli Abruzzi, Italy) and three lots of Mueller-Hinton agar media were used in this study: BBL (Becton-Dickinson, Sparks, MD), Hardy (Santa Maria, CA) and Remel (Lenexa, KS). Eight laboratories participated in the study, and each site tested ten replicates over a three-day period according to the CLSI disk diffusion method (CLSI M02-A13).

Results were similar by disk lot (mean zones were 26.5 and 26.8 mm) and media (mean zones were 26.3 to 27.0 mm). Disk diffusion susceptibility testing using a disk mass of 2 µg was selected as the optimum disk mass for the establishment of QC ranges.

16.5.1.8. Post-Antibiotic Effect

Post-antibiotic effect (PAE) was observed at 5x and 10x MIC of 0.2 and 0.7 hr for 1 out of 4 *E. coli* isolates tested, specifically ATCC 35218 (TEM-1). PAE was observed at 5x MIC for 0.7 hr for *K. pneumoniae* 396798 (ESBL, CTX-M-15, SHV-1, OXA-1/30) isolate. Sulopenem demonstrated a post-antibiotic sub-inhibitory MIC effect (PAE-SME) of >5 hour at 1/2X MIC for 4 *E. coli* and 2 *K. pneumoniae* isolates. Table 166 summarizes the results.

Table 166. Sulopenem and Ertapenem PAE and PA-SME Values Against *E. Coli* and *K. Pneumoniae*

Organism	Sulopenem					Ertapenem				
	PAE (hr)			PAE-SME (hr)		PAE (hr)			PAE-SME (hr)	
	1x	5x	10x	5x		1x	5x	10x	5x	
				1/4x	1/2x				1/4x	1/2x
<i>E. coli</i> ATCC 25922	0	0	0	0.9	>5.4	0	0.5	0	>4.8	>4.8
<i>E. coli</i> NCTC 13353	0	0	0	1.0	>5.3	0	0	0	4.5	>5.2
<i>E. coli</i> ATCC 35218	0	0.2	0.7	1.7	>5.4	0	1.0	1.0	4.2	>5.3
<i>E. coli</i> 937054	0	0	0	>5.2	>5.2	0.4	0.4	0.8	3.0	>5.2
<i>K. pneumoniae</i> ATCC 700603	0	0	0	2.5	>5.3	0.9	0.9	1.1	4.6	>5.2
<i>K. pneumoniae</i> 396798	0	0.7	0	4.3	>5.4	0.9	0.2	0.2	3.7	>5.3

Source: Adapted from JMI Final Report 17-ITR -01

Abbreviations: MIC, minimum inhibitory concentration; PAE, post antibiotic effect; PAE-SME, post-antibiotic sub-inhibitory MIC effect

16.5.1.9. Metabolites of Sulopenem etzadroxil

In addition to the prodrug sulopenem etzadroxil, five metabolites M1, M2, M3, M4 and sulopenem were detected during incubation in human whole blood. Following incubation, sulopenem etzadroxil levels were observed to decrease with time and by 120 minutes the prodrug was barely detectable (Table 167).

Table 167. Quantification of Metabolites of Sulopenem-Etzadroxil During Incubation in Human Blood

Peak	% MS Response ¹				% MS Response ²			
	0 Minute	2 Minutes	10 Minutes	120 Minutes	0 Minute	2 Minutes	10 Minutes	120 Minutes
Sulopenem-etzadroxil	99.88	97.87	88.38	8.05	100	37.88	23.31	0.006
M1	ND	0.15	1.11	6.64	ND	0.06	0.29	0.05
M2	ND	1.29	9.39	23.57	ND	0.50	2.48	0.017
M3	0.003	0.48	0.54	12.42	0.003	0.19	0.14	0.009
Sulopenem	ND	0.003	0.12	49.33	ND	0.001	0.03	0.036
M4	0.11	0.21	0.45	ND	0.11	0.08	0.12	ND

¹Reported as a percentage of total compound-related material. ²Reported relative to the MS peak area for sulopenem-etzadroxil in the control sample. ND, not detected.

Source: 17TT003-2017_06_30_Iterum Therapeutics (b) (4)-00, Tables 2 and 3.

16.5.2. Animal Infection Model Studies

Sulopenem and its oral prodrug sulopenem etzadroxil were evaluated for *in vivo* activity in three animal infection models:

- The mouse systemic infection model against *S. pneumoniae* and *K. pneumoniae*;
- The mouse pulmonary infection model against *S. pneumoniae*; and
- The Mongolian gerbil otitis media model against *H. influenzae*.

16.5.2.1. Systemic Infection Models

Summaries of the in vivo activities of sulopenem and its prodrug, sulopenem etzadroxil dosed orally (PO) or subcutaneously (SC) are presented below:

Study RR 810-00093: Briefly, CF1 mice (n=10) were infected via an intraperitoneal (IP) challenge with 3.5×10^7 CFU/mouse of *K. pneumoniae* 53A1109 isolate. This is an ESBL-producing strain that contains the TEM-1, OXA-9, multiple SHVs and AmpC β -lactamase genes with a sulopenem MIC value of 0.25 μ g/mL. Compounds in this study were dosed PO or SC at 0.5- and 4.0-hours post-infection to determine the protective dose for 50% of the tested animals (PD50). Sulopenem failed when dosed PO (PD50 >50 mg/kg) but was efficacious when dosed SC, with a PD50 of 3.4 mg/kg, as shown in Table 168. Prodrug sulopenem etzadroxil dosed orally exhibited a PD50 of 9.0 mg/kg in this model.

Study RR 810-00093: CF1 mice (n=10) were infected via an IP challenge with 1.3×10^2 CFU/mouse of *S. pneumoniae* 02J1095. This is a macrolide-resistant, penicillin-tolerant strain with sulopenem MIC value of 0.25 to 0.5 μ g/mL. Compounds were administered at 0.5- and 4-hr post-infection. Sulopenem failed when dosed PO (PD50>50 mg/kg) but was efficacious when dosed SC, with a PD50 of 4.3 mg/kg (Table 168). Sulopenem etzadroxil dosed orally exhibited a PD50 of 6.3 mg/kg.

Study RR04-25-2006: CF1 female mice (n=8) were infected via IP injection with 3.5×10^2 CFU/mouse of *S. pneumoniae* 02J1095 strain with sulopenem MIC value of 0.25 to 0.5 μ g/mL. Compounds were administered at 0.5- and 4-hr post-infection. When dosed PO, sulopenem failed with a PD50 of >50 mg/kg but was efficacious when dosed SC (PD50 6.3 mg/kg) as shown in Table 168. Sulopenem etzadroxil demonstrated an oral PD50 of 12.5 mg/kg.

Table 168. Efficacy (PD50 in mg/kg) of Sulopenem, Sulopenem Etzadroxil and Comparators Against Murine Systemic Infections

Organism	Sulopenem (sc)	Sulopenem-etzadroxil (po)	IMI (sc)	CIP (po)	CFZ (sc)	CFT (sc)	AMX (po)	CLR (po)	Source
<i>K. pneumoniae</i> 53A1109	3.4 (2.6 – 4.3)	9.0 (8.7 – 9.3)	1.4 (1.37 – 1.39)	49.4 (28.1 – 70.8)	>50	-	-	-	RR 810-00093
<i>S. pneumoniae</i> 02J1095	4.3 (4.2 – 4.5)	6.3 (1.5 – 11.1)	-	-	-	6.3 (3.4 – 9.1)	20.8 (18.4 – 23.1)	>100	RR 810-00093
<i>S. pneumoniae</i> 02J1095	6.3 (3.4 – 9.1)	12.5 (12.4 – 12.6)	-	-	-	6.3 (3.4 – 9.1)	14.1 (14.0 – 14.3)	>100	RR-04-25-2006

IMI, imipenem; CIP, ciprofloxacin; CFZ, ceftazidime; CFT, ceftriaxone; AMX, amoxicillin; CLR, clarithromycin. 95% confidence intervals shown in parentheses.

Source: [adapted from RR 810-00093](#)

Abbreviations: PD50, 50% of protective dose

16.5.2.2. Pulmonary Infection Models

The in vivo activity of sulopenem and its prodrug was evaluated in mouse pulmonary infection models caused by different gram-positive organisms in two studies: RR 810-00093 and RR-05-01-2006.

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

Study RR 810-00093: Briefly, CF-1 mice were infected via the intranasal route with 1.3×10^6 CFU/mouse of *S. pneumoniae* 02J1095 (macrolide-resistant, penicillin-tolerant strain with sulopenem MIC value of 0.25 to 0.5 µg/mL). Mice were treated twice per day for two days starting 18 hours post-infection. Sulopenem demonstrated a PD50 of >50 mg/kg when dosed PO, whereas, the PD50 was 13.9 mg/kg when dosed SC in this model (Table 169). Sulopenem etzadroxil had a PD50 of 12.5 mg/kg when dosed PO.

Table 169. Efficacy (PD50 in mg/kg) of Sulopenem, Sulopenem-Etzadroxil and Comparators Against Murine Pulmonary Infections

Organism	Sulopenem (sc)	Sulopenem-etzadroxil (po)	AMX (po)	CFT (sc)	CLR (po)	Source
<i>S. pneumoniae</i> 02J1095	13.9 (0.05 – 27.7)	12.5 (5.6 – 19.4)	35.6 (26.8 – 44.3)	13.8 (9.5 – 18.0)	>100	RR 810-00093
<i>S. pneumoniae</i> 02J1095	14.3 (-2.8 – 31.5)	16.4 (9.8 – 23.0)	16.3 (8.2 – 24.5)	9.4 (0.47 – 18.3)	>100	RR-05-01-2006

AMX, amoxicillin; CFT, ceftriaxone; CLR, clarithromycin. 95% confidence intervals shown in parentheses.

Source: adapted from RR 810-00093 and RR-05-01-2006

Abbreviations: PD50, 50% of protective dose

Study RR-05-01-2006: A second study was conducted to evaluate the activity of sulopenem and the prodrug. Mice were infected with 1.04×10^6 CFU/mouse via intranasal infection with *S. pneumoniae* 02J1095. Compounds were dosed twice per day for two days starting 18 hours post-infection. Sulopenem PD50 values were 14.3 and >50 mg/kg for when dosed PO and SC, respectively. Sulopenem etzadroxil had an oral PD50 of 16.4 mg/kg in this model.

16.5.2.3. Gerbil Otitis Media Models

The in vivo activity of sulopenem, and the prodrug sulopenem-etzadroxil was investigated in a gerbil model of otitis media caused by *H. influenzae* Rd/AH5-3 strain (β-lactamase-negative, ampicillin-resistant with sulopenem MIC value of 0.015 to 0.06 µg/mL). Briefly, gerbils were infected via direct injection into the middle ear with 1.25×10^7 CFU/gerbil; therapy was initiated 18 hr post-infection and continued three times daily for two days. In this model, sulopenem failed when dosed PO with a PD50 of >50 mg/kg but was efficacious when administered SC with a PD50 of 4.3 mg/kg (Table 170). Sulopenem etzadroxil had an oral PD50 of 4.5 mg/kg.

Table 170. Efficacy (ED50 in mg/kg) of Sulopenem, Sulopenem-Etzadroxil and Comparators Against Gerbil Otitis Media

Organism	Sulopenem (sc)	Sulopenem-etzadroxil (po)	AUG (po)	CEF (po)	IMI (sc)	CLR (po)	Source
<i>H. influenzae</i> Rd/AH5-3	4.3 (4.2 – 4.5)	4.5 (4.4 – 4.6)	3.4 (3.4 – 3.5)	>50	2.5 (1.4 – 3.7)	>100	RR 810-00093

AUG, Augmentin (7:1 amoxicillin); CEF, Cefaclor; IMI, imipenem; CLR, clarithromycin. 95% confidence intervals shown in parentheses.

Source: adapted from RR 810-00093

Abbreviations: ED50, 50% effective dose

16.5.3. Pharmacokinetics/Pharmacodynamics Studies

(For a detailed review of the PK/PD studies, PTA analysis, and Monte-Carlo simulation, please refer to the Clinical Pharmacology section 6.3.2 of this unireview)

To evaluate the PK/PD relationship for sulopenem, a mouse thigh infection study was conducted using clinical isolates of *S. pneumoniae*, *S. pyogenes*, *E. coli* and *K. pneumoniae* with different resistant phenotypes. Based on preclinical data, the Applicant states that $fT > MIC$ was the PK/PD target that best correlated with efficacy. However, the FDA Clinical Pharmacology reviewer found significant issues related to the data presented for the PK/PD studies and the data suggest that the PK/PD target index for sulopenem is predicted to be C_{max}/MIC based on plasma concentration.

Clinical Microbiology Reviewer's Comments: Although the Applicant stated that $T > MIC$ is the PK/PD target for sulopenem that best correlates with efficacy, the FDA Clinical Pharmacology reviewer found significant issues related to the data presented for the PK/PD studies.

16.5.4. Clinical Study For Sulopenem: uUTI

The Applicant conducted a single Phase 3 clinical study (IT001-301) to determine the safety and efficacy of a 5-day course of oral sulopenem etzadroxil/probenecid against a 3-day course of oral ciprofloxacin for the treatment of adult female patients (≥ 18 years of age) with uUTI. Additionally, supporting safety data for sulopenem were submitted from two different failed Phase 3 clinical studies conducted for complicated urinary tract infections (cUTI; IT001-302) and complicated intra-abdominal infections (cIAI; IT001-303). The three Phase 3 clinical trials are summarized in Table 171. However, this review focuses primarily on the uUTI trial (IT001-301).

Clinical Microbiology Reviewer's Comments: The study results in this section were largely taken from the Applicant's analyses and were used to assist in review of the clinical microbiology data for an initial assessment of possible susceptibility test interpretive criteria/breakpoints. The Clinical Microbiology reviewer defers to the Statistical reviewer for analysis and comment on the Agency's assessment of the efficacy results as noted in Section 8.1 of this unireview.

Table 171. Summary of Designs for Key Studies in Support of Sulopenem-Etzadroxil NDA

Clinical Study	IT001-301	IT001-302	IT001-303
Phase; Year completed	Phase 3; 2020	Phase 3; 2020	Phase 3; 2019
Indication	uUTI	cUTI	cIAI
Population	Adult females with uUTI (1,671 total)	Adults with cUTI (1395 total)	Adults with cIAI (674 total)
Comparator (N)	Ciprofloxacin Q12h PO (787)	Ertapenem IV with ciprofloxacin PO or amoxicillin-clavulanate step-down (698)	Ertapenem IV with ciprofloxacin PO and metronidazole or amoxicillin-clavulanate step-down (336)
Sulopenem/Sulopenem-etzadroxil Dose/Route (N)	500 mg sulopenem etzadroxil/ 500 mg probenecid bilayer tablet Q12h/PO (803)	1000 mg sulopenem IV QD with 500 mg sulopenem etzadroxil/ 500 mg probenecid Q12h step-down (697)	1000 mg sulopenem IV QD with 500 mg sulopenem etzadroxil/ 500 mg probenecid Q12h step-down (336)

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

Clinical Study		IT001-301	IT001-302	IT001-303
Therapy Duration		5 days (sulopenem etzadroxil/probenecid) 3 days (ciprofloxacin)	5 days (IV sulopenem) followed by sulopenem etzadroxil/probenecid to complete 7 to 10 total days	≥5 days (IV sulopenem) followed by sulopenem etzadroxil/probenecid to complete 7 to 10 total days or ertapenem IV for ≥5 days followed by ciprofloxacin and metronidazole or amoxicillin-clavulanate to complete 7 to 10 total days
Time points	Baseline	D-1 to D1	D-1 to D1	D-1 to D1
Intermediate				
	EOT	Day 5 ± 1 day	Day 10 ± 1 day	Day 11 - 14 ± 1 day
	TOC	Day 12 ± 1 day	Day 21 ± 1 day	Day 28 ± 1 day
	FV	Day 28 ± 2 days	Day 28 ± 3 days	Day 28 ± 1 day
Stratification Factors and Enrollment Limits at Randomization			Infection type	Infection type
Primary Endpoints		Overall response (clinical and microbiological) in micro-MITTS and micro-MITTR populations at TOC	Overall response (clinical and microbiological success) at TOC in the micro-MITT population	Clinical response at Day 28 (TOC) visit in the micro-MITT population
Key Clinical Efficacy Secondary Endpoints		- Clinical Response - Microbiologic Response - Overall Response in microMITT population	- Clinical Response - Microbiological response	Clinical response at the EOT Visit in the micro-MITT population

uUTI, uncomplicated urinary tract infection; cUTI, complicated urinary tract infection; cIAI, complicated intra-abdominal infection; EOT, End of Treatment; TOC, Test-of-Cure; FV, Final Visit

Source: NDA submission

In Study 301, the microbiological modified intent-to-treat (MMITT) population comprised all subjects who had at least one or a maximum of two baseline urinary bacterial pathogen(s) identified from urine with $\geq 10^5$ CFU/mL. A total of 830 (sulopenem arm, dosed BID for five days) and 829 (ciprofloxacin arm, dosed twice daily for three days) patients were included in the modified intent-to-treat (MITT) population. The primary endpoint for the study was the overall response (clinical and microbiological success) on Day 12 (± 1 day) at the test-of-cure (TOC) visit.

