SULOPENEM ETZADROXIL PLUS PROBENECID FOR ORAL ADMINISTRATION

FOR TREATMENT OF ACUTE UNCOMPLICATED URINARY TRACT INFECTIONS

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADME	absorption, distribution, metabolism, and excretion
ADR	adverse drug reaction
AE	adverse event
ALT	alanine transaminase
AP	alkaline phosphatase
AST	aspartate transaminase
bid	twice daily
BMI	body mass index
BUN	blood urea nitrogen
CI	confidence interval

CMH	Cochran-Mantel-Haenszel
CrCl	creatinine clearance
CRF	case report form
CSR	clinical study report
CV	Cardiovascular
ECG	Electrocardiogram
ENT	ear, nose and throat
ESBL	extended-spectrum beta lactamase
FDA	Food and Drug Administration
GGT	gamma glutamyl transferase
Hct	Hematocrit
Hgb	Hemoglobin
IND	Investigational New Drug
IRB	Institutional Review Board
ISS	Integrated Summary of Safety
ITT	intent-to-treat
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
PCS	potentially clinically significant
PO	per os (by mouth)
PT	preferred term
qd	once daily
RBC	red blood cell (count)
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SOC	System Organ Class
TEAE	treatment-emergent adverse event

TESS	treatment-emergent signs and symptoms
ULN	upper limit of normal
uUTI	Uncomplicated urinary tract infection
WBC	white blood cell (count)

1 EXECUTIVE SUMMARY

1.1 CHEMISTRY AND PHARMACEUTICAL SUMMARY

Sulopenem etzadroxil, an orally-active prodrug of sulopenem, is a broad-spectrum, thiopenem antibacterial drug. The chemical name of sulopenem etzadroxil is 4-Thia-1-azabicyclo[3.2.0]hept-2-ene-2-carboxylic acid, 6-[(1*R*)-1-hydroxyethyl]-7-oxo-3-[[(1*R*,3*S*)- tetrahydro-1-oxido-3-thienyl]thio]-, (2-ethyl-1-oxobutoxy)methyl ester, (5*R*,6*S*)-. See Section 3 for sulopenem etzadroxil chemical structure and chemical formula. The molecular weight of sulopenem etzadroxil is 477.61 g/mol.

Probenecid is a uricosuric and renal tubular transport blocking agent. The chemical name for probenecid is 4-[(dipropylamino) sulfonyl] benzoic acid. See Section 3 for probenecid chemical structure and chemical formula. The molecular weight of probenecid is 285.36 g/mol.

Each sulopenem etzadroxil/probenecid tablet for oral use contains 500 mg of sulopenem etzadroxil and 500 mg of probenecid and the following inactive ingredients: microcrystalline cellulose, croscarmellose sodium, magnesium stearate, lactose monohydrate, hydroxypropylcellulose, polyvinyl alcohol, titanium dioxide, talc, lecithin (soya), xanthan gum, and carmine.

1.2 PROPOSED INDICATION

Sulopenem etzadroxil/probenecid tablets, a fixed-dose combination product consisting of sulopenem etzadroxil, a penem antibacterial prodrug, and probenecid, a renal tubular transport blocking agent, is indicated in adult women ≥ 18 years of age for the treatment of uncomplicated urinary tract infections caused by designated susceptible microorganisms.

1.3 UNMET MEDICAL NEED

Among the most common infections caused by multidrug resistant Enterobacterales are those involving the urinary tract. Uncomplicated urinary tract infections treated in the outpatient setting account for as many as 40 million prescriptions in the United States every year [Eversana Pharmacy and Longitudinal Claims, data on file]. Historically, a variety of antibiotics were used to treat uUTI, including β-lactams, quinolones, trimethoprim-sulfamethoxazole, and nitrofurantoin (Table 1). Resistance rates for these agents, as observed in Iterum's uUTI clinical trials, are noteworthy, and surveillance data collected by Iterum as part of this development program indicate that they are now at or exceed the 20% threshold at which the IDSA recommends that, rather than empiric treatment with that agent, a urine culture be performed to guide therapy.

Table 1: Resistance in Enterobacterales from Outpatient Urinary Cultures

Antibacterial Class	IT004-401 (2017-2018) N=124 %	IT001-301 (2018-2020) N=1,071 %	IT001-310 (2022-2023) N=990 %	Iterum/BD (2011-2020) N=2,228,515 %
Quinolone	16.9	27.4	26.4	21.9
β-lactam	-	64.4	29.7	56.1
ESBL positive		13.5	9.9	9.4
Trimethoprim- sulfamethoxazole	-	31.6	30.3	23.9
Nitrofurantoin	-	17.9	15.4	22.3

Source: IT004-401: Table 14.2.2.1.1; IT001-301: Table 14.1.3.11.1; IT001-310: Table 14.1.11.1 and Table 14.2.2.2.1; Dunne 2022

The importance of co-resistance to multiple oral agents can also be appreciated in this program (Table 2). Surveillance data collected by Iterum as part of this development program [Aronin 2022, Dunne 2022] indicate 5.5-6.4% of ambulatory Enterobacterales isolates are non-susceptible to ≥3 classes of antibiotics. For ambulatory patients who received a prescription for an oral antibiotic temporally related to the urine culture collection date, 3.6% and 0.9% of isolates were non-susceptible to ≥3 classes of antibiotics and 4 classes of antibiotics, respectively. To put that in perspective, if 5% of 40,000,000 UTI episodes per year are multidrug resistant, 2,000,000 women per year are receiving inadequate antibacterial therapy. These co-resistance rates are consistent with what others have reported in the literature [Kaye, 2021; Kaye, 2024].

Table 2 Ambulatory Urinary Isolates Resistant to Multiple Classes of Antibiotics

[Source] / Years	Number of Evaluable Ambulatory Urinary Isolates	Findings
[Dunne 2022] / 2011-2020	2,228,515	5.5% non-susceptible to ≥3 classes of antibiotics; 21.2% of ESBL-positive isolates non-susceptible to TMP-SMX, FQ, and NFT; 1.4% of all isolates non-susceptible to TMP-SMX, FQ, and NFT
[Dunne 2022] / 2015-2017	5,395*	3.6% non-susceptible to ≥3 classes of antibiotics; 0.9% non-susceptible to 4 classes of antibiotics
[Aronin 2022] / 2018-2020	980,354	6.4% non-susceptible to ≥3 classes of antibiotics

*Ambulatory UTI episodes in patients who received a prescription for an oral antibiotic temporally related to the urine culture collection date

Iterum conducted two Phase 3 studies in uUTI: IT001-301 and IT001-310. In these two clinical trials of the 2061 symptomatic adult women with a positive baseline urine culture for $\geq 10^5$ CFU/mL of a uropathogen (micro-MITT population), nearly 10% of patients had an infecting organism non-susceptible to β-lactams, quinolones and trimethoprim-sulfamethoxazole, and over 3% had an infecting organism non-susceptible to all four of the commonly available classes of oral antibiotics for uUTI (β-lactams, quinolones, trimethoprim-sulfamethoxazole and nitrofurantoin) (Table 3).

Table 3: Patients with uUTI Due to Baseline Pathogen with Co-resistance to Multiple Oral Antimicrobials, Studies IT001-301 and IT001-310, micro-MITT Population

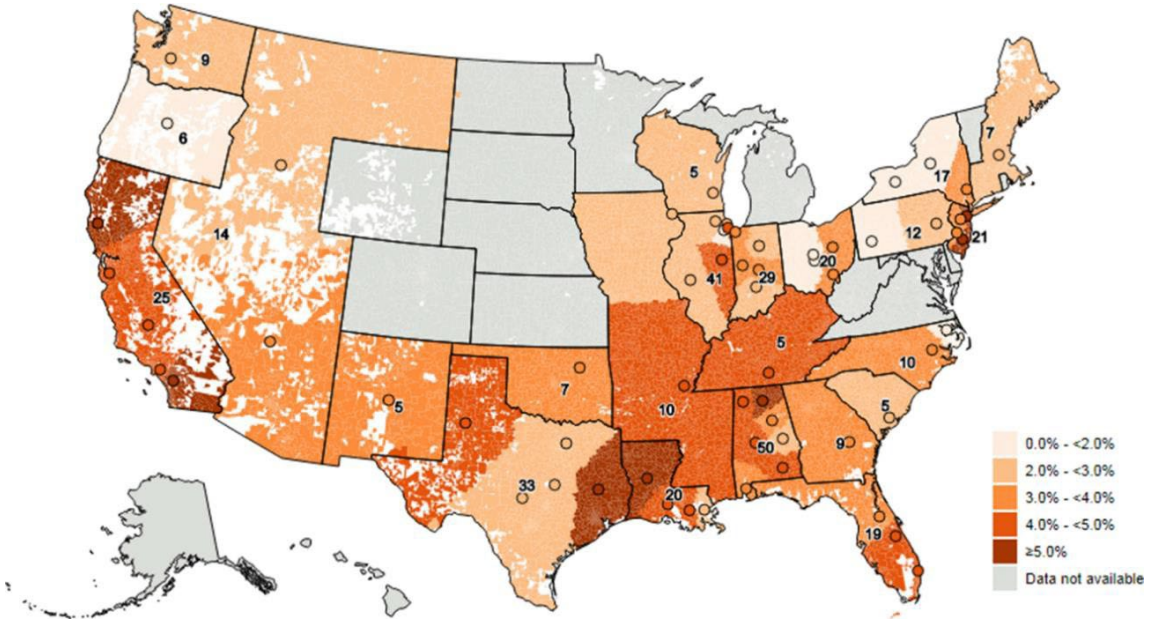
Study / Years / Location	N	≥1 isolate non-susceptible to β-lactams, FQ and TMP-SMX n (%)	≥1 isolate non-susceptible to β-lactams, FQ, TMP-SMX and NFT n (%)
IT001-301 / 2018-2020 / US, Russia, Ukraine	1071	116 (10.8)	53 (4.9)
IT001-310 / 2022-2023 / US	990	84 (8.5)	12 (1.2)
Total / 2018-2023	2061	200 (9.7)	65 (3.2)

Source: IT001-301 CSR: Table 44, IT001-310 CSR: Table 25, Table 64
Abbreviations: US = United States; FQ = fluoroquinolone; TMP-SMX = trimethoprim-sulfamethoxazole; NFT = nitrofurantoin; n = number of patients; N = number of patients in the micro-MITT population

A substantial number of women will become infected with an organism for which oral treatment options are severely limited and for which the wrong choice of empiric therapy carries a number of risks: increased morbidity directly related to the infection, additional adverse events related to a second antibiotic prescription, and the selection of more resistant pathogens in their colonizing flora.

Iterum's surveillance study results for sulopenem are supported by an epidemiologic study of the impact of mismatched empiric outpatient treatment of uUTIs at 400 healthcare institutions in the United States in 2017. A heatmap, broken down by zip code, of the incidence of multidrug resistant infections, defined as pathogens non-susceptible to quinolones and trimethoprim-sulfamethoxazole and ESBL positive among the most common pathogens responsible for uUTI, is provided in Figure 1. Multidrug resistant uropathogens are found in most major cities throughout the US, primarily concentrated in the Southern half of the country.

Figure 1 The incidence of Extended Spectrum β-Lactamase (ESBL) Positive, Quinolone and Trimethoprim-sulfamethoxazole Non-susceptible *E. Coli, K. pneumoniae, P. mirabilis* and *K. oxytoca* from Outpatient Urine Cultures in the United States in 2017



Rate of non-duplicate outpatient ESBL Positive and Quinolone NS and TMP/Sulfa-NS *E. coli, K. pneumoniae, P. mirabilis, K. oxytoca* isolates per total isolates tested for Q2 2017 across 379 acute care facilities. Data has been aggregated into geographic clusters of five or more hospitals from two or more IDNs. Each cluster's geographic centroid is represented with shaded circles. Each zip code tabulation area (ZCTA) has been attributed a rate based on that ZCTA's proximity to the nearest cluster's geographic centroid, which are represented with shaded circles. Within each state, the number of hospitals in each cluster is distributed equally, and the total number of hospitals at the state level is labeled on the map. Data for contiguous states that each contain less than five hospitals has been aggregated (AZ,MT,NV,ID,UT,AR,MS,MO,IA, ME,NH,MA,CT, KY,TN).

In a subset of this same cohort, we observed that the need for a second prescription for the initial uUTI episode increased from 16% to 36% if a patient was treated with a quinolone for an infection due to a quinolone non-susceptible pathogen [Dunne 2022]. Based on these data, among the approximately 40 million prescriptions written every year for uUTI, a substantial number of women will become infected with an organism for which oral treatment options are severely limited and for which the wrong empiric choice of therapy brings with it extended morbidity directly related to the infection, additional adverse events related to the second antibiotic prescription as well as the risk of selecting for more resistant pathogens in their colonizing flora. These findings are consistent with what others have published in the literature [Trautner, 2022].

Available treatment options for uUTI, when the pathogens demonstrate in vitro susceptibility, have limitations, as shown in Table 4.

Table 4: Limitations of Available Oral Treatment for uUTI

Antibiotic Class	Prescribing Considerations
Quinolones	• Should be reserved for patients who have no other treatment options for uUTI, as risks outweigh benefits: o Tendinitis, tendon rupture, peripheral neuropathy, central nervous system effects and exacerbation of myasthenia gravis, aortic aneurysm and dissection; • Risk is further increased in older patients
Nitrofurantoin	• Should not be used for pyelonephritis o does not reach therapeutic concentrations in kidneys • Avoid use in elderly due to age-related decline in renal function o 'creatinine clearance under 60 mL per minute or clinically significant elevated serum creatinine are contraindications.' • Acute, subacute, or chronic pulmonary reactions have been observed in patients treated with nitrofurantoin • Peripheral neuropathy, which may become severe or irreversible, has occurred. Fatalities have been reported.
Trimethoprim-sulfamethoxazole	• Monitor patients for adverse events (rash, hyperkalemia) or use an alternate antibiotic • Contraindicated in patients with marked hepatic damage or with severe renal insufficiency when renal function status cannot be monitored. • Fatalities associated with the administration of sulfonamides, although rare, have occurred due to severe reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia and other blood dyscrasias.
Pivmecillinam and other β-lactams	• Severe cutaneous adverse reactions including acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), Steven-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with pivmecillinam • Clinically significant hypocarnitinemia has been observed with pivmecillinam in patients at risk for reductions in serum carnitine; alternative antibacterial therapy should be considered in patients with significant renal impairment or decreased muscle mass and those patients requiring long term antimicrobial treatment; concurrent treatment with pivmecillinam and valproic acid, valproate or other pivalate-generating drugs should be avoided due to increased risk of carnitine depletion • Pivmecillinam is contraindicated in patients with porphyria as it has been associated with acute attacks of porphyria • β-lactams in general are associated with inferior efficacy and more adverse effects compared with other UTI antimicrobials

Source: USPI Ciprofloxacin; USPI Nitrofurantoin; USPI Trimethoprim-sulfamethoxazole; USPI Pivmecillinam; IDSA treatment recommendations for acute uncomplicated cystitis 2010

There is a clear medical need for new, safe and well tolerated orally bioavailable antibacterial agents with in vitro activity against multidrug resistant pathogens. An orally bioavailable prodrug of sulopenem, sulopenem etzadroxil, was discovered and developed in order to address this unmet medical need.

1.4 DEVELOPMENT AND REGULATORY HISTORY

1.4.1 Corporate Sponsorship of Sulopenem

The development of sulopenem dates to the mid-1980s. Pfizer, Inc. filed INDs for both a parenteral form and an oral pro-drug, sulopenem etzadroxil. Iterum Therapeutics acquired the rights to both the oral and parenteral formulations of sulopenem from Pfizer in 2015.

1.4.2 United States Regulatory History

Pfizer filed INDs for intravenous (IV) sulopenem in February 1986. Its initial IND for the oral prodrug, sulopenem etzadroxil, was filed in August 2007. The IND was opened by a Phase 1 study that evaluated the pharmacokinetics, safety and tolerability of single and multiple doses of sulopenem etzadroxil in healthy adult subjects and tested the effect of probenecid on sulopenem etzadroxil. Subsequent filings to the IND included protocols investigating the effects of different variables on the PK of sulopenem etzadroxil, among them different doses of probenecid, food intake, gastric pH modifiers and varying degrees of renal impairment.

Pfizer granted Iterum Therapeutics International Ltd (Iterum) an exclusive license to sulopenem and sulopenem etzadroxil. On 1 March 2016, Iterum submitted an IND in order to continue the clinical development of sulopenem. Sulopenem etzadroxil was granted QIDP status by the Division on 29 July 2016, while sulopenem etzadroxil/probenecid bilayer tablets (oral sulopenem) were granted QIDP status on 27 October 2017.

Iterum expressed its intent to conduct studies in uUTI (IT001-301, or Study 301), cUTI (IT001-302, or Study 302) and cIAI (IT001-303, or Study 303). Major meetings were held with the FDA in February, July and August of 2017, at which Phase 3 study design, statistical analyses and hypothesis testing were extensively discussed. Special Protocol Assessment (SPA) status was requested and granted for all three studies. On 15 March 2019, a Fast Track Status designation was granted to sulopenem etzadroxil/ probenecid tablets for the treatment of uUTI. The basis of the designation was the potential for treatment of a serious infection caused by quinolone non-susceptible organisms and the ability to address an unmet medical need via provision of alternative therapy against these pathogens, for which there are limited treatment options.

A pre-NDA meeting was held on 28 September 2020. While the outcomes of the cUTI and cIAI studies, 302 and 303, respectively, were not considered supportive of claims for those indications, the superiority of oral sulopenem over ciprofloxacin in the subpopulation of women in Study 301 with uUTI caused by quinolone non-susceptible pathogens was, as agreed upon under the SPA for that study. Safety data from all three studies were considered satisfactory support.

The NDA for oral sulopenem tablets for the treatment of uUTI was submitted to the Agency on 25 November 2020. On 23 July 2021, Iterum received a Complete Response Letter (CRL) from the Division stating that the Application could not be approved in its present form. The need for a second adequate and well-controlled uUTI trial was recommended.

Following the issue of the CRL, major meetings were held with the FDA in September 2021, December 2021, March 2022 and May 2022, at which Phase 3 uUTI study design, statistical analyses and hypothesis testing were extensively discussed. Special Protocol Assessment (SPA) status was requested and granted for the additional study in uUTI (IT001-310, or Study 310). Study 310 was completed and the NDA for oral sulopenem tablets for the treatment of uUTI was resubmitted to the Agency on 25 April 2024.

1.5 OVERVIEW OF THE SULOPENEM DEVELOPMENT PROGRAM

Pfizer's legacy clinical development program for sulopenem included two Phase 1 studies of IV sulopenem, a study in individuals with varying degrees of renal impairment, six Phase 1 studies of sulopenem etzadroxil, a study evaluating the effect of gastric pH modifiers on sulopenem etzadroxil, and a small Phase 2 study of IV sulopenem stepped down to oral sulopenem etzadroxil in patients with community-acquired pneumonia requiring hospitalization.

This document highlights Iterum's development program for sulopenem etzadroxil, which comprises five Phase 1 studies (Table 5) and four Phase 3 studies (Table 6), two in uncomplicated urinary tract infections (uUTI), and one each in complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI). Iterum's NDA is targeting the uUTI indication, with safety data from the cUTI and cIAI studies supporting the claim.

Table 5: Phase 1 Studies Conducted by Iterum

Study Number	Study Title	No. of Subjects Who Received Sulopenem	Sulopenem or Sulopenem Etzadroxil Dosage Regimen	Number of Subjects Who Received Comparator or Placebo
IT001-101	A Phase 1 Study to Evaluate the Safety, Tolerability and Pharmacokinetics of PF-04064900 and PF-03709270 (sulopenem etzadroxil) 500 mg BID Multiple Dose Administration in Healthy Adult Subjects in Fed and Fasted Conditions and With or Without Co-Administration of Probenecid	64 40 8	500 mg PO BID x 7 days 500 mg PO x 1 1000 mg PO x 1	64 (placebo)
IT001-102	A Phase 1, Randomized, Open-label, Single-dose, Four-Way Crossover Study to Determine the Plasma Pharmacokinetics of Sulopenem after Administration of Single Dose Sulopenem Etzadroxil as Powder in Bottle (PIB) Co-administered with Either Probenecid, Gallic Acid or Tannic Acid Under Fasting Conditions	36	500 mg PO x 1	NA
IT001-103	A Phase 1, Open-Label, 2-Period, 4-Sequence, Parallel Study to	48	500 mg PO x 1	62 (itraconazole)

	Estimate the Effects of Multiple-Dose Administration of Itraconazole on the Pharmacokinetics of Sulopenem in Healthy Adult Subjects	16	1000 mg IV x 1	
IT001-104	A Phase 1, Open-Label, 2-Period, 3-Sequence, Parallel Study to Estimate the Effects of Sulopenem Multiple-Dose Administration on the Pharmacokinetics of Valproic Acid in Healthy Adult Male Subjects	19 10	500 mg PO BID x 2 1000 mg IV QD x 3	30 (valproic acid)
IT001-105	A Phase 1, Open-Label, Single-Center, Four-Sequence, Three-Period, Parallel Study to Assess the Absolute Bioavailability of Sulopenem in Healthy Volunteers	34 33 12	500 mg PO x 1 366 mg IV x 1 1000 mg IV x 1	NA

Table 6: Phase 3 Studies Conducted by Iterum

Study Number	Indication	No. of Subjects Who Received Sulopenem	Sulopenem Dosage Regimen	Number of Subjects Who Received Comparator or Placebo	Comparator Dosage Regimen
IT001-301	uUTI	833	500 mg sulopenem etzadroxil + 500 mg probenecid PO BID x 5 days	827	Ciprofloxacin 250 mg PO BID x 3 days
IT001-310	uUTI	1107	500 mg sulopenem etzadroxil + 500 mg probenecid PO BID x 5 days	1107	Amoxicillin/clavulanate 875/125 mg PO BID x 5 days
IT001-302	cUTI	695	1000 mg sulopenem IV QD for at least 5 days then sulopenem etzadroxil 500 mg + 500 mg probenecid BID to	697	Ertapenem 1000 mg IV QD for at least 5 days then ciprofloxacin 500 mg or amoxicillin-clavulanate 875 mg PO BID to complete 7-10 days total

			complete 7-10 days total		
IT001-303	cIAI	335	1000 mg sulopenem IV QD for at least 5 days then sulopenem etzadroxil 500 mg + 500 mg probenecid BID to complete 7-10 days total	333	Ertapenem 1000 mg IV QD for at least 5 days then ciprofloxacin 500 mg PO BID and metronidazole 500 mg PO QID or amoxicillin-clavulanate 875 mg PO BID to complete 7-10 days total

Summaries of microbiology and clinical pharmacology, as well as overviews of efficacy and safety, are provided in the remainder of this executive summary (Section 1). Subsequent sections provide more detailed and additional information related to nonclinical information (Section 4), clinical pharmacology (Section 5), clinical microbiology (Section 6), clinical efficacy (Section 7) and safety (Section 8). A discussion of benefits and risks is provided in Section 9.

1.5.1 Product Characteristics

Sulopenem is a broad-spectrum, parenteral β-lactam antibiotic of the thiopenem class that exerts its potent bactericidal activity by binding to and inhibiting key penicillin binding proteins in bacterial cell walls, thereby inhibiting cell division.

Sulopenem etzadroxil is an oral prodrug of sulopenem that, itself, has minimal *in vitro* antibacterial activity. Following absorption, it is rapidly hydrolyzed to generate the microbiologically active moiety, sulopenem, along with non-active moieties including formaldehyde and 2-ethylbutyric acid (2-EBA). Because sulopenem is the primary active circulating moiety following oral administration of the prodrug, the nonclinical and clinical effects are primarily attributable to sulopenem.

Sulopenem etzadroxil has been co-formulated with probenecid, which prolongs the serum half-life and allows twice daily dosing in a bilayer tablet. This bilayer tablet of 500 mg sulopenem etzadroxil plus 500 mg probenecid provides an option for stepdown from IV to oral therapy, thus potentially minimizing in-hospital patient stays, as well as providing an oral agent for the treatment of uncomplicated infections entirely in the outpatient setting.

1.5.2 Summaries of Microbiology and Clinical Pharmacology

Summaries of microbiology and clinical pharmacology are provided below in Sections 1.5.2.1 and 1.5.2.2. A more detailed description of microbiology is provided in Section 6.

1.5.2.1 Microbiology

1.5.2.1.1 Spectrum of Activity

Sulopenem has broad spectrum activity against gram-positive and gram-negative aerobes and anaerobes consistent with that of ertapenem, a currently-marketed carbapenem.

Activity against key uUTI pathogens is presented in Table 7. The potency of sulopenem against Enterobacterales based on $MIC_{50/90}$ values and MIC distributions is similar to that of meropenem and ertapenem.

Table 7: Comparative MICs for Enterobacterales

	E. coli **(N = 635)**		***K. pneumoniae*** **(N = 163)**		***P. mirabilis*** **(N = 70)**	
	MIC_{90}	**%R**	**MIC_{90}**	**%R**	**MIC_{90}**	**%R**
Sulopenem	0.03	-	0.06	-	0.5	-
Imipenem	≤0.12	0.2	0.25	0.6	4	78.6
Meropenem	0.03	0.2	0.03	0.6	0.12	0.0
Ertapenem	0.03	0.3	0.06	1.8	0.015	0.0

JMI Surveillance study 2019 (Ertapenem: *E. coli* N=983, *K. pneumoniae* N=273, *P. mirabilis* N=91) and JMI Surveillance Study 2023

1.5.2.1.2 Mechanism of Action

Sulopenem's mechanism of action is similar to that of members of the carbapenem class of antibiotics: interfering with bacterial cell wall synthesis. Studies on the mechanism of action of sulopenem have shown that this compound has a high affinity for penicillin binding proteins (PBPs) prepared from cell membranes from *E. coli* in particular for PBP2. The relative order of affinity for sulopenem for *E. coli* PBPs was PBP2 >PBP1A > PBP 1B > PBP 4 > PBP 3 > PBP 5 or 6. In addition, it was determined through a hydrolysis study with crude β-lactamases that sulopenem was highly stable to type I cephalosporinases, as well as to plasmid-encoded enzymes TEM-1, SHV-1 and PSE-2. Against PRSP, sulopenem exhibited higher-affinity binding to PBPs 1a, 1b, 2a and 2b compared with amoxicillin. As would be expected given its class and mechanism of action, sulopenem showed bactericidal activity against *E. coli* and *K. pneumoniae* at ≥ 4X the MIC in separate time-kill studies and also was bactericidal against pneumococci at ≥ 2X the MIC.

1.5.2.1.3 Resistance Development

The development of resistance to sulopenem was evaluated using two methods: by determining the spontaneous mutation frequency in *E. cloacae* isolates and during serial passage in clinical isolates of *E. coli* and *K. pneumoniae*. In the spontaneous mutation study against the *E. cloacae* strains, colonies were isolated at a frequency of 1×10^{-8} but these were observed to display a ≤ 2-fold MIC increase. In the serial passage study, in two of the three *E. coli* strains, MIC values to sulopenem were observed to increase 16-fold during 15 serial passages and were unchanged for the third strain; for one *K. pneumoniae* isolate, MIC values increased 8-fold during serial passage, and for the other, MIC values increased from 0.5 to 256 µg/mL. The ertapenem control behaved similarly in all cases but the last, suggestive of a carbapenem class effect. It has been shown that these types of assays are not predictive of the risk of development of resistance in the clinical setting [Smulek, 2022]. Sulopenem is affected by resistance mechanisms that have been well-characterized for other carbapenem-class agents, namely KPC, metallo-β-lactamases, OXAs, porin/efflux proteins, etc. In a 2018 evaluation of *in vitro* activity of sulopenem against a collection of carbapenem-non-susceptible Enterobacterales (CRE), sulopenem exhibited similar

activity to the carbapenem comparators against CRE, including IMP-, KPC-, NDM-, OXA-, VIM- positive isolates. The mechanism of resistance to sulopenem has been studied utilizing a pair of clinical isolates of *K. pneumoniae* differentially resistant to sulopenem and imipenem collected from the same patient in 1998. Studies showed that resistance to sulopenem and imipenem was not conferred by the plasmid carried by both isolates, but rather to outer membrane changes rendering one strain more susceptible to sulopenem than the other. Previous investigators have shown similar mechanisms for carbapenem resistance, through acquisition of a plasmid-encoded β-lactamase followed by porin changes to further improve susceptibility.

1.5.2.1.4 *In Vivo* Efficacy

The *in vivo* efficacy of sulopenem was evaluated in a variety of infection models against organisms chosen based on their resistance phenotypes. In both protective systemic infection models and in models of tissue burden reduction, sulopenem demonstrated efficacy against organisms with demonstrated tolerance/resistance to ampicillin or with ESBLs. It is worth noting that duplicate studies were performed on different days and sulopenem produced consistent results against these challenging organisms. Sulopenem etzadroxil demonstrated equivalent efficacy to sc-dosed sulopenem when given via the oral route in these studies, indicative of its rapid conversion, an important feature in the systemic infection models.

1.5.2.1.5 Target Attainment and Dose Selection

Upon hydrolysis of sulopenem etzadroxil, the active moiety sulopenem is released and is ultimately responsible for the antibacterial activity observed following oral dosing. *In vitro* evaluations of the biologic activity of sulopenem indicate that the MIC_{90} values against targeted bacterial strains is 0.06-0.12 µg/mL. As the pharmacokinetic-pharmacodynamic (PKPD) parameter of interest for sulopenem is the percent of time that free drug concentration exceeds the MIC, clinical doses should provide sulopenem exposures in plasma and tissues at or exceeding 0.12 µg/mL. Dose selection of oral sulopenem targeted an MIC of 0.5 µg/mL, higher than the MIC_{90}, in order to inhibit growth of >90% of all pathogens in the target indications.

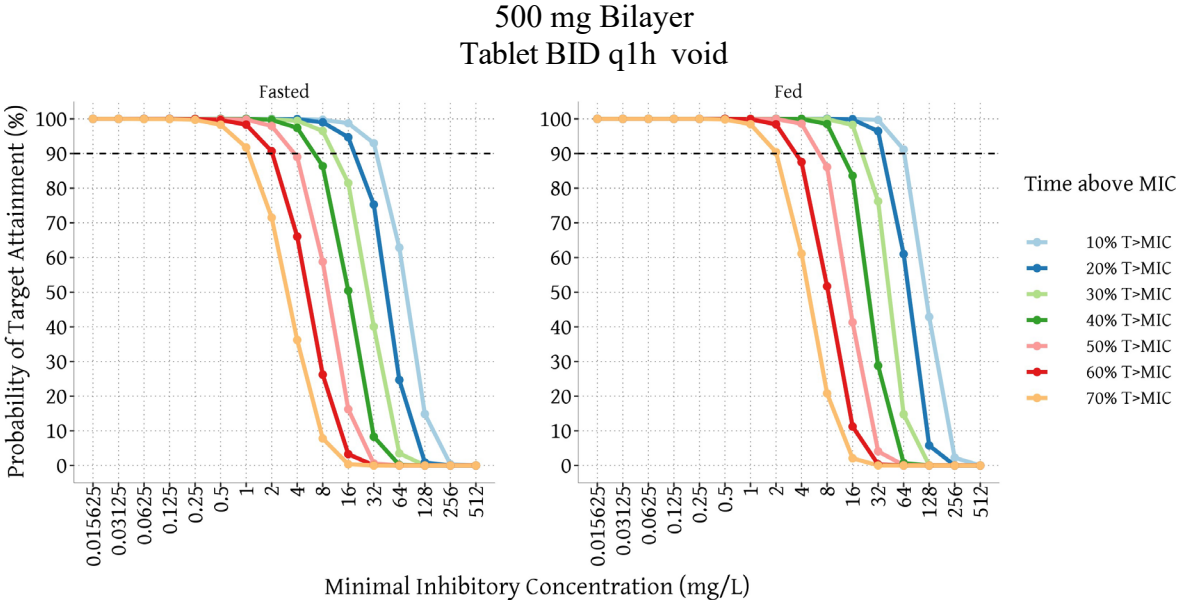
The mouse thigh infection model was used to evaluate the PK/PD relationship for sulopenem against *S. pneumoniae*, *S. pyogenes*, *E. coli* and *K. pneumoniae* strains with different resistant phenotypes, and the results indicated that T>MIC was the PK parameter that best correlated with efficacy with some contribution by concentration. The PK/PD target for attainment of efficacy for sulopenem was ~20% to ~24% *f*T>MIC for stasis and one $\log_{10}$ CFU reduction, based on preclinical data. This finding is consistent with results for other carbapenems [Bhavnani; Drusano]. A one-compartment *in vitro* model was also used to further explore the effect of sulopenem on a number of clinically relevant bacterial strains [ICPD Report 00671]. In this one-compartment *in vitro* system, the median %T>MIC values associated with achieving net bacterial stasis, 1- and 2-$\log_{10}$ reductions in bacterial burden across the Enterobacterales panel were determined to be 40.9, 50.2 and 62.6%, respectively.

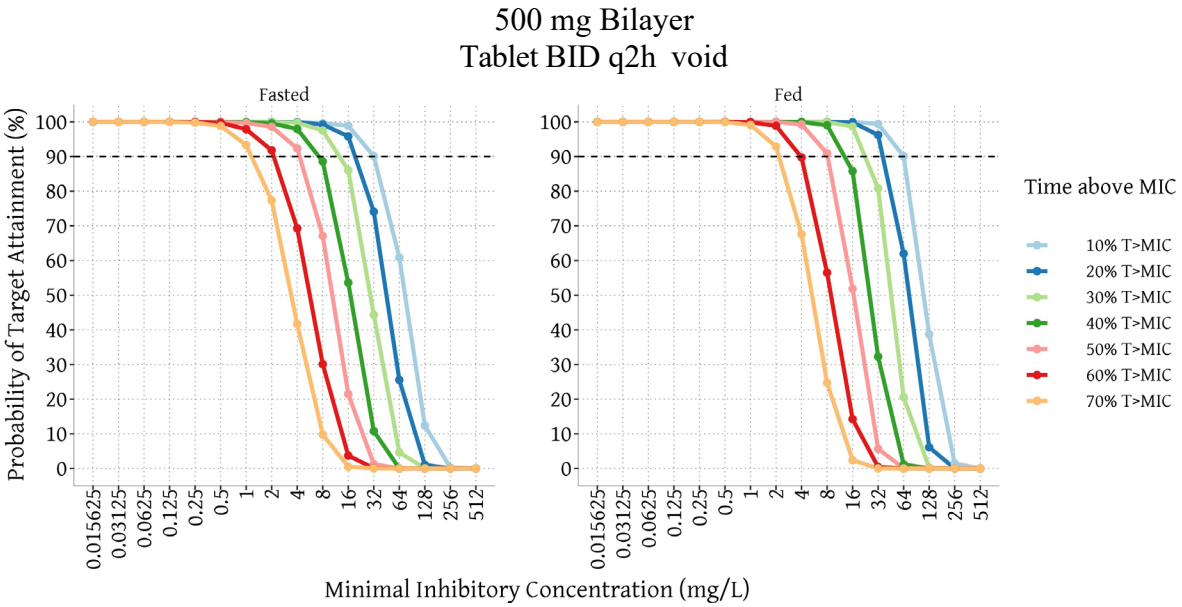
Simulations of target attainment in serum were performed based on Phase 1 and Phase 3 final PK model and actual MIC distributions from the total Phase 3 patient population. Simulations following both IV sulopenem 1000 mg with 3hr infusion and sulopenem etzadroxil assuming a 500 mg bilayer tablet, with and without food (oral dosing only) were performed. Simulations of target attainment demonstrated satisfactory treatment effect at the clinically relevant doses and administering IV sulopenem with probenecid and oral sulopenem etzadroxil bilayer tablet with food resulted in the greatest target

attainment, although all dosing regimens were predicted to achieve good target attainment. For uUTI, the exposure in urine is more relevant than exposure in serum with regards to target attainment. Urine samples collected from uUTI and cUTI patients show that sulopenem levels in urine are well above the target minimal inhibitory concentration of 0.5 µg/mL for the entire dosing interval.

The extended final plasma and urine PopPK model was used in simulation mode to obtain single dose plasma and urine PK predictions and derive probability of target attainment (PTA) by treatment regimen and bladder emptying frequency. The results of the target attainment predictions in urine are graphically presented in Figure 2 and Figure 3. These modeling results, as well as the breakpoints at which MIC from the simulated range of values is reached in 90% of the simulated subjects, stratified by prandial status, support the proposed oral sulopenem dosage regimen of 500 mg BID for patients with uUTI.

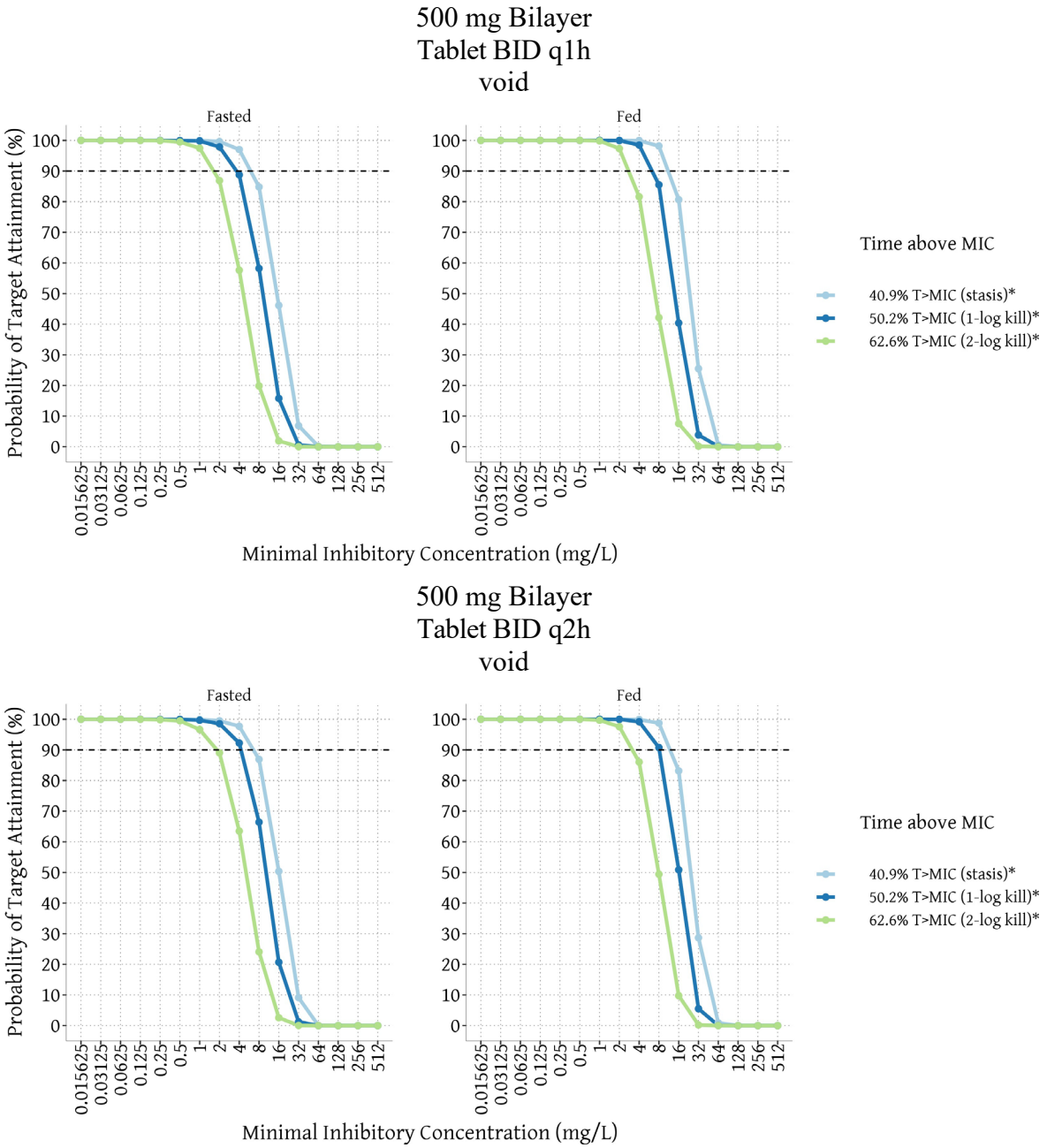
Figure 2: Probability of Target Attainment Predictions in Urine





Dashed Line: 90% of simulated subjects (n=5000) reaching the respective T>MIC target.

Figure 3**:** Probability of Target Attainment Predictions in Urine - *In vitro E.coli* and *K.pneumoniae* Bacterial Stasis, 1-log, and 2-log Kill Targets



Dashed Line: 90% of simulated subjects (n=5000) reaching the respective T>MIC target. **In vitro E.coli* and *K.pneumoniae* bacterial stasis, 1-log kill, and 2-log kill %T>MIC targets.

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1.5.2.2 Clinical Pharmacology

1.5.2.2.1 Overview of Sulopenem Pharmacokinetics

Upon oral administration, sulopenem etzadroxil is rapidly hydrolyzed to the active moiety sulopenem with peak sulopenem plasma concentrations attained in approximately 1 to 2 hours. The absolute bioavailability of sulopenem from sulopenem etzadroxil after administration of the bilayer tablet was 40% when taken in the fasted state and 64% when taken after a high-fat meal (Table 8). PopPK modelling estimated the food effect for the bilayer tablet to be 47.2%.

Table 8: Pharmacokinetics of Sulopenem in Plasma after Single Dose Administration of the Sulopenem etzadroxil and Probenecid Bilayer Tablet in Healthy Subjects

	Food State	N	Sulopenem Pharmacokinetic Parameter				
			Cmax[a] (µg/mL)	Tmax[b] (h)	t1/2[c] (h)	AUCinf[a] (µg*h/mL)	TAMIC0.5 (h)
Sulopenem etzadroxil 500 mg + Probenecid 500 mg in a bilayer tablet	Fasted	13	1.84 (39.1)	1.0 (0.5 – 3.0)	1.18 (23.8)	4.85 (25.3)	3.44 (0.54)
	Fed	13	2.66 (43.6)	2.0 (1.0 – 3.0)[e]	1.28 (48.8)	7.41 (22.7)[d]	4.11 (0.78)

[a]Data presented as geometric mean (CV%); [b]Data presented as median (range); [c]Data presented as arithmetic mean (CV%); [d]n=12; TAMIC0.5 = time over mean inhibitory concentration of 0.5 µg/mL

Highlights of sulopenem PK characteristics are as follows:

- At clinically relevant doses the elimination of sulopenem is expected to be linear.
- Co-administration of 500 mg sulopenem etzadroxil with 500 mg probenecid increased sulopenem exposure by 48.5% compared to 500 mg sulopenem etzadroxil alone.
- Patients were estimated to have slightly slower absorption as compared to healthy volunteers.
- Females were estimated to have 14.5% lower maximum rate of elimination (T_M) as compared to males.
- Sulopenem has a rapid $t_{1/2}$ of 1.1 hours and therefore there is no relevant accumulation of sulopenem following repeat dose administration of either PO or IV regimens, including the bilayer tablet.
- The CL_{cr} was estimated to have an impact on the maximum rate of elimination (T_M), resulting in 8.35% decrease in T_M for every 10 mL/min change in CL_{cr}. Dose adjustment of intravenously delivered sulopenem may be warranted in subjects with severe renal insufficiency.
- The simulations of target attainment demonstrated satisfactory treatment effect at the clinically relevant doses and administering IV sulopenem with probenecid and oral sulopenem etzadroxil/probenecid bilayer tablet with food resulted in the greatest target attainment. The sulopenem levels in urine, specifically relevant for uUTI patients, are well above the target concentration for the entire dosing interval.
- *In vitro* studies in cell systems expressing human transporters showed that sulopenem had a low potential for the risk of clinically relevant drug-drug interactions.

- Sulopenem was not a substrate for the MATE1, MATE2-K, OAT1, OATP1B1, OATP1B3, OCT1, or OCT2 transporters *in vitro*. Therefore, the propensity for sulopenem to interact with substrates or inhibitors of those transporters is unlikely.
- Sulopenem was an avid substrate for OAT3 with an over 34-fold accumulation in cells expressing OAT3. The *in vitro* uptake and the accumulation of sulopenem in OAT3-expressing cells was reduced to less than 1.5 fold in the presence of probenecid in support of the clinical use of probenecid to increase systemic exposure to sulopenem.
- Drug interactions were not observed between oral sulopenem and either valproic acid or itraconazole.
- Concomitant use of probenecid and ketoprofen is contraindicated [Toradol USPI] so, by extension, the use of oral sulopenem with ketorolac should be avoided.

1.5.3 Uncomplicated Urinary Tract Infections

Oral sulopenem efficacy in uUTI is supported by data from Study 301 (Dunne, 2023) and Study 310 (summarized below, with additional details and data provided in Section 7.5). Supportive data from Study 302 (Dunne, 2023) are presented in Section 7.5.3.

1.5.3.1 IT001-301 (Study 301)

1.5.3.1.1 Study Design

This prospective Phase 3, randomized, multicenter, double-blind, double-dummy, controlled study compared oral sulopenem to oral ciprofloxacin for the treatment of patients with uUTI. Approximately 1364 adult women with uUTI were to be randomized in a 1:1 fashion 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 oral sulopenem tablets twice daily for 5 days. The primary efficacy assessment was overall response (percentages of patients with combined clinical and microbiologic response [success, failure or indeterminate]) on Day 12 (± 1 day).

The key analysis population of interest was the microMITT population, defined as all patients who:

- Received at least a single dose of study medication;
- Had a uUTI, as defined in the study protocol;
- Had a positive urine culture, defined as $\geq 10^5$ 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 with $\geq 10^5$ CFU/mL.

Patients were to be programmatically categorized as a success, failure, or indeterminate based on data in the eCRF and from the microbiology lab. Patients with missing data or who were lost to follow-up were defined as indeterminate for the primary analyses and were included in the denominator for the calculation of the success rate.

The primary objective of this study was to compare the outcomes in patients with quinolone susceptible organisms as well as, in parallel, in patients with quinolone non-susceptible pathogens. The primary comparisons for regulatory approval are in these two mutually exclusive populations as defined by a baseline characteristic. If either of the two analyses were positive (i.e., reject null

hypothesis), the efficacy of sulopenem was to have been established consistent with the primary objective of the trial. These two populations were defined as follows:

The micro-MITTS population

This population was a subset of the micro-MITT population in which the baseline pathogen was determined to be susceptible to the comparator study drug, ciprofloxacin. For this population, a non-inferiority (NI) test of the overall success rate was to be conducted.

The NI hypothesis test was a 1-sided hypothesis test performed at the 2.5% level of significance. The primary analysis was based on the CI computed using the method proposed without stratification by Miettinen and Nurminen, which corresponded to the p-value approach of the Farrington-Manning test. If the lower limit of the 95% CI for difference in success rates in the microMITT-S population was greater than -10%, the null hypothesis was to be rejected and the NI of oral sulopenem to ciprofloxacin was to be concluded.

The micro-MITTR population

This population was a subset of the microMITT population in which the baseline pathogen was determined to be non-susceptible to the comparator study drug, ciprofloxacin. For this population, a superiority test was to be conducted.

A 2-sided 95% CI for the observed treatment difference in success rates was to be determined using the method without stratification of Miettinen and Nurminen. If the lower bound of the 95% CI was greater than 0%, the null hypothesis was to be rejected and superiority of oral sulopenem to ciprofloxacin was to be concluded.

The primary efficacy endpoint was to be based on the outcome of overall response in the microMITT-S and, separately, in the microMITT-R at TOC (Day 12 [±1 day). Additional analyses of the primary efficacy endpoint were to be performed to provide guidance to the practicing physician in the setting where culture results were not available. To do this, all randomized patients who received drug (modified intent-to-treat, MITT) were to be analyzed together as this population was more consistent with what the practicing physician is faced with every day.

The hierarchical testing procedure of Westfall and Krishen was used to continue testing hypotheses of the primary efficacy endpoint. If NI or superiority was declared for the primary comparisons, the secondary comparisons were to be statistically tested in the order presented below (Table 9). Testing was to proceed to the next comparison, only in the case where the null hypothesis in the previous comparison was rejected. When testing in a sequential manner with pre-planned testing, no adjustment to the alpha level was required.

1. NI test of overall success in the microMITT population. The number and percentage of patients in each treatment group with an overall response of success, failure, and indeterminate was to be provided for the microMITT population. A 2-sided 95% CI for the observed treatment difference in success rates was to be determined. If the lower bound of the 95% CI was greater than -10%, the null hypothesis was to be rejected and the NI of oral sulopenem to ciprofloxacin in the microMITT population was to be concluded.
2. Superiority test of overall success, H_0: $P_1 = P_2$ and H_A: $P_1 \neq P_2$, in the microMITT population. If the lower bound of the 95% CI (calculated for the hypothesis test in #1) was greater than 0%, the null hypothesis was to be rejected and the superiority of oral sulopenem to ciprofloxacin in the microMITT population was to be concluded.

Table 9: Study 301 Hypothesis Testing

Analysis	Populations	
First step	1. microMITT-S (if non-inferior then test #2)	1. microMITT-R (if superior then test #2)
Second step	2. NI in microMITT (if non-inferior then test #3)	2. NI in microMITT (if non-inferior then test #3)
	3. Superiority in microMITT (if superior then test #4)	3. Superiority in microMITT (if superior then test #4)
	4. NI in MITT* (if NI then test#5)	4. NI in MITT* (if NI then test#5)
	5. Superiority in MITT*	5. Superiority in MITT*

Abbreviations: MITT = modified intent-to-treat; microMITT = microbiologic modified intent-to-treat; microMITT-R = resistant microbiologic modified intent-to-treat; microMITT-S = susceptible microbiologic modified intent-to-treat; NI = non-inferior.
*Based on clinical response

1.5.3.1.2 Patient Enrollment

Following 2 pre-planned blinded interim analyses to ensure that the point estimate of overall response (combined clinical and microbiologic response) used in the estimation of sample size was valid for this study, the DMC recommended the addition of as many as 400 patients to the study to maintain study power. On December 20, 2019, enrollment was completed at 1671 randomized patients. Data from 1071 subjects were analyzed for the primary endpoint in the microMITT population, and data from 1660 subjects were analyzed for safety, as 11 subjects did not receive any study drug. Data from 252 randomized subjects were collected for the PK analysis of sulopenem etzadroxil coadministered with probenecid.

1.5.3.1.3 Demographics and Baseline Characteristics

Demographics across each treatment group were balanced at baseline.

A comparison of the demographic and other baseline characteristics for the microMITT-S and microMITT-R populations is provided in Table 10. Compared to the microMITT-S population, patients in the microMITT-R population were more often older (>65 years), Hispanic, diabetic, obese (BMI >30 kg/m^2), and with impaired renal function (creatinine clearance 30-60 mL/min).

Table 10: Study 301 Comparison of Baseline Demographics in microMITT-S and microMITT-R Populations

Parameter	Total microMITT-S	Total microMITT-R
N	785	286
Age (years)		
Mean (SD)	50.4 (18.8)	55.4 (19.7)
Median	51.0	57.0
Min, max	18.0, 96.0	18.0, 89.0
Age group, n (%)		
<65 years	564 (71.8)	170 (59.4)
≥65 years	221 (28.2)	116 (40.6)
Ethnicity, n (%)		

Hispanic or Latina	184 (23.4)	111 (38.8)
Not Hispanic or Latina	598 (76.2)	174 (60.8)
Not Reported	2 (0.3)	1 (0.3)
Unknown	1 (0.1)	0 (0.0)
Geographic region, n (%)		
US	406 (51.7)	163 (57.0)
Non-US	379 (48.3)	123 (43.0)
Race, n (%)		
American Indian or Alaska Native	4 (0.5)	0 (0.0)
Black or African American	67 (8.5)	26 (9.1)
Asian	6 (0.8)	2 (0.7)
White	706 (89.9)	256 (89.5)
Native Hawaiian or Pacific Islander	0 (0.0)	0 (0.0)
Other	2 (0.3)	2 (0.7)
Diabetes at Baseline, n (%)		
Present	91 (11.6)	53 (18.5)
Absent	694 (88.4)	233 (81.5)
Weight (kg)		
N	775	284
Mean (SD)	73.1 (17.8)	74.0 (18.4)
Median	70.1	70.9
Min, max	38.1, 154.4	42.5, 156.0
Categorized BMI (kg/m^2), n (%)		
<25	343 (43.7)	91 (31.8)
25-30	206 (26.2)	86 (30.1)
>30	226 (28.8)	107 (37.4)
Creatinine clearance (mL/min)[a]		
N	785	286
Mean (SD)	78.4 (26.2)	72.7 (28.2)
Median	77.0	68.0
Min, max	14.0, 199.0	17.0, 153.0

[a]Calculated by Cockcroft-Gault method.

1.5.3.1.4 Efficacy

1.5.3.1.4.1 microMITT-R population

There were 286 patients in the microMITT-R efficacy population, 147 in the oral sulopenem arm and 139 in the ciprofloxacin arm. Overall success in the microMITT-R population was seen in 62.6% of patients in the oral sulopenem group and 36.0% of patients in the ciprofloxacin group (Table 11). The primary endpoint was met and oral sulopenem was superior to ciprofloxacin in the microMITT-R population. Superiority of oral sulopenem was not only demonstrated for key

secondary endpoints of clinical success at TOC, microbiologic success at TOC, and overall success at the EOT visit, but was also observed across a range of subgroups.

Table 11: Study 301 Outcomes at TOC and EOT – microMITT-R Population

Outcome	Sulopenem n (%) N=147	Ciprofloxacin n (%) N=139	Difference % (95% CI)	p-value
Overall response at TOC	92 (62.6)	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)		
Clinical success at TOC	122 (83.0)	87 (62.6)	20.4 (10.2, 30.4)	<0.001
Microbiologic success at TOC	109 (74.1)	69 (49.6)	24.5 (13.4, 35.1)	<0.001
Overall Response at EOT	95 (64.6)	42 (30.2)	34.4 (23.1, 44.8)	<0.001

Overall response at TOC was favorable for the key targeted uropathogens (Table 12).

Table 12: Study 301 Overall Response at TOC by Selected Baseline Pathogen – microMITT-R Population

Pathogen	Sulopenem n/N (%)	Ciprofloxacin n/N (%)
E. coli	75/127 (59.1)	42/120 (35.0)
K. pneumoniae	10/14 (71.5)	8/16 (50.0)
P. mirabilis	9/9 (100.0)	3/6 (50.0)

Overall response at TOC for the microMITT-R population by resistance class is presented in Table 13. Improved treatment responses are seen for patients on the sulopenem arm for pathogens with single drug resistance and with various combinations of multidrug resistance in this quinolone resistant population.

Table 13: Study 301 Overall Response at Test of Cure by Resistance Class in Patients with a Quinolone Resistant Pathogen

Resistance Class / Clinical Response	Sulopenem n/N (%)	Ciprofloxacin n/N (%)	Difference % (95% CI)	p-value
Beta-lactam resistant				
Overall responder	86/129 (66.7)	43/121 (35.5)	31.1 (18.9, 42.4)	<0.001
Overall non-responder	37/129 (28.7)	73/121 (60.3)		
Indeterminate	6/129 (4.7)	5/121 (4.1)		
Beta-lactam, quinolone, and TMP-SMX resistant				
Overall responder	38/63 (60.3)	16/47 (34.0)	26.3 (7.4, 43.2)	0.006
Overall non-responder	22/63 (34.9)	26/47 (55.3)		
Indeterminate	3/63 (4.8)	5/47 (10.6)		
Beta-lactam, quinolone, TMP-SMX, and nitrofurantoin resistant				
Overall responder	19/24 (79.2)	11/27 (40.7)	38.4 (11.4, 60.1)	0.005
Overall non-responder	5/24 (20.8)	16/27 (59.3)		
Indeterminate	0/24 (0.0)	0/27 (0.0)		

Clinical response rates among sulopenem etzadroxil-treated patients were higher than those for ciprofloxacin at all three study visits at which assessments were done: EOT, TOC and Final Visit (Table 14).

Table 14: Study 301 Clinical Response by Visit – microMITT-R Population

Timepoint/Response	Sulopenem n (%) N=147	Ciprofloxacin n (%) N=139	Difference % (95% CI)	p-value
End of Treatment (D5)				
Clinical Success	99 (67.3)	83 (59.7)	7.6 (-3.5, 18.7)	0.180
Clinical Failure	46 (31.3)	55 (39.6)		
Indeterminate	2 (1.4)	1 (0.7)		
Test of Cure (D12)				
Clinical Success	122 (83.0)	87 (62.6)	20.4 (10.2, 30.4)	<0.001
Clinical Failure	22 (15.0)	46 (33.1)		
Indeterminate	3 (2.0)	6 (4.3)		
Final Visit (D28)				
Clinical Success	122 (83.0)	82 (59.0)	24.0 (13.7, 34.0)	<0.001
Clinical Failure	19 (12.9)	43 (30.9)		
Indeterminate	6 (4.1)	14 (10.1)		

Efficacy in the microMITT-R population, including clinical and microbiologic outcomes, is discussed in extensive detail in Section 7.5.1

1.5.3.1.4.2 microMITT Population

Following the pre-planned hierarchical testing sequence for the primary outcome measure, NI was tested in the microMITT population. For the microMITT population, the overall response at the Test of Cure visit is shown in Table 15. Overall success was seen in 65.6% of patients on oral sulopenem and 67.9% of patients on the ciprofloxacin arm [treatment difference; (95%CI): -2.3%, (-7.9, 3.3)].

Clinical success was seen in 81.6% of patients on oral sulopenem and 78.7% of patients on ciprofloxacin [treatment difference, (95% CI): 2.9%, (-1.1, 6.6)]. Microbiologic success was seen in 76.6% of patients on oral sulopenem and 79.1% of patients on ciprofloxacin [treatment difference, (95% CI): -2.5%, (-7.5, 2.5)].

A descriptive analysis is also provided in the MITT population, defined as all patients who had symptoms consistent with uUTI and a urinalysis positive for leukocyte esterase and nitrite, who were randomized and received study drug but did not necessarily have a baseline urine culture positive for $\geq 10^5$ CFU/mL of a uropathogen. This population, in which the clinical response was similar in the two arms, is comparable to that of empirically treated patients who don't have a culture performed prior to receiving antibiotics in a clinical practice setting.

Table 15: Study 301 Overall Response at TOC in the microMITT and MITT Population

Population/ Outcome	Sulopenem n/N (%)	Ciprofloxacin n/N (%)	Difference % (95% CI)	Difference % (99% CI)
MicroMITT				
Overall responder	339/517 (65.6)	376/554 (67.9)	-2.3 (-7.9, 3.3)	-2.3 (-9.7, 5.1)
Clinical success	422/517 (81.6)	436/554 (78.7)	2.9 (-1.9, 7.7)	
Microbiologic success	396/517 (76.6)	438/554 (79.1)	-2.5 (-7.5, 2.5)	
Overall response at EOT	335/517 (64.8)	313/554 (56.5)	8.3 (2.4, 14.1)	
MITT				
Clinical success	647/785 (82.4)	638/794 (80.4)	2.1 (-1.8, 5.9)	

Efficacy in the microMITT population is discussed in extensive detail in Section 7.5.1.

1.5.3.1.4.2.1 Impact of Asymptomatic Bacteriuria on Clinical Outcome at Subsequent Visits

As shown (Table 16), the presence of asymptomatic bacteriuria did not disproportionally affect the subsequent clinical failure rate relative to patients who had been cured and does not predict subsequent clinical relapse. Of the 335 patients with clinical success at Day 5, the end of treatment visit, 31 had a clinical failure at Day 12, one week later. Only 12 patients had asymptomatic bacteriuria at Day 5 and 1 of them had clinical failure at Day 12. So having asymptomatic bacteriuria at Day 5 did not predict clinical failure one week later at Day 12. Similarly, 339 patients had a clinical success at the Day 12 test of cure visit. Of those, 20 had clinical failure at Day 28, 16 days later. 74 patients had asymptomatic bacteriuria at Day 12 and of those, 8 had clinical failure at Day 28, resulting in a rate very similar to that of patients who had previously achieved both clinical and microbiologic success. In this study, the presence of asymptomatic bacteriuria did not predict subsequent clinical failure. This finding is supported by the opinion of the Infectious Disease Society of America (Nicolle, 2019).

Table 16: Study 301 Association of Asymptomatic Bacteriuria at the End of Treatment and Clinical Response at the Test of Cure – micro-MITT Population

Sulopenem		
Overall Response at EOT (D5)	**Clinical Failure at TOC (D12) n/N (%)**	**p-value**
Success	31/335 (9.3)	1.000
Fail: ASB	1/12 (8.3)	
Overall Response at TOC (D12)	**Clinical Failure at FV (D28) n/N (%)**	**p-value**
Success	20/339 (5.8)	0.128
Fail: ASB	8/74 (10.8)	

Source: IT001-301 post hoc Table 66 and post hoc Table 73

*Reasons for failure include: death, receipt of an antibiotic (which includes any antibiotic for a UTI based on investigator assessment or programmatic outcomes), clinical symptoms alone or both urine culture positive plus clinical symptoms.
Note: micro-MITT = microbiologic modified intent-to-treat; TOC = test of cure; FV = final visit; ASB = asymptomatic bacteriuria

1.5.3.1.4.3 microMITT-S Population

In the ciprofloxacin susceptible population, oral sulopenem was not non-inferior to ciprofloxacin (Table 17). Overall success in the microMITT-S population was seen in 66.8% of patients in the oral sulopenem group and 78.6% of patients in the ciprofloxacin group (treatment difference - 11.8, 95% CI [-18.0, -5.6]). However, clinical success rates were similar across the two treatment groups at TOC.

Table 17: Study 301 Outcomes at TOC and EOT - microMITT-S Population

Outcome	Sulopenem n (%) N = 370	Ciprofloxacin n (%) N = 415	Difference % (95% CI)
Overall response at TOC	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)	
Clinical success at TOC	300 (81.1)	349 (84.1)	-3.0 (-8.4, 2.3)
Microbiologic success at TOC	287 (77.6)	369 (88.9)	-11.3 (-16.7, -6.2)
Overall Response at EOT	240 (64.9)	271 (65.3)	-0.4 (-7.1, 6.2)

The difference in overall response seen in the microMITT-S population was driven by a higher rate of asymptomatic bacteriuria in the sulopenem arm. Importantly, however, as was seen for the microMITT population above, this higher rate of asymptomatic bacteriuria did not translate to more clinical failures, compared to ciprofloxacin, at the final visit on Day 28.

Efficacy in the microMITT-S population, including clinical and microbiologic outcomes, is discussed in extensive detail in Section 7.5.3.

1.5.3.1.5 Selection for Resistant Pathogens

An assessment of the impact of antibiotic therapy on the *in vitro* susceptibility of study uropathogens (Enterobacterales and *S. saprophyticus*) identified at baseline and the TOC visit was performed in order to determine if study drug was selecting for organisms with higher MIC's, building on the distribution of colonizers. All patients in the study had a baseline urine specimen cultured for uropathogens. Those patients with $\geq 10^5$ CFU/mL of a study uropathogen in the baseline urine culture, who are patients selected to be in the microMITT population, had susceptibility testing done on all isolates in that specimen cultured at $\geq 10^2$ CFU/mL, in addition to the pathogen recovered at $\geq 10^5$CFU/mL. At the subsequent TOC visit, all isolates for those microMITT patients recovered at $\geq 10^2$ CFU/mL were again tested for *in vitro* susceptibility. Note that if an isolate was identified at TOC that was not found at $\geq 10^5$ CFU/mL at baseline, that isolate was not considered in the overall assessment of microbiologic response. In this analysis that compares the distribution of *in vitro* susceptibility to the study drug before and after therapy, those isolates are analyzed in addition to pathogens considered to be the baseline pathogen.

For patients treated with sulopenem, the total number of uropathogens is lower by ~60% as would be expected post therapy. The distribution of MIC's to sulopenem after treatment with sulopenem

is very similar to the pre-treatment distribution. The $MIC_{50/90}$ pre-treatment was 0.03/0.06 µg/mL and post-treatment it was 0.03/0.12 µg/mL. No organisms that would be considered carbapenemase resistant were identified.

For patients treated with ciprofloxacin, the number of cultured uropathogens was reduced by ~80%. However, for these patients there is an increase in the proportion with quinolone resistant uropathogens post treatment relative to baseline. The $MIC_{50/90}$ pre-treatment was $\leq$0.06/>2 µg/mL and post-treatment it was >2/>2 µg/mL. Examination of the ciprofloxacin treated patients by subgroup in the non-susceptible (microMITTR) and susceptible (microMITTS) populations was performed. In the microMITTR population, patients with a quinolone resistant organism at baseline, essentially all the isolates remain quinolone resistant at TOC. In the patients in the microMITTS population with a quinolone susceptible isolate at baseline, however, a significant increase in the proportion of isolates that are quinolone resistant at TOC is evident. Treatment with ciprofloxacin in this population significantly reduced the proportion of patients with a highly-susceptible uropathogen and, at the same time, increased the likelihood that these patients will have a quinolone resistant pathogen in their colonizing flora post-treatment, placing them at risk for a subsequent uUTI caused by an organism resistant to a quinolone, as has been observed previously [Dunne 2022].

1.5.3.2 IT001-310 (Study 310)

1.5.3.2.1 Study Design

Study IT001-310 was a prospective, Phase 3, randomized, multicenter, double-blind, double dummy, controlled study to compare oral sulopenem to oral amoxicillin/clavulanate for the treatment of patients with uUTI. Approximately 1966 adult women with uUTI were to be randomized in a 1:1 fashion to receive either oral sulopenem 500 mg/500 mg twice daily for 5 days or oral amoxicillin/clavulanate 875 mg/125 mg twice daily for 5 days. The primary efficacy assessment was overall response (combined clinical and microbiologic response [success, failure or indeterminate]) in the micro-MITT, micro-MITTS and micro-MITTR populations on Day 12 (± 1 day)/TOC.

The key analysis population of interest was the micro-MITT population, defined as all MITT patients with a positive study entry urine culture defined as $\geq 10^5$ CFU/mL of a uropathogen (Enterobacterales only) and no more than 2 species of microorganisms identified in the study entry urine culture, regardless of colony count.

Patients were to be programmatically categorized as a success, failure, or indeterminate based on data in the eCRF and from the microbiology lab. Patients with missing data or who were lost to follow-up were defined as indeterminate for the primary analyses and were included in the denominator for the calculation of the success rate.

The framework for the statistical hypothesis testing of the primary efficacy outcome, overall success (combined clinical and microbiological success) at Day 12 (± 1 day)/TOC, is defined below.

The primary comparison of the study is in the micro-MITT population (the combined population of patients with a positive baseline culture and without regard to amoxicillin/clavulanate susceptibility). These outcomes are most relevant to the practicing clinician who must choose empiric treatment of uUTI before culture results become available.

The primary comparisons for regulatory approval are in two mutually exclusive sub-populations of the micro-MITT population defined by a baseline characteristic: 1) the micro-MITTS population (the subset of the micro-MITT population in which the baseline pathogen is determined to be susceptible (MIC ≤ 8/4 mg/L) to the comparator study drug, amoxicillin/clavulanate; and 2) the micro-MITTR population (the subset of the micro-MITT population in which the baseline pathogen is determined to be non-susceptible (intermediate [MIC 16/8 mg/L] or resistant [MIC ≥ 32/16 mg/L]) to the comparator study drug, amoxicillin/clavulanate.

To control for inflation of the overall type I error rate, the hierarchical testing procedure of Westfall and Krishen [Westfall 2001] was to be used to test the hypotheses of the primary efficacy outcome in these populations in the sequential order described below. Testing was to proceed to the next comparison, only in the case where the null hypothesis in the previous comparison was rejected. When testing in a sequential manner with pre-planned testing, no adjustment to the alpha level is required.

(1) NI in the micro-MITT population. For this population, a NI test of the overall success rate was to be conducted. The null and alternative hypotheses are the following:

$$H_0 : p_1 - p_2 \leq -\Delta \text{ and } H_A : p_1 - p_2 > -\Delta,$$

where p_1 is the primary efficacy outcome rate in the oral sulopenem group, p_2 is the primary efficacy outcome rate in the amoxicillin/clavulanate group, and Δ is the non-inferiority margin of 10.0%.

The NI hypothesis test is a 1-sided hypothesis test to be performed at the 2.5% level of significance. This is based on the lower limit of the 2-sided 95% CI for the observed difference in the overall success rate (oral sulopenem group minus amoxicillin/clavulanate group). The primary analysis is based on the CI computed using the method proposed without stratification by Miettinen and Nurminen, which corresponds to the p-value approach of the Farrington-Manning test. If the lower limit of the 95% CI for difference in success rates in the micro-MITT population was greater than -10.0%, the null hypothesis was to be rejected and the NI of oral sulopenem to amoxicillin/clavulanate was to be concluded.

(2) NI in the micro-MITTS population OR superiority in the micro-MITTR population as described below:

Micro-MITTS population: the subset of the micro-MITT population in which the baseline pathogen was determined to be susceptible to the comparator study drug, amoxicillin/clavulanate. For this population, a NI test of the overall success rate was to be conducted. The null and alternative hypotheses are as follows:

$$H_0 : p_1 - p_2 \leq -\Delta \text{ and } H_A : p_1 - p_2 > -\Delta$$

A 2-sided 95% CI for the observed treatment difference in success rates was to be determined. If the lower bound of the 95% CI was greater than -10.0%, the null hypothesis was to be rejected and the NI of oral sulopenem to amoxicillin/clavulanate in the micro-MITTS population was to be concluded.

Micro-MITTR population: the subset of the micro-MITT population in which the baseline pathogen was determined to be non-susceptible to the comparator study drug, amoxicillin/clavulanate. For this

population, a superiority test was to be conducted. The null and alternative hypotheses are as follows:

$H_0 : p_1 = p_2$ and $H_A : p_1 \neq p_2$

A 2-sided 95% CI for the observed treatment difference in success rates was to be determined using the method without stratification of Miettinen and Nurminen. If the lower bound of the 95% CI was greater than 0%, the null hypothesis was to be rejected and superiority of oral sulopenem to amoxicillin/clavulanate was to be concluded in the micro-MITTR population.

Each of the 2 null hypotheses in this step were to be tested at the 2.5% level and if either hypothesis was rejected, then testing was to proceed to the next step.

(3) Superiority test of overall success in the micro-MITT population. If the lower bound of the 95% CI calculated for the hypothesis test in (1) was greater than 0%, the null hypothesis was to be rejected and the superiority of oral sulopenem to amoxicillin/clavulanate in the micro-MITT population was to be concluded.

Analysis of Secondary Efficacy Outcome Measure:

The number and percentage of patients in each treatment group with a clinical response of success, failure and indeterminate at Day 12 (±1 day)/TOC was to be presented for the MITT, micro-MITT, micro-MITTS, and micro-MITTR populations. The number and percentage of patients in each treatment group with a clinical response of success and failure at Day 12 (±1 day)/TOC was to be presented for the CE and ME populations. Two-sided 95% unstratified CIs were to be constructed for the observed difference in the clinical success rates between the treatment groups for descriptive purposes; no conclusion of NI was to be made.

The number and percentage of patients in each treatment group with a microbiologic response of success, failure and indeterminate at Day 12 (±1 day)/TOC was to be presented for the micro-MITT, micro-MITTS, and micro-MITTR populations. The number and percentage of patients in each treatment group with a microbiologic response of success and failure at Day 12 (±1 day)/TOC was to be presented for the ME population. Two-sided 95% unstratified CIs were to be constructed for the observed difference in the microbiologic success rates between the treatment groups for descriptive purposes; no conclusion of NI was to be made.

Safety analyses were to be conducted in the Safety population (all patients who received at least one dose of study drug) and were to be summarized by treatment group. Safety was to be assessed through summaries of AEs, laboratory evaluations, and vital signs.

1.5.3.2.2 Patient Enrollment

Following 1 pre-planned blinded interim analyses to ensure that the point estimate of overall success (combined clinical and microbiologic success) used in the estimation of sample size, the estimated eligibility rate, susceptibility rate, and rate of post-treatment asymptomatic bacteriuria were valid for this study, the DMC recommended that in order to maintain 80%-90% power, the trial should continue to enroll to achieve a minimum of 1966 patients (original sample size in protocol) up to a maximum of 2428 patients (to achieve 90% power). On October 23, 2023, enrollment was completed at 2222 randomized patients as the sponsor considered adequate statistical power had been achieved. Data from 990 subjects (micro-MITT population) were analyzed for efficacy, and data from 2214 subjects were analyzed for safety as 8 randomized subjects did not receive any study drug.

1.5.3.2.3 Efficacy

1.5.3.2.3.1 micro-MITT Population

The primary efficacy endpoint was overall response at the Day 12 (TOC) visit in each of the micro-MITT, micro-MITTS and micro-MITTR populations. As shown (Table 18), in the micro-MITT population, overall response of success was seen in 60.9% of patients in the sulopenem group and 55.6% of patients in the amoxicillin/clavulanate group (treatment difference 5.4%, 95% CI [-0.8, 11.5]). The study demonstrated non-inferiority of sulopenem to amoxicillin/clavulanate in the treatment of uUTI in the micro-MITT population.

Clinical success rates at TOC were similar across treatment groups (76.1% of micro-MITT patients in the sulopenem group and 76.5% of patients in the amoxicillin/clavulanate group, treatment difference -0.4%, 95% CI [-5.7, 4.9]).

The microbiologic success rate at TOC was statistically significantly higher in the sulopenem group compared to the amoxicillin/clavulanate group (74.7% of micro-MITT patients in the sulopenem group and 67.3% of patients in the amoxicillin/clavulanate group, treatment difference 7.4%, 95% CI [1.8, 13.1]).

Table 18 Study 310 Overall Response, Clinical Response and Microbiologic Response at TOC – micro-MITT Population

Outcome	Sulopenem n (%) N=522	Amoxicillin/ clavulanate n (%) N=468	Difference % (95% CI)	p-value
Overall response at TOC	318 (60.9)	260 (55.6)	5.4 (-0.8, 11.5)	0.0437
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 14.2.1.1, Table 14.2.12.1.4, Table 14.2.6.1.1

% = 100 x n/N; micro-MITT = microbiological modified intent-to-treat; CI = confidence interval; TOC = test of cure; N = number of patients in the micro-MITT population; Overall Response is defined as combined clinical and microbiologic success. Indeterminate responses are considered failures for CI calculation. CI computed using the method proposed without stratification by Miettinen and Nurminen.

The overall response at TOC by baseline pathogen in the micro-MITT population is presented, for select organisms, in Table 19 below. Patients in the sulopenem group had higher overall success rates for infections caused by *E. coli*, *K. pneumoniae* and *S. saprophyticus*.

Table 19 Study 310 Overall Response at TOC by Selected Baseline Pathogens in the micro-MITT Population

Pathogen	Sulopenem m/n (%) N=522	Amoxicillin/ clavulanate m/n (%) N=468
E. coli	263/423 (62.2)	219/387 (56.6)
K. pneumoniae	31/58 (53.4)	22/50 (44.0)
P. mirabilis	6/14 (42.9)	6/13 (46.2)
E. hormaechei	3/4 (75.0)	8/8 (100.0)
*S. saprophyticus**	8/9 (88.9)	1/3 (33.3)

Source: Table 14.2.2.1.1, Listing 16.2.9.1; Post hoc Listing 1

% = 100 x m/n; Micro-MITT = Microbiological Modified Intent-to-treat; TOC = Test of Cure; N = Number of patients in the micro-MITT population; n = Number of patients in the micro-MITT population with specific study uropathogen; m = Number of patients with an overall response of success and with specific study uropathogen; Overall Success is defined as combined clinical and microbiologic success at TOC; *not included in micro-MITT population.

Overall response at TOC for the micro-MITT population by resistance class is presented below (Table 20). 91 (9.2%) patients in the micro-MITT population had a baseline pathogen resistant to at least three of β-lactam, quinolone, trimethoprim-sulfamethoxazole, or nitrofurantoin. For this subset of patients, higher overall response rates were seen for the patients in the sulopenem treatment arm. For patients with a baseline pathogen resistant to all four classes of widely prescribed orally available antibiotics, low number of patients in this category make it difficult to draw any conclusions.

Table 20 Study 310 Overall Response at TOC by Resistance Class – micro-MITT Population

Resistance Class / Overall Response	Sulopenem n (%) N=522	Amoxicillin/ clavulanate n (%) N=468	Difference % (95% CI)
ESBL positive, N1	52	46	
Overall responder	32 (61.5)	21 (45.7)	15.9 (-4.0, 34.6)
Overall non-responder	18 (34.6)	23 (50.0)	
Indeterminate	2 (3.8)	2 (4.3)	
ESBL negative, N1	470	421	
Overall responder	286 (60.9)	239 (56.8)	4.1 (-2.4, 10.5)
Overall non-responder	159 (33.8)	161 (38.2)	
Indeterminate	25 (5.3)	21 (5.0)	
Nitrofurantoin susceptible, N1	439	398	
Overall responder	275 (62.6)	225 (56.5)	6.1 (-0.5, 12.7)
Overall non-responder	141 (32.1)	153 (38.4)	
Indeterminate	23 (5.2)	20 (5.0)	
Nitrofurantoin resistant, N1	83	69	
Overall responder	43 (51.8)	35 (50.7)	1.1 (-14.7, 16.9)
Overall non-responder	36 (43.4)	31 (44.9)	
Indeterminate	4 (4.8)	3 (4.3)	
TMP-SMX susceptible, N1	361	328	
Overall responder	216 (59.8)	186 (56.7)	3.1 (-4.2, 10.5)
Overall non-responder	122 (33.8)	124 (37.8)	
Indeterminate	23 (6.4)	18 (5.5)	
TMP-SMX resistant, N1	161	139	
Overall responder	102 (63.4)	74 (53.2)	10.1 (-1.1, 21.1)
Overall non-responder	55 (34.2)	60 (43.2)	
Indeterminate	4 (2.5)	5 (3.6)	
Quinolone susceptible, N1	392	336	
Overall responder	250 (63.8)	195 (58.0)	5.7 (-1.4, 12.8)
Overall non-responder	120 (30.6)	121 (36.0)	
Indeterminate	22 (5.6)	20 (6.0)	
Quinolone resistant, N1	130	131	
Overall responder	68 (52.3)	65 (49.6)	2.7 (-9.4, 14.7)
Overall non-responder	57 (43.8)	63 (48.1)	
Indeterminate	5 (3.8)	3 (2.3)	
Beta-lactam susceptible, N1	373	322	
Overall responder	232 (62.2)	180 (55.9)	6.3 (-1.0, 13.6)
Overall non-responder	120 (32.2)	126 (39.1)	
Indeterminate	21 (5.6)	16 (5.0)	

Resistance Class / Overall Response	Sulopenem n (%) N=522	Amoxicillin/ clavulanate n (%) N=468	Difference % (95% CI)
Beta-lactam resistant, N1	149	145	
Overall responder	86 (57.7)	80 (55.2)	2.5 (-8.8, 13.8)
Overall non-responder	57 (38.3)	58 (40.0)	
Indeterminate	6 (4.0)	7 (4.8)	
Beta-lactam resistant and quinolone resistant, N1	61	65	
Overall responder	34 (55.7)	33 (50.8)	5.0 (-12.4, 22.0)
Overall non-responder	25 (41.0)	29 (44.6)	
Indeterminate	2 (3.3)	3 (4.6)	
Beta-lactam resistant, quinolone resistant, and TMP-SMX resistant	38	46	
Overall responder	20 (52.6)	20 (43.5)	9.2 (-12.2, 29.8)
Overall non-responder	17 (44.7)	24 (52.2)	
Indeterminate	1 (2.6)	2 (4.3)	
Resistant to at least three of beta-lactam, quinolone, TMP-SMX, or NFT, N1	42	49	
Overall responder	24 (57.1)	24 (49.0)	8.2 (-12.4, 28.0)
Overall non-responder	17 (40.5)	23 (46.9)	
Indeterminate	1 (2.4)	2 (4.1)	
Resistant to all four of beta-lactam, quinolone, TMP-SMX, and NFT, N1	8	4	
Overall responder	5 (62.5)	3 (75.0)	-12.5 (-56.7, 44.4)
Overall non-responder	3 (37.5)	0 (0.0)	
Indeterminate	0 (0.0)	1 (25.0)	

Source: Table 14.2.2.2.1, post hoc Table 15

% = 100 x n/N1; Micro-MITT = Microbiological Modified Intent-to-treat; TOC = Test of Cure; CI = Confidence Interval; N1 = Number of patients in the micro-MITT population with specific resistance class; ESBL positive is defined as resistant or intermediate to ceftriaxone; ESBL negative is defined as susceptible to ceftriaxone; NFT non-susceptible is defined as resistant or intermediate to nitrofurantoin; TMP-SMX non-susceptible is defined as resistant or intermediate to trimethoprim/sulfamethoxazole; Quinolone non-susceptible is defined as resistant or intermediate to ciprofloxacin; Beta-lactam non-susceptible is defined as resistant or intermediate to 1 or more beta-lactam antibiotics in the IHMA panel including cefazolin, ertapenem, meropenem, ceftriaxone, and amoxicillin-clavulanate; Beta-lactam susceptible is defined as susceptible to all beta-lactam antibiotics in the IHMA panel including above. Indeterminate responses are considered failures for CI calculation.

As shown in Table 21 below, the clinical response for patients in the micro-MITT population was similar for the two treatment arms at the EOT, TOC and Final visit.

Table 21 Study 310 Clinical Response by Visit in the micro-MITT Population

Timepoint/Response	Sulopenem n (%) N=522	Amoxicillin/ clavulanate n (%) N=468	Difference % (95% CI)
End of Treatment (D5)			
Clinical success	305 (58.4)	289 (61.8)	-3.3 (-9.4, 2.8)
Clinical failure	204 (39.1)	163 (34.8)	
Indeterminate	13 (2.5)	16 (3.4)	
Test of Cure (D12)			
Clinical success	397 (76.1)	358 (76.5)	-0.4 (-5.7, 4.9)
Clinical failure	104 (19.9)	92 (19.7)	
Indeterminate	21 (4.0)	18 (3.8)	
Final Visit (D28)			
Clinical success	412 (78.9)	379 (81.0)	-2.1 (-7.0, 3.0)
Clinical failure	75 (14.4)	57 (12.2)	
Indeterminate	35 (6.7)	32 (6.8)	

Source: Table 14.2.13.1.4, Table 14.2.12.1.4, Table 14.2.14.1.4

1.5.3.2.3.1.1 Impact of Asymptomatic Bacteriuria on Clinical Outcome at Subsequent Visits

In the 301 Study, where sulopenem was compared to ciprofloxacin, asymptomatic bacteriuria was identified as the primary reason non-inferiority was not achieved in the comparison of sulopenem and ciprofloxacin in patients with quinolone susceptible pathogens. In Study 310, asymptomatic bacteriuria at TOC was prespecified as an additional efficacy endpoint to be assessed prospectively for the micro-MITT and ME populations. In addition, as shown below (Table 22 and Table 23), the presence of asymptomatic bacteriuria at the EOT and TOC visit was evaluated to see if it impacted clinical response at the TOC and FV visit, respectively. As shown, for both treatment arms, asymptomatic bacteriuria did not lead to clinical failure at the following visit in the micro-MITT population. In this study, the presence of asymptomatic bacteriuria did not predict subsequent clinical failure. This finding is supported by the opinion of the Infectious Disease Society of America (Nicolle, 2019).

Table 22 Study 310 Association of Asymptomatic Bacteriuria at the End of Treatment and Clinical Response at the Test of Cure – micro-MITT Population

Sulopenem			Amoxicillin/clavulanate		
Overall Response at EOT (D5)	**Clinical Success at TOC (D12) n/N (%)**	**p-value**	**Overall Response at EOT (D5)**	**Clinical Success at TOC (D12) n/N (%)**	**p-value**
Success	13/272 (4.8)	0.721	Success	17/243 (7.0)	0.527
Fail: ASB	1/30 (3.3)		Fail: ASB	2/45 (4.4)	

Source: Post hoc Table 13.1, post hoc Table 14.1, post hoc Table 16

*Reasons for failure include: death, receipt of an antibiotic (which includes any antibiotic for a UTI based on investigator assessment or programmatic outcomes), clinical symptoms alone or both urine culture positive plus clinical symptoms.

Note: micro-MITT = microbiologic modified intent-to-treat; EOT = end of treatment; TOC = test of cure; ASB = asymptomatic bacteriuria

Table 23 Study 310 Association of Asymptomatic Bacteriuria at the Test of Cure and Clinical Response at the Final Visit – micro-MITT Population

Sulopenem			Amoxicillin/clavulanate		
Overall Response at TOC (D12)	**Clinical Success at FV (D28) n/N (%)**	**p-value**	**Overall Response at TOC (D12)**	**Clinical Success at FV (D28) n/N (%)**	**p-value**
Success	22/318 (6.9)	0.656	Success	13/260 (5.0)	0.208
Fail: ASB	4/73 (5.5)		Fail: ASB	8/93 (8.6)	

Source: Post hoc Table 13.1, post hoc Table 14.1, post hoc Table 16

*Reasons for failure include: death, receipt of an antibiotic (which includes any antibiotic for a UTI based on investigator assessment or programmatic outcomes), clinical symptoms alone or both urine culture positive plus clinical symptoms.