Bacterial urinary pathogens were identified from microbiological culture from acceptable urine specimens collected at baseline, and subsequent visits.

Among the ITT population, uUTIs were predominantly caused by *E. coli* (56.0% in sulopenem treatment group and 58.4% in ciprofloxacin treatment group), *K. pneumoniae* (6.5% in sulopenem treatment group and 6.0% in ciprofloxacin treatment group), and *P. mirabilis* (2.2% in sulopenem treatment group and 2.1% in ciprofloxacin treatment group).

16.5.4.1. uUTI Phase 3 Clinical Study, SURE 1: IT001-301

Methods for Microbiological Collection, Culture, and Identification

Microbiological Sampling

For microbiological culture and analysis, mid-stream clean-catch urine specimens were collected from patients into a sterile container at Screening (Baseline), Day 3, Day 5 (EOT), Day 12 (TOC), Day 28, and for any study-related visits. All specimens were sent to the local Microbiology laboratory or the regional Microbiology Laboratory (Covance) within 24 hours after collection. In addition, an aliquot of screening/baseline urine samples were also sent to central Microbiology laboratory, International Health Management Associates for the US sites only.

For the US sites, Covance served as the regional Microbiology Laboratory where isolates were stored in duplicate and where quantitative urine culture, identification and susceptibility testing were performed at all visits. The Central Microbiology Laboratory, IHMA conducted study-specific quantitative urine culture, identification and susceptibility testing/custom MIC and urine Gram stain/reading at Screening/Baseline only. IHMA also stored duplicates of isolates at -80°C and performed re-identification and susceptibility testing of isolates received from Covance.

For the ex-US sites, [REDACTED] ^{(b) (4)} was the Central Laboratory and IHMA was the Central Microbiological Laboratory. [REDACTED] ^{(b) (4)} provided study supplies, isolate delivery, and data collection; whereas, IHMA confirmed isolate identification and conducted susceptibility testing and MIC assays, as well as staining and reading the urinary slides prepared at the local laboratories.

The flowcharts for microbiological procedures in the US sites and ex-US sites are presented in Figure 22.

**Figure 22. Flow Chart of Microbiology Procedures for the IT001-301 Study: US Sites (Top Figure);
Ex-US Sites (Bottom Figure)**



Organism Isolation And Target uUTI Pathogens

Urine specimens were plated by calibrated disposable loops (1 μ L and 10 μ L loops) on the following agar plates for colony counts, microbial identification, and susceptibility testing by following standard microbiological procedures:

- Blood agar plate
- Selective agar for gram-negative rods [e.g., MacConkey or Eosin Methylene Blue plate]

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
{sulopenem etzadroxil/probenecid}

The following organisms were considered as uropathogens when the baseline urine culture grew $\geq 10^5$ CFU/mL:

- Enterobacterales
- *Staphylococcus saprophyticus*
- *Enterococcus* spp.
- *Pseudomonas aeruginosa*

However, the MMITT population (defined below) for this study only included patients with uUTIs caused by Enterobacterales and/or *S. saprophyticus* (study uropathogens).

Microbiological-MITT (or MMITT): MMITT patients were defined as those with a positive study entry urine culture within 48 hours prior to the first dose, with $\geq 10^5$ CFU/mL of a uropathogen (Enterobacterales or *Staphylococcus saprophyticus* only) and no more than 2 species of target pathogens identified in the study entry urine culture with $\geq 10^5$ CFU/mL.

MMITTS: The MMITTS patients were those MMITT patients with a baseline uropathogen susceptible to the comparator drug, ciprofloxacin (defined as MIC ≤ 1 mg/L), and no baseline pathogen phenotypically resistant to ciprofloxacin.

MMITTR: The MMITTR patients were those MMITT patients with a baseline uropathogen resistant to the comparator drug, ciprofloxacin (defined as MIC ≥ 2 mg/L).

Microbiological Outcome Measures

The primary endpoint for the uUTI study was the outcome of Overall Response at the TOC visit which included combined clinical and microbiological responses. However, the microbiological definitions used in the assessment of the per-pathogen microbiological response are summarized in Table 172 and Table 173.

Table 172. Baseline Pathogens

Response	Definition
Eradication	A urine culture obtained at the timepoint of analysis demonstrated $< 10^3$ CFU/mL of the baseline uropathogen
Persistence	A uropathogen from urine present at baseline regardless of susceptibility grew at $\geq 10^3$ CFU/mL at the timepoint of analysis*.
Persistence with Increasing MIC	A urine culture taken after at least 2 full days of treatment grew $\geq 10^3$ CFU/mL of the baseline uropathogen and displayed ≥ 4 -fold higher MIC to study drug received at the timepoint of analysis.
Indeterminate	Patient was lost to follow-up or an assessment was not undertaken such that no urine culture was obtained (or culture results could not be interpreted) at the timepoint of analysis (contaminated results are considered a negative culture and therefore an eradication ⁶).

CFU, colony-forming unit; MIC, minimum inhibitory concentration. *The genus/species and susceptibility profiles need to match. Additional molecular testing by pulsed field gel electrophoresis (PFGE) or whole genome sequencing (WGS) was performed as needed for confirmation.

Source: NDA submission

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 {sulopenem etzadroxil/probenecid}

Table 173. Post-Baseline Pathogens

Response	Definition
Superinfection	A uropathogen not present at baseline grew with $\geq 10^5$ CFU/mL from the first dose of study drug through the EOT visit in the setting of recurrent/persistent/new uUTI symptoms requiring non-study systemic antibacterial treatment* (patient-determined clinical failure at EOT).
New Infection	Isolation of a non-baseline pathogen from a culture post-EOT visit from a urine culture specimen with $\geq 10^5$ CFU/mL in a patient with one or more new uUTI signs/symptoms requiring new systemic antibacterial treatment* after the EOT visit (patient-determined clinical failure post-EOT).
Recurrence	In a patient with clinical and microbiological success at EOT, isolation of a baseline pathogen from a urine culture specimen with $\geq 10^5$ CFU/mL post-EOT visit, along with new or recurrence of one or more uUTI signs/symptoms requiring new systemic antibacterial treatment* after the EOT visit (patient-determined clinical failure post-EOT).
Colonization	Isolation of a microorganism from the urine culture after EOT in a patient without one or more signs and symptoms of uUTI and not requiring new systemic antibiotic therapy* (patient-determined clinical success post-EOT).

* Excluding linezolid, daptomycin, vancomycin, azithromycin, metronidazole, josamycin, macrolide, nifuratel, tergynan, fluconazole, cystone, butoconazole nitrate, clindamycin hydrochloride, clotrimazole, tinidazole and clarithromycin, as well as “antibiotics and chemotherapeutics for dermatological use” and “ophthalmologicals” since they have no activity against the pathogens in the study. CFU, colony-forming unit; EOT, end of treatment; uUTI, uncomplicated urinary tract infection

Source: NDA submission

Baseline Microbiology in Clinical Studies: MMITTR Population

All urinary pathogens cultured from the MMITTR population are presented in Table 75 of this unireview under section 8.1.2. The most frequently isolated pathogens in both treatment arms were *E. coli* (87.5%), *K. pneumoniae* (9.3%), and *P. mirabilis* (4.8%).

Monomicrobial and Polymicrobial Infections at Baseline: MMITTR

About 96% of patients in the MMITTR population had monomicrobial infections as shown in Table 174.

Table 174. Monomicrobial and Polymicrobial Infections at Baseline – MMITTR Population

	Sulopenem n/N (%)	Ciprofloxacin n/N (%)	Total n/N (%)
Monomicrobial	140/147 (95.2%)	134/139 (96.4%)	274/286 (95.8%)
Polymicrobial	7/147 (4.8%)	5/139 (3.6%)	12/286 (4.2%)

Micro-MITT, microbiologic Modified Intent-to-Treat. The percentages are calculated as 100 x (n/N). Enterobacterales and *S. saprophyticus* are included in the table. Micro evaluable patients are both clinical and micro evaluable.

Source: IT001-301, Table 14.1.2.10.1

MIC Susceptibility Data of Baseline Pathogens: MMITTR

The MIC susceptibility data in the MMITTR population in the sulopenem etzadroxil/probenecid treatment group, ciprofloxacin treatment group, and both treatment groups (combined), are presented in Table 175, Table 176 and Table 177, respectively. Against 247 *E. coli* isolates from both treatment groups, the MIC_{50/90} values were 0.03/0.06 µg/mL. Against 28 *K. pneumoniae* isolates from both treatment groups, the MIC_{50/90} values were 0.12/4.0 µg/mL.

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Table 175. Activity of Sulopenem and Ciprofloxacin Against Baseline Pathogens –MMITTR Population – Sulopenem Treatment Group

Organism Antibiotic	N	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)	CLSI %S/%I/%R
<i>Escherichia coli</i>	N = 127			
Sulopenem		0.03	0.06	0/0/0
Ciprofloxacin		>2	>2	3.1/0.8/96.1
<i>Klebsiella pneumoniae</i>	N = 12			
Sulopenem		0.06	4	0/0/0
Ciprofloxacin		>2	>2	8.3/0/91.7

Note: percentages are calculated as $100 \times (n/N)$; for the %S/%I/%R column there is no breakpoint for CLSI when 0/0/0 appears. CLSI, Clinical and Laboratory Standards Institute; I, intermediate; MIC₅₀, minimum inhibitory concentration required to inhibit the growth of 50% of organism; MIC₉₀, minimum inhibitory concentration required to inhibit the growth of 90% of organism; micro-MITTR, microbiologic modified intent-to-treat resistant; N, number of pathogens identified in the micro-MITTR population; R, resistant; S, susceptible.

Source: IT001-301, Table 14.1.2.16.1

Table 176. Activity of Sulopenem and Ciprofloxacin Against Baseline Pathogens –MMITTR Population – Ciprofloxacin Treatment Group

Organism Antibiotic	N	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)	CLSI %S/%I/%R
<i>Escherichia coli</i>	N = 120			
Sulopenem		0.03	0.06	0/0/0
Ciprofloxacin		>2	>2	3.3/0/96.7
<i>Klebsiella pneumoniae</i>	N = 16			
Sulopenem		0.12	4	0/0/0
Ciprofloxacin		>2	>2	12.5/0/87.5

Note: percentages are calculated as $100 \times (n/N)$; for the %S/%I/%R column there is no breakpoint for CLSI when 0/0/0 appears. CLSI, Clinical and Laboratory Standards Institute; I, intermediate; MIC₅₀, minimum inhibitory concentration required to inhibit the growth of 50% of organism; MIC₉₀, minimum inhibitory concentration required to inhibit the growth of 90% of organism; micro-MITTR, microbiologic modified intent-to-treat resistant; N, number of pathogens identified in the micro-MITTR population; R, resistant; S, susceptible.

Source: IT001-301, Table 14.1.2.17.1

Table 177. Activity of Sulopenem and Ciprofloxacin Against Baseline Pathogens –MMITTR Population – Both Treatment Groups (Combined)

Organism Antibiotic	N	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)	CLSI %S/%I/%R
<i>Escherichia coli</i>	N = 247			
Sulopenem		0.03	0.06	0/0/0
Ciprofloxacin		>2	>2	3.2/0.4/96.4
<i>Klebsiella pneumoniae</i>	N = 28			
Sulopenem		0.12	4	0/0/0
Ciprofloxacin		>2	>2	10.7/0/89.3
<i>Proteus mirabilis</i>	N = 15			
Sulopenem		0.25	0.25	0/0/0
Ciprofloxacin		2	>2	6.7/46.7/46.7

Note: percentages are calculated as $100 \times (n/N)$; for the %S/%I/%R column there is no breakpoint for CLSI when 0/0/0 appears. CLSI, Clinical and Laboratory Standards Institute; I, intermediate; MIC₅₀, minimum inhibitory concentration required to inhibit the growth of 50% of organism; MIC₉₀, minimum inhibitory concentration required to inhibit the growth of 90% of organism; micro-MITTR, microbiologic modified intent-to-treat resistant; N, number of pathogens identified in the micro-MITTR population; R, resistant; S, susceptible.

Source: IT001-301, Table 14.1.2.18.1

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Baseline Pathogens: MMITTS Population

All urinary pathogens cultured from the qualified patients in the MMITTS population are presented in Table 178. The most commonly isolated pathogens in both treatment groups were *E. coli* (84.3%), *K. pneumoniae* (8.8%) and *P. mirabilis* (2.4%).

Table 178. Pathogens From Urine at Baseline – MMITTS Population

Organism	Sulopenem n/N (%)	Ciprofloxacin n/N (%)	Total n/N (%)
Number of Patients with at least one study uropathogen in the urine at baseline	370/370 (100)	415/415 (100)	785/785 (100)
<i>Escherichia coli</i>	313/370 (84.6)	349/415 (84.1)	662/785 (84.3)
<i>Klebsiella pneumoniae</i>	37/370 (10.0)	32/415 (7.7)	69/785 (8.8)
<i>Proteus mirabilis</i>	8/370 (2.2)	11/415 (2.7)	19/785 (2.4)
<i>Staphylococcus saprophyticus</i>	5/370 (1.4)	8/415 (1.9)	13/785 (1.7)
<i>Klebsiella aerogenes</i>	4/370 (1.1)	6/415 (0.0)	10/785 (0.3)
<i>Citrobacter freundii</i>	0/370 (0.0)	6/415 (0.7)	6/785 (0.3)
<i>Citrobacter koseri</i>	4/370 (1.1)	1/415 (0.2)	5/785 (0.6)
<i>Enterobacter cloacae</i> complex	3/370 (0.8)	2/415 (0.5)	5/785 (0.6)
<i>Klebsiella oxytoca</i>	2/370 (0.5)	3/415 (0.7)	5/785 (0.6)
<i>Klebsiella varicola</i>	4/370 (1.1)	1/415 (0.2)	5/785 (0.6)
<i>Lelliottia amnigena</i>	1/370 (0.3)	3/415 (0.7)	4/785 (0.5)
<i>Morganella morganii</i>	0/370 (0.0)	3/415 (0.7)	3/785 (0.4)
<i>Raoultella planticola</i>	0/370 (0.0)	2/415 (0.5)	2/785 (0.3)
<i>Enterobacter aerogenes</i>	0/370 (0.0)	1/415 (0.2)	1/785 (0.1)
<i>Pantoea septica</i>	0/370 (0.0)	1/415 (0.2)	1/785 (0.1)
<i>Serratia marcescens</i>	0/370 (0.0)	1/415 (0.2)	1/785 (0.1)

Note: percentages are calculated as $100 \times (n/N)$. micro-MITTS, microbiological Modified Intent-to-Treat Susceptible; n, number of patients; N, number of patients in the micro-MITTS population.