Note: micro-MITT = microbiologic modified intent-to-treat; TOC = test of cure; FV = final visit; ASB = asymptomatic bacteriuria

1.5.3.2.3.2 micro-MITTS Population

The primary efficacy endpoint was overall response at the Day 12 (TOC) visit in each of the micro-MITT, micro-MITTS and micro-MITTR populations. The table below (Table 24) presents the overall, clinical and microbiologic responses at TOC in the micro-MITTS population. Overall response of success was seen in 61.7% of patients in the sulopenem group and 55.0% of patients in the amoxicillin/clavulanate group (treatment difference 6.7%, 95% CI [0.3, 13.0]). In addition to demonstrating non-inferiority, sulopenem was also found to be superior to amoxicillin/clavulanate for the treatment of uUTI in the micro-MITTS population.

Clinical success rates at TOC were similar across treatment groups (77.3% in the sulopenem group and 76.7% in the amoxicillin/clavulanate group, treatment difference 0.6%, 95% CI [-4.8, 6.1]). Clinical response for patients in both treatment arms is described in detail in Section 7 below.

Microbiologic success rates at TOC were statistically significantly higher in the sulopenem group relative to the amoxicillin/clavulanate group (75.2% in the sulopenem group and 66.7% in the amoxicillin/clavulanate group, treatment difference 8.5%, 95% CI [2.6, 14.3]). Microbiologic response for patients in both treatment groups is described in detail in Section 7 below.

Table 24 Study 310 Overall Response, Clinical Response and Microbiologic Response at TOC – micro-MITTS Population

Outcome	Sulopenem n (%) N=480	Amoxicillin/ clavulanate n (%) N=442	Difference % (95% CI)
Overall response at TOC	296 (61.7)	243 (55.0)	6.7 (0.3, 13.0)
Overall nonresponse	160 (33.3)	177 (40.0)	
Indeterminate	24 (5.0)	22 (5.0)	
Clinical success at TOC	371 (77.3)	339 (76.7)	0.6 (-4.8, 6.1)
Microbiologic success at TOC	361 (75.2)	295 (66.7)	8.5 (2.6, 14.3)

Source: Table 14.2.1.2, Table 14.2.12.1.5, Table 14.2.6.2.1

% = 100 x n/N; micro-MITTS = microbiological modified intent-to-treat susceptible; CI = confidence interval; TOC = test of cure; N = number of patients in the micro-MITTS population; Overall Success is defined as combined clinical and microbiologic success. Indeterminate responses are considered failures for CI calculation. CI computed using the method proposed without stratification by Miettinen and Nurminen.

The overall response at TOC by baseline pathogen in the micro-MITTS population is presented, for select organisms, below (Table 25). As was seen for the entire micro-MITTS population, outcomes for patients with *E. coli* and *K. pneumoniae* were better in the sulopenem arm while outcomes for patients with infection due to *P. mirabilis* were higher in the amoxicillin/clavulanate group, though the small number of patients in this sub-group preclude any conclusions from being drawn.

Table 25 Study 310 Overall Response at TOC by Selected Baseline Pathogens in the micro-MITTS Population

Pathogen	Sulopenem m/n (%) N=480	Amoxicillin/ clavulanate m/n (%) N=442
E. coli	251/400 (62.8)	210/374 (56.1)
K. pneumoniae	31/57 (54.4)	22/50 (44.0)
P. mirabilis	5/13 (38.5)	6/13 (46.2)

Source: Table 14.2.2.1.2

Note: Percentages are calculated as 100 × (n/N). Abbreviations: micro-MITTS = Microbiological Modified intent-to-treat susceptible; TOC = Test of Cure; N = Number of patients in the micro-MITTS population; n = Number of patients in the micro-MITTS population with specific study uropathogen; m = Number of patients with Overall Success and with specific study uropathogen; Overall Success is defined as combined clinical and microbiologic success at TOC.

Overall response at TOC for the micro-MITTS population by resistance class is presented in Table 26 below. 78 (8.5%) patients in the micro-MITTS population had a baseline pathogen resistant to at least three of β-lactam, quinolone, trimethoprim-sulfamethoxazole, or nitrofurantoin.

Treatment difference in patients with various combinations of multidrug resistance were similar to the overall response in this population.

Notably, the overall success rate at TOC for sulopenem in patients with quinolone-susceptible pathogens was significantly higher than amoxicillin/clavulanate, highlighting the impact of antibiotic class-dependent asymptomatic bacteriuria on the primary endpoint.

Table 26 Study 310 Overall Response at TOC by Resistance Class in the micro-MITTS Population

Resistance Class / Overall Response	Sulopenem n (%) N=480	Amoxicillin/ clavulanate n (%) N=442	Difference % (95% CI)
ESBL positive, N1	37	45	
Overall responder	22 (59.5)	20 (44.4)	15.0 (-6.8, 35.4)
Overall non-responder	13 (35.1)	23 (51.1)	
Indeterminate	2 (5.4)	2 (4.4)	
ESBL negative, N1	443	397	
Overall responder	274 (61.9)	223 (56.2)	5.7 (-1.0, 12.3)
Overall non-responder	147 (33.2)	154 (38.8)	
Indeterminate	22 (5.0)	20 (5.0)	
Nitrofurantoin susceptible, N1	416	386	
Overall responder	264 (63.5)	217 (56.2)	7.2 (0.5, 14.0)
Overall non-responder	132 (31.7)	150 (38.9)	
Indeterminate	20 (4.8)	19 (4.9)	
Nitrofurantoin resistant, N1	64	56	
Overall responder	32 (50.0)	26 (46.4)	3.6 (-14.3, 21.1)
Overall non-responder	28 (43.8)	27 (48.2)	
Indeterminate	4 (6.3)	3 (5.4)	
TMP-SMX susceptible, N1	331	308	
Overall responder	201 (60.7)	173 (56.2)	4.6 (-3.1, 12.2)
Overall non-responder	109 (32.9)	117 (38.0)	
Indeterminate	21 (6.3)	18 (5.8)	
TMP-SMX resistant, N1	149	134	
Overall responder	95 (63.8)	70 (52.2)	11.5 (-0.0, 22.8)
Overall non-responder	51 (34.2)	60 (44.8)	
Indeterminate	3 (2.0)	4 (3.0)	
Quinolone susceptible, N1	360	314	
Overall responder	234 (65.0)	180 (57.3)	7.7 (0.3, 15.0)
Overall non-responder	107 (29.7)	114 (36.3)	
Indeterminate	19 (5.3)	20 (6.4)	

Resistance Class / Overall Response	Sulopenem n (%) N=480	Amoxicillin/ clavulanate n (%) N=442	Difference % (95% CI)
Quinolone resistant, N1	120	128	
Overall responder	62 (51.7)	63 (49.2)	2.4 (-10.0, 14.8)
Overall non-responder	53 (44.2)	63 (49.2)	
Indeterminate	5 (4.2)	2 (1.6)	
Beta-lactam susceptible, N1	373	322	
Overall responder	232 (62.2)	180 (55.9)	6.3 (-1.0, 13.6)
Overall non-responder	120 (32.2)	126 (39.1)	
Indeterminate	21 (5.6)	16 (5.0)	
Beta-lactam resistant, N1	107	120	
Overall responder	64 (59.8)	63 (52.5)	7.3 (-5.6, 20.0)
Overall non-responder	40 (37.4)	51 (42.5)	
Indeterminate	3 (2.8)	6 (5.0)	
Beta-lactam resistant and quinolone resistant, N1	51	62	
Overall responder	28 (54.9)	31 (50.0)	4.9 (-13.5, 23.0)
Overall non-responder	21 (41.2)	29 (46.8)	
Indeterminate	2 (3.9)	2 (3.2)	
Beta-lactam resistant, quinolone resistant, and TMP-SMX resistant	31	44	
Overall responder	16 (51.6)	19 (43.2)	8.4 (-14.3, 30.5)
Overall non-responder	14 (45.2)	24 (54.5)	
Indeterminate	1 (3.2)	1 (2.3)	
Resistant to at least three of beta-lactam, quinolone, TMP-SMX, or NFT, N1	32	46	
Overall responder	16 (50.0)	22 (47.8)	2.2 (-20.0, 24.2)
Overall non-responder	15 (46.9)	23 (50.0)	
Indeterminate	1 (3.1)	1 (2.2)	
Resistant to all four of beta-lactam, quinolone, TMP-SMX, and NFT, N1	6	4	
Overall responder	4 (66.7)	3 (75.0)	-8.3 (-57.5, 49.7)
Overall non-responder	2 (33.3)	0 (0.0)	
Indeterminate	0 (0.0)	1 (25.0)	

Source: Table 14.2.2.2.2, post hoc Table 15

% = 100 x n/N1; Micro-MITTS = Microbiological Modified Intent-to-treat susceptible; TOC = Test of Cure; CI = Confidence Interval; N1 = Number of patients in the micro-MITTS population with specific resistance class ESBL positive is defined as resistant or intermediate to ceftriaxone; ESBL negative is defined as susceptible to ceftriaxone; NFT non-susceptible is defined as resistant or intermediate to nitrofurantoin; TMP-SMX non-susceptible is defined as resistant or intermediate to trimethoprim/sulfamethoxazole; Quinolone non-susceptible is defined as resistant or intermediate to ciprofloxacin; Beta-lactam non-susceptible is defined as resistant or intermediate to 1 or more beta-lactam antibiotic in the testing panel including cefazolin, ertapenem, meropenem, ceftriaxone, and amoxicillin-clavulanate; Beta-lactam

susceptible is defined as susceptible to all beta-lactam antibiotics in the testing panel including above. Indeterminate responses are considered failures for CI calculation.

As shown below (Table 27), the clinical response for patients in the micro-MITTS population was similar for the two treatment arms at the EOT, TOC and Final visit. The clinical success rates in both treatment groups improved from EOT to TOC and then to FV.

Table 27 Study 310 Clinical Response by Visit in the micro-MITTS Population

Timepoint/Response	Sulopenem n (%) N=480	Amoxicillin/ clavulanate n (%) N=442	Difference % (95% CI)
End of Treatment (D5)			
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)	
Test of Cure (D12)			
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 (D28)			
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 14.2.13.1.5, Table 14.2.12.1.5, Table 14.2.14.1.5

1.5.3.2.3.3 micro-MITTR Population

Due to the small sample size in the micro-MITTR population (only 25% of planned sample size was achieved) and the imbalance in randomization to the treatment groups, there was insufficient power (approximately 20%) in the micro-MITTR population to draw any conclusions about treatment effect.

The primary efficacy endpoint was overall response at the Day 12 (TOC) visit in each of the micro-MITT, micro-MITTS and micro-MITTR populations. As shown below (Table 28), for the micro-MITTR population. overall response of success at TOC was seen in 52.4% of patients in the sulopenem group and 68% of patients in the amoxicillin/clavulanate group (treatment difference -15.6%, 95% CI [-37.5, 9.1]). The small sample size precluded any conclusions from being drawn.

Table 28 Study 310 Overall Response at TOC – micro-MITTR Population

Outcome	Sulopenem n (%) N=42	Amoxicillin/ clavulanate n (%) N=25	Difference % (95% CI)	p-value
Overall response at TOC	22 (52.4)	17 (68.0)	-15.6 (-37.5, 9.1)	0.895
Overall non-response	17 (40.5)	7 (28.0)		
Indeterminate	3 (7.1)	1 (4.0)		

Source: Table 14.2.1.3

% = 100 x n/N; micro-MITTR = microbiological modified intent-to-treat resistant; CI = confidence interval; TOC = test of cure; N = number of patients in the micro-MITTR population; Overall Success is defined as combined clinical and microbiologic success at TOC. Indeterminate responses are considered failures. 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.

Several pre-specified subgroup analyses of the primary endpoint were conducted. As for the primary endpoint analysis and sensitivity analyses in the micro-MITTR population, the small sample size and the imbalance in randomization to the treatment groups hampers the ability to draw any conclusions about treatment effect from these pre-specified subgroup analyses.

The micro-MITTR population included a total of 67 patients (42 assigned to sulopenem and 25 assigned to amoxicillin/clavulanate), much fewer than the 268 patients planned for when the study was designed. The analyses performed for the micro-MITTR population are the same as were performed for the micro-MITT and micro-MITTS populations. The low number of patients in the population and the 1.7 to 1 ratio for sulopenem to amoxicillin/clavulanate treatment assignment, however, makes it difficult to draw conclusions from these analyses. Notably, there are some random imbalances which likely contributed to the results seen in this population. First, among the micro-MITTR patients, there were differences in baseline isolates in terms of MIC to amoxicillin/clavulanate. As shown in the table below, the infecting study pathogen had intermediate susceptibility to amoxicillin/clavulanate for 40.5% and 64.0% of patients in the sulopenem and amoxicillin/clavulanate arm, respectively. The infecting study pathogen was fully resistant to amoxicillin/clavulanate for 59.5% and 36.0% of patients in the sulopenem and amoxicillin/clavulanate arm, respectively. Second, patients assigned to sulopenem were significantly more likely to have a polymicrobial baseline infection than those assigned to amoxicillin/clavulanate. Third, patients assigned to sulopenem were more likely to have a multidrug resistant baseline study pathogen than those assigned to amoxicillin/clavulanate. All three of these criteria, resistance to amoxicillin/clavulanate, polymicrobial infections at baseline and multidrug resistant baseline pathogens can be markers of failure. Overall success rate for patients with infections due to amoxicillin/clavulanate resistant isolates (MIC ≥32 µg/mL**)** is much lower than those with infections caused by pathogens with intermediate susceptibility to amoxicillin/clavulanate (55.6% vs 75.0%, respectively) in the amoxicillin/clavulanate arm, and lower than the success rate seen in the same group in the sulopenem arm (64.0%).

1.5.3.2.4 Selection for Resistant Pathogens

An assessment of the impact of antibiotic therapy on the *in vitro* susceptibility of study uropathogens (Enterobacterales) identified at baseline and the TOC visit was performed in order to

determine if study drug was selecting for organisms with higher MIC's. All patients in the study had a baseline urine specimen cultured for uropathogens. Those patients with $\geq 10^5$ CFU/mL of a study uropathogen in the baseline urine culture, who are patients selected to be in the micro-MITT population, had susceptibility testing done on all isolates in that specimen cultured at $\geq 10^2$ CFU/mL, in addition to the pathogen recovered at $\geq 10^5$CFU/mL. At the subsequent TOC visit, all isolates for those micro-MITT patients recovered at $\geq 10^2$ CFU/mL were again tested for *in vitro* susceptibility. Note that if an isolate was identified at TOC that was not found at $\geq 10^5$ CFU/mL at baseline, that isolate was not considered in the overall assessment of microbiologic response. In this analysis that compares the distribution of *in vitro* susceptibility to the study drug before and after therapy, those isolates are analyzed in addition to pathogens considered to be the baseline pathogen.

For patients treated with sulopenem, the total number of uropathogens is lower by ~65% as would be expected post therapy. The distribution of MIC's to sulopenem after treatment with sulopenem is very similar to the pre-treatment distribution. The $MIC_{50/90}$ pre-treatment was 0.03/0.06 µg/mL and post-treatment it was 0.03/0.12 µg/mL. No organisms that would be considered carbapenem-resistant were identified.

For patients treated with amoxicillin/clavulanate, the number of cultured uropathogens was reduced by ~57%. However, for these patients there is an increase in the proportion with amoxicillin/clavulanate resistant uropathogens post treatment relative to baseline. The $MIC_{50/90}$ pre-treatment was 2/8 µg/mL and post-treatment it was 4/≥32 µg/mL. Examination of the amoxicillin/clavulanate treated patients by subgroup in the non-susceptible (micro-MITTR) and susceptible (micro-MITTS) populations was performed.

In the micro-MITTR population, patients with an amoxicillin/clavulanate non-susceptible organism at baseline, the majority of TOC isolates had intermediate susceptibility to amoxicillin/clavulanate at baseline, while at TOC, the majority of them were found to be resistant to amoxicillin/clavulanate.

In the patients in the micro-MITTS population with an amoxicillin/clavulanate susceptible isolate at baseline, a ~12% increase in the proportion of isolates that are amoxicillin/clavulanate resistant is evident. Treatment with amoxicillin/clavulanate in this population significantly reduced the proportion of patients with a highly-susceptible uropathogen but, at the same time, increased the likelihood that these patients will have an amoxicillin/clavulanate resistant pathogen in their colonizing flora post-treatment and are at risk for a subsequent uUTI caused by an organism resistant to amoxicillin/clavulanate, as has been observed previously [Martinez-Casanova 2021].

1.5.3.3 Supportive Data from Study 302

The findings in Study 302, which enrolled patients with complicated UTI, were similar to those described above for the microMITTS population in Study 301. Patients randomized to the sulopenem arm received IV sulopenem followed by oral sulopenem. Patients randomized to the ertapenem arm received IV ertapenem; if their baseline pathogen was susceptible to ciprofloxacin, they stepped down to oral ciprofloxacin. If, however, their baseline pathogen was resistant to ciprofloxacin, they could either remain on IV ertapenem or step down to PO amoxicillin/ clavulanate.

Table 29 presents the overall response rate, along with the rate of asymptomatic bacteriuria, in patients with ciprofloxacin-susceptible isolates compared to all other patients.

Table 29: Study 302 Overall Response

All Patients	**Sulopenem n/N (%)**	**Ertapenem n/N (%)**	**Difference % (95% CI)**
Overall Response (TOC)	301/444 (67.8)	325/440 (73.9)	-6.1 (-12.0, -0.1)
Patients with ciprofloxacin-susceptible isolates treated with ciprofloxacin as step down	IV → PO Sulopenem	IV Ertapenem → PO Ciprofloxacin	
Overall Response (TOC)	168/248 (67.7)	186/215 (86.5)	-18.8 (-26.1, -11.0)
Reason for Failure: Asymptomatic bacteriuria	54 (21.8)	10 (4.7)	
All other patients	Sulopenem: IV +/-oral	Ertapenem: IV +/- Amoxicillin-clavulanate	
Overall Response (TOC)	133/196 (67.9)	139/225 (61.8)	6.1 (-3.1, 15.1)
Reason for Failure: Asymptomatic bacteriuria	39 (19.9)	49 (21.8)	

Patients with isolates susceptible to ciprofloxacin at baseline who were treated with sulopenem had a higher rate of asymptomatic bacteriuria and a lower overall response compared with the ertapenem-treated patients who stepped down to oral ciprofloxacin, similar to what was observed in Study 301. Interestingly, in the remaining patients treated with a β-lactam, the overall response rates in the two treatment groups were similar and the rate of asymptomatic bacteriuria was exactly the same, whether they received sulopenem, ertapenem or amoxicillin-clavulanate.

1.5.4 Overview of Safety Experience with Sulopenem

1.5.4.1 Safety in the Pooled Phase 3 Studies

1.5.4.1.1 Overview

The Phase 3 integrated analysis set includes 2970 sulopenem-treated subjects from Studies 310, 301, 302, and 303. The Phase 3 uUTI integrated analysis set includes 1940 oral sulopenem-treated subjects from Studies 310 and 301.

In the Phase 3 integrated analysis set, TEAEs (20.4% vs. 14.9%) were more common among sulopenem-treated subjects than comparator-treated subjects, while the premature discontinuation rates due to TEAEs were comparable in the two groups.

1.5.4.2 Safety in the Pooled Phase 3 uUTI Studies

1.5.4.2.1 Overview

An overview of safety in the Phase 3 uUTI integrated analysis set is presented in Table 30; TEAEs (21.4% vs. 13.0%) were more common among oral sulopenem-treated subjects than comparator-

treated subjects, while the premature discontinuation rates due to TEAEs were comparable in the two groups.

In the integrated Phase 3 uUTI set, there was one death among those receiving sulopenem and none among those receiving comparator. The one death was a patient with poorly differentiated adenocarcinoma of the lung that occurred more than 5 months after study completion and was not considered related to study drug.

Table 30 All Causality Adverse Events – Phase 3 uUTI Studies Safety Population

Preferred Term	Sulopenem (N=1940) n (%)	Comparator (N=1934) n (%)
Number of patients who experienced at least one:		
AE	419 (21.6)	252 (13.0)
TEAE	416 (21.4)	251 (13.0)
Drug-related TEAE	297 (15.3)	136 (7.0)
TEAE leading to premature discontinuation of study drug	21 (1.1)	12 (0.6)
TEAE leading to premature discontinuation from study	7 (0.4)	4 (0.2)
SAE	6 (0.3)	7 (0.4)
Treatment emergent SAE	6 (0.3)	7 (0.4)
Drug-related SAE	1 (0.1)	0
SAE leading to death	1 (0.1)	0
SAE leading to premature discontinuation of study drug	1 (0.1)	2 (0.1)

Post hoc Table 4.3.3.1a

1.5.4.2.2 Common Treatment Emergent Adverse Events

TEAEs appearing in ≥1% of patients in either treatment group are presented in Table 31. The incidence of nausea, headache and vomiting was comparable in the two groups. Diarrhea, loose stool and vulvovaginal mycotic infection were reported more frequently by patients in the sulopenem arm.

Table 31: Treatment-Emergent Adverse Events Occurring in ≥1% of Patients in Either Treatment Group – Phase 3 uUTI Studies Safety Population

Preferred Term	Sulopenem N=1940 n (%)	Comparator N=1934 n (%)
Diarrhea	172 (8.9)	59 (3.1)
Nausea	80 (4.1)	62 (3.2)
Headache	42 (2.2)	35 (1.8)
Vomiting	29 (1.5)	15 (0.8)
Loose stools	26 (1.3)	8 (0.4)
Vulvovaginal mycotic infection	20 (1.0)	6 (0.3)

Source: post hoc Table 4.3.18.1a
Notes: N = Number of patients in the Safety population. The percentages are calculated as 100 * (n/N). Version 26.1 of MedDRA was used to code adverse events.

1.5.4.2.3 Hepatic Adverse Events and Liver Function Test Abnormalities

An overview of the transaminase and bilirubin elevations seen in the Phase 3 uUTI studies safety population is presented in Table 32.

Table 32: Incidence of Elevated Transaminases and Bilirubin – Phase 3 uUTI Studies Safety Population

Parameter	Sulopenem n/N (%)	Comparator n/N (%)
Patients with an elevated ALT level		
> 3x ULN	7/1875 (0.4)	5/1862 (0.3)
> 5x ULN	1/1875 (<0.1)	3/1862 (0.2)
> 10x ULN	0/1875 (0.0)	0/1862 (0.0)
Patients with an elevated AST level		
> 3x ULN	4/1873 (0.2)	4/1861 (0.2)
> 5x ULN	2/1873 (0.1)	1/1861 (<0.1)
> 10x ULN	0/1873 (0.0)	0/1861 (0.0)
Patients with an elevated bilirubin level		
> 1.5x ULN	4/1876 (0.2)	10/1862 (0.5)
> 2x ULN	1/1876 (<0.1)	5/1862 (0.3)

Source: post hoc Table 4.3.32.1a
N = Number of patients in the Safety population with at least one post-baseline value of a given lab parameter; n = number of patients; ALT= Alanine Aminotransferase; AST= Aspartate Aminotransferase; ULN = Upper Limit of Normal. The percentages are calculated as 100 * (n/N). The worst post-baseline values are summarized in the table.
Comparator: IT001-301 - Ciprofloxacin, IT001-310 – Amoxicillin/clavulanate

The proportions of subjects who had any elevation in ALT or AST > ULN were comparable in the sulopenem and comparator groups, as were the proportions of subjects who had elevations in either ALT or AST > ULN up to 10x ULN.

1.6 RISK AND BENEFITS

1.6.1 Limitations of Approved Antibacterials

Increasing resistance has imposed limitations on the oral antibiotics available for the treatment of uUTI (Table 3). In addition to concerns about decreasing efficacy related to resistance, available agents are associated with some safety concerns.

- Treatment with a quinolone antibiotic, including ciprofloxacin, has been associated with an increased risk for 'disabling and potentially irreversible serious adverse reactions …including tendinitis and tendon rupture, peripheral neuropathy and central nervous system effects,'...and 'risk of aortic aneurysm and dissection.'
- Treatment with nitrofurantoin should be avoided in patients with creatinine clearance under 60 mL per minute or clinically significant elevated serum creatinine including the elderly with age-related decline in renal function, and adverse events have been reported such as acute, subacute, or chronic pulmonary reactions and peripheral neuropathy.
- Treatment with trimethoprim-sulfamethoxazole is associated with hyperkalemia and rash including SJS and TEN and other adverse hematologic sequelae and is contraindicated in patients with marked hepatic damage or with severe renal insufficiency when renal function status cannot be monitored.
- Treatment with pivmecillinam is associated with severe cutaneous adverse reactions including SJS, TEN, AGEP and DRESS, as well as clinically significant hypocarnitinemia. Alternative antibacterial therapy should be considered in patients with significant renal impairment or decreased muscle mass and those patients requiring long term antimicrobial treatment; concurrent treatment with valproic acid, valproate or other pivalate-generating drugs should be avoided; pivmecillinam is contraindicated in patients with porphyria.

1.6.2 Clinical Efficacy

Multiple lines of evidence support the activity of oral sulopenem in the treatment of uUTI:

Study 301:

- In the micro-MITTR population of Study 301, a clinically meaningful and highly statistically significant reduction in UTI symptom burden was documented among patients who received oral sulopenem.
- This superior outcome was seen in numerous subset analyses, including patients with infections due to multidrug resistant pathogens.
- In the assessment of overall response in the micro-MITT population, oral sulopenem was non-inferior to ciprofloxacin
- The superior outcome of treatment with oral sulopenem over an inactive control agent was supported by data from multiple sources, including:
    - The noninferiority in clinical response in comparison with ciprofloxacin in patients with quinolone susceptible pathogens

- The ciprofloxacin-resistant subset of patients in the complicated urinary tract infection study, 302

- The prespecified analysis in the combined population of patients with susceptible and non-susceptible pathogens, the microMITT, while not directed at achieving a primary regulatory claim as was originally proposed and has been done for ceftolozane/tazobactam, suggests that empiric therapy with oral sulopenem in a population where quinolone resistance is 20% or higher, will be as effective as ciprofloxacin. Given that the majority of communities in the United States now have quinolone resistance rates at this level or higher, the population level risk of harm is low.
- The risk to the patient, based on the outcome in the micro-MITTS population in Study 301, is not a higher risk of a subsequent uUTI associated with clinical symptoms but rather a risk of having asymptomatic bacteriuria which, based on IDSA Guideline recommendations, is not a condition, with certain exceptions, warranting treatment and likely reflects the patient's baseline state of bladder colonization.
- Clinical success rates at TOC for women in the MITT population, the population of patients most similar to patients encountered in clinical practice, were similar across treatment groups.

Study 310:

- In Study IT001-310, oral sulopenem was non-inferior to amoxicillin/clavulanate with respect to the trial's primary endpoint - overall response (combined clinical cure plus microbiologic eradication) at the test-of-cure (TOC) visit in the microbiological-modified-intent-to-treat susceptible (micro-MITTS) population. Oral sulopenem showed overall success in 61.7% of patients compared to 55.0% for amoxicillin/clavulanate, demonstrating statistically significant superiority of oral sulopenem versus amoxicillin/clavulanate (difference: 6.7; 95% CI = 0.3, 13.0). Once again, the point estimate for the overall success rate in the oral sulopenem arm in this study essentially matched that in the IT001-301 trial, thus virtually establishing a predictability of success in uUTI of approximately 64%, irrespective of the susceptibility of the baseline uropathogen.

- Clinical success at TOC was seen in 77.3% of patients on sulopenem and 76.7% of patients on amoxicillin/clavulanate (treatment difference -0.6%, 95% CI [-4.8, 6.1]); microbiologic success was seen in 75.2% of patients on sulopenem and 66.7% of patients on amoxicillin/clavulanate (treatment difference 8.5%, 95% CI [2.6, 14.3]).

- In the population of patients with a baseline pathogen $>10^5$ CFU/mL, regardless of susceptibility to amoxicillin/clavulanate (micro-MITT population), oral sulopenem demonstrated non-inferiority to amoxicillin/clavulanate for the primary endpoint of overall success at the Test of Cure visit as the lower limit of the 95% confidence interval on the difference in outcome rates was greater than -10% [Difference: 5.4%; 95% CI: (-0.8, 11.5); p= 0.044]. Non-inferiority was also demonstrated for clinical success at the Test of Cure visit, for microbiologic success at the Test of Cure visit, and for overall success at the End of Treatment and Final visits.

- Clinical success rates at TOC for women in the MITT population, the population of patients most similar to patients encountered in clinical practice, were similar across treatment groups.

1.6.3 Clinical Safety

Phase 3 uUTI Studies Combined:

While the use of any antibiotic is associated with risk, compared to other options available for treatment of uUTI, treatment with oral sulopenem was well tolerated.

- The only adverse event noted at a rate greater than the comparator was mild diarrhea in 8.9% overall. Diarrhea is seen with a number of oral antibiotics, most notably with amoxicillin-clavulanate in 15% of patients treated [Augmentin USPI].
- Though diarrhea was observed in patients treated with sulopenem, no patients were found to have *C. difficile*. While this does not preclude *C. difficile* being identified after broader community use, the fact that no cases were observed in the clinical program is reassuring.
- Laboratory assessments on therapy were similar in the sulopenem and comparator arms, consistent with expectations based on the lack of significant systemic toxicity in animal studies.
- No adjustment in dosing for oral sulopenem is required in patients with renal insufficiency.
- Oral sulopenem is not associated with clinically relevant drug-drug interactions, including valproic acid.
- There were no safety signals of special concern in the elderly subpopulation of patients. No notable differences in safety were observed between the elderly and overall population, an important attribute given that almost 30% of the patients in the uUTI studies were over the age of 60 and, because of age-related reductions in creatinine clearance, are not candidates for treatment with nitrofurantoin. In Study 310, compared to the entire population, the patients in the oldest subgroups had similar proportions of patients with TEAEs and drug-related TEAEs, but discontinued study therapy due to TEAEs more frequently, and had proportionally more SAEs, though none were considered treatment related. Compared to the overall population, patients in the >85 age group had more TEAEs judged to be severe in intensity, though the number of patients in this group is small, making meaningful comparisons difficult. Diarrhea, the most common adverse event overall, was less frequent in the oldest subgroups, likely reflecting the fact that most of the diarrhea occurred in studies 301 and 310, which had younger patient populations.
- The incidence of rash in the clinical program was relatively low.
- Coadministration of probenecid did not appear to introduce any adverse events not potentially attributable to sulopenem etzadroxil administered alone.
    - After over 50 years of experience, the safety profile of probenecid has been well established. Clinically significant drug interactions due to changes in plasma levels of other drugs based on the competitive effects of probenecid at the OAT receptors have not been observed to date.
- In both Study 301 and Study 310, the distribution of MIC's to sulopenem after 5 days of treatment with sulopenem is very similar to the pre-treatment distribution. The $MIC_{50/90}$ pre-treatment was 0.03/0.06 µg/mL and post-treatment it was 0.03/0.12 µg/mL. No organisms that would be considered carbapenem-resistant were identified.

1.7 CONCLUSIONS

Oral sulopenem was effective and well tolerated in the treatment of women with uUTI. In both Study 310 and Study 301, in the MITT population, the population most akin to uUTI patients encountered in clinical practice, clinical response was similar across the treatment groups. In both Study 310 and Study 301, in the micro-MITT population, the population with symptomatic women with culture-confirmed uUTI (≥100,000 CFU/mL of a uropathogen), oral sulopenem was non-inferior to the comparators. The only adverse event seen more frequently on oral sulopenem than

the comparator was mild diarrhea, that was self-limited and not associated with discontinuation of treatment.

A safe and effective oral antibiotic such as oral sulopenem would provide an important oral treatment option for the treatment of uUTI in women. Treatment of uUTIs with oral sulopenem offers women a significant clinical benefit with easily identifiable, limited and manageable risks.

2 INTRODUCTION

2.1 UNCOMPLICATED URINARY TRACT INFECTIONS: MEDICAL NEED

Among the most common infections caused by multidrug resistant Enterobacterales are those in the urinary tract. Uncomplicated urinary tract infections treated in the outpatient setting account for as many as 40 million prescriptions in the United States every year [Eversana Pharmacy and Longitudinal Claims, data on file]. Uncomplicated urinary tract infections begin with colonization of the vaginal mucosa with fecal flora which in turn, via the urethra, establish infection within the bladder [Fihn 2003, Thomas-White 2018]. Pathogens responsible for infection include *Escherichia coli, Klebsiella pneumoniae* and *Proteus mirabilis* as well as *Staphylococcus saprophyticus*. Recurrence is very common, with 25% of women experiencing recurrence within 6 months of the index episode [Hooton 2012]. Typical symptoms of infection include burning on urination, increased frequency and urgency as well as lower abdominal pain.

Historically, a variety of antibiotics were used to treat uUTI including β-lactams, quinolones, trimethoprim-sulfamethoxazole, and nitrofurantoin. Resistance rates for these agents, as described in Iterum's uUTI clinical trials (Table 1) are noteworthy, and surveillance data collected by Iterum as part of this development program indicate that resistance to all of these classes of antibiotics are now at or exceed the 20% threshold at which the Infectious Disease Society of America (IDSA) recommends that, rather than empiric treatment, a urine culture be performed to guide therapy. The IDSA uUTI treatment guidelines were last updated in 2010 (published in 2011) at which time the authors aimed to balance issues of *in vitro* resistance and collateral damage (a term describing ecological adverse effects of antimicrobial therapy, such as the selection of drug-resistant organisms and colonization or infection with multidrug-resistant organisms) when making their recommendations for optimal and alternative treatment options [Gupta 2011]. At that time, first line treatment options for uUTI included nitrofurantoin, trimethoprim-sulfamethoxazole, fosfomycin and pivmecillinam. Pivmecillinam is known to be associated with inferior efficacy [IDSA uUTI guidelines 2011] and is associated with adverse side effects (Table 3). Nitrofurantoin and fosfomycin have rising rates of resistance and are associated with inferior efficacy [Munoz-Davila 2014, Schito 2009, Wagenlehner 2024], while resistance to trimethoprim-sulfamethoxazole is uniformly above 20% and increasing prevalence of resistance to quinolones and their propensity to cause collateral damage resulted in the IDSA relegating this class of antibiotic to second line therapy for uUTI.

The importance of co-resistance to multiple oral agents can also be appreciated in this program. Surveillance data collected by Iterum as part of this development program [Aronin 2022, Dunne 2022] indicate 5.5-6.4% of ambulatory Enterobacterales isolates are non-susceptible to ≥3 classes of antibiotics. For ambulatory patients who received a prescription for an oral antibiotic temporally related to the urine culture collection date, 3.6% and 0.9% of isolates were non-susceptible to ≥3 classes of antibiotics and 4 classes of antibiotics, respectively.

In Study IT001-301 and IT001-310, of the 2061 symptomatic adult women with a positive baseline urine culture for $\geq 10^5$ CFU/mL of a uropathogen (micro-MITT population), nearly 10% of patients had an infecting organism non-susceptible to β-lactams, quinolones and trimethoprim-sulfamethoxazole, and over 3% had an infecting organism non-susceptible to all four of the commonly available classes of oral antibiotics for uUTI (β-lactams, quinolones, trimethoprim-sulfamethoxazole and nitrofurantoin) (Table 2).

A substantial number of women will become infected with an organism for which oral treatment options are severely limited and for which the wrong choice of empiric therapy carries a number of risks: increased morbidity directly related to the infection, additional adverse events related to a second antibiotic prescription, and the selection of more resistant pathogens in their colonizing flora.

Currently available treatment options for uUTIs, when the pathogens demonstrate *in vitro* susceptibility, have limitations, as shown in Table 4. There is a clear medical need for new, safe and well tolerated orally bioavailable antibacterial agents with *in vitro* activity against multidrug resistant pathogens. An orally bioavailable prodrug of sulopenem, sulopenem etzadroxil, was discovered and developed in order to address this unmet medical need.

2.2 SULOPENEM: DEVELOPMENT AND REGULATORY HISTORY

2.2.1 Sponsorship History of Sulopenem

The development of sulopenem dates to the mid-1980s. Pfizer, Inc. filed INDs for both a parenteral form and an oral pro-drug, sulopenem etzadroxil. Iterum Therapeutics acquired the rights to sulopenem from Pfizer in 2015.

2.2.2 U.S. Regulatory History

Pfizer filed INDs for IV sulopenem in Feb 1986 (#27,903, for CP-65,207) and May 2006 (#73,463, for CP-70,429). Its initial IND (#77,881) for the prodrug, sulopenem etzadroxil (PF-03709270) was filed in August 2007. The IND was opened with a Phase 1 study that evaluated the safety, tolerability and pharmacokinetics of single ascending doses of sulopenem etzadroxil. Subsequent filings to the IND included protocols investigating the effects of different variables on the PK of sulopenem etzadroxil, among them different doses of probenecid, food intake, gastric pH modifiers and varying degrees of renal impairment.

Pfizer filed its first Phase 2 protocol, to be conducted in patients with community acquired pneumonia requiring hospitalization, to the IND in Aug 2008.

Pfizer notified the FDA of its intention to withdraw both INDs covering the development of sulopenem on 18 March 2011 due to business reasons.

Pfizer granted Iterum Therapeutics International Ltd (Iterum) an exclusive license to sulopenem etzadroxil as well as consent to right of reference to the data in IND 77,881 which had been previously withdrawn without prejudice on 18 March 2011. On 1 March 2016, Iterum submitted IND #129,849 in order to continue clinical development of sulopenem. Sulopenem etzadroxil was granted QIDP status by the Division on 29 July 2016, while oral sulopenem bilayer tablets were granted QIDP status on 27 October 2017.

Iterum expressed its intent to conduct studies in uUTI (Study 301), cUTI (Study 302) and cIAI (Study 303). Major meetings were held with the FDA in February, July and August of 2017, at

which Phase 3 study design, statistical analyses and hypothesis testing were extensively discussed. Special Protocol Assessment (SPA) status was requested and granted for all three studies. On 15 March 2019, a Fast Track Status designation was granted to sulopenem etzadroxil and probenecid tablets for the treatment of uUTI. The basis of the designation was the potential for treatment of a serious infection caused by quinolone non-susceptible organisms and the ability to address an unmet medical need via provision of alternative therapy against these pathogens, for which there are limited treatment options.

A pre-NDA meeting was held on 28 September 2020. While the outcomes of the cUTI and cIAI studies, 302 and 303, respectively, were not considered supportive of claims for those indications, the superiority of oral sulopenem over ciprofloxacin in the subpopulation of women in Study 301 with uUTI due to quinolone non-susceptible pathogens was. Safety data from all three studies were considered satisfactory support.

The NDA for oral sulopenem tablets for the treatment of uUTI was submitted to the Agency on 25 November 2020. On 23 July 2021, Iterum received a Complete Response Letter (CRL) from the Division stating that the Application could not be approved in its present form. The need for a second adequate and well-controlled uUTI trial was recommended.

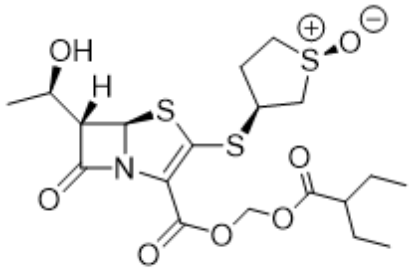
Following the issue of the CRL, major meetings were held with the FDA in September 2021, December 2021, March 2022 and May 2022, at which Phase 3 uUTI study design, statistical analyses and hypothesis testing were extensively discussed. Special Protocol Assessment (SPA) status was requested and granted for the additional study in uUTI (IT001-310, or Study 310). Study 310 was completed and the NDA for oral sulopenem tablets for the treatment of uUTI was resubmitted to the Agency on 25 April 2024.

3 CHEMISTRY AND PHARMACEUTICAL INFORMATION

3.1 DRUG SUBSTANCES

Sulopenem, like conventional penicillins and cephalosporins, is a β-lactam antibiotic, but it is classified as a penem antibiotic because a double bond is inserted into the 5-member ring of the penicillin structure (Figure 4).

Figure 4: Sulopenem Etzadroxil Chemical Structure and Formula

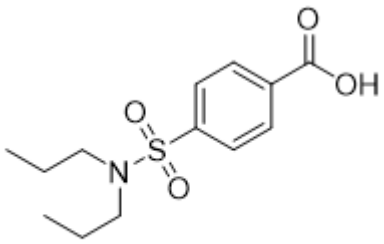


Chemical Formula: $C_{19}H_{27}NO_7S_3$

Sulopenem etzadroxil has 5 asymmetric centers with absolute configuration as indicated in the structure above (chiral centers left to right, R, S, R, S, R configuration). There are no cis/trans isomers for sulopenem etzadroxil. The etzadroxil prodrug tail is highlighted in the red box.

The chemical name for probenecid is 4-[(dipropylamino) sulfonyl] benzoic acid. See Figure 5 for probenecid chemical structure and chemical formula. The molecular weight of probenecid is 285.36 g/mol

Figure 5: Probenecid Chemical Structure and Formula



Chemical Formula: $C_{13}H_{19}NO_4S$

3.2 DRUG PRODUCT

Sulopenem etzadroxil is co-formulated with probenecid as an immediate release, fixed dose combination, film-coated tablet for oral use. The drug product is co-packaged with a 1g desiccant bag in HDPE bottles with induction seal and child-proof screw cap. The product is also packaged in an ALU-ALU blister strip. Each tablet contains 500 mg of sulopenem etzadroxil and 500 mg of probenecid in a bilayer tablet presentation with "SULO" debossed on one side.

Dosing

The highest anticipated daily dose of sulopenem etzadroxil in the oral sulopenem bilayer tablet is 1000 mg (1 tablet PO twice daily).

4 NONCLINICAL INFORMATION

4.1 PHARMACOLOGY

4.1.1 Primary Pharmacodynamics

4.1.1.1 Mechanism of Action

Sulopenem etzadroxil is rapidly hydrolyzed to the active moiety sulopenem. Sulopenem has *in vitro* activity against gram-positive and gram-negative aerobic and anaerobic bacteria. The bactericidal activity of sulopenem results from the inhibition of cell wall synthesis and is mediated through sulopenem binding to penicillin binding proteins (PBPs). In *Escherichia coli*, it has strong affinity toward PBP2 > PBP1A > PBP1B > PBP4 > PBP3 >PBP5/6.

4.1.1.2 *In Vitro Studies*

4.1.1.2.1 Antibacterial Spectrum of Activity

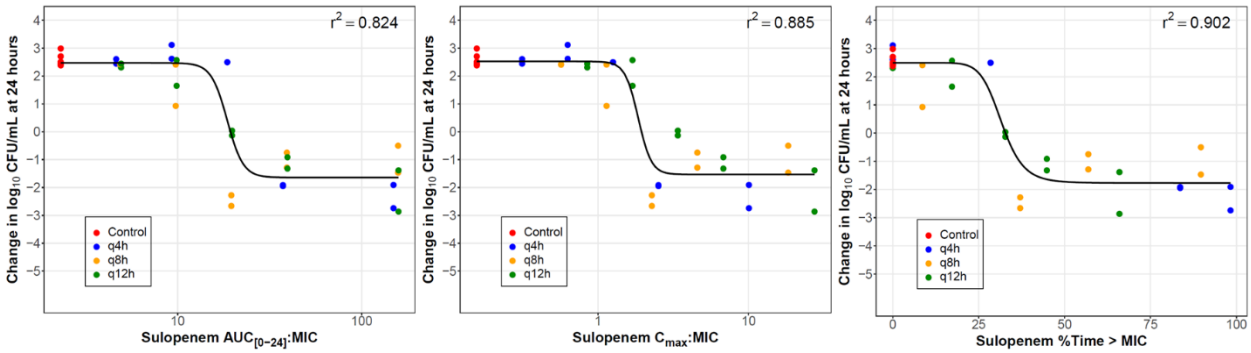
Sulopenem has broad spectrum activity against gram-positive and gram-negative aerobes and anaerobes consistent with that of the other currently-marketed carbapenems.

Activity against key uUTI pathogens is presented in Table 7, above. The potency of sulopenem against Enterobacterales based on $MIC_{50/90}$ values and MIC distributions is similar to that of meropenem and ertapenem.

4.1.1.2.2 1-compartment *In Vitro* System

The 24-hour dose-fractionation studies completed using the one-compartment *in vitro* infection model successfully evaluated the PK/PD of sulopenem. The relationships between sulopenem exposure measures and change in bacterial burden from baseline, identified %T>MIC as the exposure measure that best describes the activity of sulopenem based upon the high r^2 value of 0.90 and the dispersion of data across the fitted lines (Figure 6).

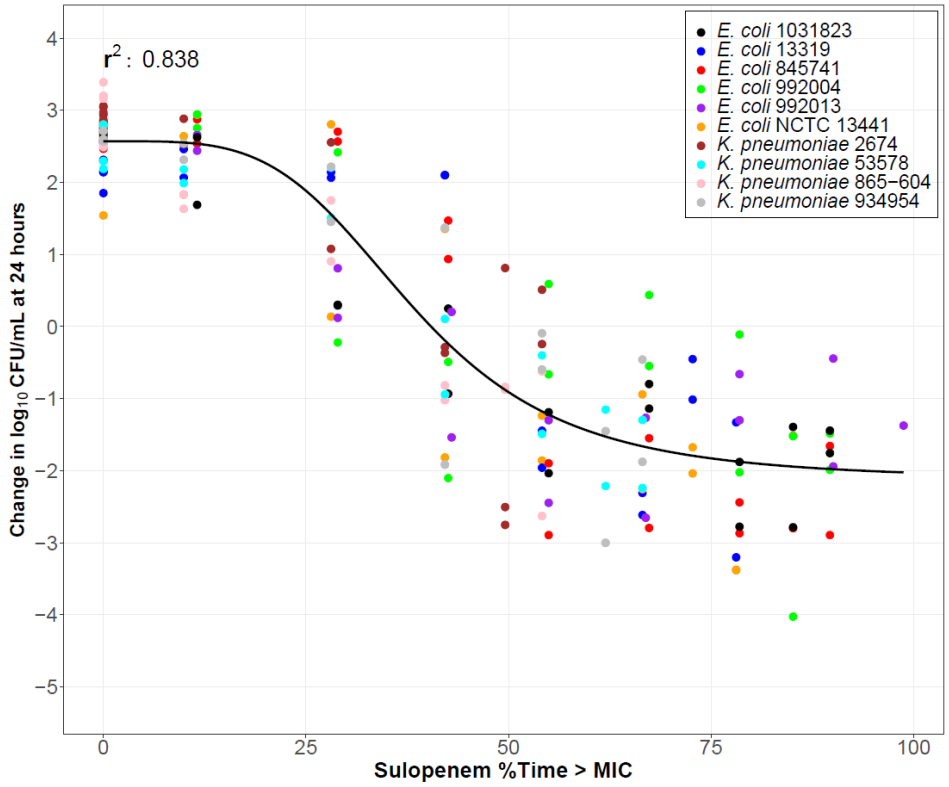
Figure 6 Relationships between free-drug sulopenem AUC_{0-24}:MIC ratio, free-drug C_{max}:MIC ratio, free-drug %T>MIC and change in bacterial burden from baseline in log_{10} CFU/mL after 24 hours of sulopenem therapy against *E. coli* NCTC 13441 in the one-compartment dose-fractionation studies.



Source: [Figure 5 ICPD report 00671]

The one-compartment *in vitro* model was also used to further explore the effect of sulopenem on a number of clinically relevant bacterial strains. The concentrations of sulopenem used were intended to mimic unbound plasma concentrations in the range observed after administration of clinical doses of sulopenem etzadroxil with probenecid. The resulting changes in log_{10} CFU at 24 hours are illustrated vs fT>MIC in Figure 7.

Figure 7 Relationships between sulopenem %T>MIC and change in log_{10} CFU/mL from baseline at 24 hours for *E. coli* and *K. pneumoniae* isolates evaluated in the sulopenem one-compartment *in vitro* model.



Source: Figure 16 ICPD Report 00671

The median %T>MIC values associated with achieving net bacterial stasis, 1- and 2-log_{10} reductions in bacterial burden across the Enterobacterales panel were determined to be 40.9, 50.2 and 62.6%, respectively in this one-compartment *in vitro* system. The time above MIC identified to be required for stasis or 1-log kill are higher than previously identified in the *in vivo* murine thigh model (both immunosuppressed and immunocompetent animals).

The 1-compartment *in vitro* study system is considered to represent a possible worst-case scenario for an uUTI indication, allowing bacteria to proliferate in growth optimal medium rather than artificial urine, and without mechanical wash-out of bacteria (bladder emptying) which would reduce the drug exposure needed to obtain stasis, one or two log kill.

The unbound plasma levels required for efficacy identified in the murine thigh model in mice with a 6h dosing interval can be considered more closely related to the *in vivo* clinical situation and applicable to discussions on MIC breakpoints in plasma, while the newly obtained *in vitro* data targets can be used as more conservative targets for MIC breakpoints in urine.

For plasma targets in uUTI, stasis is considered sufficient. The neutropenic murine thigh model estimates for stasis and one-log kill were very close due to the steepness of the curve, 17% fT>MIC rather than 16.4% was illustrated in the TA simulations. For

completeness, the *in vitro* one-compartment model targets are also visualized in the plasma target attainment simulation plots.

For PK/PD determination, the *in vitro* activity of sulopenem, the pharmacokinetics and the protein binding of the drug in mouse plasma were considered and fitted to the sigmoidal E_{max} model. As shown in Figures 8, 9 and 10, the parameter that correlates best with efficacy for sulopenem is T>MIC (r^2 of 0.84), consistent with PK/PD evaluations for β-lactam drugs (Bhavnani 2005). The PK/PD parameters AUC/MIC and C_{max}/MIC displayed weaker correlations with efficacy (r^2 values of 0.45 for both).

Figure 8 Sulopenem PK/PD Relationship of Free Plasma Cmax/MIC and Efficacy Fitted to an Emax Model

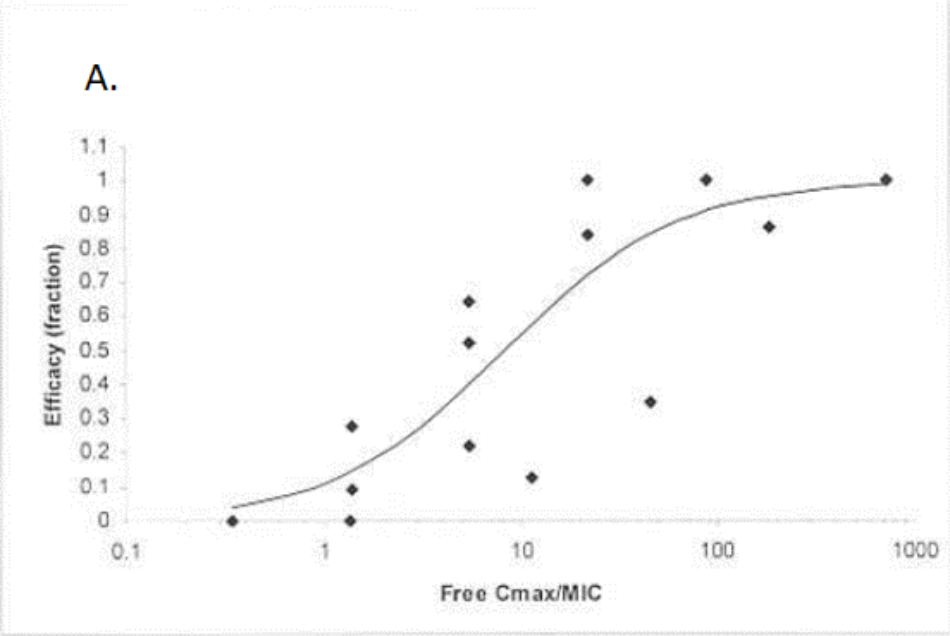


Figure 9 Sulopenem PK/PD Relationship of 24 hr AUC/MIC and Efficacy Fitted to an E_{max} Model

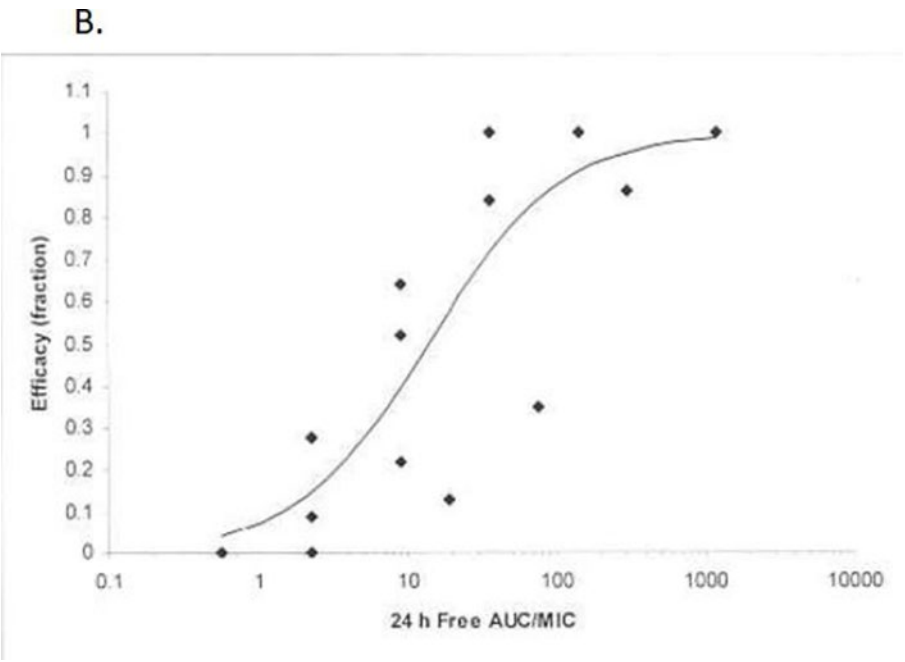
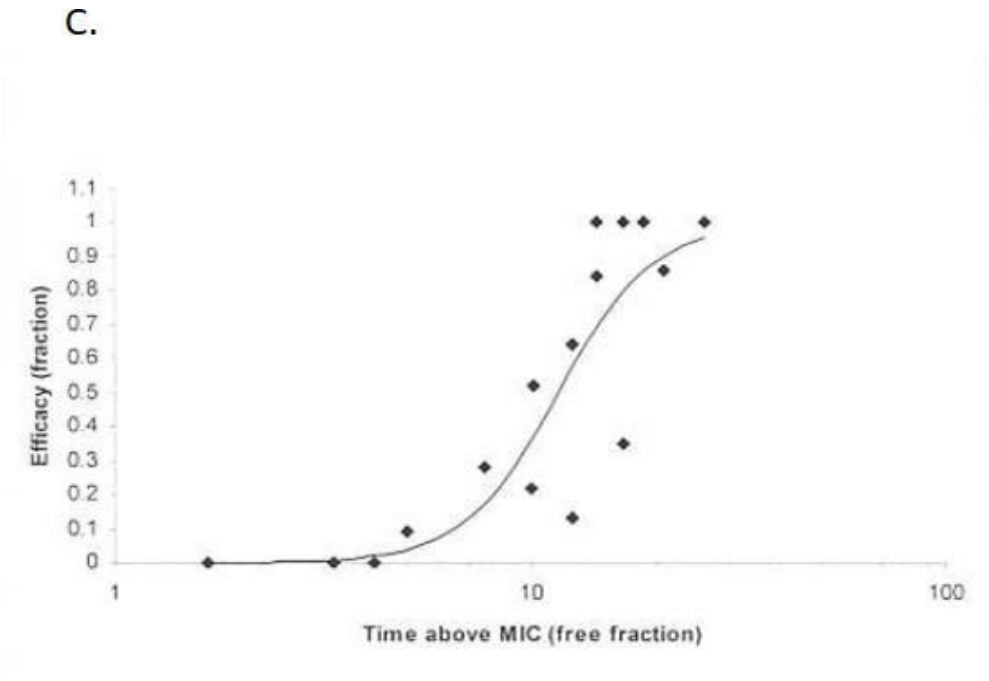


Figure 10 Sulopenem PK/PD Relationship of T>MIC and Efficacy Fitted to an E_{max} Model



Source: Study Report 810-00081, Figures 1, 2 and 3

From these data the ED_{90} can be estimated; the results show that to achieve a maximal effect (ED_{90}), the free plasma drug concentrations would need to be above the MIC for 21% of the dosing interval. These results are in agreement with those in the literature that indicate a high probability of clinical success when a target of 20 to 40% of T>MIC is reached for carbapenems (Bhavnani 2005; Cuba 2014; Drusano 2004).

Target attainment simulations were also performed using the PopPK model developed for the oral bilayer tablet at doses of 500 mg sulopenem etzadroxil BID with probenecid which was also studied in the clinical Phase 3 program. The target attainmentsimulations were performed using both fixed MIC values (0.06 and 0.5 mg/L) as well as empirical distributions of MIC values for cUTI, uUTI and cIAI, based on *in vitro* surveillance studies.

4.1.1.3 *In Vivo* Efficacy in Animal Models of Infection

Sulopenem and its oral prodrug sulopenem etzadroxil were evaluated for *in vivo* efficacy in three models of animal infection: the mouse systemic infection against *S. pneumoniae* and *K. pneumoniae*; the mouse thigh abscess infection against *K. pneumoniae*; and the Mongolian gerbil otitis media model against *H. influenzae*. In all models, the bacterial strains used to establish the infection were chosen based on their antibiotic resistance phenotypes, and appropriate positive and negative comparator antibiotics were used. *S. pneumoniae* 02J1095 is a macrolide-resistant (ermB), penicillin-tolerant strain. *K. pneumoniae* 53A1109 is an extended-spectrum β-lactamase (ESBL)-positive strain that produces OXA-9, multiple SHVs, TEM-1, and a plasmid-encoded AmpC β-lactamase that has

been shown to inactivate extended-spectrum cephalosporins such as ceftazidime; this strain also contains several mutations in the gene encoding DNA gyrase such that it has an elevated MIC to ciprofloxacin. The *H. influenzae* strain Rd/AH5-3 was derived from the laboratory strain Rd that contains a directed point mutation in PBP3 that renders it β-lactamase-negative and ampicillin-resistant (BLNAR).

In both protective systemic infection models and in models of tissue burden reduction, sulopenem demonstrated efficacy against organisms with demonstrated tolerance/resistance to ampicillin or that produced ESBLs. Duplicate studies were performed on different days and sulopenem produced consistent results against these challenging organisms. Oral sulopenem etzadroxil demonstrated equivalent efficacy to subcutaneously dosed sulopenem in these studies, indicative of its rapid conversion, an important feature in the systemic infection models.

4.1.1.4 Murine Neutropenic Thigh Infection Model

The pharmacokinetic/pharmacodynamic (PK/PD) characteristics of sulopenem were evaluated in a preclinical murine thigh infection model using representative isolates for gram-positive and gram-negative pathogens. These included 02J1095 and 02J1376 strains for *S. pneumoniae* and 53A1108 and 53A1116 for *K. pneumoniae*. PK were evaluated in parallel for each dose regimen and combined with efficacy results to determine the primary PD parameter for sulopenem. The greatest correlation with efficacy was obtained with T >MIC ($r^2 = 0.84$), compared to AUC/MIC ($r^2 = 0.45$) and C_{max}/MIC ($r^2 = 0.45$). In addition, at the ED_{90} for the pooled MIC data, T >MIC was determined to be 21% (95% CI: 13-32%). The T>MIC target of sulopenem for stasis, 1-log, and 2-log killing for each dosing interval did not vary significantly (Table 33).

Table 33: Sulopenem free-drug plasma %T>MIC targets for Enterobacterales based on data from the murine-thigh infection model

Endpoint	Free drug %T > MIC
Net bacterial stasis	16.4
1 $\log_{10}$ CFU from baseline	17.0
2 $\log_{10}$ CFU from baseline	20.1

4.1.1.5 Potential for Antagonism or Synergism

A checkerboard assay of nine other antimicrobial agents representing different drug classes against four *E. coli* and two *K. pneumoniae* isolates identified two instances of synergy, both with TMP-SMX, among the *E. coli* isolates and one instance of synergy, with gentamicin, against *K. pneumoniae*. No instances of antagonism were observed.

4.1.1.6 Studies of Selection for Resistance

The development of resistance to sulopenem was evaluated using two methods: by determining the spontaneous mutation frequency in *E. cloacae* isolates and during serial passage in clinical isolates of *E. coli* and *K. pneumoniae*. The spontaneous mutation study was conducted with the diastereomeric mixture CP-65,207, and against the *E. cloacae* strains, colonies were isolated at a frequency of 1×10^{-8} but these were observed to display a ≤2-fold MIC increase. In the serial passage study, in two of the three *E. coli* strains, MIC values to sulopenem were observed to increase 16-fold during 15 serial passages and were unchanged for the third strain; for one *K. pneumoniae* isolate, MIC values increased 8-fold during serial passage, and for the other, MIC

values increased from 0.5 to 256 µg/mL. The ertapenem control behaved similarly in all cases but the last, suggestive of a carbapenem class effect.

Sulopenem is affected by resistance mechanisms that have been well-characterized for other carbapenem-class agents, namely KPC, metallo-β-lactamases, OXAs, porin/efflux proteins, etc. The mechanism of resistance to sulopenem has been studied utilizing a pair of clinical isolates of *K. pneumoniae* differentially resistant to sulopenem and imipenem collected from the same patient in 1998. Studies showed that resistance to sulopenem and imipenem was not conferred by the plasmid carried by both isolates, but rather to outer membrane changes rendering one strain more susceptible to sulopenem than the other. Previous investigators have shown similar mechanisms for carbapenem resistance, through acquisition of a plasmid-encoded β-lactamase followed by porin changes to further improve susceptibility.

4.1.1.7 Potential for Cross-Resistance to other Antibacterials

Most isolates encountered during the surveillance studies were susceptible to carbapenems with some exceptions (e.g. MRSA, CRE, MDR and carbapenem-resistant *P. aeruginosa* and *A. baumannii*). Therefore, apart from these exceptions, cross-resistance for sulopenem with other classes is minimal.

Among gram-positive organisms, β-lactam resistance mediated by alteration to the PBP target confers cross-resistance to sulopenem and other carbapenems in *S. aureus*. For *S. pneumoniae*, despite elevated MIC values observed for sulopenem and comparators with penicillin-resistant and MDRSP isolates, potent sulopenem MIC values (≤ 2 µg/mL) are maintained for these subpopulations. There is no apparent cross-resistance with vancomycin for VISA or *E. faecalis*, nor is there cross-resistance with macrolides for β-hemolytic streptococci.

For Enterobacterales, where resistance is typically mediated by carbapenemases, cross-resistance between sulopenem and the comparator carbapenems is clear, as would be expected. Cross-resistance between sulopenem and other β-lactams is not observed for ESBL-mediated resistance, as sulopenem, like other carbapenems, maintains potent activity against ESBL-producing isolates of *E. coli* and *K. pneumoniae*, and derepressed AmpC isolates of *E. cloacae*. Cross-resistance with fluoroquinolones was not observed with *E. coli* and is not apparent for other classes as carbapenem susceptibility rates typically greatly exceed those observed with other agents from other antibiotic classes.

Finally, among lactose-nonfermenting gram-negative bacilli (e.g. *P. aeruginosa* and *A. baumannii*) where multi-drug resistance is more common, carbapenem resistance mediated by carbapenemases, porin loss, or efflux affects the activity of sulopenem in a similar fashion to that observed with comparator carbapenems. Regardless of pre-existing resistance to carbapenems, sulopenem has no appreciable activity against *P. aeruginosa*. For *A. baumannii*, cross-resistance for sulopenem and other carbapenems is evident with CRAB as expected.

4.1.1.8 *In Vitro* Data from Isolates in Phase 3 Clinical Trials

Microbiological data were obtained for isolates from 4 phase 3 double-blind, double-dummy, multicenter comparative studies of the efficacy of sulopenem in the treatment of uUTI (Study 301 and Study 310), cUTI (Study 302) and cIAI (Study 303). The bacterial pathogens isolated from clinical trial subjects were consistent with the epidemiology of the diseases under study, and the *in vitro* activity of sulopenem against the isolates was within expected MIC ranges, as observed in surveillance studies (Section 6.2).

4.1.1.9 Proposed Susceptibility Breakpoint

The proposed susceptibility interpretive criterion for sulopenem is ≤ 0.5 µg/mL for Enterobacterales, determined by broth microdilution according to CLSI [CLSI M23]. The primary considerations include wild-type MIC distribution, bactericidal activity of concentrations of sulopenem in human serum throughout the treatment period with the proposed dosage regimen, efficacy in clinical trials, and PK/PD modeling based on human clinical data and animal infection model studies.

4.1.2 Secondary Pharmacodynamic Studies

In a broad radioligand binding panel of 54 receptors, transporters, and ion channels, sulopenem etzadroxil had no affinity for any binding site, defined as IC_{50} ≥10 µM, with the exception of the COX-2 receptor for which the IC_{50} was 4.1 µM (~ 2 µg/mL).

4.1.2.1 Potential Effects on the Human Ether-a-Go-Go

Sulopenem was tested in more than one hERG assay. The study was initially done as a manual patch at body temperature in HEK293 cells which is considered the highest quality and most reproducible test system; a second test system of CHO cells with potentially different metabolic dipeptidyl peptidases was also used. HERG current was inhibited by 50% in HEK-293 cells and by 49.2% in CHO cells at 105 µg/mL which is 6.3-times the estimated Cmax of a 1200 mg IV dose in humans; no effect was observed on action potential duration in Purkinje fibers at 105 µg/mL.

Pharmacologically relevant inhibition of hERG potassium current (> 8%) was observed with sulopenem etzadroxil.

Sulopenem etzadroxil inhibited hERG between 10-20% inhibitions at approximately 5 to 10 µM. Based on typical kinetics, binding of drugs to hERG occurs at about 8-10 fold below the IC50 value, which in this case was 33.4 µM. Since oral administration of sulopenem etzadroxil is expected be associated with rapid cleavage to sulopenem, appreciable systemic plasma levels greater than 5 ng/mL (12.8 nM) of sulopenem etzadroxil are not anticipated, and any hERG binding unlikely to be of clinical concern.

4.1.2.2 Potential Effects on Coagulation

Coagulation parameters were evaluated in nonclinical studies including single-dose and repeat-dose studies in rat and monkey, using the clinical routes of administration for sulopenem and sulopenem etzadroxil. No evidence of a clinically relevant effect on platelets or coagulation parameters at projected human exposures was observed in toxicology studies (Section 4.3) or in clinical trials.

4.1.2.3 *In Vitro* Studies of Potential Effects on Other Physiologic Targets

The secondary pharmacodynamic effects of sulopenem were evaluated against a panel of receptors and ion channels. At a concentration of 100 µM, sulopenem demonstrated no affinity for any binding site. At the maximum anticipated daily clinical dose of sulopenem (1000 mg) with an associated maximum concentration of 16.6 ug/mL or 14.9 ug/mL free fraction, the estimated safety margin for off-target receptor binding is 2.3-fold.

Secondary pharmacodynamic effects of sulopenem etzadroxil were evaluated in a panel of receptors, ion channels, transporters and enzymes. At a concentration of 10 µM, sulopenem etzadroxil demonstrated no affinity for binding sites with the exception of the COX-2 enzyme

where the IC_{50} was 4.1 µM. At a concentration of 100 µM, sulopenem etzadroxil demonstrated no affinity for any binding site. At the maximum anticipated daily clinical dose of sulopenem etzadroxil (1000 mg administered at 500 mg twice daily) with an associated maximum concentration of 1.72 µg/mL or 1.38 µg/mL free fraction, the estimated safety margin for off target receptor binding is >30-fold. For Cox-2 binding, the safety margin is 1.3-fold. For the prodrug, sulopenem etzadroxil, systemic levels are undetectable in humans.

4.1.3 Safety Pharmacology Studies

Results of the *in vitro* safety pharmacology studies with sulopenem demonstrated an estimated IC_{50} of 300 µM on the hERG channel in either human embryonic kidney (HEK) or Chinese hamster ovary (CHO) cells. Results from the *in vitro* dog Purkinje fiber study showed that sulopenem had no effect on resting membrane potential, action potential amplitude or Vmax, (action potential amplitude), or duration at concentrations up to 300µM. Estimated safety margins were 6.3-fold over the maximum anticipated clinical dose based on total concentration or 7.0-fold based on free fraction of sulopenem. Sulopenem had no effect on QTc parameters when infused in anesthetized dogs at doses up to 100 mg/kg and concentrations of 258 µg/mL (15.5-fold safety margin). Sulopenem had no effect on heart rate, blood pressure or electrocardiogram (ECG) parameters including QTc interval, in conscious telemeterized monkeys up to 1000 mg/kg with associated observed maximum concentration (Cmax) levels of 2270 µg/mL sulopenem. At the maximum anticipated clinical daily dose of IV sulopenem (1000 mg), Cmax is 16.6 µg/mL. Based on exposure, the *in vivo* cardiovascular safety pharmacology studies with sulopenem in dog and monkey provide a 15.5- and 137-fold margin of safety, respectively.

There were no effects on central nervous, respiratory or gastrointestinal systems with intravenous sulopenem administration in animals. Renal effects associated with acute administration of sulopenem included increased potassium excretion at 100 mg/kg and increased potassium and chloride excretion at 300 mg/kg. Based on exposure, safety margins are estimated to be approximately 1.5-fold over exposures in humans (area under the curve [AUC]=41.9 µg*h/mL) at the maximum anticipated daily clinical dose (1000 mg).

Sulopenem etzadroxil had no effect on heart rate, blood pressure or components of the electrocardiogram, including QTc interval, in conscious telemeterized monkeys at 1000 mg/kg with mean Cmax values for sulopenem etzadroxil of 0.064 µg/mL (range <0.002-0.181 µg/mL). At the maximum anticipated clinical daily dose of sulopenem (1000 mg administered as 500 mg twice daily), Cmax is 1.72 µg/mL. Based on exposure, the *in vivo* cardiovascular safety pharmacology study with sulopenem etzadroxil in monkey provide a 4-fold margin of safety. There were no effects on the gastrointestinal and central nervous systems or respiratory parameters, with sulopenem etzadroxil administered orally at doses up to 300 mg/kg.

4.2 NONCLINICAL PHARMACOKINETICS

4.2.1 Absorption

Oral bioavailability of sulopenem etzadroxil estimated based on systemic exposure of sulopenem, was moderate in rats and monkeys, with values of 23.8% and 33.9%, respectively. Whole blood concentrations of the prodrug, sulopenem etzadroxil, were generally below the level of quantitation suggesting rapid hydrolysis or degradation of the prodrug *in vivo*. Therefore, it was not possible to fully characterize the pharmacokinetics of the prodrug. Clearance of sulopenem was moderate to high in rodents and low to moderate in higher species. Steady state volume of distribution of

sulopenem was greater than total body water in mice and rats, and less than total body water in dogs and monkeys.

4.2.2 Distribution

In preclinical pharmacokinetic studies, circulating levels of the prodrug, sulopenem etzadroxil, were generally below the limits of quantitation; therefore, distribution was not characterized. The active moiety, sulopenem, exhibits low plasma protein binding in rats, monkeys, and humans (fraction unbound 70.6% to 100%).

4.2.3 Metabolism

It is expected that the prodrug, sulopenem etzadroxil, is rapidly hydrolyzed to the active moiety sulopenem, formaldehyde, and 2-EBA either in the intestine or in the circulation. This is supported by the absence of significant concentrations of prodrug in whole blood of rats and monkeys following oral dosing of sulopenem etzadroxil. *In vivo* metabolism of the active moiety sulopenem was evaluated following intravenous dosing in cynomolgus monkeys.

4.2.4 Excretion

Excretion of sulopenem etzadroxil following oral dosing has not been investigated. However, following a single intravenous 200 mg/kg dose of 14C labeled sulopenem to cynomolgus monkeys, 72.9% and 73.5% of the dose was recovered in the urine of males and females, respectively. Unchanged drug accounted for 16.8% and 19.8% of the dose excreted in urine. In humans, 36% to 73% of an IV dose of sulopenem is excreted as unchanged drug in the urine suggesting renal clearance plays a major role in the elimination of the compound.

4.3 TOXICOLOGY

4.3.1 Toxicology Overview

The toxicology of sulopenem administered by intravenous (IV) injection, and sulopenem etzadroxil administered orally, were evaluated in nonclinical studies using the clinical routes of administration. The completed toxicology studies include single-dose and repeat-dose studies in rat and monkey, safety pharmacology studies, *in vitro* and *in vivo* genotoxicity studies, reproductive and developmental toxicity studies, juvenile toxicity studies in rat and *in vitro* phototoxicity evaluations. In addition, a 2-week rat toxicity study was conducted with sulopenem etzadroxil in combination with probenecid. Repeat dose toxicology studies were conducted with micronucleus evaluations in rat and cardiovascular evaluations in monkey. All toxicology studies were conducted in compliance with Good Laboratory Practices (GLPs).

In the repeat-dose toxicology studies, sulopenem and sulopenem etzadroxil were tolerated at high doses. The primary effects were due to the pharmacologic effects of the active moiety, sulopenem, and known effects of penem antibiotics. Target organs were typical for carbapenem antibiotics and were identified as the gastrointestinal tract (loose stool and increased cecum weight), renal (increased weight), hematologic, or cardiovascular.

After oral administration of sulopenem etzadroxil, exposures of the prodrug, sulopenem etzadroxil and the cleavage product, formaldehyde, were not detectable. Exposures of the active moiety, sulopenem, and the cleavage product for sulopenem etzadroxil, 2-ethylbutyric acid (2-EBA), were substantial across both species.

4.3.2 Systemic Effects

4.3.2.1 Target Organ Effects

Target organs identified in the toxicity studies included the hematopoietic, cardiovascular, kidney, and gastrointestinal systems. Target organs were typical for carbapenem antibiotics and were identified as the gastrointestinal tract (loose stool and increased cecum weight), renal (increased weight), hematologic, or cardiovascular. Sulopenem was weakly clastogenic *in vitro* but was negative *in vivo* without mutagenic effect.

The primary toxicity noted with sulopenem was related to the pharmacologic action of antibiotics. For example, increased kidney weight is generally considered a physiological reaction to administration of high doses of drugs with high levels of pharmacological activity, and it is not necessarily associated with cytological damage on a histopathological level. There were no *in vivo* genetic toxicology findings or indications of any mutagenic potential that would raise any concerns regarding the short-term use of this product in a broad patient population. Likewise, there were no preclinical safety alerts regarding reproductive toxicity that would be of concern with the intended short duration of use for this product.

4.3.2.2 Genotoxicity Studies

Sulopenem etzadroxil was assessed in the bacterial mutagenicity assay with and without exogenous metabolic activation using concentrations up to those limited by cytotoxicity or insolubility. Sulopenem etzadroxil was not genotoxic in this *in vitro* assay.

A screening *in vitro* micronucleus study and *in vitro* human lymphocyte study with sulopenem etzadroxil were positive for chromosomal aberrations; however, formaldehyde release during hydrolysis is likely to have contributed to the clastogenic response in these assays. An *in vivo* micronucleus study conducted using rat bone marrow was negative for chromosomal aberrations at doses up to 2000 mg/kg. A full battery of genetic toxicology studies has also been conducted with the active moiety, sulopenem. Sulopenem etzadroxil was negative in bacterial cell and mammalian cell mutagenicity assays. Weak clastogenic effects were observed *in vitro* at a single cytotoxic concentration of 4000 μg/mL, but no clastogenic effects were observed *in vivo* in the bone marrow of mice or rats.

Based on the overall test profile, there are no perceived genetic safety risks for sulopenem etzadroxil or sulopenem.

4.3.2.3 Reproductive Toxicology Studies

For sulopenem, reproductive and developmental toxicity studies with the active moiety sulopenem were uneventful, and there were no adverse effects on male or female fertility, pregnancy parameters, embryo-fetal development, or F1 generation development. The studies were all conducted using the IV route of administration. In the fertility study, there was no effect at 600 mg/kg in male and female rats. In the teratology studies in rats and rabbits, doses as high as 1000 and 90 mg/kg/day, respectively, of the active delivered during organogenesis had no effect on the developing fetus or offspring and was not teratogenic. In the pre- and post-natal development study, the highest dose tested (1000 mg/kg sulopenem) was the NOAEL .

Safety margins for fertility was 3.8-fold for rats, 1.9-fold for embryofetal development in rat and 4.3-fold for rabbits, and 7.4-fold for postnatal development in rats. Sulopenem has no reproductive

toxicity or developmental effects with acceptable safety margins for tolerability, embryo-fetal and post-natal development during pregnancy.

For sulopenem etzadroxil, reproductive and developmental toxicity studies were uneventful, and there were no adverse effects on male or female fertility, pregnancy parameters, embryo-fetal development, or F1 generation development. The studies were all conducted using the oral route of administration. In the fertility study, there was no effect at 2000 mg/kg in male and female rats. In the teratology studies in rats and rabbits, doses as high as 2000 and 5 mg/kg/day, respectively, administered orally during organogenesis had no effect on the developing fetus or offspring and was not teratogenic. In the pre- and post-natal development study, the highest dose tested (1000 mg/kg sulopenem etzadroxil) was the NOAEL.

Safety margins for fertility was 14.5-fold for male rats and 7.9-fold for female rats, 1.1-fold for embryofetal development in rat and <1-fold for rabbits, and 9.9-fold for postnatal development in rats. Sulopenem has no reproductive toxicity or developmental effects with acceptable safety margins for tolerability, embryo-fetal and post-natal development during pregnancy.

Fertility and Embryonic Development

Male and female fertility and early embryonic development was examined in rats (20/sex/group) dosed orally with sulopenem etzadroxil at 100, 400, or 2000 mg/kg. Treatment with sulopenem etzadroxil did not affect reproduction including estrous cycle length, mating and fertility rates, implantation, conceptus viability, sperm concentration and motility or accessory male sex glands weights. Based on the results of this study, the NOAEL for reproductive toxicity was 2000 mg/kg.

Embryo-Fetal Development

Embryo-fetal development was examined in rats (38 dams/group) at 100, 400 or 2000 mg/kg and rabbits (15 dams/group) at 5, 15 or 50 mg/kg sulopenem etzadroxil administered orally.

Sulopenem etzadroxil was not teratogenic at any dose tested. In rats, the NOAEL for maternal toxicity was 100 mg/kg based upon reduced body weight and food consumption and the NOAEL was 100 mg/kg for developmental toxicity in fetuses and offspring based on increased early resorptions and growth retardation.

2-EBA was also tested in pregnant rats at 75, 150 and 300 mg/kg. 2-EBA was well tolerated with a NOAEL at the highest dose.

Sulopenem etzadroxil was tested in pregnant rabbits at 5, 15 and 50 mg/kg. The NOAEL was 5 mg/kg for developmental toxicity and was not teratogenic at any dose level tested.

Prenatal and Postnatal Development and Maternal Function

The pre and post-natal development study in rat was conducted with sulopenem etzadroxil administered orally at 100, 300 or 1000 mg/kg. There was no test- article related mortality. With sulopenem etzadroxil, there was minimal maternal toxicity at >300 mg/kg (decreased body weight gain and food consumption). There were no other adverse effects with sulopenem etzadroxil administered by oral gavage. The maternal and fetal NOAEL was 1000 mg/kg with an associated C_{max} of 30.1 and 0.31 µg/mL, respectively.

4.3.2.4 Toxicology Studies in Juvenile Animals

The juvenile toxicity study in rats was conducted with sulopenem etzadroxil administered orally from postnatal day (PND) 5 to 90 at 25, 75 or 225 mg/kg. There was no sulopenem-related toxicity observed in either sex in regard to mean body weight gain, mean body weight, food consumption, development, neurological assessments, or necropsy findings.

Sulopenem related but non-adverse toxicity was noted through an increase in kidney weight with microscopic findings which included hypertrophy of tubule epithelial cells observed at 60 or 200 mg/kg/day which were considered adaptive. Therefore, based upon these data, a no observable adverse effect level (NOAEL) was determined to be 800 mg/kg/day for juvenile animals administered sulopenem.

There was no sulopenem etzadroxil related toxicity observed in either sex in regard to clinical observations, mean body weight gain, mean body weight, food consumption, development, or necropsy findings. Sulopenem etzadroxil-related but non-adverse toxicity was noted via decreases in locomotor assessments (basic movements and X+Y ambulations) during the recovery period for animals administered 225 mg/kg/day. Sulopenem etzadroxil related toxicity was also noted through an increase in kidney weight with microscopic findings which included hypertrophy of tubule epithelial cells observed ≥25 mg/kg/day.

Overall, incidence and kidney weights were lower in the recovery phase. Therefore, based upon these data, a NOAEL was determined to be 225 mg/kg/day for juvenile animals administered sulopenem etzadroxil.

Sponsor's Commentary:

In Cohort I, no animals given 800 mg/kg/day IV sulopenem survived to completion of the PND 90 treatment endpoint. Morbidity and mortality were associated primarily with excessive damage to the tail at the injection site, leading to a large number of animals being sacrificed early for humane reasons. The early deaths or sacrifice of animals at this dose level precluded any meaningful conclusions regarding potential sulopenem-related adverse effects following necropsy in that dose group. As such, and in conjunction with correspondence with the Division, the Sponsor has concluded that the 800 mg/kg/day dose cannot be considered the NOAEL and has therefore excluded that high-dose treatment group from the safety analysis. In the lowest (60 mg/kg/day - males) and mid-dose (200 mg/kg/day - females) treatment groups, sulopenem-related toxicities were noted through an increase in kidney weight with microscopic findings which included hypertrophy of tubule epithelial cells observed at 60 or 200 mg/kg/day which were considered adaptive in the final study report. With the highest dose tested in this juvenile rat toxicology study excluded from the analysis, NOAELs would be 60 mg/kg/day for males and 200 mg/kg/day for females based on the minimal degeneration of proximal tubule cells.

In Cohort II, similar renal toxicity findings with administration of prodrug sulopenem etzadroxil as described above with Cohort I. Treatment levels at 25, 75 and 225 mg/kg/day afforded a reassessment of the NOAELs by sex to be 75 mg/kg/day in males and 225 mg/kg/day for females, based on the degeneration of proximal tubule cells.

4.4 CONCLUSIONS FROM NONCLINICAL SAFETY STUDIES

Overall, the nonclinical safety studies support the use of intravenous sulopenem and oral sulopenem etzadroxil as an antibiotic in patients with infection. Pharmacology studies demonstrate that sulopenem and sulopenem etzadroxil inhibit microbial growth in animal models of infection.

Toxicokinetic evaluations show that sulopenem and sulopenem etzadroxil are safe at multiples above the intended clinical doses. Toxicology studies demonstrated that the primary toxicity associated with sulopenem and sulopenem etzadroxil is reversible and related to the pharmacologic action of the antibiotic (GI, renal and hematopoietic changes). The combination toxicology study indicates that sulopenem etzadroxil coadministered with probenecid is safe at multiples above the maximum daily human dose. Taken together, these studies demonstrate that both sulopenem and the prodrug, sulopenem etzadroxil are safe and well-tolerated.

5 CLINICAL PHARMACOLOGY

5.1 HUMAN PHARMACOKINETICS

5.1.1 Basic Pharmacokinetic Properties of Sulopenem

5.1.1.1 Absorption

Peak plasma sulopenem concentrations are attained in approximately 1 to 2 h after administration of sulopenem etzadroxil as the bilayer tablet. Moderately enhanced bioavailability and improved tolerability occurs when the bilayer tablet is taken in the fed state. The absolute bioavailability of sulopenem from sulopenem etzadroxil after administration of the bilayer tablet was 40% when taken in the fasted state and 64% when taken after a high-fat meal.

5.1.1.2 Distribution

The unbound fraction of sulopenem in human plasma was 0.893 and was independent of concentration over the 100-fold concentration range evaluated. Given the low degree of protein binding and the lack of concentration dependence, protein binding is unlikely to be a clinically significant consideration for use of sulopenem. Moreover, these same characteristics make sulopenem an unlikely perpetrator of drug-drug interactions for highly protein-bound medicines administered concurrently with sulopenem. The volume of distribution at steady-state for sulopenem in healthy subjects was greater than 75 L, suggesting distribution of sulopenem into total body water.

5.1.1.3 Metabolism

Upon oral administration, sulopenem etzadroxil is rapidly hydrolyzed either in the intestine or in the systemic circulation to the active moiety sulopenem and non-active moieties including formaldehyde and 2-ethylbutyric acid (2-EBA). The etzadroxil prodrug was not quantifiable in any blood samples collected after administration to human subjects. Furthermore, no sulopenem etzadroxil was observed in excreta after oral administration of [^{14}C]-sulopenem etzadroxil. *In vivo* metabolism of the active moiety sulopenem was evaluated following intravenous dosing in cynomolgus monkeys. Profiling of urine and plasma suggested sulopenem undergoes multiple concurrent metabolic changes including β-lactam cyclic amide bond hydrolysis, dehydrogenation, decarboxylation, sulfide cleavage, and acetylation. There is low potential for drug interactions at therapeutic concentrations of sulopenem.