Source: IT001-301, Table 14.1.1.9.1

Monomicrobial and Polymicrobial Infections at Baseline: MMITTS

As shown in Table 179, over 96% of patients in the MMITTS population had monomicrobial infections, and 3.3% of patients in this group had polymicrobial infections.

Table 179. Monomicrobial and Polymicrobial Infections at Baseline – MMITTS Population

	Sulopenem n/N (%)	Ciprofloxacin n/N (%)	Total n/N (%)
Monomicrobial	359/370 (97.0%)	400/415 (96.4%)	759/785 (96.7%)
Polymicrobial	11/370 (3.0%)	15/415 (3.6%)	26/785 (3.3%)

Micro-MITT, microbiologic Modified Intent-to-Treat. The percentages are calculated as $100 \times (n/N)$. Enterobacterales and *S. saprophyticus* are included in the table. Micro evaluable patients are both clinical and micro evaluable.

Source: Table 14.1.1.10.1

Susceptibility of Baseline Pathogens: MMITTS

The MIC susceptibility data in the MMITTS populations for the sulopenem etzadroxil/probenecid treatment group, ciprofloxacin treatment group, and both treatment groups combined are presented in Table 180, Table 181 and Table 182, respectively. Against 653 *E. coli* isolates from both treatment groups, the MIC_{50/90} values were 0.03/0.03 µg/mL.

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

Against 68 *K. pneumoniae* isolates from both treatment groups, the MIC_{50/90} values were 0.03/0.12 µg/mL. Against 17 *P. mirabilis* isolates from both treatment groups, the MIC_{50/90} values were 0.25/0.25 µg/mL.

Table 180. Activity of Sulopenem and Ciprofloxacin Against Baseline Pathogens – MMITTS Population – Sulopenem Treatment Group

Organism Antibiotic	N	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)	CLSI %S/%I/%R
<i>Escherichia coli</i>	N = 310			
Sulopenem		0.03	0.03	0/0/0
Ciprofloxacin		≤0.06	0.25	99.0/1.0/0
<i>Klebsiella pneumoniae</i>	N = 36			
Sulopenem		0.03	0.12	0/0/0
Ciprofloxacin		≤0.06	0.5	97.2/0/2.8

Note: percentages are calculated as 100 × (n/N); for the %S/%I/%R column there is no breakpoint for CLSI when 0/0/0 appears. CLSI, Clinical and Laboratory Standards Institute; I, intermediate; MIC₅₀, minimum inhibitory concentration required to inhibit the growth of 50% of organism; MIC₉₀, minimum inhibitory concentration required to inhibit the growth of 90% of organism; micro-MITTS, microbiologic modified intent-to-treat susceptible; N, number of pathogens identified in the micro-MITT population; R, resistant; S, susceptible.

Source: IT001-301, Table 14.1.1.16.1

Table 181. Activity of Sulopenem and Ciprofloxacin Against Baseline Pathogens –MMITTS Population – Ciprofloxacin Treatment Group

Organism Antibiotic	N	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)	CLSI %S/%I/%R
<i>Escherichia coli</i>	N = 343			
Sulopenem		0.03	0.03	0/0/0
Ciprofloxacin		≤0.06	0.5	98.3/0.6/1.2
<i>Klebsiella pneumoniae</i>	N = 32			
Sulopenem		0.03	0.12	0/0/0
Ciprofloxacin		≤0.06	≤0.06	100.0/0/0

Note: percentages are calculated as 100 × (n/N); for the %S/%I/%R column there is no breakpoint for CLSI when 0/0/0 appears. CLSI, Clinical and Laboratory Standards Institute; I, intermediate; MIC₅₀, minimum inhibitory concentration required to inhibit the growth of 50% of organism; MIC₉₀, minimum inhibitory concentration required to inhibit the growth of 90% of organism; micro-MITTS, microbiologic modified intent-to-treat susceptible; N, number of pathogens identified in the micro-MITT population; R, resistant; S, susceptible.

Source: IT001-301, Table 14.1.1.17.1

Table 182. Activity of Sulopenem and Ciprofloxacin Against Baseline Pathogens –MMITTS Population – Both Treatment Groups

Organism Antibiotic	N	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)	CLSI %S/%I/%R
<i>Escherichia coli</i>	N = 653			
Sulopenem		0.03	0.03	0/0/0
Ciprofloxacin		≤0.06	0.5	98.6/0.8/0.6
<i>Klebsiella pneumoniae</i>	N = 68			
Sulopenem		0.03	0.12	0/0/0
Ciprofloxacin		≤0.06	0.12	98.5/0/1.5
<i>Proteus mirabilis</i>	N = 17			
Sulopenem		0.25	0.25	0/0/0
Ciprofloxacin		≤0.06	0.12	100.0/0/0
<i>Staphylococcus saprophyticus</i>	N = 13			
Sulopenem		0.25	0.25	0/0/0
Ciprofloxacin		0.25	0.5	100.0/0/0
<i>Klebsiella aerogenes</i>	N = 10			
Sulopenem		0.06	0.12	0/0/0
Ciprofloxacin		≤0.06	≤0.06	100.0/0/0

Note: percentages are calculated as $100 \times (n/N)$; for the %S/%I/%R column there is no breakpoint for CLSI when 0/0/0 appears. CLSI, Clinical and Laboratory Standards Institute; I, intermediate; MIC₅₀, minimum inhibitory concentration required to inhibit the growth of 50% of organism; MIC₉₀, minimum inhibitory concentration required to inhibit the growth of 90% of organism; micro-MITTS, microbiologic modified intent-to-treat susceptible; N, number of pathogens identified in the micro-MITT population; R, resistant; S, susceptible.

Source: IT001-301, Table 14.1.1.18.1

Baseline Pathogens-Overall Population: MMITT

All urinary pathogens cultured from the qualified patients of overall MMITT (MMITTS and MMITTR) population are presented in Table 183. The most commonly isolated pathogens in both treatment groups were *E. coli* (84.9%), *K. pneumoniae* (9.2%) and *P. mirabilis* (3.2%).

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

Table 183. Pathogens From Urine at Baseline – MMITT Population

Organism	Sulopenem n/N (%)	Ciprofloxacin n/N (%)	Total n/N (%)
Number of Patients with at least one study uropathogen in the urine at baseline	517/517 (100)	554/554 (100)	1071/1071 (100)
<i>Escherichia coli</i>	440/517 (85.1)	469/554 (84.7)	909/1071 (84.9)
<i>Klebsiella pneumoniae</i>	51/517 (9.9)	48/554 (8.7)	99/1071 (9.2)
<i>Proteus mirabilis</i>	17/517 (3.3)	17/554 (3.1)	34/1071 (3.2)
<i>Staphylococcus saprophyticus</i>	5/517 (1.0)	8/554 (1.4)	13/1071 (1.2)
<i>Klebsiella aerogenes</i>	4/517 (0.8)	6/554 (1.1)	10/1071 (0.9)
<i>Morganella morganii</i>	3/517 (0.6)	4/554 (0.7)	7/1071 (0.7)
<i>Citrobacter freundii</i>	0/517 (0.0)	6/554 (1.1)	6/1071 (0.6)
<i>Enterobacter cloacae</i> complex	4/517 (0.8)	2/554 (0.4)	6/1071 (0.6)
<i>Citrobacter koseri</i>	4/517 (0.8)	1/554 (0.2)	5/1071 (0.5)
<i>Klebsiella oxytoca</i>	2/517 (0.4)	3/554 (0.5)	5/1071 (0.5)
<i>Klebsiella variicola</i>	4/517 (0.8)	1/554 (0.2)	5/1071 (0.5)
<i>Lelliottia amnigena</i>	1/517 (0.2)	3/554 (0.5)	4/1071 (0.4)
<i>Raoultella planticola</i>	0/517 (0.0)	2/554 (0.4)	2/1071 (0.2)
<i>Enterobacter aerogenes</i>	0/517 (0.0)	1/554 (0.2)	1/1071 (0.1)
<i>Pantoea septica</i>	0/517 (0.0)	1/554 (0.2)	1/1071 (0.1)
<i>Providencia stuartii</i>	0/517 (0.0)	1/554 (0.2)	1/1071 (0.1)
<i>Serratia marcescens</i>	0/517 (0.0)	1/554 (0.2)	1/1071 (0.1)

Note: percentages are calculated as $100 \times (n/N)$. micro-MITT, microbiological modified intent-to-treat; n, number of patients; N, number of patients in the micro-MITT population.

Source: IT001-301, 14.1.3.9.1

Monomicrobial and Polymicrobial Infections at Baseline: MMITT

As shown in Table 184, approximately 96% of patients in the MMITT population had monomicrobial infections, and 3.5% of patients in this group had polymicrobial infections.

Table 184. Monomicrobial and Polymicrobial Infections at Baseline – MMITT Population

	Sulopenem n/N (%)	Ciprofloxacin n/N (%)	Total n/N (%)
Monomicrobial	499/517 (96.5%)	534/554 (96.4%)	1033/1071 (96.5%)
Polymicrobial	18/517 (3.5%)	20/554 (3.6%)	38/1071 (3.5%)

Micro-MITT, microbiologic Modified Intent-to-Treat. The percentages are calculated as $100 \times (n/N)$.

Enterobacterales and *S. saprophyticus* are included in the table. Micro evaluable patients are both clinical and micro evaluable.

Source: Table 14.1.3.10.1

MIC Susceptibility Data of Baseline Pathogens: MMITT

The MIC susceptibility data in the overall MMITT populations for the sulopenem etzadroxil/probenecid treatment group, ciprofloxacin treatment group, and both treatment groups combined are presented in Table 185, Table 186, and Table 187, respectively. Against 900 *E. coli* isolates from both treatment groups, the MIC_{50/90} values were 0.03/0.06 µg/mL. Against 96 *K. pneumoniae* isolates from both treatment groups, the MIC_{50/90} values were 0.06/0.12 µg/mL. Against 32 *P. mirabilis* isolates from both treatment groups, the MIC_{50/90} values were 0.25/0.25 µg/mL.

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

Table 185. Activity of Sulopenem and Ciprofloxacin Against Baseline Pathogens –MMITT Population – Sulopenem Treatment Group

Organism Antibiotic	N	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)	CLSI %S/%I/%R
<i>Escherichia coli</i>	N = 437			
Sulopenem		0.03	0.06	0/0/0
Ciprofloxacin		≤0.06	>2	71.2/0.9/27.9
<i>Klebsiella pneumoniae</i>	N = 48			
Sulopenem		0.03	0.12	0/0/0
Ciprofloxacin		≤0.06	>2	75.0/0/25.0
<i>Proteus mirabilis</i>	N = 17			
Sulopenem		0.25	0.25	0/0/0
Ciprofloxacin		0.5	>2	52.9/23.5/23.5

Note: percentages are calculated as $100 \times (n/N)$; for the %S/%I/%R column there is no breakpoint for CLSI when 0/0/0 appears. CLSI, Clinical and Laboratory Standards Institute; I, intermediate; MIC₅₀, minimum inhibitory concentration required to inhibit the growth of 50% of organism; MIC₉₀, minimum inhibitory concentration required to inhibit the growth of 90% of organism; micro-MITT, microbiologic modified intent-to-treat; N, number of pathogens identified in the micro-MITT population; R, resistant; S, susceptible.

Source: [Table 14.1.3.16.1](#)

Table 186. Activity of Sulopenem and Ciprofloxacin Against Baseline Pathogens –MMITT Population – Ciprofloxacin Treatment Group

Organism Antibiotic	N	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)	CLSI %S/%I/%R
<i>Escherichia coli</i>	N = 463			
Sulopenem		0.03	0.06	0/0/0
Ciprofloxacin		≤0.06	>2	73.7/0.4/25.9
<i>Klebsiella pneumoniae</i>	N = 48			
Sulopenem		0.06	0.25	0/0/0
Ciprofloxacin		≤0.06	>2	70.8/0/29.2
<i>Proteus mirabilis</i>	N = 15			
Sulopenem		0.25	0.5	0/0/0
Ciprofloxacin		≤0.06	>2	60.0/20.0/20.0

Note: percentages are calculated as $100 \times (n/N)$; for the %S/%I/%R column there is no breakpoint for CLSI when 0/0/0 appears. CLSI, Clinical and Laboratory Standards Institute; I, intermediate; MIC₅₀, minimum inhibitory concentration required to inhibit the growth of 50% of organism; MIC₉₀, minimum inhibitory concentration required to inhibit the growth of 90% of organism; micro-MITT, microbiologic modified intent-to-treat; N, number of pathogens identified in the micro-MITT population; R, resistant; S, susceptible.

Source: [Table 14.1.3.17.1](#)

Table 187. Activity of Sulopenem and Ciprofloxacin Against Baseline Pathogens –MMITT Population – Both Treatment Groups

Organism Antibiotic	N	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)	CLSI %S/%I/%R
<i>Escherichia coli</i>	N = 900			
Sulopenem		0.03	0.06	0/0/0
Ciprofloxacin		≤0.06	>2	72.4/0.7/26.9
<i>Klebsiella pneumoniae</i>	N = 96			
Sulopenem		0.06	0.12	0/0/0
Ciprofloxacin		≤0.06	>2	72.9/0/27.1
<i>Proteus mirabilis</i>	N = 32			
Sulopenem		0.25	0.25	0/0/0
Ciprofloxacin		0.12	>2	56.3/21.9/21.9
<i>Staphylococcus saprophyticus</i>	N = 13			
Sulopenem		0.25	0.25	0/0/0
Ciprofloxacin		0.25	0.5	100/0/0
<i>Klebsiella aerogenes</i>	N = 10			
Sulopenem		0.06	0.12	0/0/0
Ciprofloxacin		≤0.06	≤0.06	100/0/0

Note: percentages are calculated as $100 \times (n/N)$; for the %S/%I/%R column there is no breakpoint for CLSI when 0/0/0 appears. CLSI, Clinical and Laboratory Standards Institute; I, intermediate; MIC₅₀, minimum inhibitory concentration required to inhibit the growth of 50% of organism; MIC₉₀, minimum inhibitory concentration required to inhibit the growth of 90% of organism; micro-MITT, microbiologic modified intent-to-treat; N, number of pathogens identified in the micro-MITT population; R, resistant; S, susceptible.

Source: Table 14.1.3.18.1

Discordant Ciprofloxacin Susceptibility Results Between Local and Central Lab

The Applicant stated that approximately 4% (42/1071) of the total isolates in the MMITT population had discordant ciprofloxacin susceptibility culture results between local and central laboratory that required gyrase-polymerase chain reaction (PCR) confirmation in order to assign to either the resistant or susceptible sub-population. A summary of the microbiological results for all such patients is provided in Table 188.