5.1.1.4 Excretion

Renal clearance of sulopenem after administration of sulopenem etzadroxil was 18.8 L/h and 15.7 L/h in the fed and fasted states, respectively. In comparison, the total systemic clearance of IV

administration in the fed and fasted states was 40.0 and 35.1 L/h, respectively, indicating that renal clearance of unchanged sulopenem is a major route of excretion accounting for nearly half of the total systemic clearance.

5.1.2 Pharmacokinetics in Healthy Volunteers

The proposed clinical dose is BID dosing of a bilayer tablet of sulopenem etzadroxil and probenecid (500 mg of each component). Disproportionality was observed in studies using sulopenem etzadroxil. Increases in sulopenem AUC were proportional to the increase in sulopenem etzadroxil dose up to 4000 mg. However, sulopenem AUC increased in a greater than dose-proportional fashion after a single oral dose of 8000 mg sulopenem etzadroxil which was the maximum dose of sulopenem etzadroxil administered. Repeated doses of sulopenem etzadroxil of up to 2000 mg BID alone and up to doses of 1200 mg sulopenem etzadroxil and 1000 mg probenecid have been administered for 10 days. Potential effects of probenecid on dose-dependent changes in sulopenem pharmacokinetics were not investigated. However, systemic exposure to sulopenem increased when the dose of probenecid increased from 500 to 1000 mg with 500 mg sulopenem etzadroxil. The population PK model describes the non-linearity in elimination using Michaelis Menten kinetics. The relatively high K_M suggest that at the clinically relevant doses the elimination of sulopenem is expected to be linear. Owing to its rapid half-life ($t_{1/2}$) of 1.1 hours, there is no relevant accumulation of sulopenem following repeat dose administration of either PO or IV regimens, including the bilayer tablet.

5.1.3 Special Populations

5.1.3.1 Race and Ethnicity

No individual studies to determine PK based on race and ethnicity have been conducted.

5.1.3.2 Pediatric Patients

No studies have been conducted in pediatric patients to date.

5.1.3.3 Age and Gender

5.2.3.3 No individual studies to determine PK based on age and gender have been conducted.

5.1.3.4 Renal Impairment

The renal impairment study was an open-label, 2-way crossover study to investigate the pharmacokinetics, safety and tolerability of single doses of IV sulopenem and oral sulopenem etzadroxil in subjects with varying degrees of renal impairment and normal renal function. The study was conducted in 4 groups of 8 subjects each, with varying degrees of renal function. In Period 1, subjects with normal renal function, and mild (CLcr >50 and ≤80 mL/minute) or moderate (CLcr ≥30 and ≤50 mL/minute) renal impairment received a single dose of sulopenem 800 mg given as a 1.5-h IV infusion. Subjects with severe renal function received a single dose of 200 mg sulopenem as a 1.5-h IV infusion (1 subject with severe impairment received a dose of 800 mg as a 1.5-h IV infusion and was excluded from data summaries). Subjects received a single oral dose of 1000 mg sulopenem etzadroxil as tablets. Serial blood samples for PK analysis were collected for up to 48 hours after dosing. Urine for PK analysis was collected for 24 hours after dosing. Results from this study showed that the systemic exposure (AUC_{inf}) of sulopenem was increased in subjects with mild, moderate and

severe renal function by 2.1 fold, 3.5 fold and 7.4 fold, respectively, as compared to normal renal function after a single oral dose of 1000 mg sulopenem etzadroxil. Sulopenem AUC_{inf} in subjects with mild and moderate renal impairment was increased 170% and 250%, respectively, compared to subjects with normal renal function after an 800 mg IV dose. Following a dose reduction to 200 mg from 800 mg the severe renal impairment group showed similar exposures to that of the normal renal function group given the 800 mg dose.

5.1.3.5 Hepatic Impairment

No formal studies have been performed with sulopenem etzadroxil in hepatic impaired patients as renal clearance is the major route of excretion for unchanged sulopenem.

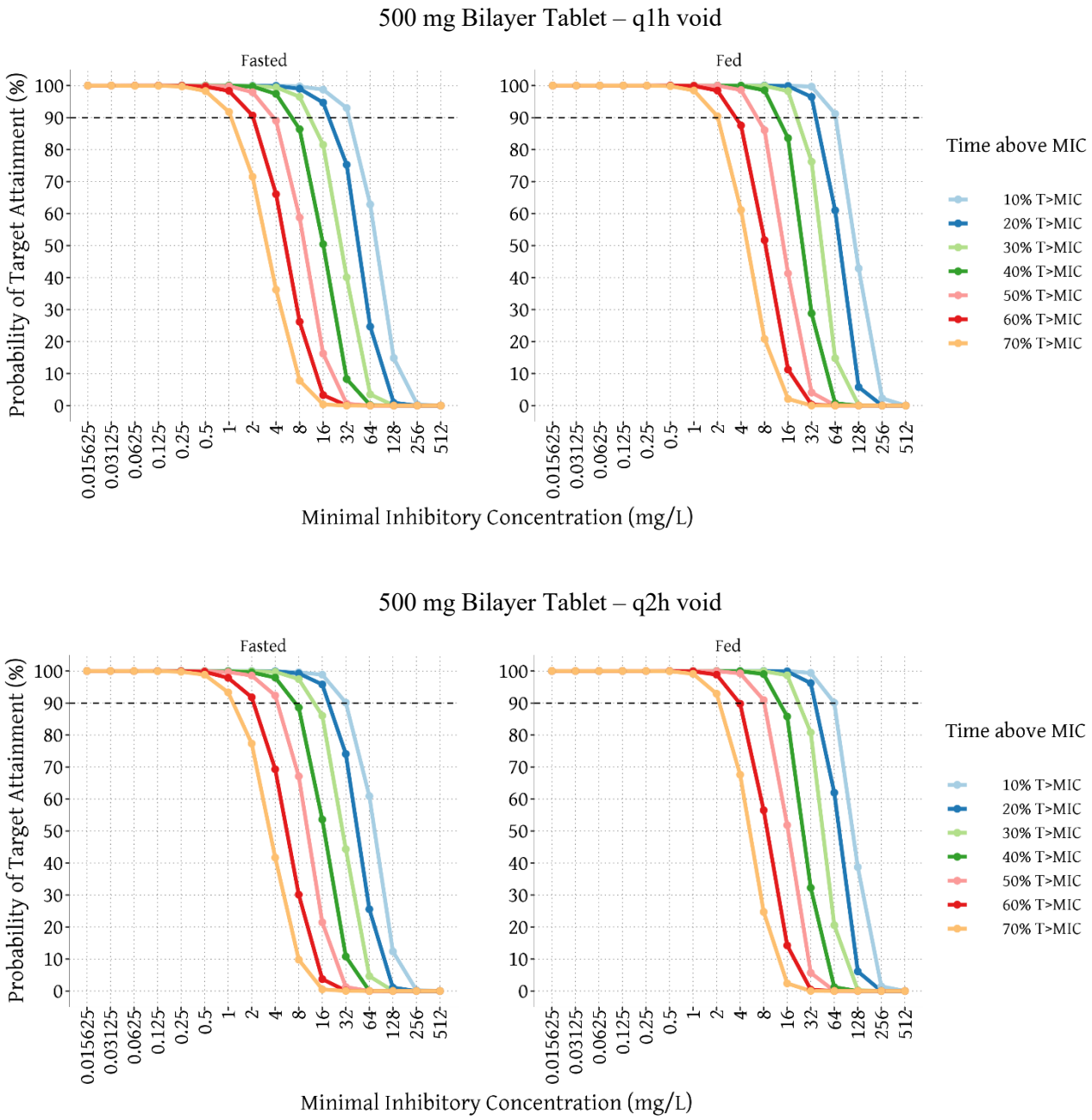
5.1.4 Population Pharmacokinetics

The aim of this analysis was to develop a model to describe the time course of sulopenem pharmacokinetics (PK) following single and multiple dosing, with and without probenecid coadministration and with and without food, as well as to explore the impact of patient characteristics on relevant PK parameters. The population pharmacokinetics (PopPK) analysis was initially based on Phase 1 data in healthy volunteers and was subsequently updated based on sparse samples obtained from the patients in the Phase 3 studies. In addition, the PopPK model was used for target attainment simulations to predict the proportion of subjects achieving specified target exposures. The overall PK profile was well described a three-compartment model, with non-linear elimination at higher doses.

For the clinically relevant doses, the elimination of sulopenem is expected to be dose-proportional. Absorption was described using two parallel transit compartment absorption models (TCAMs) to adequately capture the observed double peaks in the sulopenem PK profile. The bioavailability of sulopenem etzadroxil was estimated to be 21.1%. The bioavailability increased by 51.8% with food as compared to the fasted state for the bilayer tablet. Administrating IV sulopenem and oral sulopenem etzadroxil with 500 mg probenecid reduced the elimination by 31.5%, increasing sulopenem exposure by 46.5% following 500 mg sulopenem etzadroxil. Patients were estimated to have slightly slower absorption as compared to healthy volunteers, with 36.9% higher mean transit time (MTT) for uUTI and cUTI patients and 67.4% higher MTT for cIAI patients as compared to the healthy volunteers in the Phase 1 studies.

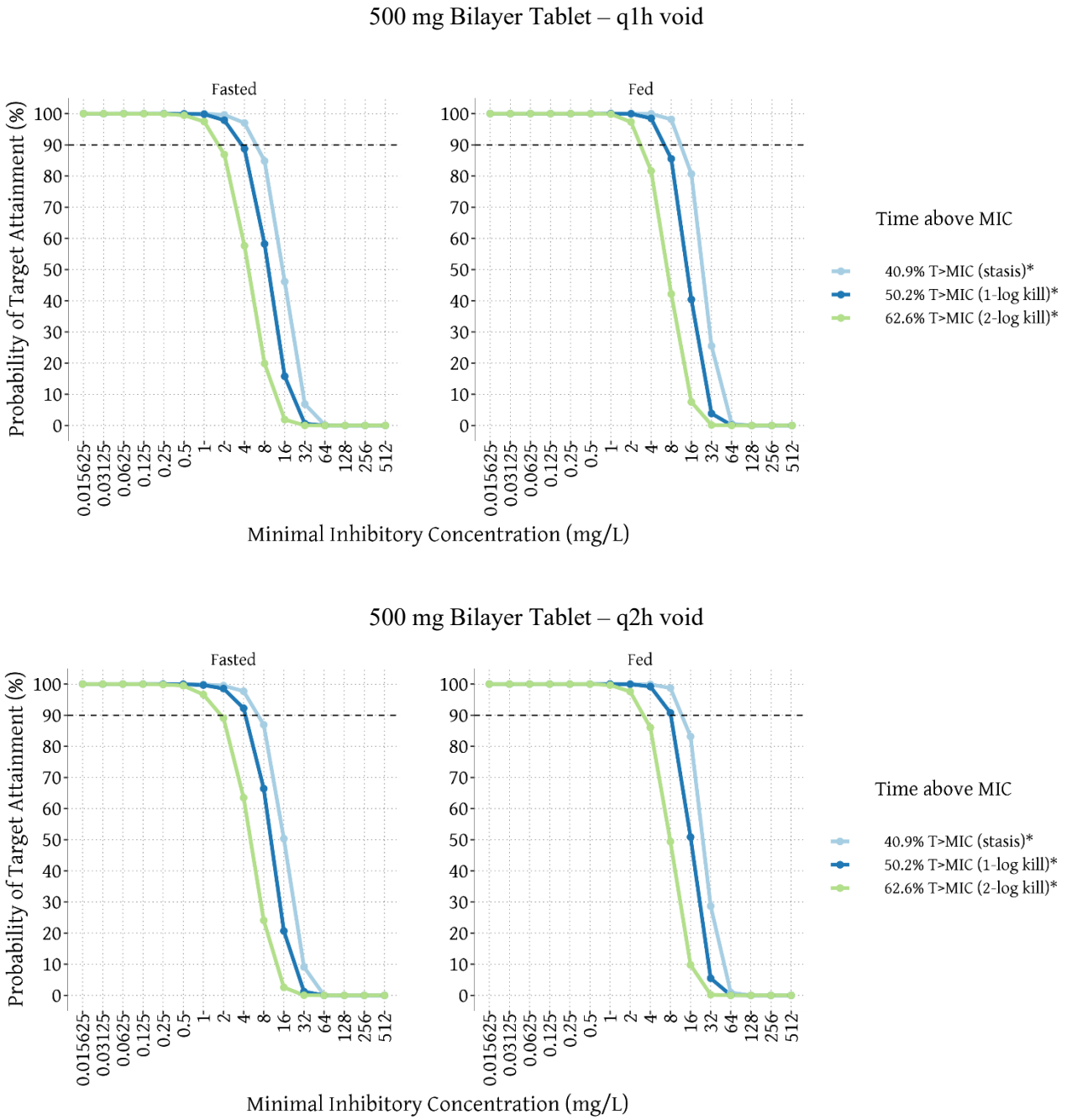
The Phase 1 and Phase 3 final PopPK model was used for simulations of target attainment in plasma and urine (Figure 11) using the same %T>MIC targets as was done before (ICPD Report 00475, 2017), 17% (1-log kill) and 20.2% (2-log kill) from Girard et al. (2008). The simulations show that this is expected to be achieved in more than 90% of the patients at the clinically relevant doses based on both fixed MIC values (0.06 and 0.5 mg/L) as well as simulations using actual MIC distribution in the Phase 3 patients, and would exceed 30% time above MIC with all formulations based on the distribution of MIC in each of the indications studied. In addition, the sulopenem levels in urine are well above the target concentration for at least 80% of the dosing interval. The target attainment predictions in urine of 500 mg bi-layer tablet BID regimen under fed and 2h voiding conditions, demonstrated adequate coverage (in at least 90% of the simulated subjects) of the bacterial stasis (40.9%), 1-log kill (50.2%), and 2-log kill (62.6%) targets, for MICs up to 8, 8 and 2 mg/L, respectively (Figure 12). A similar exercise in plasma yielded coverage in at least 90% of the simulated subjects of the murine thigh model 1-log kill (17%) and 2-log kill (20.2%), and *in vitro* bacterial stasis (40.9%) targets, for MICs up to 0.5, 0.5 and 0.25 mg/L, respectively.

Figure 11 Probability of Target Attainment Predictions in Urine



Dashed Line: 90% of simulated subjects (n=5000) reaching the respective %T>MIC target. Source: Population PK Report Figure 33.

Figure 12 Probability of Target Attainment Predictions in Urine -Preclinical *E.coli* and *K. pneumoniae* Bacterial Stasis, 1-log, and 2-log Kill Targets



Dashed Line: 90% of simulated subjects (n=5000) reaching the respective %T>MIC target. ***** *In vitro* E. coli and K. pneumoniae bacterial stasis, 1-log kill, and 2-log kill %T>MIC targets. Source: Population PK Report Figure 34.

All together, these analyses support the dose recommendations and labeling in the target population and in special populations.

5.2 POTENTIAL FOR DRUG-DRUG INTERACTIONS

Sulopenem did not inhibit or induce any of the major CYP enzymes tested nor inhibit any of the transporters tested *in vitro*. Sulopenem did inhibit OAT1 *in vitro*, but only at the highest concentration tested (150 µM). Therefore, the risk of clinically relevant effects of sulopenem on the disposition of concomitantly administered medications by interactions with CYP enzymes and the major transporters is deemed low.

Concomitant administration of carbapenem antibiotics and valproic acid (VPA) has been associated with a clinically significant reduction in serum VPA concentrations, resulting in a loss of seizure control [Huang]. Multiple doses of IV sulopenem 1.0 g infused over 3 hours decreased VPA $AUC_{0\text{-}tau}$ and $C_{max,ss}$ by approximately 33% and 28%, respectively, relative to administration of VPA alone. Administration of a sulopenem etzadroxil tablet without probenecid decreased VPA AUC_{tau} and $C_{max,ss}$ by approximately 25% and 19%, respectively, relative to administration of VPA alone. These results are consistent with observations after concomitant administration of VPA and carbapenem antibiotics.

In contrast, multiple doses of oral sulopenem as the bilayer tablet had no effect on VPA $AUC_{0\text{-}tau}$ and $C_{max,ss}$ relative to administration of VPA alone. The mechanism of the negation of the effect of sulopenem on VPA pharmacokinetics is not clear. However, these results demonstrated that loss of seizure control is unlikely with concomitant administration of VPA and the bilayer tablet, potentially providing patients taking VPA for seizure control with an option to use a penem antibiotic not previously available.

A Phase 1, open-label, 2-period, 4-sequence, parallel study was conducted to estimate the effects of multiple-dose administration of itraconazole on the pharmacokinetics of sulopenem in healthy adult subjects. There was no drug-drug interaction between itraconazole and IV sulopenem or 500 mg sulopenem etzadroxil tablet. Itraconazole did not change the plasma sulopenem AUCs and T_{free}>MIC of the 500 mg sulopenem etzadroxil/500 mg probenecid bilayer tablet, at both fasted or fed states. Itraconazole produced a small increase in sulopenem Cmax of a single dose of 500 mg sulopenem etzadroxil/500 mg probenecid bilayer tablet, in the fed state.

5.3 PHARMACOKINETIC-PHARMACODYNAMIC RELATIONSHIPS

5.3.1 Dose Regimen Justification for Achievement of Clinical Efficacy

Dosing recommendations for treatment of uUTI with oral sulopenem are based on data from *in vitro* surveillance studies of the pathogens expected in this indication, results from the murine thigh model of infection from which PKPD targets are derived, multiple studies of pharmacokinetics in health volunteers followed by population PK data from patients in the Phase 3 program. All of this data was then utilized in a Monte Carol model which provided support for the selected dose. *In vitro* evaluations of the biologic activity of sulopenem indicate that the MIC_{90} values against targeted bacterial strains is 0.06-0.12 µg/mL, depending on the specific infection, and the MIC_{99} is 0.5 µg/mL. The pharmacokinetic-pharmacodynamic (PK/PD) parameter of interest for sulopenem is the percent of time that free drug concentration exceeds the MIC (%T_{free}>MIC) which was determined from the murine thigh infection model to be ~17% for stasis of growth and ~20% for a 1 log CFU/mL reduction in bacterial burden. The clinical dose was then selected so as to provide, at a minimum, an exposure in plasma of 17-20% of the dosing interval over 0.12 µg/mL. To be conservative, dose selection of oral sulopenem targeted the MIC_{99} of 0.5 µg/mL.

For PK/PD determination, the *in vitro* activity of sulopenem, the pharmacokinetics and the protein binding of the drug in mouse plasma were considered and fitted to the sigmoidal E_{max} model. The results show that for sulopenem, the parameter that correlates best with efficacy is T>MIC, consistent with PK/PD evaluations for β-lactam drugs (Bhavnani 2005). The PK/PD parameters AUC/MIC and C_{max}/MIC) displayed weaker correlations with efficacy (r^2 values of 0.45 for both). From these data the ED_{90} could be estimated; the results showed that to achieve a maximal effect (ED_{90}), the free plasma drug concentrations would need to be above the MIC for 21% of the dosing interval. These results are in agreement with those in the literature that indicate a high probability of clinical success when a target of 20 to 40% of T>MIC is reached for carbapenems (Bhavnani 2005; Cuba 2014; Drusano 2004).

Target attainment simulations were also performed using the PopPK model developed for the oral bilayer tablet at doses of 500 mg sulopenem etzadroxil/500 mg probenecid which was also studied in the clinical Phase 3 program. The target attainment simulations were performed, using both fixed MIC values (0.006 and 0.5 mg/L) as well as empirical distributions of MIC values for cUTI, uUTI and cIAI, based on *in vitro* surveillance studies. Simulations were performed with and without probenecid and with and without food, showing the largest target attainment (with a probability close to 100%) in the presence of probenecid and food, although all dosing regimens were predicted to achieve good target attainment.

6 CLINICAL MICROBIOLOGY

6.1 SUSCEPTIBILITY DETERMINATION METHODOLOGY

The principal target pathogens in uUTI are Enterobacterales species such as *E. coli*, *Klebsiella pneumoniae*, and *Proteus mirabilis*.

There was little to no impact of non-standard test conditions on the perceived *in vitro* activity of sulopenem against quality control isolates from the ATCC, demonstrating the overall stability of this method for the susceptibility testing of sulopenem. Despite this stability, it is important to highlight strict adherence to CLSI guidelines during broth microdilution susceptibility testing and the incorporation of quality control ranges as established by CLSI for the susceptibility testing of sulopenem against both aerobes (broth microdilution) and anaerobes (agar dilution). Agar dilution susceptibility testing was demonstrated to be a suitable method for evaluating the susceptibility of aerobes including methicillin-susceptible staphylococci, streptococci, and Enterobacterales but not methicillin-resistant staphylococci or *H. influenzae*. Disk diffusion susceptibility testing was found to be feasible for sulopenem over a wide range of disk masses, with ultimately a disk mass of 2 µg being selected as the optimum disk mass for which quality control ranges were subsequently established.

6.2 SURVEILLANCE STUDIES

6.2.1 Overview of Surveillance Studies

Table 34 lists the surveillance studies that have evaluated the activity of sulopenem and comparators against clinical isolates from the US, Canada and Europe. Susceptibility testing performed in each of the five surveillance studies was conducted under the most current guideline from the CLSI available at the time of testing (M07, M11, and M100).

Table 34 Surveillance Studies Assessing *In Vitro* Activity of Sulopenem

Study	Source of Isolates	No. of Isolates	Methodology
IHMA, Schaumburg, IL (2013-2015)	Urinary tract, intra-abdominal	873	CLSI broth microdilution
JMI Laboratories, North Liberty, IA (2016-2017)	Urinary tract, intra-abdominal	1,918	CLSI broth microdilution
Health Sciences Centre, Winnipeg, Manitoba, Canada (2016)	Respiratory tract, skin, urinary tract, blood	3,126	CLSI broth microdilution
JMI Laboratories, North Liberty, IA (2019)	Blood, intra-abdominal, urinary tract	1,647	CLSI broth microdilution
JMI Laboratories, North Liberty, IA (2023)	Blood, intra-abdominal, urinary tract	1,086	CLSI broth microdilution

6.2.2 Activity Against Aerobic Gram-Negative Bacteria

A summary of the $MIC_{50/90}$ values for sulopenem against gram-negative aerobic bacteria is presented in Table 35. The activity of sulopenem was consistent against isolates of US, European, and Canadian origin.

Table 35: $MIC_{50/90}$ 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	1,515	0.03	0.25
	Canada	2016	1,055	0.03	0.25
	US	2019	1,647	0.03	0.25
	US	2023	1,086	0.03	0.25
E. coli	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
	Canada	2014-2021	1248	0.03	0.06
	US	2019	983	0.03	0.03
	US	2023	635	0.03	0.03
K. pneumoniae	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

	Canada	2014-2021	200	0.06	0.12
	US	2019	273	0.03	0.06
	US	2023	163	0.03	0.06
K. oxytoca	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
	Canada	2014-2021	35	0.06	0.06
	US	2019	41	0.03	0.06
	US	2023	31	0.03	0.06
K. aerogenes	US-Europe	2013-2015	60	0.12	0.25
	US	2019	33	0.12	0.25
	US	2023	22	0.12	0.25
P. mirabilis	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
	Canada	2014-2021	88	0.25	0.5
	US	2019	91	0.25	0.25
	US	2023	70	0.25	0.5
E. cloacae complex	US-Europe	2013-2015	66	0.12	0.5
	US-Europe	2016-2017	75	0.06	1
	Canada	2016	92	0.12	0.5
	Canada	2014-2021	47	0.12	0.5
	US	2019	110	0.12	0.5
	US	2023	48	0.12	0.5
C. freundii 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
	US	2023	28	0.06	0.12
C. koseri	US-Europe	2013-2015	29	0.03	0.03
	US-Europe	2016-2017	60	0.03	0.06

	US	2019	9	0.03	-
	US	2023	20	0.03	0.03
S. marcescens	US-Europe	2013-2015	60	0.25	2
	Canada	2016	60	0.5	4
	US	2019	36	0.5	2
	US	2023	29	0.5	4
M. morgannii	US-Europe	2013-2015	22	0.5	1
	US-Europe	2016-2017	79	0.5	1
	US	2019	20	1	1
	US	2023	13	1	1
P. aeruginosa	US-Europe	2013-2015	66	>16	>16
	Canada	2016	324	>8	>8
	Canada	2014-2021	75	>8	>8
A. baumannii	US-Europe	2013-2015	63	16	>64
H. influenzae	Canada	2016	133	0.12	0.5

US, United States; MIC, minimum inhibitory concentration; MIC_{50}, MIC against 50% of the isolates; MIC_{90}, MIC against 90% of the isolates.

6.2.3 Sulopenem Potency Compared With Other Antimicrobials

The activity of sulopenem and comparator carbapenems against US, European and Canadian isolates of Enterobacterales overall is presented in Table 36. Sulopenem and meropenem had similar potency, and both were slightly less potent than ertapenem; sulopenem, meropenem and ertapenem were all more potent than imipenem.

Table 36: $MIC_{50/90}$ Values (µg/mL) of Sulopenem and Comparators against Enterobacterales - Surveillance

Drug	Study	Year	Type	N	MIC_{50}	MIC_{90}	%S	%R
Sulopenem	IHMA_2757	2013-2015	US-Europe	682	0.06	0.5	-	-
			UTI	371	0.06	0.5	-	-
			IAI	311	0.03	0.25	-	-
			US	330	0.06	0.5	-	-
			Europe	352	0.06	0.5	-	-
			US-Europe	1,515	0.03	0.25	-	-
			UTI	1,279	0.03	0.25	-	-

	17-ITR-05	2016-2017	IAI	236	0.03	0.5	-	-
			US	1,008	0.03	0.25	-	-
			Europe	507	0.03	0.5	-	-
	CANWARD 2016	2016	Canada	1,055	0.03	0.25	-	-
			UTI	247	0.03	0.06	-	-
			BSI	531	0.03	0.12	-	-
	18-ITR-03	2019	US	1,647	0.03	0.25	-	-
			UTI	999	0.03	0.12	-	-
			IAI	261	0.03	0.25	-	-
			BSI	387	0.03	0.25	-	-
	22-ITR-03	2023	US	1,096	0.03	0.25	-	-
			UTI	728	0.03	0.25	-	-
			IAI	86	0.03	0.5	-	-
			BSI	272	0.03	0.25	-	-
Ertapenem	IHMA_2757	2013-2015	US-Europe	682	0.015	0.25	92.5	3.1
	17-ITR-05	2016-2017	US-Europe	1515	≤0.008	0.06	97.4	1.5
	CANWARD 2016	2016	Canada	1055	≤0.03	0.06	99.1	0.4
	18-ITR-03	2019	US	1,647	≤0.008	0.06	98.3	0.9
Meropenem	IHMA_2757	2013-2015	US-Europe	682	0.03	0.12	98.4	1.3
	17-ITR-05	2016-2017	US-Europe	1515	0.03	0.06	98.8	0.9
	CANWARD 2016	2016	Canada	1055	≤0.03	0.06	99.9	0.0
	18-ITR-03	2019	US	1,647	≤0.015	0.06	99.7	0.2
	22-ITR-03	2023	US	1,096	≤0.015	0.06	99.7	0.3
Imipenem	IHMA_2757	2013-2015	US-Europe	682	0.25	2	88.6	3.7
	17-ITR-05	2016-2017	US-Europe	1515	≤0.12	2	88.8	2.6
	CANWARD 2016	2016	Canada	1055	0.12	0.5	98.0	0.7
	18-ITR-03	2019	US	1,647	≤0.12	1	92.0	0.2
	22-ITR-03	2023	US	1,096	≤0.12	1	92.9	1.7

US, United States; MIC, minimum inhibitory concentration; MIC_{50}, MIC against 50% of the isolates; MIC_{90}, MIC against 90% of the isolates; %S, percent susceptible, %R, percent resistant, UTI, urinary tract infection source, IAI, intraabdominal infection source.

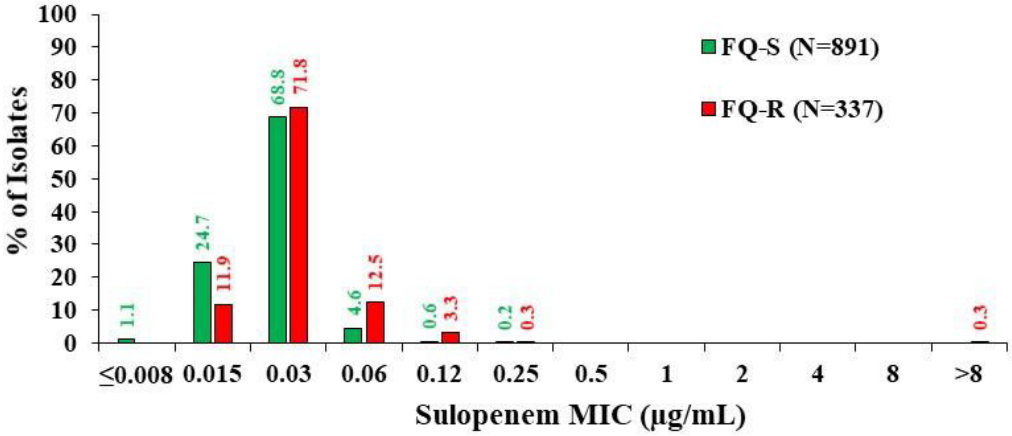
6.2.4 Activity of Sulopenem Against Bacteria Resistant to Other Classes of Antimicrobial Agents

The *in vitro* activity of sulopenem against selected pathogens with important resistance phenotypes is discussed below by pathogen. Using relevant data from both large profiling studies and surveillance studies as needed, an *ad hoc* analysis of integrated sulopenem MIC data by resistance phenotype was performed below. Key resistance phenotypes evaluated include, but are not limited to, those relevant to the targeted indications (e.g. CRE, fluoroquinolone-resistant [FQ-R] *E. coli*, and Enterobacterales positive for ESBLs).

6.2.4.1 *Escherichia coli* (FQ-R, ESBL, CRE)

Among the evaluated *E. coli* surveillance isolates, a high degree of fluoroquinolone resistance was observed. The sulopenem MIC distribution against fluoroquinolone-susceptible (FQ-S) and FQ-R isolates is shown in Figure 13. Sulopenem had an $MIC_{50/90}$ value of 0.03/0.03 µg/mL against FQ-S isolates compared to 0.03/0.06 µg/mL for FQ-R isolates. The similarity in $MIC_{50/90}$ between the FQ-S and FQ-R subpopulations and the nearly identical MIC distribution shows that sulopenem activity is not impacted by fluoroquinolone-resistance among *E. coli*.

Figure 13: Sulopenem MIC Distribution against FQ-S and FQ-R E. coli

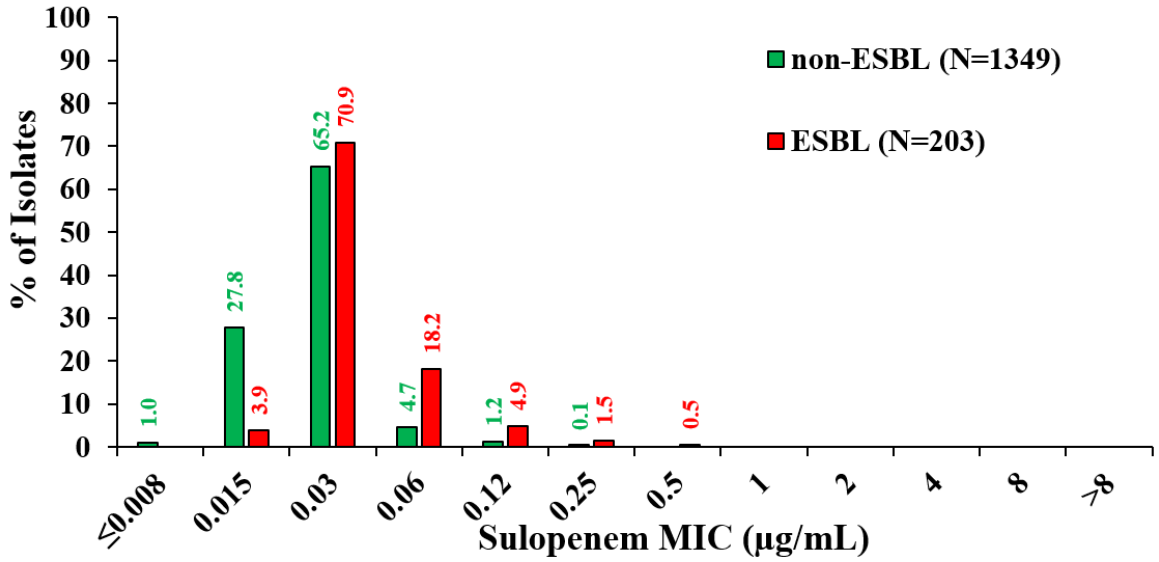


FQ, fluoroquinolone; S, susceptible; R, resistant.

ESBL screen-positive isolates (based on ceftriaxone MIC values ≥2 µg/mL; [CLSI M100]) were also frequently encountered during surveillance. The sulopenem MIC distribution against non-ESBL and ESBL isolates is shown in Figure 14. Sulopenem had an $MIC_{50/90}$ value of 0.03/0.03 µg/mL against non-ESBL isolates compared to 0.03/0.06 µg/mL for ESBL isolates. The similarity in $MIC_{50/90}$ between the non-ESBL and ESBL subpopulations and the nearly identical MIC distribution shows that sulopenem activity is not impacted by the presence of ESBL among *E. coli*.

Of note, during surveillance only 2 carbapenem-resistant *E. coli* were encountered and sulopenem had MIC values of 4 and >16 µg/mL against these isolates, similar to meropenem and ertapenem.

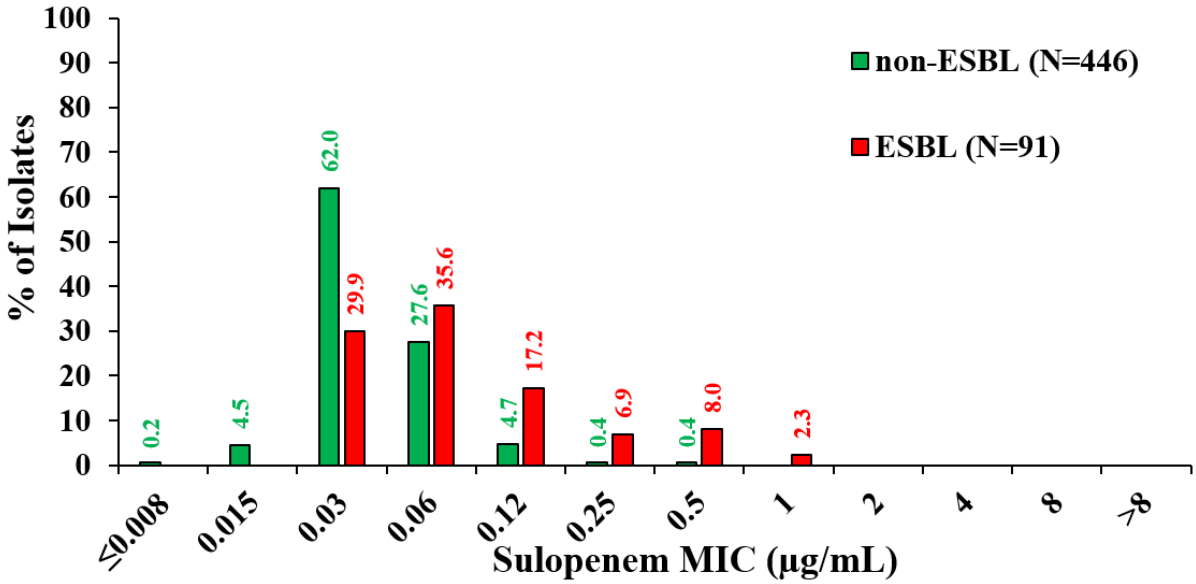
Figure 14: Sulopenem MIC Distribution against non-ESBL and ESBL E. coli



6.2.4.2 *Klebsiella pneumoniae* (ESBL, CRE)

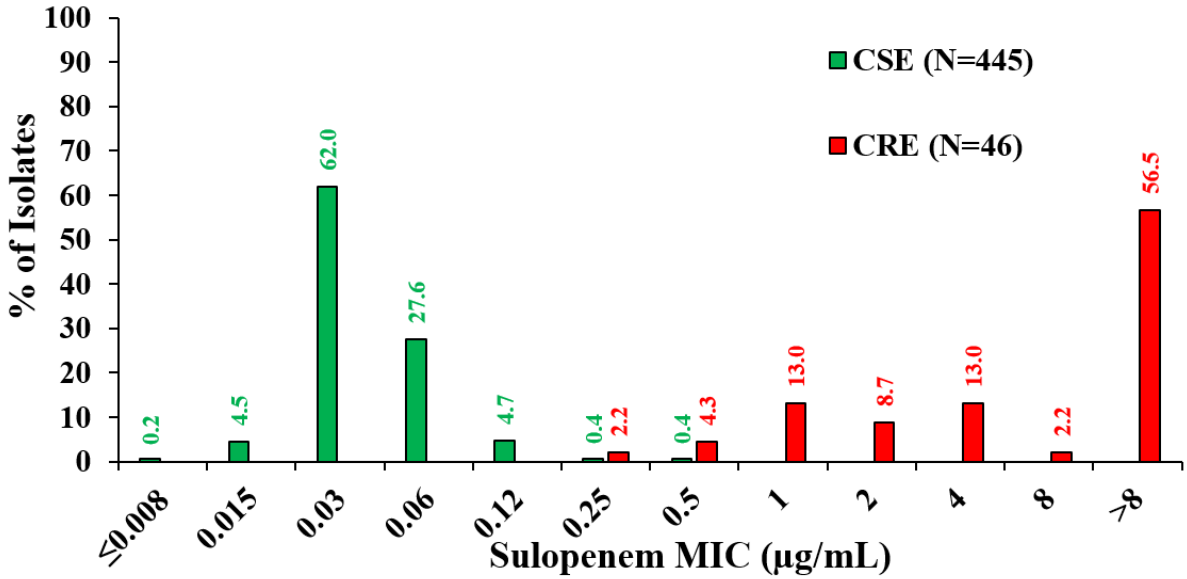
ESBL screen-positive isolates (based on ceftriaxone MIC values ≥2 µg/mL; [CLSI M100]) were also frequently encountered among *K. pneumoniae* during surveillance. The sulopenem MIC distribution against non-ESBL and ESBL isolates is shown in Figure 15. Sulopenem had an $MIC_{50/90}$ value of 0.03/0.06 µg/mL against non-ESBL isolates compared to 0.06/0.5 µg/mL for ESBL isolates. Despite the difference in MIC_{90} between the non-ESBL and ESBL subpopulations the MIC distribution largely overlaps showing that sulopenem activity is not affected for the majority of ESBL isolates of *K. pneumoniae*. Of note, sulopenem MIC values did not exceed 1 µg/mL against the ESBL subpopulation.

Figure 15: Sulopenem MIC Distribution against non-ESBL and ESBL *K. pneumoniae*



Carbapenem-resistant *K. pneumoniae* isolates were infrequently encountered during routine surveillance but were also tested as part of profiling studies. The sulopenem MIC distribution against carbapenem-susceptible (CSE) and CRE isolates is shown in Figure 16. Sulopenem had an $MIC_{50/90}$ value of 0.03/0.06 µg/mL against CSE isolates compared to >8/>8 µg/mL for CRE. These results demonstrate that carbapenem-resistance among *K. pneumoniae* affects sulopenem activity, as expected.

Figure 16: Sulopenem MIC Distribution against CSE and CRE K. pneumoniae



6.2.4.3 Carbapenem-resistant Enterobacterales (CRE)

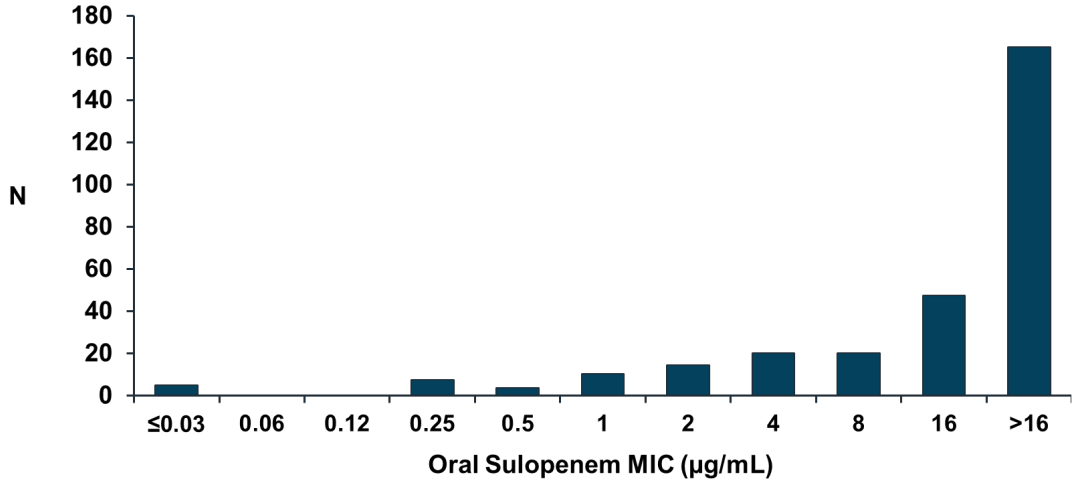
A total of 300 genetically-characterized CRE isolates underwent susceptibility testing for sulopenem and comparators. A breakdown of isolates by species and resistance mechanism is shown in Table 37. The sulopenem MIC distribution against these isolates is shown in Figure 17. Sulopenem had an $MIC_{50/90}$ of >16/>16 µg/mL for Enterobacterales expressing IMP (N=50), KPC (N=50), NDM (N=50), and OXA (N=50) carbapenemases, 16/>16 µg/mL those expressing VIM (N=50) carbapenemases, and 1/4 µg/mL for Enterobacterales that were CRE but were negative for known carbapenemases. Taken together, these results suggest that sulopenem, like other carbapenems, is susceptible to known carbapenemases.

Table 37: Total isolate counts by species and phenotype

Organism	Genotype (n)						Species Total
	IMP	KPC	NDM	OXA	VIM	Cpnase	
Citrobacter freundii	15			1	4		20
Enterobacter cloacae	12	1	11	1	21	8	54
Enterobacter kobei	1						1
Escherichia coli	2	4	7	3		14	30
Klebsiella aerogenes	2			1			3
Klebsiella oxytoca	4	2		1	3		10
Klebsiella pneumoniae	10	43	29	37	14	28	161

Providencia rettgeri			3				3
Providencia stuartii					6		6
Raoultella ornithinolytica				2			2
Raoultella planticola				3			3
Serratia marcescens	4			1	2		7
Genotype total	50	50	50	50	50	50	300

Figure 17: Sulopenem MIC Distribution against Genetically-characterized CRE (N=300)



6.2.4.4 Assessment of Cross-Resistance

With some exceptions (e.g. MRSA, CRE, MDR and carbapenem-resistant *P. aeruginosa* and *A. baumannii*), most isolates encountered during the surveillance studies were susceptible to carbapenems. Apart from these exceptions, cross-resistance for sulopenem with other classes is minimal.

For Enterobacterales, in which resistance is typically mediated by carbapenemases, cross-resistance between sulopenem and the comparator carbapenems is clear as would be expected. Cross-resistance between sulopenem and other β-lactams is not observed for ESBL-mediated resistance, as sulopenem, like carbapenems, maintains potent activity against ESBL isolates of *E. coli* and *K. pneumoniae*, and derepressed AmpC isolates of *E. cloacae*. Cross-resistance with fluoroquinolones was not observed with *E. coli* and is not apparent for other classes as carbapenem susceptibility rates typically greatly exceed those observe with other agents from other antibiotic classes.

Among lactose-nonfermenting gram-negative bacilli (e.g., *P. aeruginosa* and *A. baumannii*) where multi-drug resistance is more common, carbapenem resistance mediated by carbapenemases, porin loss, or efflux affects the activity of sulopenem in a similar fashion to that observed with comparator carbapenems. Regardless of pre-existing resistance to carbapenems, sulopenem has no appreciable activity against *P. aeruginosa*. For *A. baumannii*, cross-resistance for sulopenem and other carbapenems is evident with carbapenem resistant *A. baumannii* as expected.

Among gram-positive organisms, β-lactam resistance mediated by alteration to the PBP target confers cross-resistance to sulopenem and other carbapenems in *S. aureus*. For *S. pneumoniae*, despite elevated MIC values observed for sulopenem and comparators with penicillin-resistant and MDRSP isolates, potent sulopenem MIC values (≤ 2 µg/mL) are maintained for these

subpopulations. There is no apparent cross-resistance with vancomycin for VISA or *E. faecalis*, nor is there cross-resistance with macrolides for β-hemolytic streptococci.

7 CLINICAL EFFICACY

7.1 OVERVIEW OF THE SULOPENEM CLINICAL DEVELOPMENT PROGRAM

Based on sulopenem's spectrum of antibacterial activity, the Phase 3 development program focused on three indications: uncomplicated urinary tract infections (uUTI), complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI). Iterum has filed an NDA for the indication of uUTI; safety and efficacy data from the cUTI and cIAI studies were included in the NDA as supportive data.

7.1.1 Proposed Indication

Oral sulopenem tablets, a fixed-dose combination product consisting of sulopenem etzadroxil, a penem antibacterial prodrug, and probenecid, a renal tubular transport blocking agent, are indicated in adult women ≥ 18 years of age for the treatment of uncomplicated urinary tract infections caused by designated susceptible microorganisms.

7.2 TRIAL DESIGN

Oral sulopenem efficacy in uUTI is supported by data from Study 301 and Study 310, with additional details and data provided in Section 7.5. Supportive data from Study 302 are presented in Section 7.6.2.

7.2.1 Study 301

7.2.1.1 Patient Selection Criteria

The patient population in Study 301 was intended to include adult women with signs and symptoms of uncomplicated urinary tract infection, further refined by the study inclusion and exclusion criteria provided below.

Inclusion Criteria

Patients had to meet all of the following criteria to be considered for inclusion in this study:

- Female patients ≥18 years of age with ≥24 hours and ≤96 hours of urinary symptoms attributable to a urinary tract infection
- Two or more 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** from the same specimen
    - Evidence of pyuria defined as either:
        - A machine-read dipstick positive for leukocyte esterase **OR**
        - At least 10 white blood cells (WBCs)/mL^3 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 any study enrollment

Exclusion Criteria

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

- Presence of signs and symptoms suggestive of acute pyelonephritis defined as: fever (temperature >38°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., nonsteroidal 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 vesicoureteral 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/mm^3
    - Neutropenia (defined as absolute neutrophil count <1000 cells/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 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 study to the first dose of study drug, or prior participation in any sulopenem clinical trial

7.2.1.2 Choice of Comparator

The dose of oral ciprofloxacin was 250 mg BID for 3 days, consistent with the ciprofloxacin US Prescribing Information.

7.2.2 Study 310

7.2.2.1 Patient Selection Criteria

The patient population in Study 310 was intended to include adult women with signs and symptoms of uncomplicated urinary tract infection, further refined by the study inclusion and exclusion criteria provided below.

Inclusion Criteria

Patients had to meet all of the following criteria to be considered for inclusion in this study:

- Female patients ≥18 years of age with ≥24 hours and ≤96 hours of urinary symptoms attributable to a urinary tract infection;
- Two of the following signs and symptoms of a 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 esterase **OR,**
    - Evidence of pyuria as defined as either:
        - A machine-read dipstick positive for large leukocyte esterase, **OR**
        - At least 10 white blood cells (WBCs)/mL^3 on microscopic analysis of unspun urine, **OR**
        - WBC count ≥10 cells/high power field (HPF) in the sediment of a spun urine sample;
- Given written informed consent to participate in the study.

Exclusion Criteria

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

- Presence of signs and symptoms suggestive of acute pyelonephritis defined as: fever (temperature >38°C), chills, costovertebral angle tenderness, flank pain, nausea, and/or vomiting;
- Receipt of antibacterial drug therapy potentially effective as treatment of a 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). Note: Patients could be included if these medications were previously taken and have 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 is positive for more than two microorganisms regardless of colony count (contaminated), or confirms a fungal UTI;
- Patient is receiving hemodialysis, hemofiltration, peritoneal dialysis, or had a renal transplant;
- Patient known to be immunocompromised as evidenced by any of the following:
    - Known HIV positive, with either a recent (in the past six months) AIDS-defining condition or a CD4+ T lymphocyte count <200/mm^3
    - Known neutropenia (defined as absolute neutrophil count <1,000 cells/mm^3);
    - Systemic or hematological malignancy requiring chemotherapeutic or radiation/immunologic interventions within six 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 five days or more in the 30 days prior to randomization).
- Known liver function abnormalities as defined by the following laboratory criteria:
    - ALT or AST >3 × Upper Limit of Normal (ULN) and/or
    - Total bilirubin >2 × ULN
- Females of child-bearing potential who are unable to take adequate contraceptive precautions (refer to Sections 4.4 and 4.5), have a positive pregnancy test result within 24 hours prior to study entry, are otherwise known to be pregnant, or are currently breastfeeding;
- Poorly controlled diabetes mellitus including the presence of ketoacidosis and hyperosmolar hyperglycemia;
- Patients with a history of seizures;
- Patients with a history of blood dyscrasias;
- Patients with a history of uric acid kidney stones;

- Patients with acute (current) gouty arthritis;
- Concomitant administration of valproic acid;
- Patients with a history of allergy or hypersensitivity to carbapenems, β-lactams, 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 study to the first dose of study drug, or prior participation in any sulopenem clinical trial.

7.2.2.2 Choice of Comparator

The FDA approved dose of 875/125 mg oral amoxicillin/clavulanate administered twice daily for 5 days was used for treatment of uncomplicated UTI. Though the usual adult dose for amoxicillin/clavulanate per the Augmentin USPI is 500/125 mg orally twice daily, a higher dose indicated for more severe infections was chosen for this study to justify the use of amoxicillin/clavulanate CLSI breakpoints for uUTI (M100 Performance Standards for Antimicrobial Susceptibility Testing, 32nd edition).

7.3 CRITERIA FOR EVALUATION OF EFFICACY

7.3.1 Study 301

7.3.1.1 Primary Efficacy Outcomes

The primary efficacy endpoint was to be based on the outcome of overall response (combined clinical and microbiological response) in the microMITT-S and, separately, in the microMITT-R populations (see Section 7.4.1 for population definitions) at TOC (Day 12 [±1] day).

A patient was to be defined as a success [responder] at a given timepoint [Day 3, End of Treatment (EOT), TOC (Day 12), and Final Visit (FV) (Day 28) [±1 day]] if the following criteria were met:

Clinical response was defined as:

- The patient was alive
- The patient had received no non-study antibacterial therapy for uUTI (excluding linezolid, daptomycin, vancomycin, azithromycin, metronidazole, josamycin, macrolide, nifuratel, tergynan, 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 antibiotic 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 Patient Symptom Assessment Questionnaire [PSAQ]). Missing PSAQ questions were to be treated as missing; thus, the outcome was indeterminate.

Microbiological response was defined as:

- Urine culture collected at the follow-up visit demonstrated $<10^3$ CFU/mL of the baseline uropathogen.

7.3.1.2 Secondary Efficacy Outcomes

The number and percentage of patients with a per-patient microbiologic response of success (eradication) or failure (persistence or persistence with increasing MIC) at the TOC visit were to be determined in each treatment group in the ME-TOCS and ME-TOCR populations (see Section 7.4.1 for population definitions). The observed difference in percentage of patients with microbiologic success (eradication) (oral sulopenem group minus the ciprofloxacin group) was to be determined and a 2-sided 95% CI for the observed difference was to be computed using the unstratified method of Miettinen and Nurminen.

7.3.2 Study 310

7.3.2.1 Primary Efficacy Outcomes

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

Overall Response (at a given visit) was assessed using the definitions listed below:

A patient was to be defined as a success if the following criteria are met (programmatically, based on the data on the eCRF):

- The patient was alive
- The patient had received no rescue therapy for uUTI
  - If an antibiotic active against the urinary tract pathogen was given for other 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 uUTI symptoms (based on the Patient Symptom Assessment Questionnaire)
  - Baseline symptoms associated with another known condition (eg, overactive bladder) do not need to be resolved.
- Urine culture demonstrates $<10^3$ CFU/mL of the baseline uropathogen based on results of quantitative cultures performed on collected urine specimens.

7.3.2.2 Secondary Efficacy Outcomes

The number and percentage of patients in each treatment group with a clinical response of success, failure and indeterminate at Day 12 (±1 day)/TOC were to be presented for the MITT, micro-MITT, micro-MITTS, and micro-MITTR populations. The number and percentage of patients in each treatment group with a clinical response of success and failure at Day 12 (±1 day)/TOC were to be presented for the CE and ME populations. Two-sided 95% unstratified CIs were to be constructed for the observed difference in the clinical success rates between the treatment groups for descriptive purposes; no conclusion of NI was to be made.

The number and percentage of patients in each treatment group with a microbiologic response of success, failure and indeterminate at Day 12 (±1 day)/TOC were to be presented for the micro-MITT, micro-MITTS, and micro-MITTR populations. The number and percentage of patients in each treatment group with a microbiologic response of success and failure at Day 12 (±1 day)/TOC were to be presented for the

ME populations. Two-sided 95% unstratified CIs were to be constructed for the observed difference in the microbiologic success rates between the treatment groups for descriptive purposes; no conclusion of NI was to be made.

7.4 STATISTICAL METHODOLOGY

7.4.1 Study 301

7.4.1.1 Analysis Populations

The following main patient populations were identified for the safety and efficacy analyses:

- Intent to Treat (ITT) Population
    - All randomized patients regardless of whether the patient received study drug.
- Safety Population
    - All patients in the ITT population who received at least a single dose of study medication.
- Modified Intent to Treat (MITT)
    - 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.
- Microbiologic MITT (microMITT)
    - All MITT patients with a positive study entry urine culture within 48 hours prior to first dose, defined as $\geq 10^5$ 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 with $\geq 10^5$ CFU/mL.
- Susceptible microMITT (microMITT-S)
    - All microMITT patients with a baseline uropathogen susceptible to the comparator drug, ciprofloxacin (ciprofloxacin MIC ≤1 mg/L), and no baseline pathogen non-susceptible to ciprofloxacin.
- Resistant microMITT (microMITT-R)
    - All microMITT patients with a baseline uropathogen non-susceptible (defined as MIC ≥2 mg/L) to the comparator drug, ciprofloxacin

7.4.1.2 Analysis of Primary Efficacy Data

The primary efficacy endpoint was to be based on the outcome of overall response (combined clinical and microbiological response [success, failure, or indeterminate]) in the microMITT-S and, separately, in the microMITT-R at TOC (Day 12 [±1 day).

Patients were to be programmatically categorized as a success, failure, or indeterminate based on data in the eCRF and from the microbiology lab. Patients with missing data or who were lost to

follow-up were defined as indeterminate for the primary analyses and were included in the denominator for the calculation of the success rate. The number and percentage of patients with success, failure, and indeterminate response were to be determined in each treatment group in the microMITT-S and microMITT-R populations.

The primary objective of this study was to compare the outcomes in patients with quinolone susceptible organisms as well as, in parallel, in patients with quinolone non-susceptible pathogens. The primary comparisons for regulatory approval were in these two mutually exclusive populations as defined by a baseline characteristic. If either of the two analyses were positive (i.e., reject null hypothesis), the efficacy of sulopenem was to have been established consistent with the primary objective of the trial. These two populations were defined as follows:

The microMITT-R population

This population was a subset of the microMITT population in which the baseline pathogen was determined to be non-susceptible to the comparator study drug, ciprofloxacin. For this population, a superiority test was to be conducted. The null and alternative hypotheses were as follows:

H_0: $P_1 = P_2$

H_A: $P_1 \neq P_2$

A 2-sided 95% CI for the observed treatment difference in success rates was to be determined using the method without stratification of Miettinen and Nurminen. If the lower bound of the 95% CI was greater than 0%, the null hypothesis was to be rejected and superiority of oral sulopenem to ciprofloxacin was to be concluded.

The microMITT-S population

This population was a subset of the microMITT population in which the baseline pathogen was determined to be susceptible to the comparator study drug, ciprofloxacin. For this population, a NI test of the overall success rate was to be conducted. The null and alternative hypotheses were as follows:

H_0: $P_1 - P_2 \leq -\Delta$

H_A: $P_1 - P_2 > -\Delta$

Where:

P_1 = the primary efficacy endpoint rate in the oral sulopenem group, P_2 = the primary efficacy endpoint rate in the ciprofloxacin group, and Δ = the non-inferiority margin of 10%.

The NI hypothesis test was a 1-sided hypothesis test performed at the 2.5% level of significance. This was based on the lower limit of the 2-sided 95% CI for the observed difference in the overall success rate (oral sulopenem group minus ciprofloxacin group). The primary analysis was based on the CI computed using the method proposed without stratification by Miettinen and Nurminen, which corresponded to the p-value approach of the Farrington-Manning test. If the lower limit of the 95% CI for difference in success rates in the microMITT-S population was greater than -10%, the null hypothesis was to be rejected and the NI of oral sulopenem to ciprofloxacin was to be concluded.

Additional Hypothesis Testing of the Primary Efficacy Outcome

Additional analyses were to be performed to provide guidance to the practicing physician in the setting where culture results were not available. To do this, all randomized patients who received

drug were to be analyzed together as this population was more consistent with what the practicing physician is faced with every day. Table 38 presents a family of analyses to be conducted in the study populations and the sequence in which they were to be conducted. The regulatory outcomes are focused on the primary analyses. The secondary analyses, which sequentially progress towards an assessment in the randomized population prior to the benefit of culture data, provide guidance to physicians who need to choose an empiric treatment regimen without the support of a urine culture.

Table 38: Study 301 Additional Hypothesis Testing

Analysis	Populations	
First step	1. microMITT-S (if non-inferior then test #2)	1. microMITT-R (if superior then test #2)
Second step	2. NI in microMITT (if non-inferior then test #3)	2. NI in microMITT (if non-inferior then test #3)
	3. Superiority in microMITT (if superior then test #4)	3. Superiority in microMITT (if superior then test #4)
	4. NI in MITT* (if NI then test#5)	4. NI in MITT* (if NI then test#5)
	5. Superiority in MITT*	5. Superiority in MITT*

MITT = modified intent-to-treat; microMITT = microbiologic modified intent-to-treat; microMITT-R = resistant microbiologic modified intent-to-treat; microMITT-S = susceptible microbiologic modified intent-to-treat; NI = non-inferior. *Based on clinical response

To control for inflation of the overall type I error rate in assessment of the secondary analyses, the hierarchical testing procedure of Westfall and Krishen was to be used to continue testing hypotheses of the primary efficacy endpoint. If NI or superiority was declared for the primary comparisons, the secondary comparisons were to be statistically tested in the order presented below. Testing was to proceed to the next comparison, only in the case where the null hypothesis in the previous comparison was rejected. When testing in a sequential manner with pre-planned testing, no adjustment to the alpha level was required.

1. NI test of overall success, H_0: $P_1 - P_2 \leq -\Delta$ and H_A: $P_1 - P_2 > -\Delta$, in the microMITT population. The number and percentage of patients in each treatment group with an overall response of success, failure, and indeterminate was to be provided for the microMITT population. A 2-sided 95% CI for the observed treatment difference in success rates was to be determined. If the lower bound of the 95% CI was greater than -10%, the null hypothesis was to be rejected and the NI of oral sulopenem to ciprofloxacin in the microMITT population was to be concluded.
2. Superiority test of overall success, H_0: $P_1 = P_2$ and H_A: $P_1 \neq P_2$, in the microMITT population. If the lower bound of the 95% CI (calculated for the hypothesis test in #1) was greater than 0%, the null hypothesis was to be rejected and the superiority of oral sulopenem to ciprofloxacin in the microMITT population was to be concluded.

7.4.1.3 Interim Analysis

To ensure that the point estimate of overall response (combined clinical and microbiologic response) used in the estimation of sample size was valid for this study, two interim analyses for sample size re-estimation were to be performed when response data at Day 12 (± 1 day; TOC) were available for approximately 33% and 66% of the patients (approximately 450 and 900 patients, respectively). The FDA Guidance "Non-inferiority Clinical Trials", 2016 notes that such a sample

size re-estimation if based on the blinded overall response rates is not only acceptable but is advisable. The interim analysis was to involve a sample size re-estimation to either confirm the initial sample size estimate was adequate or increase the sample size (number of randomized patients) to ensure the study had adequate power for determining whether oral sulopenem is NI to oral ciprofloxacin for the primary outcome measure in the microMITT-S population. The sample size was not to be decreased. In addition, the sample size could be increased based on a lower than expected evaluability rate (i.e., percentage of the ITT population in the microMITT population) or lower than expected percentage of patients with a susceptible pathogen. The sample size re-estimation was to be based on the blinded overall (not by treatment group) outcome and evaluability rates.

The blinded interim analyses proceeded as follows:

1. The percentage of patients with a baseline pathogen (micro-MITT population) was determined
2. The percentages of patients with a susceptible (to comparator study drug, ciprofloxacin) pathogen (micro-MITTS population) and a non-susceptible (to ciprofloxacin) pathogen (micro-MITTR population) were determined
3. The overall success rate aggregated across treatment groups in the micro-MITTS population was determined
4. Whether there was sufficient power (80-90%) in the micro-MITTS to show NI with the planned sample size based on the observed aggregated (across treatment groups) overall success rate was determined
    a. If NO, then the sample size in the micro-MITTS population was increased to have sufficient power.

In addition, the micro-MITT rate (i.e. evaluability rate) and proportion of patients with a susceptible pathogen (micro-MITTS evaluability rate) was used to determine the total number of patients needed.

In order to determine whether the sample size was sufficient to determine whether oral sulopenem was superior to ciprofloxacin in the patients whose baseline pathogens were non-susceptible to ciprofloxacin, a conditional power analysis for the superiority hypothesis in the micro-MITTR population was conducted when 66% of patients had been enrolled (unblinded interim analysis). A conditional power analysis using the approach of Lan and Wittes was conducted to determine whether the sample size needed to be adjusted. The sample size adjustment would be conducted as described by Mehta and Pocock. If the conditional power was <40%, no change to the sample size would be made. If the conditional power was 40%-<80%, the sample size for micro-MITTR population would be calculated based on the observed overall success rates in each treatment group and increased to a maximum number. If the conditional power was ≥80%, no change to the sample size would be made. The final sample size in the ITT population would be adjusted to take into account the proportion of patients in the micro-MITT population and the micro-MITTR population. No adjustment to the overall alpha level was needed.

The sample size re-estimations were to be conducted by an independent, unblinded statistician. A DMC was to be provided the results of the interim analyses by the independent, unblinded statistician and was to make a recommendation regarding changes to the sample size. A detailed

DMC charter was developed outlining the analyses to be completed, statistical rules, the potential changes to the sample size, and the recommendations that could be made to the Sponsor.

7.4.1.4 Sample Size Justification

The study was designed to determine whether oral sulopenem is NI to oral ciprofloxacin for the outcome measure of overall response (combined clinical and microbiologic success) at Day 12 (± 1 day) in the microMITT-S population and/or whether oral sulopenem was superior to oral ciprofloxacin for overall success at Day 12 (± 1 day) in the microMITT-R population. The primary outcome measure of overall response (combined clinical and microbiologic success) was defined as resolution of the symptoms of uUTI present at trial entry (and no new symptoms) and the demonstration that the bacterial pathogen found at trial entry was reduced to $<10^3$ CFU/mL on urine culture (microbiological success [eradication]).

The proposed sample size in the microMITT-S population was 441 patients per arm (total of 882 patients) based on the method of Farrington and Manning. This assumed a non-inferiority margin of 10%, a power of 90%, a one-sided alpha level of 0.025, and a 70% treatment success rate. With 105 patients per treatment group in the microMITT-R population, there was 90% power to show superiority given a 66% and 43% overall success rate in the oral sulopenem and ciprofloxacin groups, respectively. Assuming that 22% of the patients had non-susceptible pathogens and 83% of the randomized patients met criteria for inclusion into the microMITT population (1132 patients), the sample size for the ITT population was 1364.

Following 2 interim analyses, the DMC recommended the addition of 400 patients to the study to maintain study power and sufficient number of microMITT patients, bringing the total number of potential patients to approximately 1764. On December 20, 2019, enrollment was completed at 1671 randomized patients as the sponsor considered that adequate statistical power had been achieved at that point.

The primary populations for this study were: the micro-MITTS population, defined as all randomized patients with a positive baseline urine culture defined as $\geq 10^5$ CFU/mL of a uropathogen (and no more than 2 species of microorganisms), with a pathogen susceptible to the comparator study drug, ciprofloxacin (ciprofloxacin MIC ≤1 mg/L); and the micro-MITTR population defined as all randomized patients with a positive baseline urine culture defined as $\geq 10^5$ CFU/mL of a uropathogen (and no more than 2 species of microorganisms), with a pathogen non-susceptible to the comparator study drug, ciprofloxacin (ciprofloxacin MIC ≥2 mg/L; includes strains with intermediate susceptibility and resistance to ciprofloxacin).

A review of the literature showed that only approximately 60% of symptomatic uUTI patients will have $\geq 10^5$ CFU/mL of a uropathogen. Thus, in order to optimize the enrollment of patients with $\geq 10^5$ CFU/mL of a uropathogen, the inclusion criteria were designed to require a urine dipstick analysis to be positive for nitrite in addition to having evidence of pyuria, as this has been shown to increase the sensitivity and specificity of enrolling patients with $\geq 10^5$ CFU/mL of a uropathogen to 84% and 98%, respectively [Semeniuk].

7.4.2 Study 310

7.4.2.1 Analysis Populations

- Intent to Treat (ITT) Population

- All randomized patients regardless of whether or not the patient received study drug.

- Safety Population
  - All patients in the ITT population who received at least one dose of study medication.
- Modified Intent to Treat (MITT)
  - All patients in the ITT population who received at least a single dose of study medication.
- Microbiologic MITT (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 only) and no more than 2 species of microorganisms identified in the study entry urine culture, regardless of colony count.
- Susceptible microMITT (micro-MITTS)
  - All microMITT patients with a baseline uropathogen susceptible (defined as MIC ≤8/4 mg/L) to the comparator drug, amoxicillin/clavulanate, and no baseline pathogen non-susceptible to amoxicillin/clavulanate. If a patient has 2 uropathogens at baseline, both need to be susceptible.
- Resistant microMITT (micro-MITTR)
  - All microMITT patients with a baseline uropathogen non-susceptible (defined as intermediate (MIC 16/8 mg/L) or resistant (MIC ≥32/16 mg/L) to the comparator drug, amoxicillin/clavulanate.

7.4.2.2 Analysis of Primary Efficacy Data

The primary efficacy endpoint was defined as the outcome of overall success (combined clinical and microbiologic success) at TOC in each of the micro-MITT, micro-MITTS and micro-MITTR populations.

Patients were to be programmatically categorized as a success, failure, or indeterminate based on the data in the e-CRF and from the microbiology lab. The number and percentage of patients with success, failure and indeterminate response was to be determined in each treatment group in the micro-MITT, micro-MITTS and micro-MITTR populations.

The primary comparison of the study is in the micro-MITT population (the combined population of patients with a positive baseline culture and without regard to amoxicillin/clavulanate susceptibility). These outcomes are most relevant to the practicing clinician who must choose empiric treatment of uUTI before culture results become available, hence these results will help put into context the outcomes in the culture and susceptibility-driven sub-populations.

To control for the inflation of the overall type I error rate, the hierarchical testing procedure of Westfall and Krishen [Westfall 2001] was to be used to test the hypotheses of the

primary efficacy outcome in these populations in the sequential order described below. Testing was to proceed to the next comparison, only in the case where the null hypothesis in the previous comparison was rejected. When testing in a sequential manner with pre-planned hierarchy, no adjustment to the alpha level is required.

1. NI in the micro-MITT population:

   For this population, a NI test of the overall success rate was to be conducted. The null and alternative hypotheses are the following:

$$H_0 : p_1 - p_2 \leq -\Delta \text{ and } H_1 : p_1 - p_2 > -\Delta ,$$

where p_1 is the overall success rate in the oral sulopenem treatment group, p_2 is the overall success rate in the amoxicillin/clavulanate group, and Δ is the non-inferiority margin of 10%.

The NI hypothesis test is a 1-sided hypothesis test performed at the 2.5% level of significance. This was to be based on the lower limit of the 2-sided 95% CI for the observed difference in the overall success rates (oral sulopenem group minus amoxicillin/clavulanate group). The primary analysis was to be based on the CI computed using the method proposed without stratification by Miettinen and Nurminen, which corresponds to the p-value approach of the Farrington-Manning test. If the lower limit of the 95% CI for difference in success rates in the micro-MITT population was greater than -10%, the null hypothesis was to be rejected and the NI of oral sulopenem to amoxicillin/clavulanate was to be concluded and testing was to proceed to the next step.

2. NI in the micro-MITTS population OR superiority in the micro-MITTR population as described below:

   Micro-MITTS population: For this population, a NI test of the overall success rate was to be conducted. The null and alternative hypotheses are the following:

$$H_0 : p_1 - p_2 \leq -\Delta \text{ and } H_1 : p_1 - p_2 > -\Delta ,$$

where p_1 is the overall success rate in the oral sulopenem treatment group, p_2 is the overall success rate in the amoxicillin/clavulanate group, and Δ is the non-inferiority margin of 10%. The NI hypothesis test is a 1-sided hypothesis test performed at the 2.5% level of significance. A 2-sided 95% CI for the observed treatment difference in success rates was to be determined using the method without stratification of Miettinen and Nurminen. If the lower bound of the 95% CI was greater than -10%, the null hypothesis was to be rejected and the NI of oral sulopenem to amoxicillin/clavulanate in the micro- MITTS population was to be concluded.

Micro-MITTR population: For this population, a superiority test was to be conducted. The null and alternative hypotheses are the following:

$$H_0 : p_1 = p_2 \text{ and } H_1 : p_1 \neq p_2$$

A 2-sided 95% CI for the observed treatment difference in success rates was to be determined using the method without stratification of Miettinen and Nurminen. The 1-sided p-value corresponding to the lower bound of the 95% CI was to be reported. If the lower bound of the 95% CI was greater than 0%, the null hypothesis was to be rejected

and superiority of oral sulopenem to amoxicillin/clavulanate was to be concluded in the micro-MITTR population.

If either of these 2 null hypotheses was rejected, then testing was to proceed to the next step.

3. Superiority in the micro-MITT population

The null and alternative hypotheses are: $H_0 : p_1 = p_2$ and $H_1 : p_1 \neq p_2$.

The 1-sided p-value corresponding to the lower bound of the 95% CI calculated for the hypothesis test in (1) was to be reported. If the lower bound of the 95% CI (for the hypothesis test in (1)) was greater than 0%, the null hypothesis was to be rejected and the superiority of oral sulopenem to amoxicillin/clavulanate in the micro- MITT population was to be concluded.

For regulatory approval, the primary comparisons are in two mutually exclusive sub-populations of the micro-MITT population defined by a baseline characteristic, the micro-MITTS and micro-MITTR populations. To control for the inflation of the overall type I error rate, the following hierarchical testing procedure was to be used to test the hypotheses of the primary efficacy outcome in these populations in the sequential order described below.

Testing was to proceed to the next comparison, only in the case where the null hypothesis in the previous comparison was rejected. When testing in a sequential manner with pre-planned hierarchy, no adjustment to the alpha level is required.

(1) NI in the micro-MITTS population OR superiority in the micro-MITTR population as described below:

Micro-MITTS population: For this population, a NI test of the overall success rate was to be conducted. The null and alternative hypotheses are the following:

$$H_0 : p_1 - p_2 \leq -\Delta \text{ and } H_1 : p_1 - p_2 > -\Delta ,$$

where p_1 is the overall success rate in the oral sulopenem treatment group, p_2 is the overall success rate in the amoxicillin/clavulanate group, and Δ is the non-inferiority margin of 10%. The NI hypothesis test is a 1-sided hypothesis test performed at the 2.5% level of significance. A 2-sided 95% CI for the observed treatment difference in success rates was to be determined using the method without stratification of Miettinen and Nurminen. If the lower bound of the 95% CI is greater than -10%, the null hypothesis was to be rejected and the NI of oral sulopenem to amoxicillin/clavulanate in the micro- MITTS population was to be concluded.

Micro-MITTR population: For this population, a superiority test was to be conducted. The null and alternative hypotheses are the following:

$$H_0 : p_1 = p_2 \text{ and } H_1 : p_1 \neq p_2$$

A 2-sided 95% CI for the observed treatment difference in success rates was to be determined using the method without stratification of Miettinen and Nurminen. The 1-sided p-value corresponding to the lower bound of the 95% CI was to be reported. If the lower bound of the 95% CI is greater than 0%, the null hypothesis was to be rejected and superiority of oral sulopenem to amoxicillin/clavulanate was to be concluded in the micro-MITTR population.

If either of these 2 null hypotheses was rejected, then testing was to proceed to the next step.

(2) Superiority in the micro-MITT population

The null and alternative hypotheses are: $H_0 : p_1 = p_2$ and $H_1 : p_1 \neq p_2$.

A 2-sided 95% CI for the observed treatment difference in success rates was to be determined using the method without stratification of Miettinen and Nurminen. The 1-sided p-value corresponding to the lower bound of the 95% CI was to be reported. If the lower bound of the 95% CI is greater than 0%, the null hypothesis was to be rejected and the superiority of oral sulopenem to amoxicillin/clavulanate in the micro- MITT population was to be concluded.

The reasons for failure and indeterminate were to be tabulated for the primary efficacy endpoint at TOC in each of the micro-MITT, micro-MITTS and micro-MITTR populations.

7.4.2.3 Interim Analysis

To ensure that the point estimate of overall success (combined clinical and microbiologic success) used in the estimation of sample size, the estimated eligibility rate, susceptibility rate, and rate of post-treatment asymptomatic bacteriuria is valid for this study, an interim analysis for sample size re-estimation was to be performed when clinical and microbiologic response data at TOC are available for 50% of the patients (approximately 983 patients). The FDA Guidance "Non-inferiority Clinical Trials to Establish Effectiveness" [FDA Guidance 2016] notes that such a sample size re-estimation if based on the blinded overall response rates is not only acceptable but is advisable. The interim analysis was to involve a sample size re-estimation to either confirm the initial sample size estimate is adequate or increase the sample size (number of randomized patients) to ensure the study had adequate power for determining whether oral sulopenem was NI to oral amoxicillin/clavulanate for the primary outcome measure in the micro-MITTS population. This would ensure that the study was sufficiently powered to test the primary endpoint in the micro-MITT. The sample size was not be decreased. In addition, the sample size could be increased based on a lower-than-expected evaluability rate (i.e., percentage of the micro-MITT population in the ITT population), lower-than-expected percentage of patients with a susceptible pathogen and a lower-than-expected overall success rate. The sample size re-estimation was to be based on the blinded overall (not by treatment group) pooled data.

The blinded interim analysis was to proceed as follows:

(1) Determine the percentage of patients with a baseline pathogen $\geq 10^5$ CFU/mL (micro-MITT population), which is the micro-MITT eligibility rate

(2) Determine the percentage of patients with a susceptible (to comparator study drug, amoxicillin/clavulanate) pathogen (micro-MITTS population) and a non-susceptible (to amoxicillin/clavulanate) pathogen (micro-MITTR population) at baseline

(3) Determine the overall success rate and overall rate of asymptomatic bacteriuria at TOC aggregated across treatment groups in the micro-MITTS population

(4) Determine if there is sufficient power (80-90%) in the micro-MITTS to show NI with the planned sample size based on the observed aggregated (across treatment groups) overall success rate

a. If NO, then increase the sample size in the micro-MITTS population to have sufficient power.

(5) If the aggregated overall success rate in the micro-MITTS population is higher than 70%, or if the aggregated rate of asymptomatic bacteriuria is significantly lower than anticipated, then a futility analysis may be conducted to assess if the study should continue. The futility analysis will be done by computing the conditional power at the interim analysis, given the observed overall success rates in each treatment group in the micro-MITTS population.

The (blinded) sample size re-estimation was to be conducted by a blinded statistician and the (unblinded) futility analysis was to be conducted by an independent, unblinded statistician. A Data Monitoring Committee (DMC) was to be provided the results of the interim analysis to make a recommendation regarding changes to the sample size and if the study should continue. A detailed DMC charter was developed to outline the analyses to be completed, statistical rules, potential changes to the sample size and the recommendations that can be made to the sponsor.

7.4.2.4 Sample Size Justification

The study was designed to determine whether oral sulopenem is non-inferior to oral amoxicillin/clavulanate for the outcome measure of overall success (combined clinical and microbiologic success) at Day 12 (± 1 day)/TOC in both the micro-MITT and micro-MITTS populations and whether oral sulopenem is superior to oral amoxicillin/clavulanate for overall success at Day 12 (± 1 day)/TOC in the micro-MITTR population. The primary outcome measure of overall success (combined clinical and microbiologic success) was defined as resolution of the symptoms of uUTI present at trial entry (and no new symptoms) and the demonstration that the bacterial pathogen found at trial entry was reduced to $<10^3$ CFU/mL on urine culture (microbiological success [eradication]).

The proposed sample size in the micro-MITTS population was 505 patients per arm (total of 1010 patients) based on the method of Farrington and Manning. This assumed a non-inferiority margin of 10%, a power of 90%, a one-sided alpha level of 0.025, 60% overall success rate with amoxicillin/clavulanate and 60% overall success rate with oral sulopenem. Assuming that 21% of the patients would have non-susceptible pathogens and assuming 85% power to show superiority in the micro-MITTR population (micro-MITT=1278 patients), 67% of the randomized patients would meet criteria for inclusion into the micro-MITT population (MITT=1907 patients) and allowing for a dropout rate of 3%, the sample size for the ITT population was 1966. With 134 patients per treatment group in the micro-MITTR population, there was at least 85% power to show superiority at the one-sided 2.5% alpha level given a 51% and 33% overall success rate in the oral sulopenem and amoxicillin/clavulanate groups, respectively. With 1278 patients in the micro-MITT population, there was at least 95% power to show non-inferiority (non-inferiority margin of 10.0%) at the one-sided alpha level of 0.025 with the treatment success rates of the oral sulopenem and amoxicillin/clavulanate groups assumed to be 58% in this population.

One blinded interim analysis for sample size re-estimation was planned. Following the blinded interim analysis, the DMC recommended that in order to maintain 80%-90% power, the trial should continue to enroll to achieve a minimum of 1966 patients (original sample size in protocol) up to a maximum of 2428 patients (to achieve 90% power). On October 23, 2023, enrollment was completed at 2222 randomized patients as the sponsor considered that adequate statistical power had been achieved at that point.

7.5 RESULTS

7.5.1 Study 301

A summary of the outcomes for patients in the microMITT-R population will be presented first, followed by the microMITT population, and then the microMITT-S population. Because the primary endpoint was met in the microMITT-R and not in the microMITT-S population, data from the microMITT-R population, and from the analysis of the combined population, provide evidence for the treatment of patients with a uUTI due to a quinolone non-susceptible pathogen.

7.5.1.1 MicroMITT-R Population

7.5.1.1.1 Baseline Demographics

The demographic characteristics of patients randomized to each treatment regimen were similar (Table 39).

Table 39: Study 301 Demographic Characteristics of Patients in the microMITT-R Population

Parameter	Sulopenem N=147	Ciprofloxacin N=139
Age, years (SD)	54.5 (19.3)	56.3 (20.1)
Min, max	18.0, 89.0	18.0, 87.0
Female, n (%)	147 (100)	139 (100)
Ethnicity, n (%) Hispanic/Latino Not Hispanic/Latino	 58 (39.5) 89 (60.5)	 53 (38.1) 85 (61.2)
Geographic Region, n (%) US Ex-US	 81 (55.1) 66 (44.9)	 82 (59.0) 57 (41.0)
Race, n (%) Black Asian White Other	 14 (9.5) 2 (1.4) 130 (88.4) 1 (0.7)	 12 (8.6) -- 126 (90.6) 1 (0.7)
Diabetes present at Baseline, n (%)	27 (18.4)	26 (18.7)
BMI (kg/m^2) Median Min, max	 28.3 (16.7, 52.1)	 27.5 (15.2, 53.4)
Creatinine clearance (mL/min)[a] Median Range	 69.0 (17.0, 143.0)	 68.0 (23.0, 153.0)

Source: Table 14.1.2.4.1

[a]Calculated by Cockcroft-Gault method.

7.5.1.1.2 Baseline Pathogens

Pathogens cultured from urine that qualified patients for the microMITT-R population are presented in Table 40. The most commonly identified pathogens in both groups were *E. coli*

(86.4%), *K. pneumoniae* (10.5%), and *P. mirabilis* (5.2%), balanced between arms and consistent with the distribution reported in the uUTI literature.

Table 40: Study 301 Pathogens from Urine at Baseline - microMITT-R Population

Organism	Sulopenem n (%) N=147	Ciprofloxacin n (%) N=139
Number of Patients with at least one study uropathogen in the urine at baseline	147 (100)	139 (100)
Escherichia coli	127 (86.4)	120 (86.3)
Klebsiella pneumoniae	14 (9.5)	16 (11.5)
Proteus mirabilis	9 (6.1)	6 (4.3)
Morganella morganii	3 (2.0)	1 (0.7)
Enterobacter cloacae complex	1 (0.7)	0 (0.0)
Providencia stuartii	0 (0.0)	1 (0.7)

Source: Table 14.1.2.9.1
Note: percentages are calculated as 100 × (n/N). Abbreviations: microMITT-R = microbiologic modified intent-to-treat resistant; n = number of patients; N = number of patients in the microMITT-R population.

7.5.1.1.2.1 Distribution of Baseline Study Uropathogens by Antibiotic Resistance

A total of 91 patients, just under 32% of microMITT-R patients, had at least 1 baseline Enterobacterales pathogen that was ESBL-positive, as determined by having a ceftriaxone MIC of >1 μg/mL (Table 41). In this quinolone resistant population, isolates were also frequently resistant to other classes of antibacterials (38.5% were also β-lactam and trimethoprim-sulfamethoxazole resistant; 17.8% were also β-lactam, trimethoprim-sulfamethoxazole, and nitrofurantoin resistant). Notably, there are a small number of microMITT-R patients with a quinolone susceptible isolate. This is because there are a small number of isolates with discordant ciprofloxacin susceptibility culture results between the two labs that processed the initial urine samples and that required PCR confirmation in order to assign to either the resistant or susceptible sub-population. This could have resulted in a patient analyzed in the quinolone resistant population who, at least by the IHMA culture results, had a quinolone susceptible culture. In some cases, the patient had two organisms at baseline, one susceptible and one resistant; in that case they would be grouped into the microMITT-R population but would have a second organism that was ciprofloxacin susceptible.

Table 41: Study 301 Distribution of Pathogens by ESBL status and Quinolone, Trimethoprim- Sulfamethoxazole and Nitrofurantoin Susceptibility – microMITT-R Population

Parameter	Sulopenem n (%) N=147	Ciprofloxacin n (%) N=139
ESBL Status		
Negative	97 (66.0)	98 (70.5)
Positive	50 (34.0)	41 (29.5)
Quinolone		
Susceptible	2 (1.4)	2 (1.4)
Non-susceptible	145 (98.6)	137 (98.6)
Trimethoprim-sulfamethoxazole		
Susceptible	53 (36.1)	61 (43.9)
Non-susceptible	94 (63.9)	78 (56.1)
Nitrofurantoin		
Susceptible	108 (73.5)	101 (72.7)
Non-susceptible	39 (26.5)	38 (27.3)
Quinolone Resistant/ β-lactam resistant	129 (87.8)	121(87.1)
Quinolone Resistant/ β-lactam resistant /Trimethoprim-sulfamethoxazole resistant	63 (42.9)	47 (33.8)
Quinolone Resistant/ β-lactam resistant /Trimethoprim-sulfamethoxazole resistant/ Nitrofurantoin Resistant	24 (16.3)	27 (19.4)

Source: Table 14.1.2.11.1, Table 14.2.2.1.1.4
Note: Percentages are calculated as 100 × (n/N). Patients were considered ESBL-positive if they had a baseline urine specimen or blood culture positive for at least 1 Enterobacterales with a ceftriaxone MIC of >1 µg/mL; Abbreviations: MIC = minimum inhibitory concentration; microMITT-R = microbiologic modified intent-to-treat resistant; ESBL = extended spectrum beta-lactamase; TMP-SMX = trimethoprim-sulfamethoxazole; n = number of patients; N = number of patients in a population.