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

Table 188. Summary of Patients in the MMITT Population With PCR Assignment to Study Population Due to Baseline Isolate Discordance of Ciprofloxacin Susceptibility by Culture

PID	IHMA	Covance	IHMA-c	Local	Local-c	DNA Gyrase	Micro-MITT Population
(b) (6)	<i>E. coli</i> - S	<i>E. coli</i> - R	<i>E. coli</i> - S			Not detected	S
	<i>E. coli</i> - R	<i>E. coli</i> - S	<i>E. coli</i> - S			Not detected	S
	<i>E. coli</i> - S	<i>E. coli</i> - R	<i>E. coli</i> - S	<i>P. mirabilis</i> - S		Not detected	S
	<i>E. coli</i> - S	<i>E. coli</i> - R	<i>E. coli</i> - S			Not detected	S
	<i>E. coli</i> - R	<i>E. coli</i> - S	<i>E. coli</i> - S	<i>E. coli</i> - S		Not detected	S
				<i>E. coli</i> - S	<i>E. coli</i> - R	Not detected	S
				<i>E. coli</i> - S	<i>E. coli</i> - R	Not detected	S
	<i>E. coli</i> - R	<i>E. coli</i> - S	<i>E. coli</i> - R			Not detected	S
				<i>E. cloacae</i> - R	<i>E. cloacae</i> - S	NA	S
				<i>C. freundii</i> - R	<i>C. freundii</i> - S		
				<i>E. coli</i> - R	<i>E. coli</i> - S	Not detected	S
				<i>E. coli</i> - S	<i>E. coli</i> - R	Not detected	S
				<i>E. coli</i> - S	<i>E. coli</i> - R	Not detected	S
				<i>K. pneumoniae</i> - S	<i>K. pneumoniae</i> - R	Not detected	S
				<i>K. pneumoniae</i> - R	<i>K. pneumoniae</i> - S	Not detected	S
				<i>E. coli</i> - S	<i>E. coli</i> - R	Not detected	S
	<i>E. coli</i> - S	<i>E. coli</i> - S	<i>E. coli</i> - R			Not detected	S
	<i>E. coli</i> - S	<i>E. coli</i> - S	<i>E. coli</i> - S	<i>E. coli</i> - R		Not detected	S
	<i>E. coli</i> - S	<i>E. coli</i> - S	<i>E. coli</i> - S	<i>E. coli</i> - R		Not detected	S
		<i>E. coli</i> - S	<i>E. coli</i> - R			Not detected	S

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

PID (b) (6)	IHMA	Covance	IHMA-c	Local	Local-c	DNA Gyrase	Micro- MITT Population
	<i>E. coli</i> - R	<i>E. coli</i> - R	<i>E. coli</i> - S			Detected	R
	<i>E. coli</i> - S			<i>K. pneumoniae</i> - R		NA	R
	<i>K. pneumoniae</i> - S	<i>K. pneumoniae</i> - R	<i>K. pneumoniae</i> - R			Detected	R
	<i>E. coli</i> - R	<i>E. coli</i> - R	<i>E. coli</i> - S			Detected	R
	<i>E. coli</i> - R	<i>E. coli</i> - R	<i>E. coli</i> - S			Detected	R
				<i>E. coli</i> - R	<i>E. coli</i> - S	Detected	R
				<i>E. coli</i> - R	<i>E. coli</i> - S	Detected	R
				<i>K. pneumoniae</i> - S	<i>K. pneumoniae</i> - S		
	<i>E. coli</i> - R	<i>E. coli</i> - R	<i>E. coli</i> - R			Detected	R
	<i>E. coli</i> - S						
	<i>E. coli</i> - R					Detected	R
	<i>E. cloacae</i> - S						
	<i>E. coli</i> - R	<i>E. coli</i> - S	<i>E. coli</i> - S			Detected	R
	<i>E. coli</i> - S						
	<i>E. coli</i> - R	<i>E. coli</i> - R	<i>E. coli</i> - R			Detected	R
	<i>E. coli</i> - S						
	<i>E. coli</i> - S	<i>E. coli</i> - R	<i>E. coli</i> - R			Detected	R
	<i>P. mirabilis</i> -S	<i>P. mirabilis</i> -R	<i>P. mirabilis</i> -R			NA	R
		<i>E. coli</i> - R	<i>E. coli</i> - R	<i>K. pneumoniae</i> - S		NA	R
				<i>P. mirabilis</i> -S	<i>P. mirabilis</i> -R	NA	R
				<i>E. coli</i> - R	<i>E. coli</i> - R	NA	R
				<i>E. coli</i> - S	<i>E. coli</i> - S		
				<i>E. coli</i> - R	<i>E. coli</i> - R	NA	R
				<i>E. coli</i> - S	<i>E. coli</i> - S		
				<i>P. mirabilis</i> -R	<i>P. mirabilis</i> -R	NA	R
				<i>E. coli</i> - S	<i>E. coli</i> - S		
				<i>P. mirabilis</i> -S	<i>P. mirabilis</i> -R	NA	R
				<i>M. organii</i> - S	<i>M. organii</i> - S		

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

PID	IHMA	Covance	IHMA-c	Local	Local-c	DNA Gyrase	Micro-MITT Population
(b) (6)				<i>E. coli</i> - R	<i>E. coli</i> - R	NA	R
				<i>E. coli</i> - S	<i>E. coli</i> - S		
				<i>P. mirabilis</i> -S	<i>P. mirabilis</i> -R	NA	R
	<i>E. coli</i> - S	<i>E. coli</i> - R	<i>E. coli</i> - R			Not detected	R
	<i>E. coli</i> - R						
	<i>K. pneumoniae</i> - S	<i>K. pneumoniae</i> - S	<i>K. pneumoniae</i> - S			NA	R
	<i>E. coli</i> - R	<i>E. coli</i> - R	<i>E. coli</i> - R				

Notes: PID, patient identification; IHMA, primary baseline culture result from central laboratory; Covance, primary baseline culture result from Covance local laboratory (U.S.); IHMA-c, confirmatory baseline culture result of Covance isolate as determined by central laboratory; Local, primary baseline culture result from local laboratory (ex-U.S or U.S.); Local-c, confirmatory baseline culture result of local laboratory isolate as determined by central laboratory; R, resistant; S, susceptible; NA, test not performed; DNA Gyrase assay was performed using Acuitas® Antimicrobial Resistance Gene Panel testing (multiplexed, semi-quantitative real-time PCR, OpGen® Inc.) to identify the presence or absence of DNA gyrase mutations. For patient (b) (6), there was no discordance (eg, a resistant strain of *E. coli* was detected by both IHMA and Covance), so the patient was assigned to the micro-MITT population even though DNA gyrase was not detected. See IT001-301 QC Analyses for details on R/S assignment convention.

Source: NDA submission

Abbreviations: MMITT, microbiological modified intent-to-treat; PCR polymerase chain reaction

Clinical Microbiology Reviewer's Comments: The Agency differed with the Applicant's approach for resolving discordant cipro-susceptibility results and whether or not to assign these subjects to the MMITT population. The Agency provided guidance that if a subject is found with a cipro-resistant isolate from either a central lab IHMA culture or IHMA confirmatory identification of the local laboratory isolates, then the subject should be included in the MMITT population. The ciprofloxacin susceptibility should be determined by IHMA based on the MIC broth microdilution assay only. The IHMA in vitro MIC susceptibility results should have priority irrespective of the gyrase PCR results. The Agency found that the proposed PCR for gyrase mutation was not sufficient to determine cipro-susceptibility since other gene mutations may also be involved in determining quinolone-resistance (e.g., parC, parE) as per current literature. Additionally, the presence of other plasmid-mediated quinolone resistance genes may also confer quinolone resistance.

Summary of Baseline Culture Results: ITT Population

Approximately 67% of the ITT patients (1072/1590) from both treatment arms had a baseline urine culture with at least one target uropathogen in a quantity of $\geq 10^5$ CFU/mL, thus qualifying for the MMITT population. The most-frequently isolated uropathogens from urine at concentrations $\geq 10^5$ CFU/mL in the ITT population are summarized in Table 189. More than half the pathogens isolated were *E. coli* (57.2%; 910/1590); whereas 6.2% were *K. pneumoniae*, 2.1% were *P. mirabilis*, and less than 1% were *S. saprophyticus*.

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

Table 189. Distribution of Study Uropathogens at Baseline – ITT Population

Study Uropathogen	Sulopenem n/N (%)	Ciprofloxacin n/N (%)	Total n/N (%)
<i>Escherichia coli</i>	441/785 (56.0%)	469/803 (58.4%)	910/1590 (57.2%)
<i>Klebsiella pneumoniae</i>	51/878 (6.5%)	48/803 (6.0%)	99/1590 (6.2%)
<i>Proteus mirabilis</i>	17/787 (2.2%)	17/803 (2.1%)	34/1590 (2.1%)
<i>Staphylococcus saprophyticus</i>	5/787 (0.6%)	8/803 (1.0%)	13/1590 (0.8%)

Note: only isolates with $\geq 5 \times 10^5$ CFU/mL urine are shown. ITT, Intent-to-Treat. The percentages are calculated as $100 \times (n/N)$.

Source: Table 14.1.3.12.2

Efficacy Analysis: Clinical and Microbiological Outcomes

The combined clinical and microbiological response and microbiological response at TOC of the analysis populations are covered in section 8.1 of this unireview. The Clinical Microbiology reviewer defers to the results of the efficacy analysis conducted by the Statistical Reviewer.

Correlation of Overall Response and Sulopenem MICs of Key Target Pathogens: MMITT

The overall response by target pathogens *E. coli* (N=437), *K. pneumoniae* (N=48) and *P. mirabilis* (N=17) and their MICs for sulopenem in the overall MMITT population are shown in Figure 23, Figure 24, and Figure 25, respectively. Against *E. coli*, the overall rate of success was between 40 and 66.8% across an MIC range of ≤ 0.015 to 0.25 $\mu\text{g/mL}$. Against *K. pneumoniae*, an overall success rate of 43 to 100% with an MIC range of ≤ 0.015 to 8 $\mu\text{g/mL}$, however, no isolates with an MIC of 0.25 to 2.0 $\mu\text{g/mL}$ were present. Against *P. mirabilis*, success rates were observed between 50 to 100% with an MIC range 0.03 to 0.25 $\mu\text{g/mL}$.

Figure 23. Overall Response Per Pathogen for MIC to Sulopenem – MMITT Population – *E. coli* (N=437)

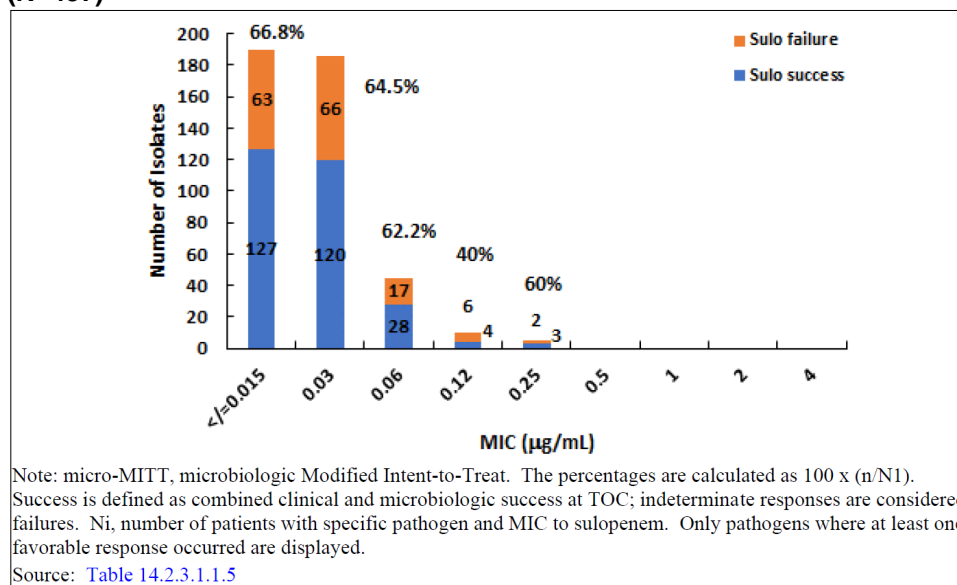


Figure 24. Overall Response Per Pathogen for MIC to Sulopenem – MMITT Population – *K. pneumoniae* (N=48)

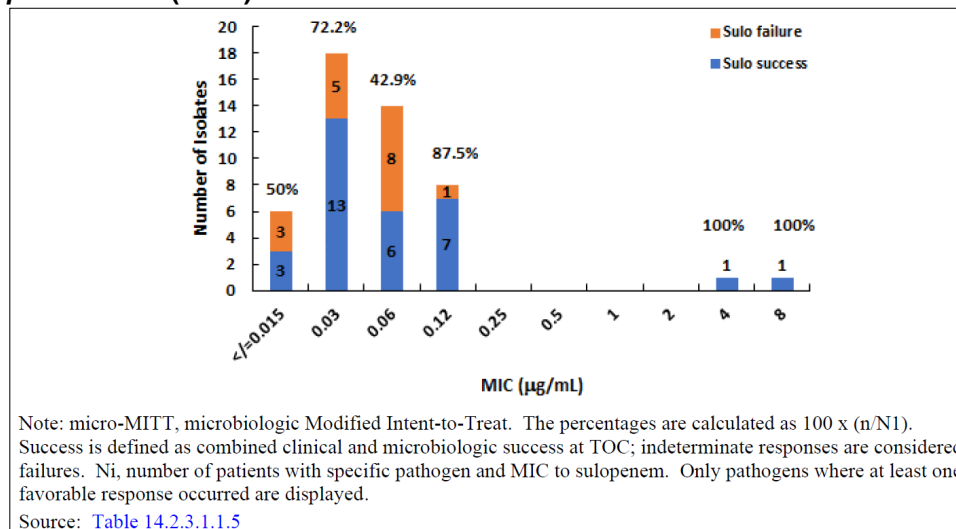
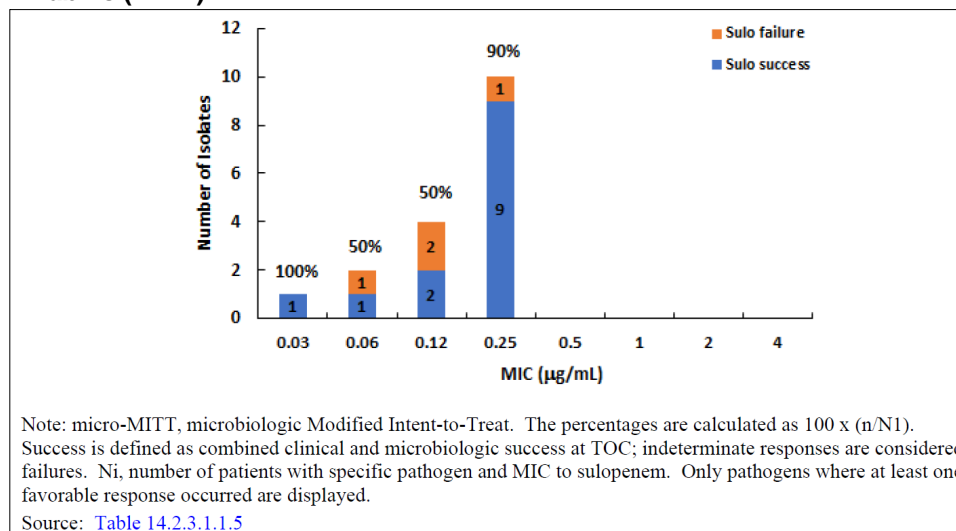


Figure 25. Overall Response Per Pathogen for MIC to Sulopenem – MMITT Population – *P. mirabilis* (N=17)



16.5.4.2. Emergence of Resistance During Therapy

Impact of Treatment on the Distribution of Susceptibility to the Treatment Regimen

In this study, no post baseline isolate was observed with a sulopenem MIC that had increased by ≥ 4 -fold relative to a baseline isolate of the same genus and species. However, there was one patient that was reported to have an MIC increase of ≥ 16 -fold during therapy. Patient 129-1001 was a 73-year-old woman that had a baseline *E. coli* with an MIC of 0.015 µg/mL and an *E. coli* with an MIC of 0.25 µg/mL was identified at TOC. The baseline isolate with the lowest MIC was compared to the TOC isolate as it was having a ≥ 4 x MIC change and was investigated for further analysis. It was revealed that the patient also had an *E. coli* at baseline with the same whole

genome sequence with an MIC of 0.25 µg/mL. All three *E. coli* isolates were susceptible to ertapenem and the patient had fully resolved all uUTI symptoms at the TOC visit. Furthermore, this indicated that a sub-population of the same bacterial species with different MIC values may have been present at baseline.

Treatment with sulopenem had very little impact on the distribution of MIC's between the pre-treatment and post-treatment isolates. Overall, the MIC_{50/90} values were 0.03/0.06 µg/mL and 0.03/0.12 µg/mL against pre-treatment and post-treatment isolates, respectively.

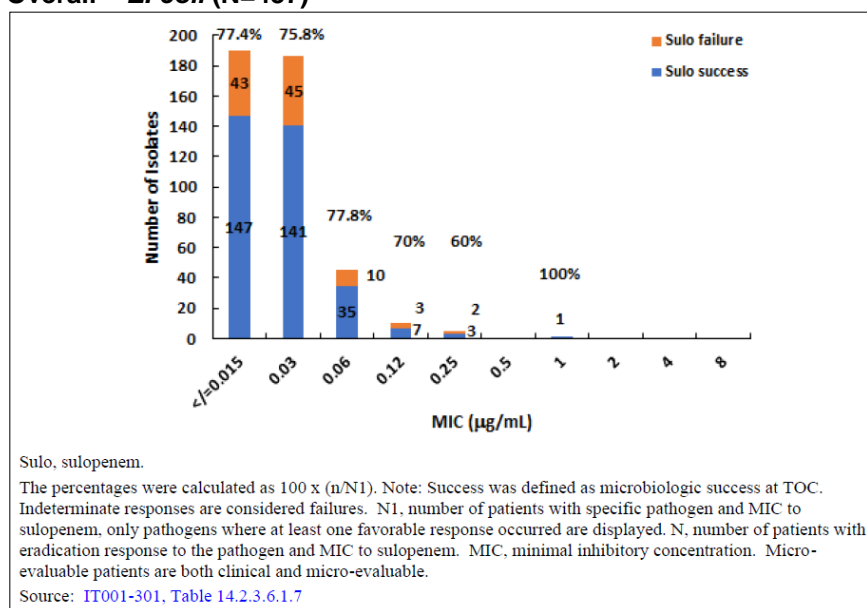
Correlation of MIC Values of the Baseline Isolates to Microbiologic Outcome at TOC: MMITT, MMITTS and MMITTR Populations

The per pathogen microbiologic response of *E. coli*, *K. pneumoniae*, and *P. mirabilis* at TOC by baseline MIC to sulopenem was determined as percent success for the MMITT (overall), the MMITTS and the MMITTR populations. Microbiologic response was defined as microbiologic success at TOC in the microbiologically evaluable (ME-TOC) patients, that is, those that were both clinically and microbiologically evaluable.

E. coli

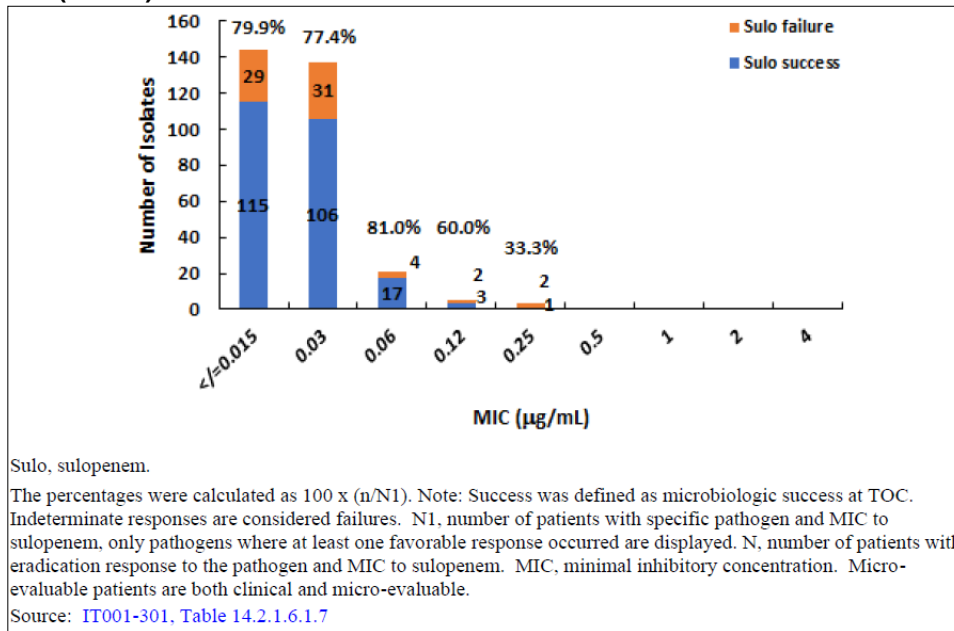
The microbiologic response for the baseline *E. coli* population is shown by sulopenem MIC from overall MMITT (N=437), MMITTS (N=310) and in the MMITTR (N=127), in Figure 26, Figure 27, and Figure 28, respectively. Against *E. coli*, the rate of microbiologic success ranged from 33.3 to 100% over the MIC range of ≤0.015 to 1.0 µg/mL, with very low numbers of isolates at the higher MIC values (0.25 to 1.0 µg/mL).

Figure 26. Microbiologic Response Per Pathogen for MIC to Sulopenem – MMITT Population Overall – *E. coli* (N=437)



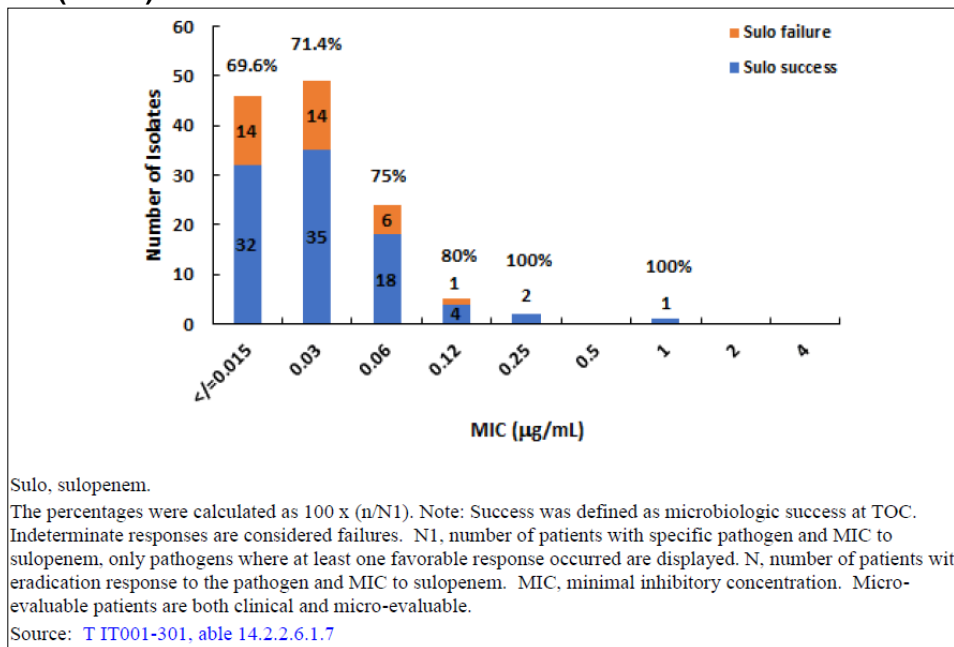
Abbreviations: MMITT, microbiological modified intent-to-treat.

Figure 27. Microbiologic Response Per Pathogen for MIC to Sulopenem – MMITTS Population – *E. coli* (N=310)



Abbreviations: MMITT, microbiological modified intent-to-treat.

Figure 28. Microbiologic Response Per Pathogen for MIC to Sulopenem – MMITTR Population – *E. coli* (N=127)



Abbreviations: MMITT, microbiological modified intent-to-treat.

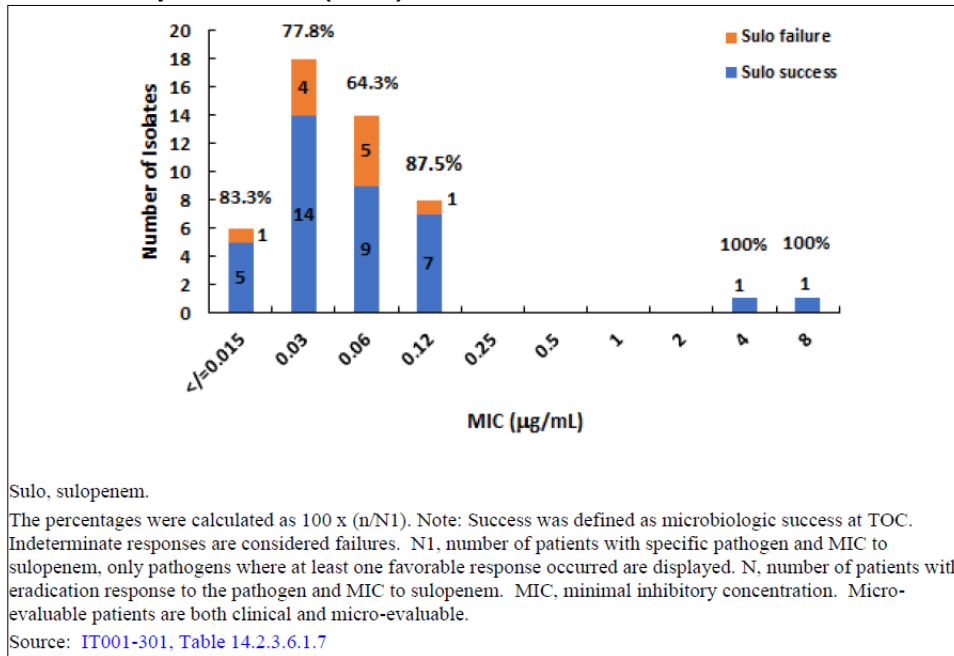
K. pneumoniae

The microbiologic response for the baseline *K. pneumoniae* population is shown by sulopenem MIC in Figure 29, Figure 30, and Figure 31 for the MMITT (N=48), MMITTS (N=36) and MMITTR

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 {sulopenem etzadroxil/probenecid}

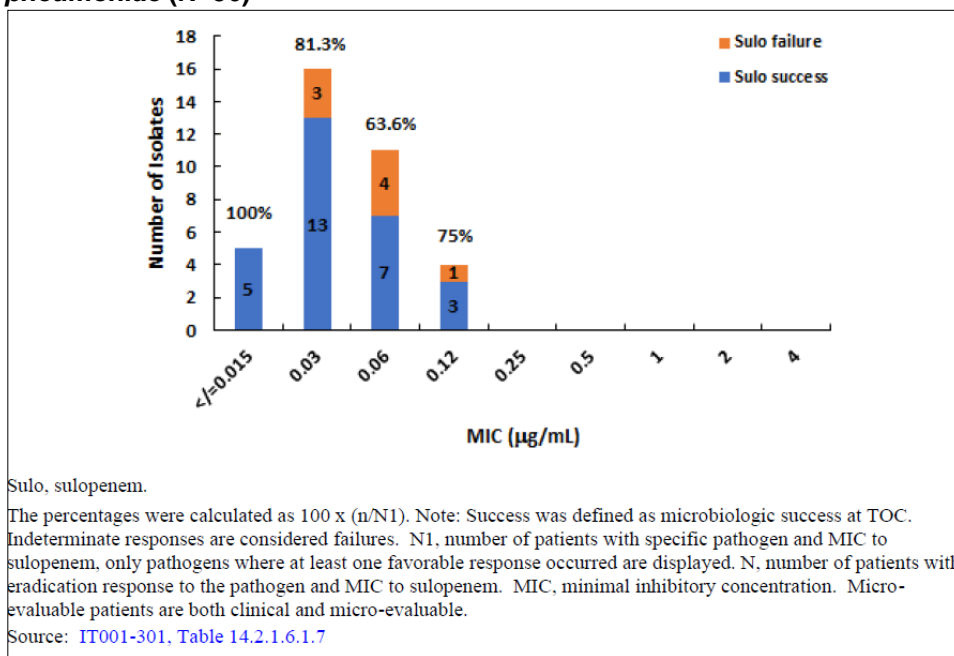
(N=12), respectively. Against *K. pneumoniae*, the rates of microbiologic success ranged from 0 to 100% over the MIC range of ≤ 0.015 to 8.0 $\mu\text{g/mL}$, with very low numbers of isolates at the higher MIC values (0.25 to 8 $\mu\text{g/mL}$).

Figure 29. Microbiologic Response Per Pathogen for MIC to Sulopenem – MMITT Population Overall – *K. pneumoniae* (N=48)



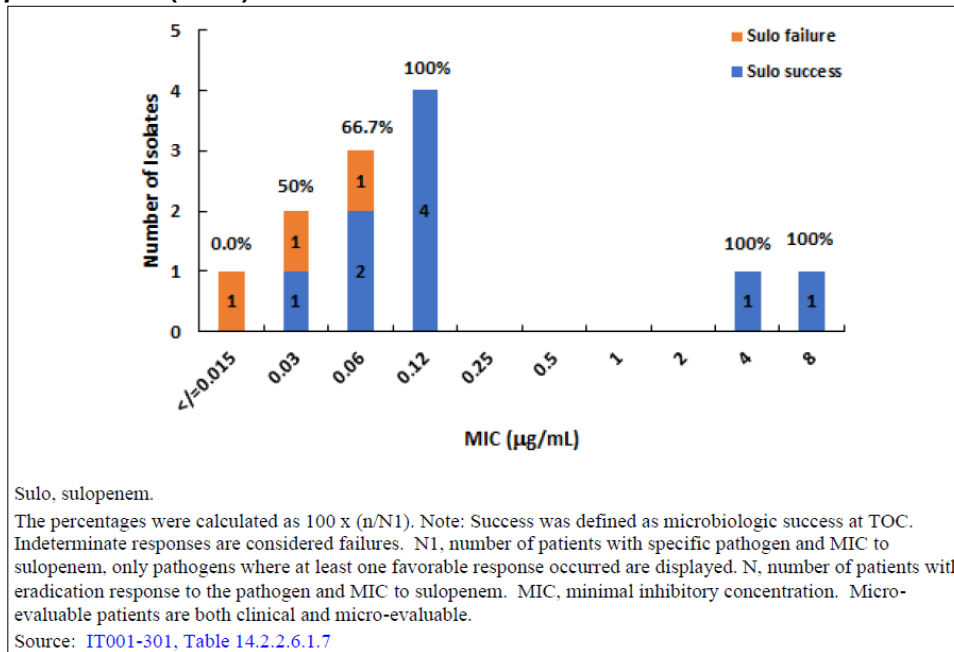
Abbreviations: MMITT, microbiological modified intent-to-treat.

Figure 30. Microbiologic Response Per Pathogen for MIC to Sulopenem – MMITTS Population – *K. pneumoniae* (N=36)



Abbreviations: MMITT, microbiological modified intent-to-treat.

Figure 31. Microbiologic Response Per Pathogen for MIC to Sulopenem – MMITR Population – *K. pneumoniae* (N=12)

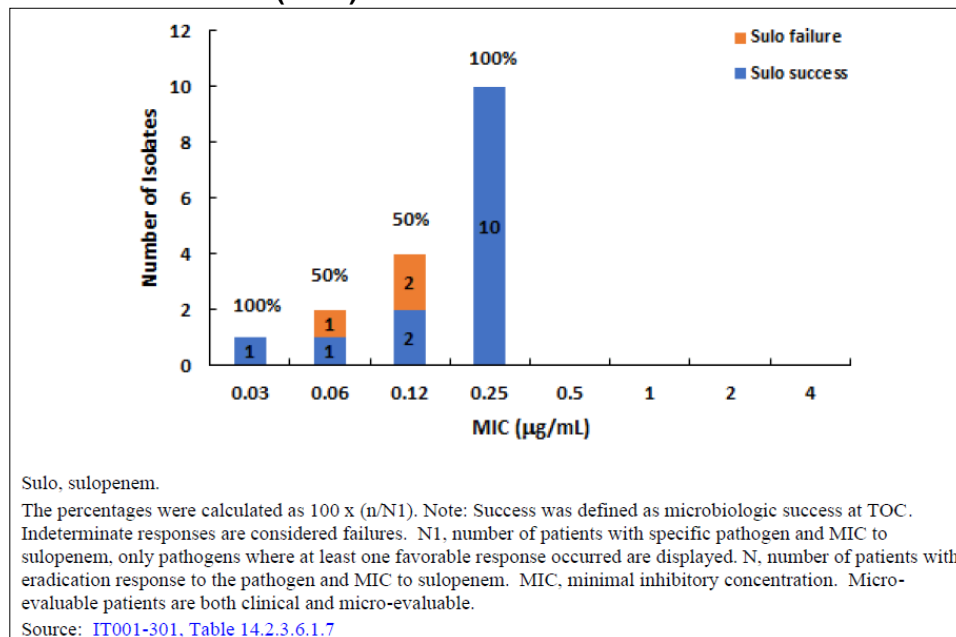


Abbreviations: MMITT, microbiological modified intent-to-treat.