7.5.1.1.2.2 Susceptibility of Baseline Pathogens

For patients in the microMITT-R populations, susceptibility data for baseline pathogens isolated in at least 10 patients total, are presented for both treatment groups in Table 42.

Table 42 Study 301 Activity of Sulopenem and Ciprofloxacin Against Baseline Pathogens – microMITT-R Population – Both Treatment Groups

Organism Antibiotic	N	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	CLSI %S/%I/%R
Escherichia coli	N = 247			
Sulopenem		0.03	0.06	NA
Ciprofloxacin		>2	>2	3.2/0.4/96.4
Klebsiella pneumoniae	N = 28			
Sulopenem		0.12	4	NA
Ciprofloxacin		>2	>2	10.7/0/89.3
Proteus mirabilis	N = 15			
Sulopenem		0.25	0.25	NA
Ciprofloxacin		2	>2	6.7/46.7/46.7

Source: Table 14.1.2.18.1
Note: percentages are calculated as 100 × (n/N); for the %S/%I/%R column there is no breakpoint for CLSI when NA appears.
Abbreviations: CLSI = Clinical and Laboratory Standards Institute; I = intermediate; MIC_{50} = minimum inhibitory concentration required to inhibit the growth of 50% of organism; MIC_{90} = minimum inhibitory concentration required to inhibit the growth of 90% of organism; microMITT-R = microbiologic modified intent-to-treat resistant; N = number of pathogens identified in the microMITT-R population; R = resistant; S = susceptible.

7.5.1.1.3 Overall Response

In the population of patients in Study 301 with baseline pathogens resistant to quinolones (microMITT-R), oral sulopenem demonstrated superiority to ciprofloxacin [Difference: 26.6; p <0.001] for the primary endpoint of overall success at the TOC visit (Table 43). The most common reason for overall non-response in the oral sulopenem and ciprofloxacin groups was that the urine culture at the follow-up visit demonstrated $\geq 10^3$ CFU/mL of the baseline uropathogen, unassociated with any concomitant UTI symptoms. Overall failure due to both lack of resolution of clinical symptoms and persistence of the baseline pathogen, as well as receipt of non-study antibacterial therapy for uUTI, occurred more frequently for patients randomized to ciprofloxacin.

Table 43: Study 301 Overall Response at TOC and Reasons for Overall Non-response - microMITT-R Population

	Sulopenem n (%) N=147	**Ciprofloxacin n (%) N=139**	**Difference % (95% CI)**	**p-value**
Overall response	92 (62.6)	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)		
Reasons for Overall Non-response				
Total number of non-responders	49 (33.3)	84 (60.4)		
Urine culture at TOC visit demonstrates $\geq 10^3$ CFU/mL of the baseline uropathogen (**microbiologic failure only**)	27 (18.4)	38 (27.3)		
No resolution or worsening of symptoms of uUTI present at trial entry and/or new uUTI symptoms (**clinical failure only**)	17 (11.6)	13 (9.4)		
Urine culture $\geq 10^3$ CFU/mL and at least one symptom not resolved (**both clinical and microbiologic failure**)	5 (3.4)	25 (18.0)		
Receipt of non-study antibacterial therapy for uUTI	0 (0.0)	11 (7.9)		
Antibacterial therapy alone	0 (0.0)	8 (5.8)		
Death due to uUTI	0 (0.0)	0 (0.0)		

Source: Tables 14.2.2.1.1.1, Table 14.2.2.1.2.1

7.5.1.1.4 Clinical Response

The clinical response and reasons for clinical non-response as determined by the patient and the investigator at TOC for the microMITT-R population are provided in Table 44 and Table 45, respectively. Both patient-determined and investigator-assessed clinical response rates were higher for patients receiving sulopenem.

Table 44: Study 301 Clinical Response (Patient-Determined) and Reasons for Clinical Non-response at TOC in the microMITT-R Population

	Sulopenem n (%) N=147	Ciprofloxacin n (%) N=139	Difference % (95% CI)	p-value
Clinical success	122 (83.0)	87 (62.6)	20.4 (10.2, 30.4)	<0.001
Clinical failure	22 (15.0)	46 (33.1)		
Indeterminate	3 (2.0)	6 (4.3)		
Reasons for Clinical Non-response				
uUTI symptoms not resolved/developed new symptoms	22 (15.0)	38 (27.3)		
Rescue therapy received	0 (0.0)	11 (7.9)		
Death	0 (0.0)	0 (0.0)		

Source: Table 14.2.2.10.1.1, Table 14.2.2.10.2.1

Table 45: Study 301 Clinical Response (Investigator-Determined) and Reasons for Clinical Non-response at TOC in the microMITT-R Population

	Sulopenem n/N (%)	Ciprofloxacin n/N (%)	Difference % (95% CI)
Clinical success	126/144 (87.5)	90/134 (67.2)	20.3 (10.7, 30.0)
Clinical failure	18/144 (12.5)	42/134 (31.3)	
Indeterminate	0/144 (0.0)	2/134 (1.5)	
Reasons for Clinical Non-response			
Persistence/progression of any pre-therapy uUTI signs/symptoms	18/144 (12.5)	35/134 (26.1)	
Use of additional antibiotics for the current infection	1/144 (0.7)	16/134 (11.9)	
Previously met criteria for failure and received rescue antibiotics	0/144 (0.0)	7/134 (5.2)	
Death related to uUTI prior to EOT	0/144 (0.0)	0/134 (0.0)	

Source: Table 14.2.2.14.1.1, Table 14.2.2.14.2.1. Note in this analysis of the investigator response, 'indeterminate' was a specific option for the reason for failure and missing data was not considered as a reason for failure.

7.5.1.2 MicroMITT Population

Per the prespecified hierarchical testing plan, non-inferiority in the microMITT population would be assessed if superiority had been established in the microMITT-R population.

7.5.1.2.1 Baseline Demographics

Demographic characteristics were similar for patients in the microMITT population randomized to either oral sulopenem or ciprofloxacin (Table 46).

Table 46: Study 301 Demographic Characteristics of Patients in the microMITT Population

Parameter	Sulopenem N=517	Ciprofloxacin N=554
Age, years (SD)	51.9 (19.2)	51.5 (19.2)
Min, max	18.0, 89.0	18.0, 96.0
Female, n (%)	517 (100)	554 (100)
Ethnicity, n (%)		
Hispanic/Latino	141 (27.3)	154 (27.8)
Not Hispanic/Latino	373 (72.1)	399 (72.0)
Not reported	2 (0.4)	1 (0.2)
Unknown	1 (0.2)	--
Geographic Region, n (%)		
US	269 (52.0)	300 (54.2)
Ex-US	248 (48.0)	254 (45.8)
Race, n (%)		
American Indian or Alaska Native	4 (0.8)	--
Black	47 (9.1))	46 (8.3)
Asian	5 (1.0)	3 (0.5)
White	460 (89.0)	502 (90.6)
Other	1 (0.2)	3 (0.5)
Diabetes present at Baseline, n (%)	69 (13.3)	75 (13.5)
BMI (kg/m^2)		
Median	27.8	27.6
Min, max	(38.1, 156.0)	(15.2, 53.4)
Creatinine clearance (mL/min)[a]		
Median	74.0	77.0
Range	(14.0, 161.0)	(23.0, 199.0)

Source: Table 14.1.3.4.1; [a]Calculated by Cockcroft-Gault method. Abbreviations: BMI = body mass index; n = number of patients in study population; N = Number of randomized patients; SD = standard deviation; US = United States.

7.5.1.2.2 Baseline Pathogens

Pathogens cultured from urine, and that qualified patients for the microMITT population, are presented in Table 47. The most commonly identified pathogens in both groups were *E. coli* (84.9%), *K. pneumoniae* (9.2%), and *P. mirabilis* (3.2%) and were balanced between the treatment arms.

Table 47: Study 301 Pathogens from Urine at Baseline - microMITT Population

Organism	Sulopenem n (%) N=517	Ciprofloxacin n (%) N=554
Number of Patients with at least one study uropathogen in the urine at baseline	517 (100)	554 (100)
Escherichia coli	440 (85.1)	469 (84.7)
Klebsiella pneumoniae	51 (9.9)	48 (8.7)
Proteus mirabilis	17 (3.3)	17 (3.1)
Staphylococcus saprophyticus	5(1.0)	8 (1.4)
Klebsiella aerogenes	4 (0.8)	6 (1.1)
Morganella morganii	3 (0.6)	4 (0.7)
Citrobacter freundii	0 (0.0)	6 (1.1)
Enterobacter cloacae complex	4 (0.8)	2 (0.4)
Citrobacter koseri	4 (0.8)	1 (0.2)
Klebsiella oxytoca	2 (0.4)	3 (0.5)
Klebsiella variicola	4 (0.8)	1 (0.2)
Lelliottia amnigena	1 (0.2)	3 (0.5)
Raoultella planticola	0 (0.0)	2 (0.4)
Enterobacter aerogenes	0 (0.0)	1 (0.2)
Pantoea septica	0 (0.0)	1 (0.2)
Providencia stuartii	0 (0.0)	1 (0.2)
Serratia marcescens	0 (0.0)	1 (0.2)

Source: Table 14.1.3.9.1
Note: percentages are calculated as 100 × (n/N).
Abbreviations: microMITT = microbiologic modified intent-to-treat; n = number of patients; N = number of patients in the microMITT population.

7.5.1.2.2.1 Distribution of Baseline Study Uropathogens by Antibiotic Resistance

A total of 145 patients, just under 14% of study patients overall, had at least 1 baseline Enterobacterales pathogen that was ESBL-positive, as determined by having a ceftriaxone MIC of >1 μg/mL (Table 48). A total of 293 (27.4%) and 338 (31.6%) of study patients overall had at least 1 baseline Enterobacterales pathogen that was non-susceptible to quinolones and trimethoprim-sulfamethoxazole, respectively. Notably, 11% had a baseline organism non- susceptible to β-lactams, quinolones and trimethoprim-sulfamethoxazole, and 5% had a baseline organism non-susceptible to all orally available classes of antibiotics tested (β-lactams, quinolones, trimethoprim-sulfamethoxazole, and nitrofurantoin). As noted previously, there are a small number of microMITT isolates with discordant ciprofloxacin susceptibility culture results between the two labs that required PCR confirmation in order to assign to either the resistant or susceptible sub-population.

Table 48: Study 301 Distribution of Pathogens by ESBL, Quinolone, Trimethoprim-Sulfamethoxazole and Nitrofurantoin Status – microMITT Population

Parameter	Sulopenem n (%) N=517	Ciprofloxacin n (%) N=554
ESBL Status		
Positive	73 (14.1)	72 (13.0)
Negative	436 (84.3)	467 (84.3)
Missing	8 (1.5)	15 (2.7)
Quinolone Susceptibility Status		
Susceptible	363 (70.2)	404 (72.9)
Non-susceptible	150 (29.0)	143 (25.8)
Missing	4 (0.8)	7 (1.3)
Trimethoprim-sulfamethoxazole Susceptibility Status		
Susceptible	342 (66.2)	380 (68.6)
Non-susceptible	171 (33.1)	167 (30.1)
Missing	4 (0.8)	7 (1.3)
Nitrofurantoin Susceptibility Status		
Susceptible	416 (80.5)	452 (81.6)
Non-susceptible	97 (18.8)	95 (17.1)
Missing	4 (0.8)	7 (1.3)
Quinolone Resistant/ β-lactam resistant /Trimethoprim-sulfamethoxazole resistant	65 (12.6)	51 (9.2)
Quinolone Resistant/ β-lactam resistant /Trimethoprim-sulfamethoxazole resistant/ Nitrofurantoin Resistant	25 (4.8)	28 (5.1)

Source: Table 14.1.3.11.1, Table 14.2.3.1.1.4
Note: Percentages are calculated as 100 × (n/N). Patients were considered ESBL-positive if they had a baseline urine specimen or blood culture positive for at least 1 Enterobacterales with a ceftriaxone MIC of >1 µg/mL;
Abbreviations: MIC = minimum inhibitory concentration; microMITT = microbiologic modified intent-to-treat; ESBL = extended spectrum beta-lactamase; n = number of patients; N = number of patients in a population.

7.5.1.2.2.2 Susceptibility of Baseline Pathogens

Susceptibility data for both treatment groups combined, for baseline pathogens isolated in at least 10 patients total, are presented in Table 49. There were four patients in the microMITT population with baseline infection due to carbapenem-resistant *K. pneumoniae*, two on each arm. Approximately 4% (42/1071) of isolates in the microMITT population had discordant ciprofloxacin susceptibility culture results that required PCR confirmation in order to assign to either the resistant or susceptible sub-population.

Table 49: Study 301 Activity of Sulopenem and Ciprofloxacin Against Baseline Pathogens in the microMITT Population – Both Treatment Groups

Organism Antibiotic	N	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	CLSI %S/%I/%R
Escherichia coli	N = 900			
Sulopenem		0.03	0.06	NA
Ciprofloxacin		≤0.06	>2	72.4/0.7/26.9
Klebsiella pneumoniae	N = 96			
Sulopenem		0.06	0.12	NA
Ciprofloxacin		≤0.06	>2	72.9/0/27.1
Proteus mirabilis	N = 32			
Sulopenem		0.25	0.25	NA
Ciprofloxacin		0.12	>2	56.3/21.9/21.9
Staphylococcus saprophyticus	N = 13			
Sulopenem		0.25	0.25	NA
Ciprofloxacin		0.25	0.5	100/0/0
Klebsiella aerogenes	N = 10			
Sulopenem		0.06	0.12	NA
Ciprofloxacin		≤0.06	≤0.06	100/0/0

Source: Table 14.1.3.18.1
Note: percentages are calculated as 100 × (n/N); for the %S/%I/%R column there is no breakpoint for CLSI when NA appears.
Abbreviations: CLSI = Clinical and Laboratory Standards Institute; I = intermediate; MIC_{50} = minimum inhibitory concentration required to inhibit the growth of 50% of organism; MIC_{90} = minimum inhibitory concentration required to inhibit the growth of 90% of organism; microMITT = microbiologic modified intent-to-treat; N = number of pathogens identified in the microMITT population; R = resistant; S = susceptible.

7.5.1.2.3 Overall Response

For the microMITT population, the overall response at the Test of Cure visit, along with the reasons for non-response, are shown in Table 50. Overall success was seen in 65.6% of patients on oral sulopenem and 67.9% of patients on the ciprofloxacin [treatment difference; (95%CI): -2.3%, (-7.9, 3.3)]

In the MITT population, which would represent truly empirically treated patients without value of a culture result prior to antibiotic administration and defined as all patients who had symptoms consistent with uUTI, a urinalysis that was positive for leukocyte esterase and nitrite, who were randomized and received study drug though did not necessarily have a positive urine culture at $\geq 10^5$ CFU/mL at baseline, the clinical response was also similar between the two regimens.

Table 50: Study 301 Overall Response at TOC and Reasons for Overall Non-response microMITT Population

	Sulopenem n/N (%)	Ciprofloxacin n/N (%)	Difference % (95% CI)	Difference % (99% CI)
Overall response	339/517 (65.6)	376/554 (67.9)	-2.3 (-7.9, 3.3)	-2.3 (-9.7, 5.1)
Overall non-response				
Indeterminate				
Reasons for Overall Non-response	154 (29.8)	149 (26.9)		
Total number of non-responders				
Urine culture at the TOC visit demonstrates $\geq 10^3$ CFU/mL of the baseline uropathogen (**microbiologic failure only**)	74 (14.3)	54 (9.7)		
No resolution or worsening of symptoms of uUTI present at trial entry and/or new uUTI symptoms (**clinical failure only**)	55 (10.6)	55 (9.9)		
Urine culture $\geq 10^3$ CFU/mL and at least one symptom not resolved (**both clinical and microbiologic failure**)	23 (4.4)	29 (5.2)		
Receipt of non-study antibacterial therapy for uUTI	4 (0.8)	16 (2.9)		
Antibacterial therapy alone	2 (0.4)	11 (2.0)		
Death due to uUTI	0 (0.0)	0 (0.0)		

Source: Table 14.2.3.1.1.1; Table 14.2.3.10.1.1; Table 14.2.3.6.1.1; Table 14.2.3.4.1.1; Table 14.2.3.10.1.1; post-hoc Table 83. CI = confidence interval; microMITT = microbiologic modified intent-to-treat; n = number of patients in study population; N = Number of randomized patients; TOC = test of cure; EOT = end of treatment; ASB = asymptomatic bacteriuria.; Not all patients in MITT population had culture data so clinical response is provided.

The most common reason for overall nonresponse in the oral sulopenem and ciprofloxacin groups was that the urine culture at the TOC visit demonstrated $\geq 10^3$ CFU/mL of the baseline uropathogen without associated clinical symptoms (asymptomatic bacteriuria), seen in 14.3% and 9.7% in patients receiving sulopenem and ciprofloxacin, respectively. Overall nonresponse at TOC due to both clinical and microbiologic failure occurred in 4.4% and 5.2% of patients in the oral sulopenem arm and ciprofloxacin arm, respectively; receipt of non-study antibacterial therapy for uUTI occurred less frequently on oral sulopenem (0.8%) than ciprofloxacin (2.9%).

7.5.1.2.4 Clinical Response

The clinical response and reasons for clinical non-response as determined by the patient and the investigator at TOC for the microMITT population are provided in Table 51 and Table 52, respectively. Both patient-determined and investigator-assessed clinical response rates were similar for the two treatment arms.

Table 51: Study 301 Clinical Response (Patient-Determined) and Reasons for Clinical Non-response at TOC in the microMITT Population

Clinical Response	Sulopenem n (%) N=517	Ciprofloxacin n (%) N=554	Difference % (95% CI)
Clinical success	422 (81.6)	436 (78.7)	2.9 (-1.9, 7.7)
Clinical failure	80 (15.5)	95 (17.1)	
Indeterminate	15 (2.9)	23 (4.2)	
Reasons for Clinical Non-response			
uUTI symptoms not resolved/developed new symptoms	78 (15.1)	84 (15.2)	
Rescue therapy received	4 (0.8)	16 (2.9)	
Death	0 (0.0)	0 (0.0)	

Source: Table 14.2.3.10.1.1, Table 14.2.3.10.2.1

Table 52: Study 301 Clinical Response (Investigator-Determined) and Reasons for Clinical Non-response at TOC in the microMITT Population

Investigator's Assessment of Clinical Response	Sulopenem n/N (%)	Ciprofloxacin n/N (%)	Difference % (95% CI)
Clinical success	446/503 (88.7)	463/531 (87.2)	1.5 (-2.5, 5.5)
Clinical failure	57/503 (11.3)	65/531 (12.2)	
Indeterminate	0/503 (0.0)	3/531 (0.6)	
Reasons for Clinical Non-response			
Persistence/progression of any pre-therapy uUTI signs/symptoms	54/503 (10.7)	56/531 (10.5)	
Use of additional antibiotics for the current infection	11/503 (2.2)	25/531 (4.7)	
Previously met criteria for failure and received rescue antibiotics	3/503 (0.6)	9/531 (1.7)	
Death related to uUTI prior to EOT	0 (0.0)	0 (0.0)	

Source: Table 14.2.3.14.1.1, Table 14.2.3.14.2.1

7.5.1.2.5 Microbiologic Response

The microbiologic response per patient at TOC for the microMITT population is provided in Table 53. The microbiologic response was similar for the two arms.

Post-baseline isolates with sulopenem MICs that had increased by more than four-fold (i.e., four dilutions) relative to baseline isolates of the same genus and species were not observed in this study.

Table 53: Study 301 Microbiologic Response Per Patient and Reasons for Microbiologic Nonresponse at TOC in the microMITT Population

Microbiologic Response per Patient	Sulopenem n (%) N=517	Ciprofloxacin n (%) N=554	Difference % (95% CI)
Microbiologic success	396 (76.6)	438 (79.1)	-2.5 (-7.5, 2.5)
Microbiologic failure	97 (18.8)	83 (15.0)	
Reasons for Microbiologic Non-response			
Persistence	93 (18.0)	82 (14.8)	
Persistence with increasing MIC	4 (0.8)	1 (0.2)	
Presumed persistence	0 (0.0)	0 (0.0)	
Indeterminate	24 (4.6)	33 (6.0)	

Source: IT001-301, Table 14.2.3.6.1.1
Note: CI = confidence interval; MIC = minimum inhibitory concentration; TOC = test of cure; the percentages are calculated as 100 x (n/N); persistence with increasing MIC means a ≥4-fold MIC increase from baseline visit; microbiologically evaluable patients are both clinically evaluable and microMITT.

Table 54 presents the microbiologic response at TOC by MIC to sulopenem for patients treated with either oral sulopenem or ciprofloxacin. Among those patients treated with oral sulopenem, there does not appear to be a difference in success rates across MICs, acknowledging that there are small numbers in some subcategories.

Table 54: Study 301 Microbiologic Response at TOC by Pathogen for MIC to Sulopenem in the microMITT Population

Pathogen / MIC (µg/mL)	Sulopenem n/N (%)	Ciprofloxacin n/N (%)
E. coli, N	437	463
≤0.015	147/190 (77.4)	162/195 (83.1)
0.03	141/186 (75.8)	167/215 (77.7)
0.06	35/45 (77.8)	24/38 (63.2)
0.12	7/10 (70.0)	10/13 (76.9)
0.25	3/5 (60.0)	2/2 (100)
0.50	-	-
1.0	1/1 (100)	-
K. pneumoniae, N	48	48
≤0.015	5/6 (83.3)	1/2 (50.0)
0.03	14/18 (77.8)	15/19 (78.9)
0.06	9/14 (64.3)	10/11 (90.9)
0.12	7/8 (87.5)	9/11 (81.8)
0.25	-	1/1 (100)
0.50	-	1/2 (50.0)
1.0	-	-
2.0	-	-
4.0	1/1 (100)	1/2 (50.0)
8.0	1/1 (100)	-
P. mirabilis, N	17	15
≤0.015	-	-
0.03	1/1 (100)	-
0.06	1/2 (50.0)	-
0.12	2/4 (50.0)	5/7 (71.4)
0.25	10/10 (100)	6/6 (100)
0.5	-	1/2 (50.0)

Source: Table 14.2.3.6.1.7
Note: microMITT = Microbiologic Modified Intent-to-treat; The percentages are calculated as 100 x (n/N) where n = number of patients with Eradication response to the pathogen and MIC to Sulopenem and N = number of patients with specific pathogen and MIC to Sulopenem; only pathogens where at least one favorable response occurred are displayed; success is defined as microbiologic success at TOC; indeterminate responses are considered failures; MIC = Minimum Inhibitory Concentration.

7.5.1.2.6 Additional Analyses of the Primary Endpoint

7.5.1.2.6.1 Overall Response at TOC by MIC to Sulopenem

Table 55 presents the overall response at TOC by MIC to sulopenem for patients treated with either oral sulopenem or ciprofloxacin. Among patients treated with oral sulopenem, there does not appear to be a difference among MICs, acknowledging limitations due to small numbers in subcategories.

Table 55: Study 301 Overall Response at TOC by Pathogen for MIC to Sulopenem in the microMITT Population

Pathogen / MIC (µg/mL)	Sulopenem n/N (%)	Ciprofloxacin n/N (%)
E. coli, N	437	463
≤0.015	127/190 (66.8)	136/195 (69.7)
0.03	120/186 (64.5)	144/215 (67.0)
0.06	28/45 (62.2)	18/38 (47.4)
0.12	4/10 (40.0)	7/13 (53.8)
0.25	3/5 (60.0)	2/2 (100)
0.50	-	-
1.0	0/1 (0.0)	-
K. pneumoniae, N	48	48
≤0.015	3/6 (50.0)	1/2 (50.0)
0.03	13/18 (72.2)	14/19 (73.7)
0.06	6/14 (42.9)	7/11 (63.6)
0.12	7/8 (87.5)	9/11 (81.8)
0.25	-	0/1 (0.0)
0.50	-	1/2 (50.0)
1.0	-	-
2.0	-	-
4.0	1/1 (100)	1/2 (50.0)
8.0	1/1 (100)	-
P. mirabilis, N	17	15
≤0.015	-	-
0.03	1/1 (100)	-
0.06	1/2 (50.0)	-
0.12	2/4 (50.0)	5/7 (71.4)
0.25	9/10 (90.0)	6/6 (100)
0.5	-	1/2 (50.0)

Source: Table 14.2.3.1.1.5
Note: microMITT = Microbiologic Modified Intent-to-treat; The percentages are calculated as 100 x (n/N) where N = number of patients with specific pathogen and MIC to Sulopenem; only pathogens where at least one favorable response occurred are displayed; success is defined as combined clinical and microbiologic success at TOC; indeterminate responses are considered failures; MIC = minimum inhibitory concentration.

7.5.1.2.6.2 Overall Response at TOC by MIC to Ciprofloxacin

In comparing the outcomes of patients with a uUTI treated with sulopenem or ciprofloxacin, different conclusions can be drawn depending on the ciprofloxacin MIC threshold used to divide the treatment population. Using ≥2 µg/mL as the threshold, consistent with generally accepted thresholds for ciprofloxacin *in vitro* susceptibility and to define the populations in this trial, results in outcome measures as noted in Table 56, 'Primary Analyses: Ciprofloxacin MIC breakpoint of ≥2 µg/mL'. In order to gain confidence that the superiority outcome is not overly sensitive to the selected breakpoint, we examined the overall response on each treatment regimen by MIC to

ciprofloxacin. As see in Table 56, statistical superiority would be observed even if the threshold MIC was as low as 0.03 µg/mL.

A number of observations follow from this data presentation. With regard to ciprofloxacin activity against Enterobacterales in the urine, there appear to be three types of response.

- One, associated with organisms with an MIC > 2 µg/mL, results in an overall response outcome of ~40%, consistent with placebo effects, in which drug concentrations, presumably all in the urine, are inadequate to affect a microbiologic response.
- A second overall response of ~65% occurs for organisms ≥ 0.03 µg/mL but <2 µg/mL, presumably reflecting adequate urinary concentrations of drug to cause a microbiologic response.
- A third type of response is seen in the 'highly-susceptible' organisms that have MIC's ≤ 0.03 µg/mL, which likely benefit from the urinary concentrations of drug but in which another factor is influencing the response rate.

Of interest, at 0.06 µg/mL the ratio of $AUC_{0\text{-}24}$/MIC for ciprofloxacin 250 mg bid is 160, the PK/PD ratio which reflects adequate tissue concentrations to cause a microbiologic effect for a quinolone; at 0.03 µg/mL the $AUC_{0\text{-}24}$/MIC is 327. The two tissues relevant to uUTI would be the bladder wall and the vaginal mucosa. Evidence to support infection of the bladder epithelium in the etiology of a uUTI remains controversial. Colonization of the vaginal mucosa, however, has been proposed to precede bladder colonization [Thomas-White] and has been demonstrated to be impacted by treatment with ciprofloxacin to a greater degree than a β-lactam [Hooten 2005; Hooton 2012]. If that is the case, then ciprofloxacin is selectively reducing the colonizing flora in the vaginal mucosa for organisms that have an MIC ≤ 0.03 µg/mL.

Table 56: Study 301 Overall Response at TOC by Ciprofloxacin MIC – microMITT Population

All isolates, N MIC (µg/mL)	Sulopenem n/N (%) 529 Overall Response	Ciprofloxacin n/N (%) 564 Overall Response	Primary Analyses: Ciprofloxacin MIC breakpoint of ≥2 µg/mL	Ciprofloxacin MIC breakpoint of >0.03 µg/mL
0.004	1/1 (100.0)	1/1 (100.0)	247/370 (66.8%) vs 326/415 (78.6%) -11.8% (-18.0, -5.6)	193/296 (65.2%) vs 253/314 (80.6%) -15% (-22.3, -8.4)
0.008	10/19 (52.6)	11/17 (64.7)		
0.015	137/196 (69.9)	169/208 (81.3)		
0.03	45/80 (56.3)	72/88 (81.8)		
0.06	12/15 (80.0)	12/14 (85.7)		153/233 (65.7%) vs 131/250 (52.4%) p=0.003
0.12	7/10 (70.0)	9/12 (75.0)		
0.25	20/30 (66.7)	26/35 (74.3)		
0.5	15/22 (68.2)	24/34 (70.6)		
1	6/8 (75.0)	5/11 (45.5)		
≥2	93/148 (62.8)	55/144 (38.2)	P<0.001	

Source: Post-hoc Table 34

This effect of ciprofloxacin on the ciprofloxacin 'highly-susceptible' flora disproportionately impacts the difference in the rate of asymptomatic bacteriuria (ASB) between the two regimens (Table 57). In fact, sulopenem did not achieve non-inferiority with ciprofloxacin solely because of asymptomatic bacteriuria in this 'highly-susceptible' population. At MIC's from 0.06 µg/mL to 1 µg/mL, there were 10 and 8 cases of ASB on sulopenem and ciprofloxacin, respectively. All the ASB difference is seen among organisms with MIC's ≤ 0.03 µg/mL (40 vs 8 cases on sulopenem and ciprofloxacin, respectively). It is not all patients with ciprofloxacin-susceptible uropathogens in which a difference in outcomes is seen but predominantly those patients with colonizing flora that is affected by the tissue levels achieved by 250 mg bid of ciprofloxacin.

Table 57: Study 301 Overall Response at TOC and Proportion of Patients with Asymptomatic Bacteriuria by Ciprofloxacin MIC in the microMITT Population

	Overall Response		Asymptomatic Bacteriuria	
	Sulopenem n/N (%)	**Ciprofloxacin n/N (%)**	**Sulopenem n/N (%)**	**Ciprofloxacin n/N (%)**
All isolates, N	**529**	**564**	**529**	**564**
Ciprofloxacin MIC (µg/mL)				
0.004	1/1 (100.0)	1/1 (100.0)	0/1 (0.0)	0/1 (0.0)
0.008	10/19 (52.6)	11/17 (64.7)	4/19 (21.1)	0/17 (0.0)
0.015	137/196 (69.9)	169/208 (81.3)	22/196 (11.2)	6/208 (2.9)
0.03	45/80 (56.3)	72/88 (81.8)	14/80 (17.5)	2/88 (2.3)
0.06	12/15 (80.0)	12/14 (85.7)	1/15 (6.7)	1/14 (7.1)
0.12	7/10 (70.0)	9/12 (75.0)	2/10 (20.0)	2/12 (16.7)
0.25	20/30 (66.7)	26/35 (74.3)	4/30 (13.3)	3/35 (8.6)
0.5	15/22 (68.2)	24/34 (70.6)	2/22 (9.1)	1/34 (2.9)
1	6/8 (75.0)	5/11 (45.5)	1/8 (12.5)	1/11 (9.1)
≥2	93/148 (62.8)	55/144 (38.2)	27/148 (18.2)	38/144 (26.4)

Source: Post-hoc Table 34; post-hoc Table 35

7.5.1.2.6.3 Covariate Analysis of the Overall Response in the microMITT Population

Covariate analysis of the overall response at TOC in the microMITT population is provided in Table 58. Extension of the pre-specified covariate analysis identified 9 statistically significant variables related to overall response at the TOC Visit. Treatment conditional on baseline susceptibility to a quinolone was the most significant variable. Having diabetes, a higher symptom score, an ESBL positive uropathogen (which was frequently associated with quinolone resistance), and lower creatinine clearance was associated with relatively lower overall response at the TOC visit.

Table 58: Study 301 Significant Covariates from Stepwise Selection Associated with Overall Response at Test of Cure – microMITT Population

Covariate	Odds Ratio (95% CI)	p-value
Treatment (Sulopenem vs Ciprofloxacin)		<0.001
Susceptible	0.55 (0.40, 0.77)	
Resistant	3.17 (1.89, 5.32)	
Creatinine Clearance		<0.001
Susceptible	1.01 (1.00, 1.02)	
Resistant	1.02 (1.01, 1.04)	
Randomization Order Group	1.06 (1.01, 1.11)	0.023
Diabetes	0.64 (0.43, 0.95)	0.025
Baseline Susceptibility Group		<0.001
Sulopenem and Creatinine clearance (76.6 mL/min)	0.92 (0.59, 1.43)	
Ciprofloxacin and Creatinine clearance (76.6 mL/min)	5.24 (3.35, 8.20)	
ESBL status (positive)	0.66 (0.44, 0.99)	0.044
Symptom Score	0.94 (0.89, 0.99)	0.031
Treatment X Baseline Susceptibility Group Interaction Term		<0.001
Creatinine clearance X Baseline Susceptibility Group Interaction Term		0.012

Source: post-hoc Table 22.
Note: potential baseline covariates include age, race, *E. coli* as baseline uropathogen, baseline uropathogen, ciprofloxacin susceptibility group, ESBL status, diabetes, creatinine clearance, randomization period (10^{th} percentiles), PSAQ symptom score, and treatment regimen; baseline covariates that were identified in the first three steps of the model to go into the final analysis include age, race, *E. coli* as baseline uropathogen, ciprofloxacin susceptibility group, ESBL status, diabetes, creatinine clearance, randomization period (10^{th} percentiles), treatment regimen, treatment x ciprofloxacin susceptibility group interaction term, and creatinine clearance x ciprofloxacin susceptibility group interaction term.

7.5.1.2.6.4 Overall Response at TOC Using All Sites Including Sites 202 and 218

Throughout the study period, surveillance of microbiologic data was performed to identify results possibly impacted by cross-contamination. This process identified questionable culture results from two sites (site 202 and site 218). Evaluation of the questionable isolates by pulse-field gel electrophoresis, in addition to concerns about PK data collection from site 202, led to the conclusion that data from these sites was not reliable, leading to the removal of both sites from the efficacy analyses. Overall response at TOC when these two sites are included, shown in Table 59, is similar to when the two sites are excluded.

Table 59: Study 301 Overall Response at TOC Using All Sites Including Sites 202 and 218 – MicroMITT and ME-TOC Populations

Population/Overall Response	Sulopenem n/N (%)	Ciprofloxacin n/N (%)	Difference % (95% CI)
MicroMITT			
Overall Responder	361/546 (66.1)	388/572 (67.8)	-1.7 (-7.2, 3.8)
Overall Non-responder	157/546 (28.8)	152/572 (26.6)	
Indeterminate	28/546 (5.1)	32/572 (5.6)	
ME-TOC			
Overall Responder	321/458 (70.1)	349/475 (73.5)	-3.4 (-9.2, 2.4)
Overall Non-responder	137/458 (29.9)	126/475 (26.5)	

Source: Table 14.2.3.1.1.18.
Note: CI = confidence interval; microMITT = microbiologic modified intent-to-treat; ME = microbiologically evaluable; 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 are considered failures; microbiologically evaluable patients are both clinically evaluable and microMITT.

7.5.1.2.6.5 Impact of Asymptomatic Bacteriuria on Clinical Outcomes at Subsequent Visits

As previously described (Table 16), the presence of asymptomatic bacteriuria did not disproportionally affect the subsequent clinical failure rate relative to patients who had been cured and does not predict subsequent clinical release. In this study, the presence of asymptomatic bacteriuria did not predict subsequent clinical failure. This finding is supported by the opinion of the Infectious Disease Society of America (Nicolle, 2019).

7.5.1.3 MicroMITT-S Population

Per the prespecified hierarchical testing plan, non-inferiority in the microMITT-S population was assessed in parallel to assessing superiority in the microMITT-R population.

7.5.1.3.1 Baseline Demographics

The demographic characteristics of patients randomized to each treatment regimen were similar (Table 60).

Table 60: Study 301 Demographic Characteristics of Patients in the microMITT-S Population

Parameter	Sulopenem N=370	Ciprofloxacin N=415
Age, years (SD)	50.9 (19.0)	49.9 (18.6)
Min, max	18.0, 89.0	18.0, 96.0
Female, n (%)	370 (100)	415 (100)
Ethnicity, n (%)		
Hispanic/Latino	83 (22.4)	101 (24.3)
Not Hispanic/Latino	284 (76.8)	314 (75.7)
Not Reported	2 (0.5)	--
Unknown	1 (0.3)	--
Geographic Region, n (%)		
US	188 (50.8)	218 (52.5)
Ex-US	182 (49.2)	197 (47.5)
Race, n (%)		
American Indian or Alaska Native	4 (1.1)	--
Black	33 (8.9)	34 (8.2)
Asian	3 (0.8)	3 (0.7)
White	330 (89.2)	376 (90.6)
Other	--	2 (0.5)
Diabetes Present at Baseline, n (%)	42 (11.4)	49 (11.8)
BMI (kg/m^2)		
Median	26.3	25.5
Min, max	(16.0, 57.1)	(17.0, 52.4)
Creatinine clearance (mL/min)[a]		
Median	75.0	79.0
Range	(14.0, 161.0)	(26.0, 199.0)

Source: IT001-301 Table 14.1.1.4.1
[a]Calculated by Cockcroft-Gault method

7.5.1.3.2 Baseline Pathogens

Pathogens cultured from urine, and that qualified patients for the microMITT-S population, are presented in Table 61. The most commonly identified pathogens in both groups were *E. coli* (84.3%), *K. pneumoniae* (8.8%), and *P. mirabilis* (2.4%) and were balanced between the two treatment arms.

Table 61: Study 301 Pathogens from Urine at Baseline - microMITT-S Population

Organism	Sulopenem n (%) N=370	Ciprofloxacin n (%) N=415
Number of Patients with at least one study uropathogen in the urine at baseline	370 (100)	415 (100)
Escherichia coli	313 (84.6)	349 (84.1)
Klebsiella pneumoniae	37 (10.0)	32 (7.7)
Proteus mirabilis	8 (2.2)	11 (2.7)
Staphylococcus saprophyticus	5 (1.4)	8 (1.9)
Klebsiella aerogenes	4 (1.1)	6 (1.4)
Citrobacter freundii	0 (0.0)	6 (1.4)
Citrobacter koseri	4 (1.1)	1 (0.2)
Enterobacter cloacae complex	3 (0.8)	2 (0.5)
Klebsiella oxytoca	2 (0.5)	3 (0.7)
Klebsiella variicola	4 (1.1)	1 (0.2)
Lelliottia amnigena	1 (0.3)	3 (0.7)
Morganella morganii	0 (0.0)	3 (0.7)
Raoultella planticola	0 (0.0)	2 (0.5)
Enterobacter aerogenes	0 (0.0)	1 (0.2)
Pantoea septica	0 (0.0)	1 (0.2)
Serratia marcescens	0 (0.0)	1 (0.2)

Source: Table 14.1.1.9.1
Note: percentages are calculated as 100 × (n/N).
Abbreviations: microMITT-S = microbiologic modified intent-to-treat susceptible; n = number of patients; N = number of patients in the microMITT-S population.

7.5.1.3.2.1 Distribution of Baseline Study Uropathogens by Antibiotic Resistance

A total of 54 patients, just under 7% of microMITT-S patients, had at least 1 baseline Enterobacterales pathogen that was ESBL-positive, as determined by having a ceftriaxone MIC of >1 μg/mL (Table 62). In this quinolone susceptible population, approximately 20% and 15% were resistant to trimethoprim-sulfamethoxazole and nitrofurantoin, respectively. Notably, there are a small number of microMITT-S patients with a quinolone non-susceptible isolate. This is because there are a small number of isolates with discordant ciprofloxacin susceptibility culture results between the two labs that processed the initial urine samples and that required PCR confirmation in order to assign to either the resistant or susceptible sub-population. This could have resulted in a patient analyzed in the quinolone susceptible population who, at least by the IHMA culture results, had a quinolone non-susceptible culture.

Table 62: Study 301 Distribution of Pathogens by ESBL, Quinolone, Trimethoprim-Sulfamethoxazole and Nitrofurantoin Status – microMITT-S Population

Parameter	Sulopenem n (%) N=370	Ciprofloxacin n (%) N=415
ESBL Status		
Positive	23 (6.2)	31 (7.5)
Negative	339 (91.6)	369 (88.9)
Missing	8 (2.2)	15 (3.6)
Quinolone Susceptibility Status		
Susceptible	361 (97.6)	402 (96.9)
Non-susceptible	5 (1.4)	6 (1.4)
Missing	4 (1.1)	7 (1.7)
Trimethoprim-sulfamethoxazole Susceptibility Status		
Susceptible	289 (78.1)	319 (76.9)
Non-susceptible	77 (20.8)	89 (21.4)
Missing	4 (1.1)	7 (1.7)
Nitrofurantoin Susceptibility Status		
Susceptible	308 (83.2)	351 (84.6)
Non-susceptible	58 (15.7)	57 (13.7)
Missing	4 (1.1)	7 (1.7)

Source: Table 14.1.1.11.1, Table 14.2.1.1.1.4
Note: Percentages are calculated as 100 × (n/N). Patients were considered ESBL-positive if they had a baseline urine specimen or blood culture positive for at least 1 Enterobacterales with a ceftriaxone MIC of >1 µg/mL; Abbreviations: MIC = minimum inhibitory concentration; microMITT-S = microbiologic modified intent-to-treat susceptible; ESBL = extended spectrum beta-lactamase; TMP-SMX = trimethoprim- sulfamethoxazole; n = number of patients; N = number of patients in a population.

7.5.1.3.3 Susceptibility of Baseline Pathogens

For patients in the microMITT-S populations, susceptibility data for both treatment groups combined are presented in Table 63. There are no isolates non-susceptible to carbapenems in the microMITT-S population. There are a small number of isolates with discordant ciprofloxacin susceptibility culture results that required PCR confirmation in order to assign to either the resistant or susceptible sub-population.

Table 63 Study 301 Activity of Sulopenem and Ciprofloxacin Against Baseline Pathogens – microMITT-S Population – Both Treatment Groups

Organism Antibiotic	N	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	CLSI %S/%I/%R
Escherichia coli	N = 653			
Sulopenem		0.03	0.03	NA
Ciprofloxacin		≤0.06	0.5	98.6/0.8/0.6
Klebsiella pneumoniae	N = 68			
Sulopenem		0.03	0.12	NA
Ciprofloxacin		≤0.06	0.12	98.5/0/1.5
Proteus mirabilis	N = 17			
Sulopenem		0.25	0.25	NA
Ciprofloxacin		≤0.06	0.12	100.0/0/0
Staphylococcus saprophyticus	N = 13			
Sulopenem		0.25	0.25	NA
Ciprofloxacin		0.25	0.5	100.0/0/0
Klebsiella aerogenes	N = 10			
Sulopenem		0.06	0.12	NA
Ciprofloxacin		≤0.06	≤0.06	100.0/0/0

Source: Table 14.1.1.18.1
Note: percentages are calculated as 100 × (n/N); for the %S/%I/%R column there is no breakpoint for CLSI when NA appears.
Abbreviations: CLSI = Clinical and Laboratory Standards Institute; I = intermediate; MIC_{50} = minimum inhibitory concentration required to inhibit the growth of 50% of organism; MIC_{90} = minimum inhibitory concentration required to inhibit the growth of 90% of organism; microMITT-S = microbiologic modified intent-to-treat susceptible; N = number of pathogens identified in the microMITT population; R = resistant; S = susceptible.