P. mirabilis

The microbiologic response by sulopenem MIC for the baseline *P. mirabilis* population for the MMITT (N=17) is shown in Figure 32. Against a much smaller number of *P. mirabilis* baseline isolates, the rates of microbiologic success ranged from 50 to 100% over the MIC range of 0.03 to 0.25 µg/mL.

Figure 32. Microbiologic Response Per Pathogen for MIC to Sulopenem – MMITT Population Overall – *P. mirabilis* (N=17)



Abbreviations: MMITT, microbiological modified intent-to-treat.

Clinical Microbiology Reviewer's Comment: Favorable responses were observed for patients with baseline isolates of E. coli and P. mirabilis that had MIC values of ≤ 0.015 up to 0.25 µg/mL. No baseline isolate of E. coli with MIC 0.5 µg/mL was observed and a single isolate with MIC 1.0 µg/mL was observed but was associated with a microbiologic failure. No baseline isolate of P. mirabilis with MIC 0.5 µg/mL or higher was observed. An overall favorable response was observed for patients with baseline isolates of K. pneumoniae that had MIC values of ≤ 0.015 up to 0.12 µg/mL. No baseline isolates of K. pneumoniae were observed that had MIC values between 0.25 to 2 µg/mL, however, two isolates with MIC 4 and 8 µg/mL were observed and this was associated with a favorable outcome.

16.5.5. Supporting Microbiology Data From Other Phase 3 Studies

As mentioned earlier, the Applicant conducted two additional Phase 3 studies to evaluate the safety and efficacy of sulopenem for the treatment of cUTI and cIAI indications. Data from both cUTI and cIAI studies were submitted in this NDA application to support the safety of sulopenem administration in uUTI treatment.

This review only summarizes the microbiological data from cUTI Phase 3 study only (SURE2, IT001-302).

16.5.5.1. cUTI Phase 3 Study: SURE 2 (Study IT001-302)

The IV sulopenem alone or followed by PO sulopenem etzadroxil/probenecid was compared with IV ertapenem followed by PO ciprofloxacin or amoxicillin-clavulanate in this study for the

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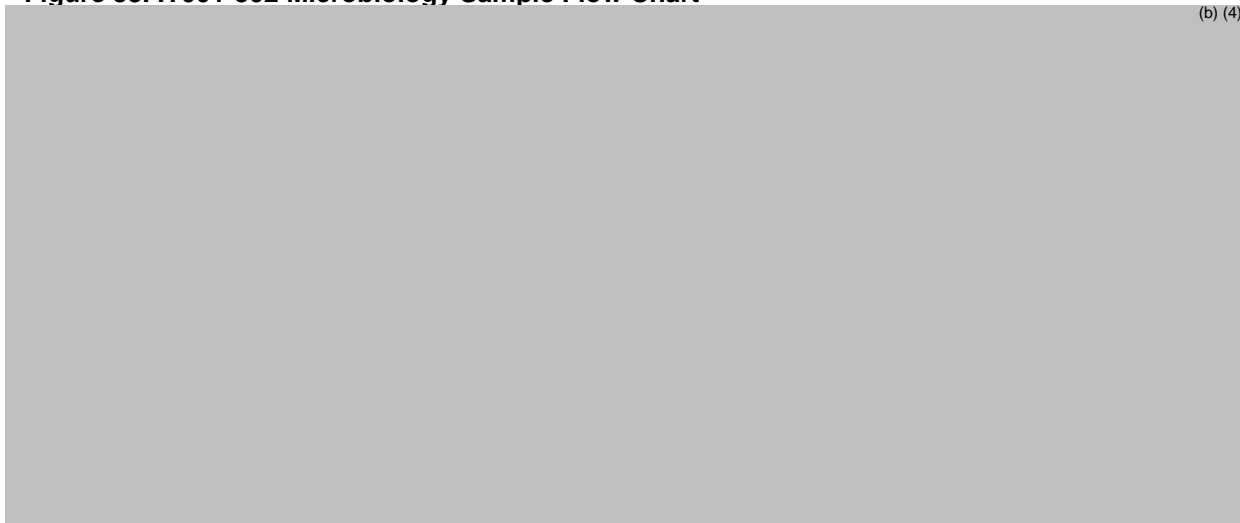
treatment of adult patients with cUTI at the TOC visit (Day 21±1 day). A total of 1356 patients were randomized (1:1 fashion) in this study.

Microbiological Sampling, Culture and Pathogen Identification: cUTI

Urine specimens were collected for culture at Screening (Baseline), Day 5, Day 10 (±1 day; EOT), Day 21 (±1 day; TOC), and any study-related visits by following standard procedures.

Additionally, two sets of blood culture bottles were to be collected aseptically at each visit (one aerobic and one anaerobic) by following a standard procedure. According to the Applicant, (b) (4) was the Central Laboratory and IHMA was the Central Microbiological Laboratory in both the US and in Europe. Routine culture and antimicrobial susceptibility testing (except study drug) was to be performed at the local laboratories against all gram-negative pathogens. The Central Microbiology Laboratory, IHMA, only received all isolates from the local laboratories and confirmed the identification with further analysis. These procedures are outlined in the following Figure 33.

Figure 33. IT001-302 Microbiology Sample Flow Chart



In the cUTI study, the following organisms were always considered a uropathogen either present as monomicrobial or polymicrobial (not more than two target pathogens with $\geq 10^5$ CFU/mL) infections:

- Enterobacterales, including extended-spectrum beta-lactamase-positive isolates
- *Enterococci*
- *Pseudomonas aeruginosa*

Primary Clinical and Microbiological Outcome Measures: cUTI

The primary endpoint for this study was overall response at TOC in the MMITT population.

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Baseline Microbiology: cUTI

Species Distribution Among Patients at Baseline

In the cUTI study, uropathogens that were identified at baseline from urine samples of the MMITT population are summarized in Table 190 and Table 191. The most frequently isolated uropathogens were *E. coli*, *K. pneumoniae* and *P. mirabilis* as 76.2%, 11.3% and 4.4%, respectively (Table 190). Infection due to a qualifying organism in the blood was present in 9.8% of cases (87/884) and *E. coli* was the most commonly identified pathogen (8.8%; 78/884) (Table 191). Overall, 72.8% of infections at Baseline were monomicrobial (72.8% and 72.7% in the sulopenem and ertapenem groups, respectively) in the MMITT population.

Table 190. Pathogens From Urine at Baseline – MMITT Population

Organism	Sulopenem n/N (%)	Ertapenem n/N (%)	Total n/N (%)
Number of Patients with at least one study uropathogen in the urine at baseline	436/444 (98.2)	435/440 (100.0)	871/884 (98.5)
<i>Escherichia coli</i>	332/444 (74.8)	346/440 (77.7)	674/884 (76.2)
<i>Klebsiella pneumoniae</i>	55/444 (12.4)	45/440 (10.2)	100/884 (11.3)
<i>Proteus mirabilis</i>	25/444 (5.9)	14/440 (3.2)	39/884 (4.4)
<i>Enterobacter cloacae</i> complex	9/444 (2.0)	15/440 (3.4)	24/884 (2.7)
<i>Klebsiella oxytoca</i>	7/444 (1.6)	7/440 (1.6)	14/884 (1.6)
<i>Citrobacter freundii</i>	4/444 (0.9)	5/440 (1.1)	9/884 (1.0)
<i>Morganella morganii</i>	4/444 (0.9)	5/440 (1.1)	9/884 (1.0)
<i>Klebsiella varicola</i>	5/444 (1.1)	1/440 (0.2)	6/884 (0.7)
<i>Serratia marcescens</i>	3/444 (0.7)	3/440 (0.7)	6/884 (0.7)
<i>Citrobacter koseri</i>	3/444 (0.7)	2/440 (0.5)	5/884 (0.6)
<i>Klebsiella aerogenes</i>	2/444 (0.5)	2/440 (0.5)	4/884 (0.5)
<i>Proteus vulgaris</i>	0/444 (0.0)	3/440 (0.7)	3/884 (0.3)
<i>Providencia rettgeri</i>	0/444 (0.0)	3/440 (0.7)	3/884 (0.3)
<i>Raoultella ornithinolytica</i>	2/444 (0.5)	1/440 (0.2)	3/884 (0.3)
<i>Proteus hauseri</i>	1/444 (0.2)	1/440 (0.2)	2/884 (0.2)
<i>Providencia stuartii</i>	1/444 (0.2)	1/440 (0.2)	2/884 (0.2)
<i>Enterobacter</i> , non-speciated	0/444 (0.0)	1/440 (0.2)	1/884 (0.1)
<i>Klebsiella</i> , spp.	1/444 (0.2)	0/440 (0.0)	1/884 (0.1)
<i>Leclercia adecarboxylata</i>	1/444 (0.2)	0/440 (0.0)	1/884 (0.1)
<i>Raoultella planticola</i>	1/444 (0.2)	0/440 (0.0)	1/884 (0.1)
<i>Serratia liquefaciens</i>	0/444 (0.0)	1/440 (0.2)	1/884 (0.1)
<i>Serratia</i> , non-speciated	0/444 (0.0)	1/440 (0.2)	1/884 (0.1)

micro-MITT, microbiological Modified Intent-to-Treat; n, number of patients; N, number of patients in the micro-MITT population. The percentages are calculated as $100 \times (n/N)$.

Source: 14.1.11.2.1

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Table 191. Pathogens From Blood at Baseline – MMITT Population

Organism	Sulopenem n/N (%)	Ertapenem n/N (%)	Total n/N (%)
Number of Patients with at least one study uropathogen in the blood at baseline	44/444 (9.9)	43/440 (9.8)	87/884 (9.8)
<i>Escherichia coli</i>	39/444 (8.8)	39/440 (8.9)	78/884 (8.8)
<i>Klebsiella pneumoniae</i>	1/444 (0.2)	4/440 (0.9)	5/884 (0.6)
<i>Proteus mirabilis</i>	2/444 (0.5)	0/440 (0.0)	2/884 (0.2)
<i>Enterobacter cloacae</i> complex	1/444 (0.2)	0/440 (0.0)	1/884 (0.1)
<i>Morganella morganii</i>	1/444 (0.2)	0/440 (0.0)	1/884 (0.1)

micro-MITT, microbiological Modified Intent-to-Treat; n, number of patients; N, number of patients in the micro-MITT population. The percentages are calculated as $100 \times (n/N)$.

Source: 14.1.12.2.1

Antibacterial Activity Against Baseline Pathogens of Both Treatment Groups: cUTI

In vitro MIC susceptibility data for baseline pathogens from both sulopenem and ertapenem treatment groups are summarized in Table 192. Against, *E. coli* (n=827), *K. pneumoniae* (n=116), and *P. mirabilis* (n=43) isolates from both treatment groups, the sulopenem MIC_{50/90} values were 0.015/0.03, 0.03/0.12, and 0.25/0.5 µg/mL, respectively (Table 192).

Table 192. Activity of Sulopenem and Ertapenem Against Baseline Pathogens – Micro- MITT Population – Both Treatment Groups

Organism Antibiotic	N	MIC ₅₀ (µg/mL)	MIC ₉₀ (µg/mL)	CLSI %S/%I/%R
<i>Escherichia coli</i>	N = 827			
Sulopenem		0.015	0.03	0/0/0
Ertapenem		≤0.25	≤0.25	100/0/0
<i>Klebsiella pneumoniae</i>	N = 116			
Sulopenem		0.03	0.12	0/0/0
Ertapenem		≤0.25	≤0.25	100/0/0
<i>Proteus mirabilis</i>	N = 43			
Sulopenem		0.25	0.5	0/0/0
Ertapenem		≤0.25	≤0.25	100/0/0
<i>Enterobacter cloacae</i> complex	N = 27			
Sulopenem		0.06	0.25	0/0/0
Ertapenem		≤0.25	0.5	100/0/0
<i>Klebsiella oxytoca</i>	N = 14			
Sulopenem		0.03	0.06	0/0/0
Ertapenem		≤0.25	≤0.25	100/0/0
<i>Morganella morganii</i>	N = 10			
Sulopenem		0.5	0.5	0/0/0
Ertapenem		≤0.25	≤0.25	100/0/0

The percentages are calculated as $100 \times (n/N)$; for the %S/%I/%R column there is no breakpoint for CLSI when 0/0/0 appears. CLSI, Clinical and Laboratory Standards Institute; I, intermediate; MIC₅₀, Minimum Inhibitory Concentration required to inhibit the growth of 50% of organisms; MIC₉₀, Minimum Inhibitory Concentration required to inhibit the growth of 90% of organisms; micro-MITT, microbiologic Modified Intent-to-Treat; N, number of pathogens identified in the micro-MITT population; R, resistant; S, susceptible.

Source: Table 14.1.21.1

16.5.5.2. Summary of Clinical and Microbiologic Efficacy: cUTI study

Overall Response: cUTI

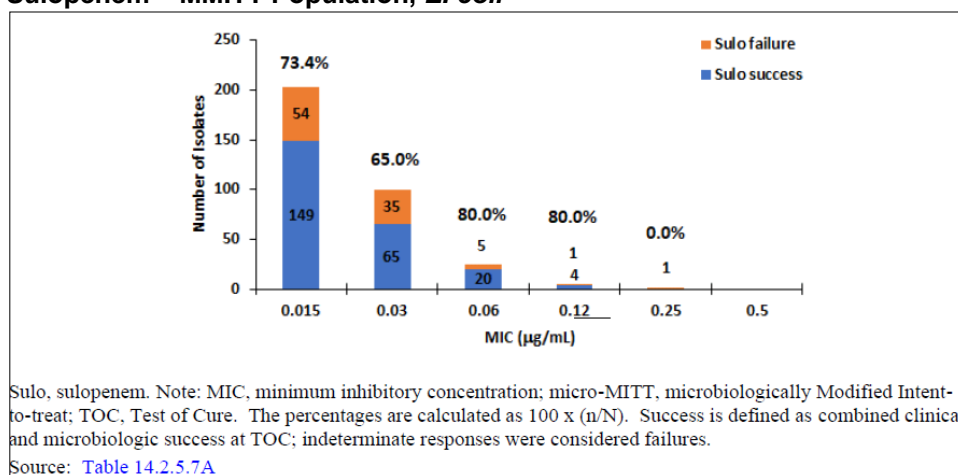
The efficacy analysis was conducted for the two Phase 3 trials in cUTI and cIAI under section 8.1.3 of this unireview. The Clinical Microbiology reviewer defers to the Statistical reviewer for analysis and comment on the Agency's assessment of the efficacy results.

Correlation of Baseline Sulopenem MIC to Microbiological Outcomes: cUTI Study

E. coli

Against *E. coli* (N=334), sulopenem demonstrated microbiological success at 65 to 80% across MIC values of ≤ 0.015 -0.12 $\mu\text{g}/\text{mL}$ (Figure 34). The overall microbiological success rate for sulopenem against *E. coli* was 71.3% (238/334).

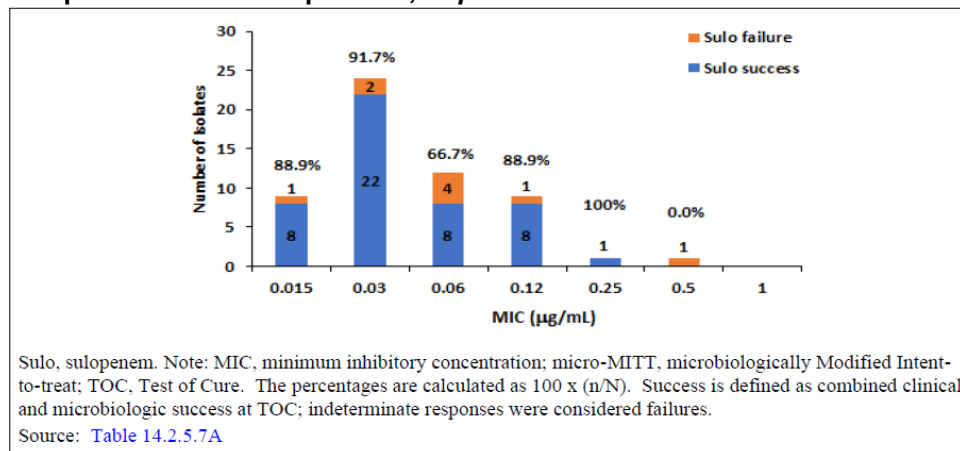
Figure 34. Microbiologic Response Per Pathogen From Urine or Blood at TOC for MIC to Sulopenem – MMITT Population, *E. coli*



K. pneumoniae

Against *K. pneumoniae* (N=56) isolates from urine or blood at TOC, the microbiological success ranged from 66.7% to 100% (Figure 35) with sulopenem MIC values of 0.015 to 0.12 $\mu\text{g}/\text{mL}$. The overall microbiologic success rate for sulopenem against *K. pneumoniae* was 83.9% (47/56).

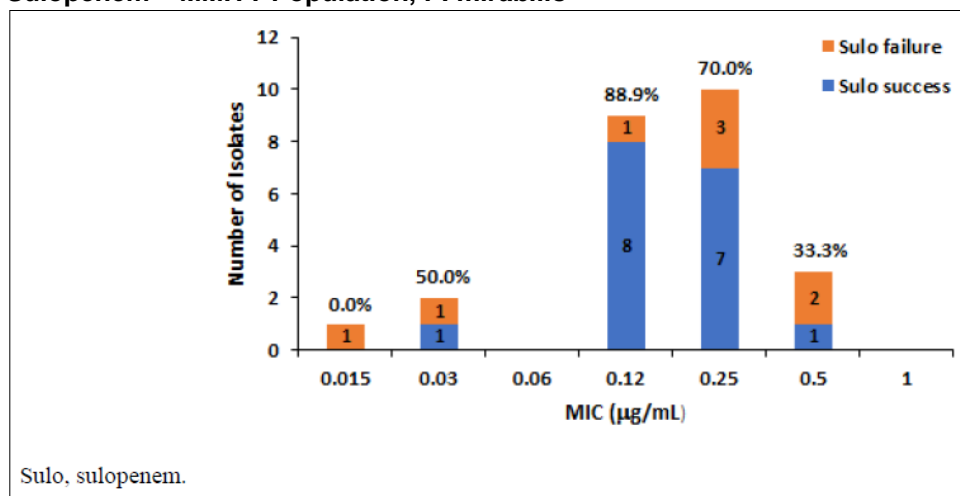
Figure 35. Microbiologic Response Per Pathogen From Urine or Blood at TOC for MIC to Sulopenem – MMITT Population, *K. pneumoniae*



P. mirabilis

Against *P. mirabilis* (N=25) isolates from urine or blood at TOC, the microbiological success ranged from 0% to 88.9% (Figure 36) with sulopenem MIC values of 0.015 to 0.5 µg/mL. The overall microbiologic success rate for sulopenem against *P. mirabilis* was 68.0% (17/25).

Figure 36. Microbiologic Response Per Pathogen From Urine or Blood at TOC for MIC to Sulopenem – MMITT Population, *P. mirabilis*



Source: Note: MIC, minimum inhibitory concentration; micro-MITT, microbiologically Modified Intent-to-treat; TOC, Test of Cure. The percentages are calculated as 100 x (n/N). Success is defined as combined clinical and microbiologic success at TOC; indeterminate responses were considered failures. [Table 14.2.5.7A](#)

Clinical Microbiology Reviewer's Comment: The in vitro activity of sulopenem against target uropathogens were comparable between the cUTI and uUTI trials with only one dilution difference for E. coli and P. mirabilis isolates. Against, E. coli (n=827), K. pneumoniae (n=116), and P. mirabilis (n=43) isolates from both treatment groups in cUTI study, the sulopenem MIC90 values were 0.03, 0.12 and 0.5 µg/mL, respectively. In contrast, against E. coli (n=900), K. pneumoniae (n=96), and P. mirabilis (n=32) isolates from both treatment groups in the uUTI

study, the sulopenem MIC₉₀ values were 0.06 µg/mL, 0.12 µg/mL, and 0.25 µg/mL, respectively. The correlation of microbiological success of the baseline isolates and their sulopenem MICs were similar to uUTI clinical study isolates.

16.5.6. Applicant's Proposed Interpretive Criteria for Sulopenem: uUTI Target Pathogens

The Applicant has proposed sulopenem broth microdilution MIC and disk diffusion susceptibility testing interpretive criteria or breakpoints (BPs) against Enterobacterales based on the following sulopenem summary data:

1. MIC frequency distributions for surveillance study and clinical study isolates for the indicated pathogens;
2. PK/PD information including target attainment analysis from Monte-Carlo simulations conducted with Phase 3 patient PK data;
3. A summary of correlation between microbiologic outcome and MIC; and
4. The generation of proposed disk diffusion interpretive criteria by correlation between zone diameter and broth microdilution MIC values in scatterplot following the CLSI error-rate bounding analysis.

The Applicant proposed BPs against Enterobacterales are summarized in the following Table 193.

Table 193. Proposed Broth Microdilution and Disk Diffusion Susceptibility Test Criteria for Sulopenem

Organism	MIC (µg/mL)	Zone Diameter ^a (mm) (b) (4)
Enterobacterales		

MIC = minimum inhibitory concentration; NA = not applicable. ^a Sulopenem 2-µg disk
Source: NDA submission

16.5.7. Recommended BPs for Sulopenem Against Target uUTI Pathogens

The following is a summary of the Clinical Microbiology team's breakpoints (BPs) rationale and labeling recommendations:

16.5.7.1. Setting the MIC BPs for Sulopenem Against uUTI Target Pathogens

For setting the MIC BPs for sulopenem against uUTI target pathogens *E. coli*, *K. pneumoniae*, and *P. mirabilis*, the Clinical Microbiology team primarily relied on:

1. Overall MIC₉₀ data from clinical and surveillance study isolates; and
2. Microbiological eradication rates at each MIC dilution of uUTI clinical study isolates.

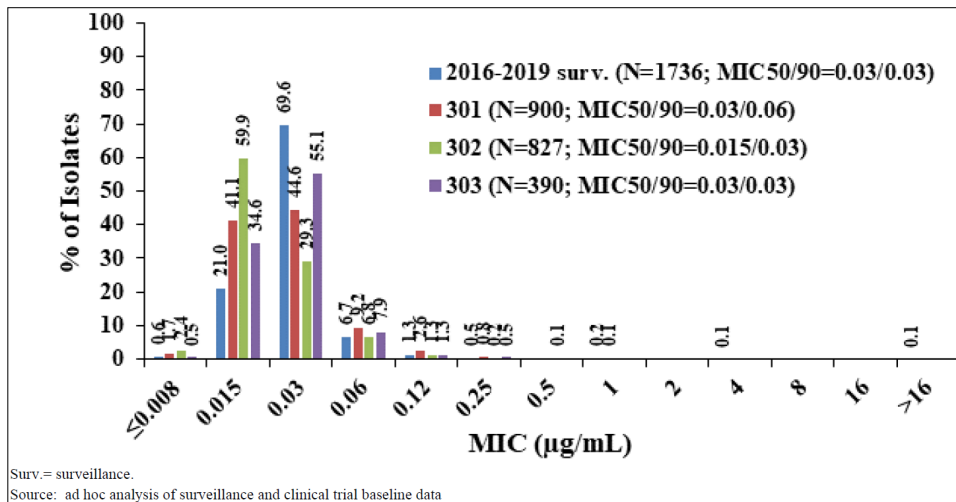
Of note, the FDA Clinical Pharmacology team has a concern with the validity of PK/PD study results.

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Overall MIC Distributions – Clinical vs. Surveillance

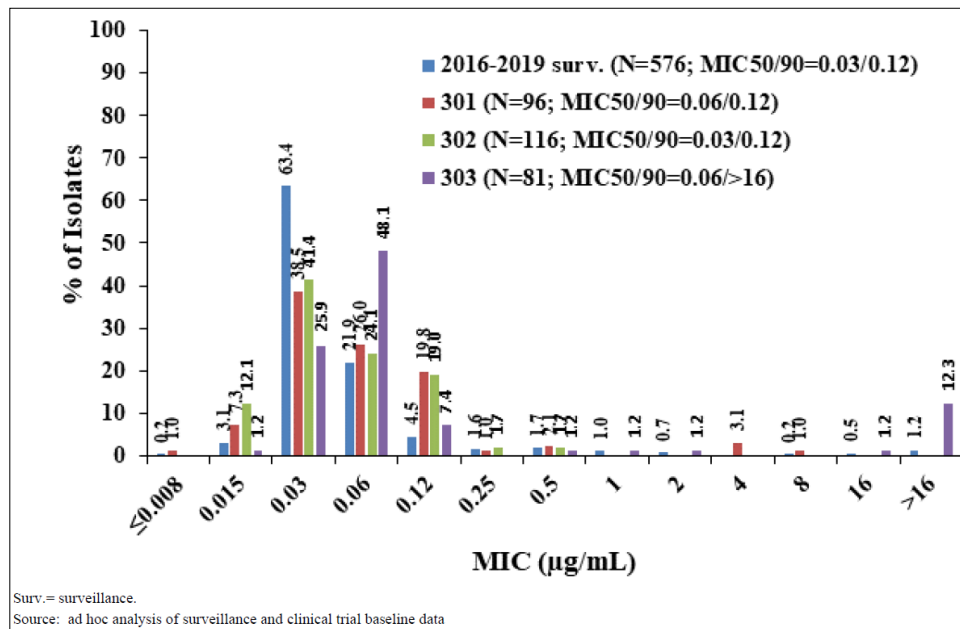
The MIC distributions of sulopenem against target pathogens isolated at baseline in clinical studies (MMITT; Study 301 uUTI, 302 cUTI, and 303 cIAI) relative to recent surveillance (US and European isolates from 2016-2019 combined) are shown in histograms for the uUTI target pathogens: *E. coli* (Figure 37), *Klebsiella pneumoniae* (Figure 38), and *Proteus mirabilis* (Figure 39). A unimodal distribution was observed for all three pathogens from both clinical and surveillance isolates.

Figure 37. MIC Distribution of Sulopenem for *E. Coli* Isolates During Recent Surveillance and Phase 3 Clinical Trials



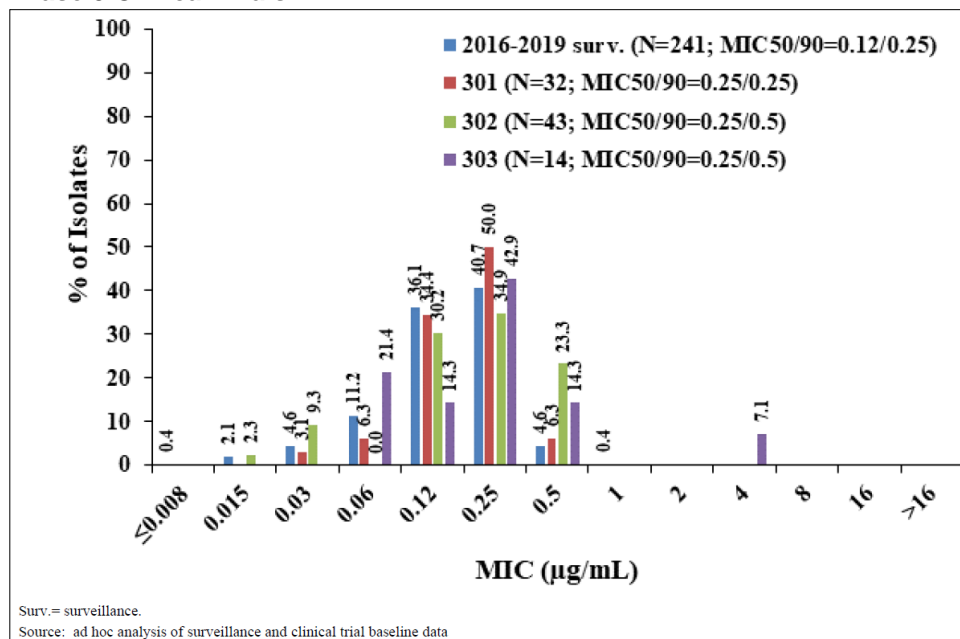
Source: Applicant's ad hoc analysis of surveillance and clinical trial baseline data
 Abbreviations: MIC, minimum inhibitory concentration

Figure 38. MIC Distribution of Sulopenem for *K. Pneumoniae* Isolates During Recent Surveillance and Phase 3 Clinical Trials



Source: Applicant's ad hoc analysis of surveillance and clinical trial baseline data
 Abbreviations: MIC, minimum inhibitory concentration

Figure 39. MIC Distribution of Sulopenem for *P. Mirabilis* Isolates During Recent Surveillance and Phase 3 Clinical Trials



Source: Applicant's ad hoc analysis of surveillance and clinical trial baseline data
 Abbreviations: MIC, minimum inhibitory concentration

Correlation of microbiological success to MIC values of baseline *E. coli*, *K. pneumoniae*, and *P. mirabilis* isolates

In the uUTI clinical study, the microbiological success in relation to MIC values of baseline *E. coli*, *K. pneumoniae*, and *P. mirabilis* isolates from the sulopenem treatment group the in MMITT (MMITTR and MMITTS) population at the TOC visit are summarized below:

- Among 437 baseline *E. coli* isolates with an MIC range of 0.015 to 1.0 µg/mL, the overall microbiological eradication rate at TOC was 76.4%. The highest sulopenem MIC that correspond to microbiological success was 0.25 µg/mL and 3/5 (60%) isolates were eradicated. Only one baseline *E. coli* isolate with a sulopenem MIC of 1 µg/mL was available but persisted. No baseline isolate with MIC values at ≥ 2 µg/mL was available. The MIC_{50/90} was 0.03/0.06 µg/mL against all *E. coli* isolates from both surveillance and clinical studies. Therefore, a susceptible BP of 0.25 µg/mL would be reasonable and will cover most *E. coli* population.
- Among 48 baseline *K. pneumoniae* isolates with an MIC range 0.015 to 8.0 µg/mL, the overall microbiological eradication rate at TOC was 77.1%. The highest sulopenem MIC that correspond to favorable microbiological eradication was 0.12 µg/mL and 7/8 (87.5%) isolates at this MIC were successfully eradicated. No baseline isolate was available with MIC values between 0.25 to 2.0 µg/mL. However, only 2 baseline isolates with MIC values 4 and 8 µg/mL were available but eradicated. The MIC_{50/90} was 0.03/0.12 against all *K. pneumoniae* isolates from both surveillance (US and Europe) and clinical studies. Therefore, a susceptible BP of 0.25 µg/mL would also be reasonable and would cover most *K. pneumoniae*.
- Among 17 baseline *P. mirabilis* isolates with an MIC range of 0.03 to 0.25 µg/mL, the overall microbiological eradication rate at TOC was 82.4%. The highest sulopenem MIC that correspond to microbiological success was 0.25 µg/mL and 10/10 (100%) isolates at this MIC were successfully eradicated. No baseline isolate was available at MIC values ≥ 0.5 µg/mL. Against *P. mirabilis* isolates from both surveillance and clinical studies, the MIC_{50/90} was between 0.12/0.25 to 0.25/0.5 µg/mL. Therefore, a susceptible BP of 0.25 µg/mL would also be reasonable and would cover most *P. mirabilis*.

In summary, the overall microbiological success was observed in patients with baseline isolates of *E. coli* and *P. mirabilis* that had MIC values of ≤ 0.015 to 0.25 µg/mL. No baseline *E. coli* isolate at MIC 0.5 µg/mL was available but a single isolate at MIC 1.0 µg/mL was available with microbiologic failure. No baseline *P. mirabilis* isolate with MIC ≥ 0.5 µg/mL was available. The overall microbiological success was observed in patients with baseline *K. pneumoniae* isolates that had MIC values of ≤ 0.015 up to 0.12 µg/mL. No baseline *K. pneumoniae* isolates with MIC values between 0.25 to 2 µg/mL were available, however, only two isolates at MIC 4 and 8 µg/mL were available with overall success outcome.

Therefore, the Clinical Microbiology team recommends revised sulopenem S/I/R MIC BPs of $\leq 0.25/0.5/\geq 1.0$ µg/mL against Enterobacteriales (*E. coli*, *K. pneumoniae*, and *P. mirabilis* only). The corresponding disk diffusion zone diameter BPs have been calculated by following CLSI

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
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error rate criteria (section 16.5.7.2). The recommended broth microdilution (MIC) and disk diffusion interpretive criteria (BPs) for sulopenem are summarized in Table 194.

Table 194. Recommended Broth Microdilution (MIC) and Disk Diffusion Interpretive Criteria (BPs) for Sulopenem

Indicated Pathogens	Broth Microdilution Method			Disk Diffusion Method Zone Diameter		
	Susceptible (µg/mL)	Intermediate (µg/mL)	Resistant (µg/mL)	Susceptible (mm)	Intermediate (mm)	Resistant (mm)
<i>E. coli</i>	≤0.25	0.5	≥1.0	≥19	16-18	≤15
<i>K. pneumoniae</i>	≤0.25	0.5	≥1.0	≥19	16-18	≤15
<i>P. mirabilis</i>	≤0.25	0.5	≥1.0	≥19	16-18	≤15

Source: Reviewer's analysis

Abbreviations: BP, breakpoint; MIC, minimum inhibitory concentration

We agree with the inclusion of *E. coli*, *K. pneumoniae* and *P. mirabilis* in the first list pathogens of 12.4 Microbiology section of the sulopenem labeling. However, inclusion of pathogens in the second list has been modified based on the relevance of uUTI indication and of having an in vitro MIC₉₀ of ≤0.25 µg/mL. The recommendation is that the following organisms could be included in the second list: *Staphylococcus saprophyticus*, *Streptococcus agalactiae*, *Citrobacter freundii*, *Citrobacter koseri*, *Enterobacter cloacae species complex*, *Klebsiella aerogenes*, *Klebsiella oxytoca*, *Proteus vulgaris*, *Providencia alcalifaciens*, and *Providencia stuartii*.

16.5.7.2. Broth MIC vs. Disk Zone Diameter Correlation and Error-Rate Bounding Analysis

The scatterplot analysis was done using the error-rate bounding method in accordance with CLSI M23 guideline (Table 195). In scatterplots, the dotted black lines represent the Applicant's analysis and the red bold lines represent the FDA Clinical Microbiology Reviewer's analysis (Figures 40-43).

Table 195. Acceptable Error Rates in Interpretation Between Test Methods (CLSI M23)

Discrepancy Rates			
1-dilution Intermediate Range	Very Major	Major	Minor
≥ I+2	< 2%	NA	< 5%
I+1 to I-1	< 10%	< 10%	< 40%
≤ I-2	NA	< 2%	< 5%

CLSI = Clinical and Laboratory Standards Institute; I, intermediate; R, resistant; S, susceptible; Very Major, false susceptible by disk; Major, false resistant by disk; MIC, minimum inhibitory concentration; Minor, false intermediate by disk or broth; NA, not applicable;

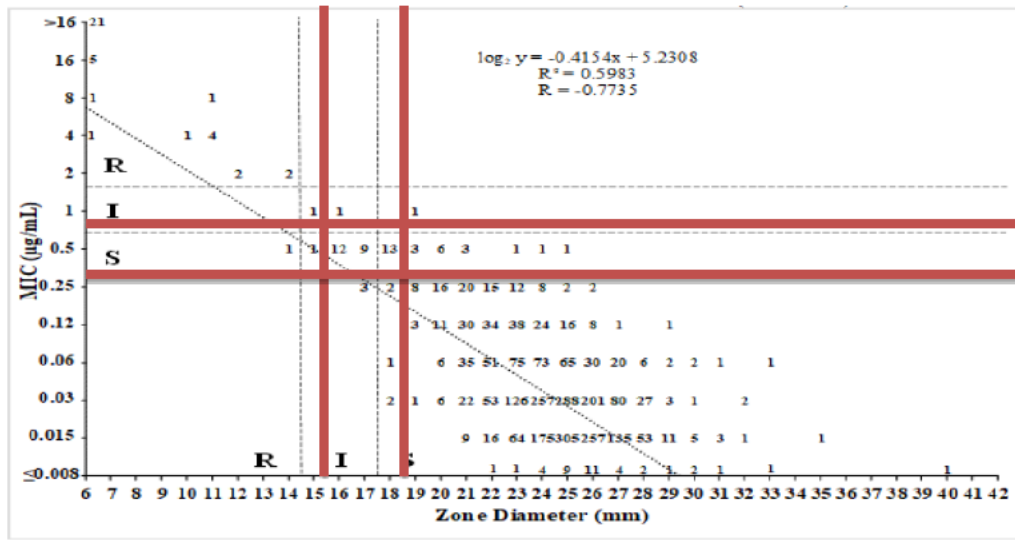
Source: CLSI M23-A3

Abbreviations: CLSI, Clinical Laboratory Standard Institute guidelines

The broth microdilution MIC and disk zone correlation is shown by scatterplot for Enterobacterales (Figure 40) and the primary pathogens: *E. coli* (Figure 41), *K. pneumoniae*, (Figure 42), and *P. mirabilis* (Figure 43). A reanalysis was conducted for all scatterplots using the Clinical Microbiology team's recommended MIC BPs for sulopenem (S/I/R of 0.25/0.5/1 µg/mL). According to the reanalysis, the Clinical Microbiology team recommends sulopenem disk interpretive criteria of ≥19 mm susceptible, 16-18 mm intermediate, and ≤15 mm resistant.

NDA Multi-disciplinary Review and Evaluation {NDA 213972}
 {sulopenem etzadroxil/probenecid}

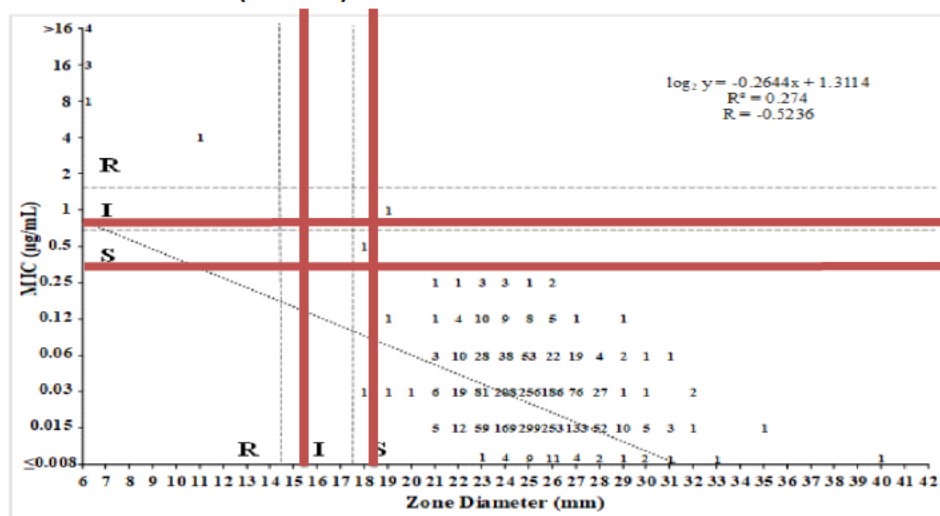
Figure 40. Correlation Between Sulopenem Broth MIC Values and Disk Diffusion for Overall Enterobacteriales (N=2856)



		Discrepancy Rates					
		Very Major		Major		Minor	
MIC range	N	n	(%)	n	(%)	n	(%)
>I+2	38	0	0	NA	NA	0	0
I+1 to I-1	142	1	0.7	0	0	23	16.2
<I-2	2676	NA	NA	0	0	3	0.1
TOTAL	2856	1	0.04	0	0	26	0.9

Source: Reviewer's analysis
 Abbreviations: MIC, minimum inhibitory concentration

Figure 41. Correlation Between Sulopenem Broth MIC Values and Disk Diffusion Zone Diameters for *E. Coli* Overall (N=2148)

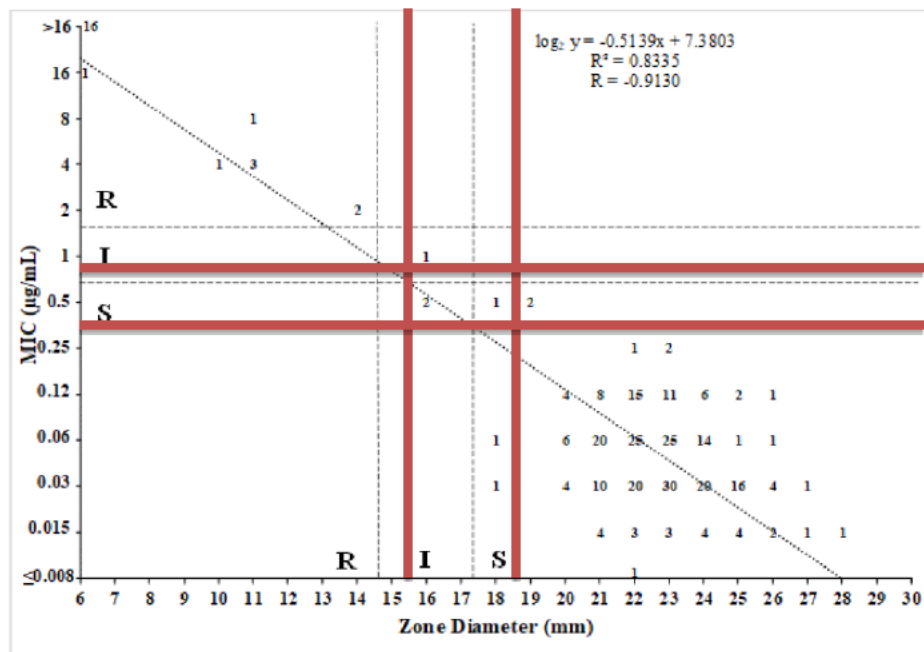


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MIC range	N	Discrepancy Rates					
		Very Major		Major		Minor	
		n	(%)	n	(%)	n	(%)
>I+2	9	0	0	NA	NA	0	0
I+1 to I-1	13	1	7.7	0	0	0	0
<I-2	2126	NA	NA	0	0	1	0.05
TOTAL	2148	1	0.05	0	0	1	0.05

Source: Reviewer's analysis
 Abbreviations: MIC, minimum inhibitory concentration

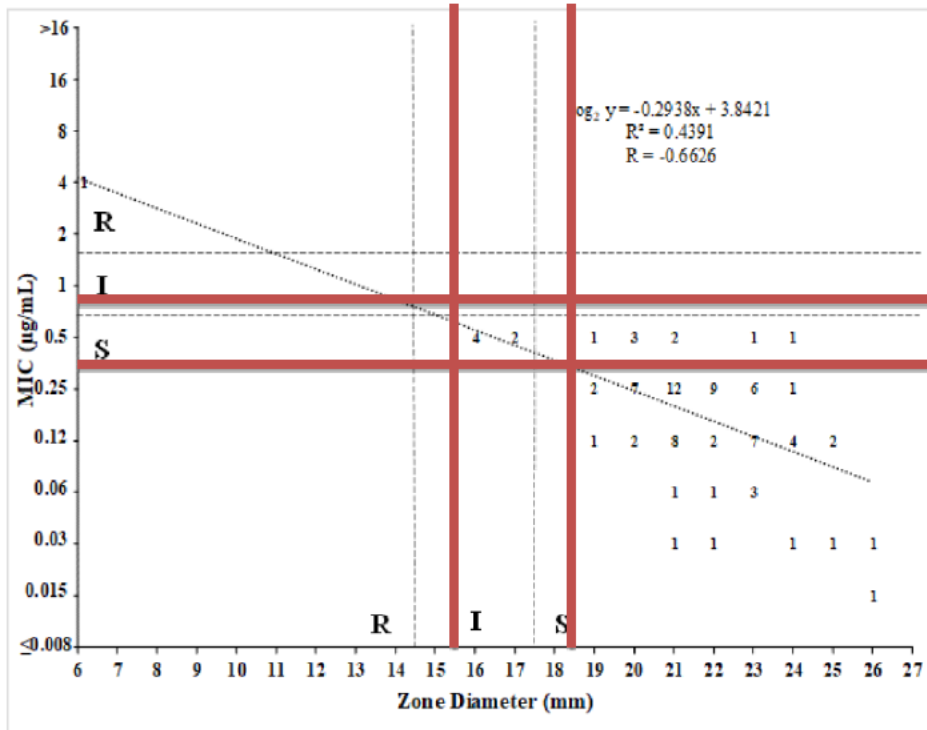
Figure 42. Correlation Between Sulopenem Broth MIC Values and Disk Diffusion Zone Diameters for *K. Pneumoniae* Overall (N=302)



MIC range	N	Discrepancy Rates					
		Very Major		Major		Minor	
		n	(%)	n	(%)	n	(%)
>I+2	7	0	0	NA	NA	0	0
I+1 to I-1	9	0	0	0	0	3	33.3
<I-2	286	NA	NA	0	0	2	0.7
TOTAL	302	0	0	0	0	5	1.7

Source: Reviewer's analysis
 Abbreviations: MIC, minimum inhibitory concentration

Figure 43. Correlation Between Sulopenem Broth MIC Values and Disk Diffusion Zone Diameters for *P. Mirabilis* Overall (N=89)



MIC range	N	Discrepancy Rates					
		Very Major		Major		Minor	
		n	(%)	n	(%)	n	(%)
>I+2	1	0	0	NA	NA	0	0
I+1 to I-1	51	0	0	0	0	8	15.7
<I-2	37	NA	NA	0	0	0	0
TOTAL	89	0	0	0	0	8	9

Source: Reviewer's analysis
 Abbreviations: MIC, minimum inhibitory concentration

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/s/

CHRISTOPHER L SMITH
07/22/2021 10:48:56 AM

JAMES S WILD
07/22/2021 11:13:27 AM

TERRY J MILLER
07/22/2021 11:28:21 AM
I am signing for myself and for Dr. Hanan Ghantous, Division Director of DPT-ID. Dr. Ghantous authorized me to sign for her on 7/22/2021.

HENRIETTA D ABODAKPI
07/22/2021 11:29:20 AM

ZHIXIA YAN
07/22/2021 12:00:54 PM

JALAL U SHEIKH
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AVERY C GOODWIN
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KELLIE S REYNOLDS
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DIONNE L PRICE

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Signing on behalf of Karen Higgins who is on leave.

ABIMBOLA O ADEBOWALE

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JUSTIN C EARP

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