7.5.1.3.4 Overall Response

In this population of patients with organisms susceptible to quinolones, sulopenem was not noninferior to ciprofloxacin for the primary endpoint as the lower limit of the 95% confidence interval on the difference in outcomes at TOC was not greater than -10% (Table 64).

The difference in outcome between the two treatment regimens in this population of patients was driven primarily by the lower rate of asymptomatic bacteriuria post treatment in patients treated with ciprofloxacin, as identified in the reasons for failure in the overall response.

Table 64 Study 301 Overall Response at TOC and Reasons for Overall Non-response - microMITT-S Population

	Sulopenem n (%) N=370	**Ciprofloxacin n (%) N=415**	**Difference (%) (95% CI)**
Overall response	247/370 (66.8)	326/415 (78.6)	-11.8 (-18.0, -5.6)
Overall nonresponse	105 (28.4)	65 (15.7)	
Indeterminate	18 (4.9)	24 (5.8)	
Reasons for Overall Non-response			
Total number of non-responders	105 (28.4)	65 (15.7)	
Urine culture at the TOC visit demonstrates $\geq 10^3$ CFU/mL of the baseline uropathogen (**microbiologic failure only**)	47 (12.7)	16 (3.9)	
No resolution or worsening of symptoms of uUTI present at trial entry and/or new uUTI symptoms (**clinical failure only**)	38 (10.3)	42 (10.1)	
Urine culture $\geq 10^3$ CFU/mL and at least one symptom not resolved (**both clinical and microbiologic failure**)	18 (4.9)	4 (1.0)	
Receipt of non-study antibacterial therapy for uUTI	4 (1.1)	5 (1.2)	
Antibacterial therapy alone	2 (0.5)	3 (0.7)	
Death due to uUTI	0 (0.0)	0 (0.0)	

Source: Table 14.2.1.1.1.1, Table 14.2.1.1.2.1
Note: TOC = test of cure; CI = Confidence interval; microMITT-S = microbiological modified intent-to-treat susceptible; uUTI = uncomplicated urinary tract infection; CFU/mL = colony forming units/milliliter

7.5.1.3.5 Clinical Response

Clinical response outcomes, which notably do not include failures due to asymptomatic bacteriuria, were similar on each regimen. Both patient-determined (Table 65) and investigator-determined (Table 66) clinical response rates were similar for the two treatment arms.

Of note, the number of patients who received non-study antibiotics for uUTI differs on these two tables as non-study antibacterial therapy for uUTI leading to failure in the patient-determined assessment must have been administered prior to the time of the study visit (and antibiotics administered on the day of the visit, after the assessment, would be captured as antibiotic-failures at the next study visit) while antibacterial therapy for uUTI administered at the same time as a study visit could be considered a reason for treatment failure in the investigator's clinical assessment at a given visit.

Table 65: Study 301 Clinical Response (Patient-Determined) and Reasons for Clinical Non-response at TOC in the microMITT-S Population

Clinical Response	Sulopenem n (%) N=370	Ciprofloxacin n (%) N=415	Difference % (95% CI)
Clinical success	300 (81.1)	349 (84.1)	-3.0 (-8.4, 2.3)
Clinical failure	58 (15.7)	49 (11.8)	
Indeterminate	12 (3.2)	17 (4.1)	
Reasons for Clinical Non-response			
uUTI symptoms not resolved/developed new symptoms	56 (15.1)	46 (11.1)	
Rescue therapy received	4 (1.1)	5 (1.2)	
Death	0 (0.0)	0 (0.0)	

Source: Table 14.2.1.10.1.1, Table 14.2.1.10.2.1
Note: TOC = test of cure; CI = Confidence interval; microMITT-S = microbiological modified intent-to-treat susceptible; uUTI = uncomplicated urinary tract infection

Table 66: Study 301 Clinical Response (Investigator-Determined) and Reasons for Clinical Non-response at TOC in the microMITT-S Population

Investigator's Assessment of Clinical Response	Sulopenem n/N (%)	Ciprofloxacin n/N (%)	Difference % (95% CI)
Clinical success	320/359 (89.1)	373/397 (94.0)	-4.8 (-9.0, -0.9)
Clinical failure	39/359 (10.9)	23/397 (5.8)	
Indeterminate	0/359 (0.0)	1/397 (0.3)	
Reasons for Clinical Non-response			
Persistence/progression of any pretherapy uUTI signs/symptoms	36/359 (10.0)	21/397 (5.3)	
Use of additional antibiotics for the current infection	10/359 (2.8)	9/397 (2.3)	
Previously met criteria for failure and received rescue antibiotics	3/359 (0.8)	2/397 (0.5)	
Death related to uUTI prior to EOT	0 (0.0)	0 (0.0)	

Source: Table 14.2.1.14.1.1, Table 14.2.1.14.2.1
Note: EOT = End of treatment; TOC = test of cure; CI = Confidence interval; microMITT-S = microbiological modified intent-to-treat susceptible; uUTI = uncomplicated urinary tract infection

Of note, the greater percentage of patients with asymptomatic bacteriuria on sulopenem at Day 12 (12.7% vs. 3.9%) did not translate into an increase in clinical failure at Day 28 Final Visit, where the clinical response rate of oral sulopenem and ciprofloxacin, again, were similar (Table 67).

Table 67 Study 301 Clinical Response at EOT, TOC and Final Visit in microMITT-S Population

Timepoint/ Clinical Response	Sulopenem n (%) N=370	Ciprofloxacin n (%) N=415	Difference % (95% CI)
EOT (D5)	256 (69.2)	290 (69.9)	-0.7 (-7.2, 5.7)
Test of Cure (D12)	300 (81.1)	349 (84.1)	-3.0 (-8.4, 2.3)
Final Visit (D28)	295 (79.7)	341 (82.2)	-2.4 (-8.0, 3.1)

Source: Table 14.2.1.12.1.1 , 14.2.1.10.1.1 Table 14.2.1.13.1.1
Note: EOT = End of treatment; TOC = test of cure; CI = Confidence interval; microMITT-S = microbiological modified intent-to-treat susceptible.

7.5.1.3.6 Microbiologic Response

The microbiologic response per patient at TOC for the microMITT-S population is provided in Table 68. The proportion of patients with microbiologic success was higher in the ciprofloxacin arm. Per pathogen microbiologic responses are also higher for patients receiving ciprofloxacin, consistent with the primary endpoint.

Table 68: Study 301 Microbiologic Response Per Patient and Reasons for Overall Non-response at TOC in the microMITT-S Population

Microbiologic Response per Patient	Sulopenem n (%) N=370	Ciprofloxacin n (%) N=415	Difference % (95% CI)
Microbiologic success	287 (77.6)	369 (88.9)	-11.3 (-16.7, -6.2)
Microbiologic failure	65 (18.7)	20 (4.9)	
Reasons for Microbiologic Non-response			
Persistence	62 (18.1)	19 (4.9)	
Persistence with increasing MIC	3 (0.6)	1 (0.0)	
Presumed persistence	0 (0.0)	0 (0.0)	
Indeterminate	18 (4.9)	26 (6.3)	

Source: IT001-301, Table 14.2.1.6.1.1
Note: CI = confidence interval; MIC = minimum inhibitory concentration; TOC = test of cure; the percentages are calculated as 100 x (n/N); persistence with increasing MIC means a 4-fold MIC increase from baseline visit

Post-baseline isolates with sulopenem MICs that had increased by more than four-fold (i.e., four dilutions) relative to baseline isolates of the same genus and species were not observed in this study. Three microMITT-S patients in the sulopenem arm ([redacted] (b) (6)) had microbiologic persistence with increasing MIC.

- The first patient was a 39-year-old obese, Hispanic woman with a creatinine clearance of 79 mL/min. Her baseline uropathogen was *E. coli* whose MIC increased from 0.015 µg/mL at the baseline visit to 0.06 µg/mL at the TOC visit; all of her symptoms were resolved at TOC and FV, without the need for additional antibiotics.
- The second patient was a 79-year-old woman with a creatinine clearance of 44 mL/min. Her baseline uropathogen was *E. coli* whose MIC increased from 0.03 µg/mL at the baseline visit to 0.12 µg/mL at the TOC visit; she fully resolved all uUTI symptoms at EOT with return of mild dysuria and mild urinary frequency that was not significantly bothersome at TOC with the use of additional antibiotics for the current infection.

- The third patient was previously described in Section 7.5.1.5.

For all three patients, baseline and TOC organisms were identical by whole genome sequencing.

7.5.1.3.7 Additional Analyses of the Primary Endpoint

7.5.1.3.7.1 Significant Covariates from Stepwise Selection Associated with Overall Response at Test of Cure in the microMITT-S Population

A covariate analysis of the overall response at TOC in the microMITT-S population is provided in Table 69. The pre-specified covariate analysis identified 4 statistically significant variables related to overall response at the TOC Visit. Treatment with sulopenem was the most significant variable affecting outcome, resulting in a lower likelihood of overall response, as was having an ESBL positive uropathogen at baseline.

The odds ratios were only marginally above one for creatine clearance and randomization order.

Table 69: Study 301 Significant Covariates from Stepwise Selection Associated with Overall Response at Test of Cure in the microMITT-S Population

Covariate	Odds Ratio (95% CI)	p-value
Treatment (Sulopenem vs Ciprofloxacin)	0.56 (0.40, 0.77)	<0.001
Creatinine clearance	1.01 (1.00, 1.02)	0.002
Randomization Order	1.06 (1.00, 1.12)	0.049
ESBL status (positive)	0.52 (0.29, 0.94)	0.03

Source: post-hoc Table 22
Note: CI = confidence interval; microMITT-S = microbiologic modified intent-to-treat susceptible; ESBL = extended spectrum β-lactamase

7.5.1.3.7.2 Overall Response at TOC Using All Sites Including Sites 202 and 218

Throughout the study period, surveillance of microbiologic data was performed to identify results possibly impacted by cross-contamination. This process identified questionable culture results from two sites (site 202 and site 218). Evaluation of the questionable isolates by pulse-field gel electrophoresis, in addition to concerns about PK data collection from site 202, led to the conclusion that data from these sites was not reliable, leading to the removal of both sites from the efficacy analyses. Overall response at TOC when these two sites are included, shown in Table 70, is similar to when the two sites are excluded.

Table 70 Study 301 Overall Response at TOC Using All Sites Including Sites 202 and 218 in the MicroMITT-S and ME-TOC Populations

Population/Overall Response	Sulopenem n/N (%)	Ciprofloxacin n/N (%)	Difference % (95% CI)
MicroMITT-S			
Overall Responder	263/388 (67.8)	335/428 (78.3)	-10.5 (-16.6, -4.4)
Overall Non-responder	105/388 (27.1)	66/428 (15.4)	
Indeterminate	20/388 (5.2)	27/428 (6.3)	
ME-TOC			
Overall Responder	234/324 (72.2)	301/356 (84.6)	-12.3 (-18.5, -6.2)
Overall Non-responder	90/324 (27.8)	55/356 (15.4)	

Source: Table 14.2.1.1.1.18.
Note: CI = confidence interval; microMITT-S = microbiologic modified intent-to-treat susceptible; ME = microbiologically evaluable; 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 are considered failures; microbiologically evaluable patients are both clinically evaluable and microMITT.

7.5.2 Study 310

7.5.2.1 MicroMITT Population

A summary of the outcomes for patients in the microMITT population will be presented first, followed by the micro-MITTS population, and then the microMITT-R population. Per the prespecified hierarchical analysis, the primary comparison of the study is in the micro-MITT population (the combined population of patients with a positive baseline culture and without regard to amoxicillin/clavulanate susceptibility). These outcomes are most relevant to the practicing clinician who must choose empiric treatment of uUTI before culture results become available, hence these results will help put into context the outcomes in the culture and susceptibility-driven sub-populations.

7.5.2.1.1 Baseline Demographics

Demographic and other baseline characteristics are summarized by treatment for patients in the micro-MITT population below (Table 71). The sulopenem group and the amoxicillin/clavulanate group were well-matched for all parameters listed. All patients were enrolled at sites in the United States; ethnicity was primarily Hispanic (63.5%); race distribution included nearly 20% non-White patients.

Table 71 Study 310 Demographics and Baseline Characteristics in micro-MITT Population

Parameter	Sulopenem	Amoxicillin/ clavulanate	Total	p-value
Age (years)				0.1233
N	522	468	990	
Mean (SD)	50.3 (17.31)	48.6 (17.18)	49.5 (17.26)	
Median	52.0	50.0	51.0	
Min, max	18, 91	18, 93	18, 93	
Age group (FDA), n (%)				0.2834
<65 years	400 (76.6)	372 (79.5)	772 (78.0)	
≥65 years	122 (23.4)	96 (20.5)	218 (22.0)	
Age group (EMA), n (%)				0.1983
<65 years	400 (76.6)	372 (79.5)	772 (78.0)	
65-74 years	73 (14.0)	67 (14.3)	140 (14.1)	
75-84 years	42 (8.0)	22 (4.7)	64 (6.5)	

≥85 years	7 (1.3)	7 (1.5)	14 (1.4)	
Gender, n (%)				NA
Female	522 (100.0)	468 (100.0)	990 (100.0)	
Ethnicity, n (%)				0.7376
N	522	468	990	
Hispanic or Latina	333 (63.8)	296 (63.2)	629 (63.5)	
Not Hispanic or Latina	189 (36.2)	171 (36.5)	360 (36.4)	
Not Reported	0 (0.0)	1 (0.2)	1 (0.1)	
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	
Race, n (%)				0.8122
N	522	468	990	
American Indian or Alaska Native	1 (0.2)	1 (0.2)	2 (0.2)	
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 Pacific Islander	0 (0.0)	1 (0.2)	1 (0.1)	
White	419 (80.3)	370 (79.1)	789 (79.7)	
Other	8 (1.5)	4 (0.9)	12 (1.2)	
Diabetes at Baseline, n (%)				0.4297
N	522	468	990	
Present	86 (16.5)	68 (14.5)	154 (15.6)	
Absent	436 (83.5)	400 (85.5)	836 (84.4)	
Height (cm)				0.5854
N	522	468	990	
Mean (SD)	161.7 (7.25)	162.0 (7.05)	161.8 (7.15)	
Median	162.0	162.0	162.0	
Min, max	125, 180	142, 185	125, 185	
Weight (kg)				0.8819
N	522	468	990	
Mean (SD)	76.08 (16.992)	76.41 (17.922)	76.23 (17.429)	
Median	73.40	73.95	73.45	
Min, max	39.0, 192.7	40.8, 163.6	39.0, 192.7	
BMI (kg/m^2)				0.7019
N	522	468	990	

Mean (SD)	29.105 (6.280)	29.135 (6.618)	29.119 (6.439)	
Median	28.125	27.884	27.972	
Min, max	15.547, 67.470	17.604, 59.800	15.547, 67.470	
Categorized BMI (kg/m^2), n (%)				0.2612
<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)	
Creatinine clearance (mL/min)				0.6077
N	519	461	980	
Mean (SD)	83.859 (27.923)	85.014 (29.286)	84.402 (28.563)	
Median	83.142	83.658	83.351	
Min, max	8.156, 178.065	16.380, 181.951	8.156, 181.951	
Categorized creatinine clearance (mL/min), n(%)				0.2337
<60	113 (21.6)	86 (18.4)	199 (20.1)	
≥60	406 (77.8)	375 (80.1)	781 (78.9)	

Source: Table 14.1.4.3

% = 100 x n/N.

micro-MITT = Microbiological Modified Intent-to-treat; EMA = European Medicines Agency; FDA = US Food and Drug Administration; NA = Not applicable; BMI = Body mass index; cm = centimeter; kg = kilogram; SD = Standard deviation; Min = Minimum value; Max = Maximum value; Central lab data are used for Creatinine Clearance calculation by Cockcroft-Gault method using ideal body weight; N = Number of patients in the micro-MITT population.

Fisher's exact test p-values comparing frequencies in two treatment arms and Wilcoxon Rank Sum test p-values comparing means are reported.

7.5.2.1.2 Baseline Pathogens

Pathogens cultured from urine that qualified patients for the micro-MITT population are presented in below (Table 72). The most commonly identified pathogens in both groups were *E. coli* (81.8%), *K. pneumoniae* (10.9%), and *P. mirabilis* (2.7%).

Table 72 Study 310 Pathogens from Urine at Baseline - microMITT Population

Organism	Sulopenem n (%) N=522	Amoxicillin/ clavulanate n (%) N=468	Total n (%) N=990
Number of Patients with at least one study uropathogen in the urine at baseline	522 (100.0)	468 (100.0)	990 (100.0)
Escherichia coli	423 (81.0)	387 (82.7)	810 (81.8)
Klebsiella pneumoniae	58 (11.1)	50 (10.7)	108 (10.9)

Organism	Sulopenem n (%) N=522	Amoxicillin/ clavulanate n (%) N=468	Total n (%) N=990
Proteus mirabilis	14 (2.7)	13 (2.8)	27 (2.7)
Enterobacter hormaechei	4 (0.8)	8 (1.7)	12 (1.2)
Klebsiella aerogenes	4 (0.8)	3 (0.6)	7 (0.7)
Klebsiella variicola	5 (1.0)	1 (0.2)	6 (0.6)
Citrobacter freundii	5 (1.0)	0 (0.0)	5 (0.5)
Citrobacter koseri	3 (0.6)	2 (0.4)	5 (0.5)
Serratia marcescens	3 (0.6)	1 (0.2)	4 (0.4)
Morganella morganii	2 (0.4)	1 (0.2)	3 (0.3)
Providencia stuartii	2 (0.4)	1 (0.2)	3 (0.3)
Klebsiella oxytoca	0 (0.0)	2 (0.4)	2 (0.2)
Klebsiella spp	1 (0.2)	1 (0.2)	2 (0.2)
Enterobacter bugandensis	0 (0.0)	1 (0.2)	1 (0.1)
Enterobacter cloacae	1 (0.2)	0 (0.0)	1 (0.1)
Enterobacter kobei	1 (0.2)	0 (0.0)	1 (0.1)
Escherichia spp	1 (0.2)	0 (0.0)	1 (0.1)
Pantoea spp	1 (0.2)	0 (0.0)	1 (0.1)

Source: Table 14.1.9.1

Note: percentages are calculated as 100 × (n/N). Abbreviations: micro-MITT = microbiologic modified intent-to-treat; n = number of patients; N = number of patients in the micro-MITT population.

7.5.2.1.2.1 Distribution of Baseline Study Uropathogens by Antibiotic Resistance

As shown in Table 73 below, a total of 98 patients, just under 10% of micro-MITT patients, had at least 1 baseline Enterobacterales pathogen that was ESBL-positive, as determined by having a ceftriaxone MIC of >1 µg/mL. A total of 300 (30.3%) and 261 (26.4%) of micro-MITT patients overall had at least 1 baseline Enterobacterales pathogen that was non-susceptible to trimethoprim-sulfamethoxazole and quinolones, respectively. Notably, 8% had a baseline organism ESBL-positive and quinolone non-susceptible, 5.8% had a baseline organism ESBL-positive, and also quinolone and trimethoprim-sulfamethoxazole non-susceptible, 0.6% had a baseline organism ESBL-positive, and also quinolone, trimethoprim-sulfamethoxazole, and nitrofurantoin non-susceptible, and 1.2% of micro-MITT patients had a baseline organism non-susceptible to all orally available classes of antibiotics tested (β-lactams, quinolones, trimethoprim-sulfamethoxazole, and nitrofurantoin).

Table 73 Study 310 Distribution of Pathogens by ESBL status and Amoxicillin/clavulanate, Quinolone, Trimethoprim-Sulfamethoxazole and Nitrofurantoin Susceptibility – microMITT Population

Parameter	Sulopenem n (%) N=522	Amoxicillin/ clavulanate n (%) N=468	Total n (%) N=990
ESBL Status			
Negative	470 (90.0)	421 (90.0)	891 (90.0)
Positive	52 (10.0)	46 (9.8)	98 (9.9)
Missing	0 (0.0)	1 (0.2)	1 (0.1)
Amoxicillin/clavulanate			
Susceptible	480 (92.0)	442 (94.4)	922 (93.1)
Non-susceptible	42 (8.0)	25 (5.3)	67 (6.8)
Missing	0 (0.0)	1 (0.2)	1 (0.1)
Nitrofurantoin			
Susceptible	439 (84.1)	398 (85.0)	837 (84.5)
Non-susceptible	83 (15.9)	69 (14.7)	152 (15.4)
Missing	0 (0.0)	1 (0.2)	1 (0.1)
Trimethoprim-sulfamethoxazole			
Susceptible	361 (69.2)	328 (70.1)	689 (69.6)
Non-susceptible	161 (30.8)	139 (29.7)	300 (30.3)
Missing	0 (0.0)	1 (0.2)	1 (0.1)
Quinolone			
Susceptible	392 (75.1)	336 (71.8)	728 (73.5)
Non-susceptible	130 (24.9)	131 (28.0)	261 (26.4)
Missing	0 (0.0)	1 (0.2)	1 (0.1)
ESBL Positive and Quinolone Non-susceptible	39 (7.5)	40 (8.5)	79 (8.0)
ESBL Positive, Quinolone Non-susceptible, and Trimethoprim-sulfamethoxazole non-susceptible	28 (5.4)	29 (6.2)	57 (5.8)
ESBL Positive, Quinolone Non-susceptible, Trimethoprim-sulfamethoxazole Non-susceptible, and Nitrofurantoin Non-susceptible	5 (1.0)	1 (0.2)	6 (0.6)
β-lactam Non-susceptible, Quinolone Non-susceptible, Trimethoprim-sulfamethoxazole Non-susceptible, and Nitrofurantoin Non-susceptible	8 (1.5)	4 (0.9)	12 (1.2)

Source: Table 14.1.11.1, post hoc Table 7

Note: percentages are calculated as 100 × (n/N). Patients were considered ESBL-positive if they had a baseline urine specimen positive for at least 1 Enterobacterales with a ceftriaxone MIC of >1 µg/mL.

Abbreviations: MIC = minimum inhibitory concentration; micro-MITT = microbiologic modified intent-to-treat; ESBL = extended spectrum beta-lactamase; n = number of patients with respective pathogen as baseline pathogen; N = number of patients in the micro-MITT population.

7.5.2.1.2.2 Susceptibility of Baseline Pathogens

Susceptibility data for the sulopenem treatment group, for baseline pathogens isolated in at least 10 patients total, are presented in Table 74 Baseline isolates non-susceptible to carbapenems and/or amoxicillin/clavulanate are included in this table. This includes two patients in the micro-MITT population with baseline infection due an Enterobacterales with intermediate susceptibility (MIC 1 µg/mL) to ertapenem (subject (b) (6) had a baseline infection due to *Escherichia coli* treated with amoxicillin/clavulanate, and subject (b) (6) had a baseline infection due to *Enterobacter hormaechei* treated with sulopenem).

Table 74 Study 310 Activity of Sulopenem and Amoxicillin/clavulanate Against Baseline Pathogens in the micro-MITT Population – Sulopenem Treatment Group

Organism/Antibiotic	N	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	CLSI %S/%I/%R
Escherichia coli	423			
Sulopenem		0.03	0.06	NA
Amoxicillin/clavulanate		4/2	8/4	94.6/3.1/2.4
Klebsiella pneumoniae	58			
Sulopenem		0.03	0.06	NA
Amoxicillin/clavulanate		1/0.5	4/2	98.3/0.0/1.7
Proteus mirabilis	14			
Sulopenem		0.12	0.5	NA
Amoxicillin/clavulanate		0.5/0.25	4/2	100.0/0.0/0.0

Source: Table 14.1.16.1

Note: percentages are calculated as 100 × (n/N) where N is number of patients in the micro-MITT population with respective study uropathogen at baseline with valid MIC values; for the %S/%I/%R columns there is no breakpoint for CLSI when NA appears. Abbreviations: CLSI = Clinical and Laboratory Standards Institute; MIC_{50} = minimum inhibitory concentration required to inhibit the growth of 50% of organism; MIC_{90} = 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; S = susceptible; I = intermediate; R = resistant.

7.5.2.1.3 Overall Response

The primary efficacy endpoint was overall response at the Day 12 (TOC) visit in each of the micro-MITT, micro-MITTS and micro-MITTR populations. Table 75 presents the results for the micro-MITT population. Overall response of success was seen in 60.9% of patients in the sulopenem group and 55.6% of patients in the amoxicillin/clavulanate group (treatment difference 5.4%, 95% CI [-0.8, 11.5]). The study demonstrated non-inferiority of sulopenem to amoxicillin/clavulanate in the treatment of uUTI in the micro-MITT population.

Clinical success rates at TOC were similar across treatment groups (76.1% of micro-MITT patients in the sulopenem group and 76.5% of patients in the amoxicillin/clavulanate group, treatment difference -0.4%, 95% CI [-5.7, 4.9]).

The microbiologic success rate at TOC was statistically significantly higher in the sulopenem group compared to the amoxicillin/clavulanate group (74.7% of micro-MITT patients in the sulopenem

group and 67.3% of patients in the amoxicillin/clavulanate group, treatment difference 7.4%, 95% CI [1.8, 13.1]).

Table 75 Study 310 Overall Response, Clinical Response and Microbiologic Response at TOC – micro-MITT Population

Outcome	Sulopenem n (%) N=522	Amoxicillin/ clavulanate n (%) N=468	Difference % (95% CI)	p-value
Overall response at TOC	318 (60.9)	260 (55.6)	5.4 (-0.8, 11.5)	0.0437
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 14.2.1.1, Table 14.2.12.1.4, Table 14.2.6.1.1

% = 100 x n/N

micro-MITT = microbiological modified intent-to-treat; CI = confidence interval; TOC = test of cure; N = number of patients in the micro-MITT population

Success is defined as combined clinical and microbiologic success. Indeterminate responses are considered failures for CI calculation. CI computed using the method proposed without stratification by Miettinen and Nurminen.

The reasons for overall failure at TOC in the micro-MITT population are shown below (Table 76). The most common reasons for overall failure in both treatment groups were that the urine culture at TOC demonstrated >10^5 CFU/mL of the baseline uropathogen, followed by no resolution/worsening of baseline uUTI symptoms and/or new uUTI symptoms at TOC.

Table 76 Study 310 Reasons for Overall Nonresponse at TOC – micro-MITT Population

Number of Non-responders/ Reasons for Overall Non-response at TOC	Sulopenem n (%) N=522	Amoxicillin/ clavulanate n (%) N=468
Total number of non-responders	177 (33.9)	185 (39.5)
Urine culture at TOC visit demonstrates ≥10^3 CFU/mL of the baseline uropathogen (**microbiologic failure only**)	74 (14.2)	93 (19.9)
No resolution or worsening of symptoms of uUTI present at trial entry and/or new uUTI symptoms (**clinical failure only**)	70 (13.4)	50 (10.7)
Urine culture ≥10^3 and at least one symptom not resolved (**both clinical and microbiologic failure**)	32 (6.1)	38 (8.1)
Antibacterial therapy alone	1 (0.2)	4 (0.9)
Death due to uUTI	0 (0.0)	0 (0.0)
Receipt of non-study antibacterial therapy for uUTI	10 (1.9)	4 (0.9)

Source: Table 14.2.2.14.1

Abbreviations: uUTI = uncomplicated urinary tract infection; micro-MITT = microbiologic modified intent-to-treat; the percentages are calculated as 100 x (n/N); TOC = test of cure.

7.5.2.1.4 Clinical Response

The clinical response at TOC and reasons for clinical non-response as determined by the patient and the investigator at TOC for the micro-MITT population are provided in Table 77 and Table 78, respectively. Both patient-determined and investigator-assessed clinical response rates for patients on sulopenem were similar to those receiving amoxicillin/clavulanate.

Table 77 Study 310 Clinical Response (Patient-Determined) at TOC and Reasons for Clinical Non-response at TOC in the micro-MITT Population

Clinical Response	Sulopenem n (%) N=522	Amoxicillin/ clavulanate n (%) N=468	Difference % (95% CI)
Clinical success	397 (76.1)	358 (76.5)	-0.4 (-5.7, 4.9)
Clinical failure	104 (19.9)	92 (19.7)	
Indeterminate	21 (4.0)	18 (3.8)	
Reasons for Clinical Non-response			
uUTI symptoms not resolved/developed new symptoms	102 (19.5)	88 (18.8)	
Rescue therapy received	10 (1.9)	4 (0.9)	
Death	0 (0.0)	0 (0.0)	

Source: Table 14.2.12.1.4, Table 14.2.12.7.4

Table 78 Study 310 Clinical Response at TOC and Reasons for Clinical Non-response as Determined by the Investigator at TOC – micro-MITT Population

Clinical Response	Sulopenem n (%) N=522	Amoxicillin/ clavulanate n (%) N=468	Difference % (95% CI)
Clinical success	456 (87.4)	405 (86.5)	0.8 (-3.4, 5.1)
Clinical failure	47 (9.0)	48 (10.3)	
Indeterminate	19 (3.6)	15 (3.2)	
Reasons for Clinical Non-response			
Persistence/progression of any pre-therapy uUTI signs/symptoms	44 (8.4)	40 (8.5)	
Use of additional antibiotics for the current infection	10 (1.9)	14 (3.0)	
Previously met criteria for failure and received rescue antibiotics	6 (1.1)	2 (0.4)	
Death related to uUTI prior to EOT	0 (0.0)	0 (0.0)	

Source: Table 14.2.15.1.4, Table 14.2.15.4.4

7.5.2.1.5 Microbiologic Response

The microbiologic response per patient at TOC for the micro-MITT population is provided in Table 79. Microbiologic success rates at TOC were statistically significantly higher for patients receiving sulopenem relative to those receiving amoxicillin/clavulanate.

Table 79 Study 310 Microbiologic Response Per Patient at TOC – micro-MITT Population

Microbiologic Response per Patient	Sulopenem n (%) N=522	Amoxicillin/ clavulanate n (%) N=468	Difference % (95% CI)
Microbiologic success	390 (74.7)	315 (67.3)	7.4 (1.8, 13.1)
Microbiologic 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: Table 14.2.6.1.1

Note: CI = confidence interval; MIC = minimum inhibitory concentration; TOC = test of cure; the percentages are calculated as 100 x (n/N); persistence with increasing MIC means a ≥ 4-dilutions higher MIC from baseline visit; microbiologically evaluable patients are both clinically evaluable and micro-MITT.

Provided below (Table 80) is the microbiologic response at TOC by MIC to sulopenem for patients treated with either sulopenem or amoxicillin/clavulanate. Focusing on patients treated with sulopenem, there does not appear to be a difference in outcomes by MICs accepting limitations due to small numbers in subcategories.

Table 80 Study 310 Microbiologic Response at TOC by Pathogen for MIC to Sulopenem in the micro-MITT Population

Pathogen / MIC (µg/mL)	Sulopenem m/n (%) N=522	Amoxicillin/ clavulanate m/n (%) N=468
E. coli, N1	423	387
≤0.008	2/3 (66.7)	3/5 (60.0)
0.015	90/127 (70.9)	54/88 (61.4)
0.03	197/258 (76.4)	189/266 (71.1)
0.06	27/37 (73.0)	19/27 (70.4)
0.12	9/12 (75.0)	3/6 (50.0)
0.25	2/2 (100.0)	1/2 (50.0)
0.5	0/0 (0.0)	2/2 (100.0)

Pathogen / MIC (µg/mL)	Sulopenem m/n (%) N=522	Amoxicillin/ clavulanate m/n (%) N=468
K. pneumoniae, N1	58	50
0.015	0/0 (0.0)	0/1 (0.0)
0.03	24/36 (66.7)	14/26 (53.8)
0.06	17/20 (85.0)	8/17 (47.1)
0.12	2/2 (100.0)	2/3 (66.7)
0.25	1/2 (50.0)	3/3 (100.0)
P. mirabilis, N1	14	13
0.015	0/1 (0.0)	0/0 (0.0)
0.03	1/1 (100.0)	1/1 (100.0)
0.06	0/1 (0.0)	1/2 (50.0)
0.12	1/4 (25.0)	6/6 (100.0)
0.25	3/4 (75.0)	1/3 (33.3)
0.5	1/3 (33.3)	0/1 (0.0)
Enterobacter hormaechei, N1	4	8
0.03	1/1 (100.0)	1/1 (100.0)
0.06	1/1 (100.0)	4/4 (100.0)
0.12	0/0 (0.0)	3/3 (100.0)
0.25	1/1 (100.0)	0/0 (0.0)
0.5	0/1 (0.0)	0/0 (0.0)

Source: Table 14.2.6.16.1

% = 100 x m/n

micro-MITT = microbiological modified intent-to-treat; TOC = Test of Cure; MIC = Minimal Inhibitory Concentration; Success is defined as microbiologic success at TOC.

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 sulopenem; m = number of patients with eradication response to the specific pathogen and MIC to sulopenem; only pathogens where at least one favorable response occurred are displayed.

7.5.2.1.6 Additional Analyses of Primary Endpoint

7.5.2.1.6.1 Overall Response at TOC by Pathogen for MIC to Sulopenem

Provided below (Table 81) is the overall response at TOC by MIC to sulopenem for patients treated with either sulopenem or amoxicillin/clavulanate. Focusing on patients treated with sulopenem, there does not appear to be a difference among MICs accepting limitations due to small numbers in subcategories.

Table 81 Study 310 Overall Response at TOC by Pathogen for MIC to Sulopenem in the micro-MITT Population

Pathogen / MIC (µg/mL)	Sulopenem m/n (%) N=522	Amoxicillin/ clavulanate m/n (%) N=468
E. coli, N1	423	387
<=0.008	2/3 (66.7)	2/5 (40.0)
0.015	80/127 (63.0)	48/88 (54.5)
0.03	154/258 (59.7)	153/266 (57.5)
0.06	24/37 (64.9)	16/27 (59.3)
0.12	7/12 (58.3)	3/6 (50.0)
0.25	2/2 (100.0)	1/2 (50.0)
0.50	0/0 (0.0)	2/2 (100.0)
K. pneumoniae, N1	58	50
0.015	0/0 (0.0)	0/1 (0.0)
0.03	16/36 (44.4)	11/26 (42.3)
0.06	13/20 (65.0)	6/17 (35.3)
0.12	2/2 (100.0)	2/3 (66.7)
0.25	1/2 (50.0)	3/3 (100.0)
P. mirabilis, N1	14	13
0.015	0/1 (0.0)	0/0 (0.0)
0.03	1/1 (100.0)	0/1 (0.0)
0.06	0/1 (0.0)	1/2 (50.0)
0.12	1/4 (25.0)	4/6 (66.7)
0.25	3/4 (75.0)	1/3 (33.3)
0.5	1/3 (33.3)	0/1 (0.0)
E. hormaechei, N1	4	8
0.03	1/1 (100.0)	1/1 (100.0)
0.06	1/1 (100.0)	4/4 (100.0)
0.12	0/0 (0.0)	3/3 (100.0)
0.25	1/1 (100.0)	0/0 (0.0)
0.5	0/1 (0.0)	0/0 (0.0)

Source: Table 14.2.2.3.1

% = 100 x m/n

Micro-MITT = Microbiological Modified Intent-to-treat; TOC = Test of Cure; MIC = Minimal Inhibitory Concentration; Success is defined as combined clinical and microbiologic success at TOC.

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; m = number of patients with overall success to the specific pathogen and MIC to sulopenem.

Only pathogens where at least one favorable response occurred are displayed.

7.5.2.1.6.2 Covariate Analysis of the Overall Response in the microMITT Population

Covariate analysis of the overall response at TOC in the micro-MITT population is provided below (Table 82). The pre-specified covariate analysis identified 3 statistically significant variables related to overall response at the TOC visit. Age was the most significant variable with younger age favoring higher overall response. Having Diabetes mellitus and lower albumin levels were associated with relatively lower overall response at the TOC visit. In the presence of these covariates, the effect of treatment with sulopenem was less significant compared to the primary endpoint.

Table 82 Study 310 Significant Covariates from Stepwise Selection Associated with Overall Response at Test of Cure – micro-MITT Population

Covariate	Odds Ratio (95% CI)	p-value
Treatment (sulopenem vs amoxicillin/clavulanate)	1.253 (0.966, 1.625)	0.090
Age	0.987 (0.979, 0.996)	0.002
Albumin	1.064 (1.017, 1.114)	0.008
Diabetes mellitus	0.678 (0.467, 0.985)	0.042

Source: Table 14.2.2.11.1

CI = Confidence interval; micro-MITT = Microbiological Modified Intent-to-treat; TOC = Test of Cure; Logistic regression with the stepwise selection method was performed using the following covariates: study drug, continuous variable age, race, *E. coli* at baseline (Y vs N), creatinine clearance, albumin, comorbidities (Diabetes (Y vs N)). Study drug is included in the model regardless of significance. The alpha level for both entering and removing a covariate was 0.10.

7.5.2.1.6.3 Impact of Asymptomatic Bacteriuria on Clinical Outcomes at Subsequent Visits

In the previous trial of uUTI where sulopenem was compared to ciprofloxacin (IT001-301), asymptomatic bacteriuria was identified as the primary reason non-inferiority was not achieved in the comparison of sulopenem and ciprofloxacin in patients with quinolone susceptible pathogens. In the current study, asymptomatic bacteriuria at TOC was prespecified as an additional efficacy endpoint to be assessed for the micro-MITT and ME populations. In addition, as shown in Table 83 and Table 84, the presence of asymptomatic bacteriuria at the EOT and TOC visit was evaluated to see if it impacted clinical response at the TOC and FV visit, respectively. As shown, for both treatment arms, asymptomatic bacteriuria did not lead to clinical failure at the following visit in the micro-MITT population. In this study, the presence of asymptomatic bacteriuria did not predict subsequent clinical failure. This finding is supported by the opinion of the Infectious Disease Society of America (Nicolle, 2019).

Table 83 Study 310 Association of Asymptomatic Bacteriuria at the End of Treatment and Clinical Response at the Test of Cure – micro-MITT Population

Sulopenem			Amoxicillin/clavulanate		
Overall Response at EOT (D5)	**Clinical Success at TOC (D12) n/N (%)**	**p-value**	**Overall Response at EOT (D5)**	**Clinical Success at TOC (D12) n/N (%)**	**p-value**
Success	259/272 (95.2)	0.721	Success	226/243 (93.0)	0.527
Fail: ASB	29/30 (96.7)		Fail: ASB	43/45 (95.6)	

Source: Post hoc Table 13.1, post hoc Table 14.1, post hoc Table 16

*Reasons for failure include: death, receipt of an antibiotic (which includes any antibiotic for a UTI based on investigator assessment or programmatic outcomes), clinical symptoms alone or both urine culture positive plus clinical symptoms.

Note: micro-MITT = microbiologic modified intent-to-treat; EOT = end of treatment; TOC = test of cure; ASB = asymptomatic bacteriuria

Table 84 Study 310 Association of Asymptomatic Bacteriuria at the Test of Cure and Clinical Response at the Final Visit – micro-MITT Population

Sulopenem			Amoxicillin/clavulanate		
Overall Response at TOC (D12)	**Clinical Success at FV (D28) n/N (%)**	**p-value**	**Overall Response at TOC (D12)**	**Clinical Success at FV (D28) n/N (%)**	**p-value**
Success	296/318 (93.1)	0.656	Success	247/260 (95.0)	0.208
Fail: ASB	69/73 (94.5)		Fail: ASB	85/93 (91.4)	

Source: Post hoc Table 13.1, post hoc Table 14.1, post hoc Table 16

*Reasons for failure include: death, receipt of an antibiotic (which includes any antibiotic for a UTI based on investigator assessment or programmatic outcomes), clinical symptoms alone or both urine culture positive plus clinical symptoms.

Note: micro-MITT = microbiologic modified intent-to-treat; TOC = test of cure; FV = final visit; ASB = asymptomatic bacteriuria

7.5.2.2 MicroMITT-S Population

7.5.2.2.1 Baseline Demographics

Demographic and other baseline characteristics are summarized by treatment for patients in the micro-MITTS population in Table 85. The sulopenem and amoxicillin/clavulanate treatment groups were well-matched with respect to all characteristics at baseline. The mean age was 49.3 years and mean BMI was 29.1 kg/m^2. Ethnicity was primarily Hispanic (63.1%), race was predominantly White (79.5%), and Diabetes was present in a minority (15.8%) of the patients.

Table 85 Study 310 Demographics and Baseline Characteristics in micro-MITTS Population

Parameter	Sulopenem	Amoxicillin/ clavulanate	Total	p-value
Age (years)				0.141
N	480	442	922	
Mean (SD)	50.1 (17.54)	48.5 (17.32)	49.3 (17.45)	
Median	51.0	49.0	50.0	
Min, max	18, 91	18, 93	18, 93	
Age group (FDA), n (%)				0.342
<65 years	367 (76.5)	350 (79.2)	717 (77.8)	
≥65 years	113 (23.5)	92 (20.8)	205 (22.2)	
Age group (EMA), n (%)				0.167
<65 years	367 (76.5)	350 (79.2)	717 (77.8)	
65-74 years	67 (14.0)	65 (14.7)	132 (14.3)	
75-84 years	39 (8.1)	20 (4.5)	59 (6.4)	
≥85 years	7 (1.5)	7 (1.6)	14 (1.5)	
Gender, n (%)				NA
Female	480 (100.0)	442 (100.0)	922 (100.0)	
Ethnicity, n (%)				0.808
N	480	442	922	
Hispanic or Latina	304 (63.3)	278 (62.9)	582 (63.1)	
Not Hispanic or Latina	176 (36.7)	163 (36.9)	339 (36.8)	
Not Reported	0 (0.0)	1 (0.2)	1 (0.1)	
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	
Race, n (%)				0.848
N	480	442	922	
American Indian or Alaska Native	1 (0.2)	1 (0.2)	2 (0.2)	
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 Pacific Islander	0 (0.0)	1 (0.2)	1 (0.1)	
White	383 (79.8)	350 (79.2)	733 (79.5)	
Other	8 (1.7)	4 (0.9)	12 (1.3)	

Diabetes at Baseline, n (%)				0.528
N	480	442	922	
Present	80 (16.7)	66 (14.9)	146 (15.8)	
Absent	400 (83.3)	376 (85.1)	776 (84.2)	
Height (cm)				0.614
N	480	442	922	
Mean (SD)	161.7 (7.27)	162.0 (7.00)	161.8 (7.14)	
Median	162.0	162.0	162.0	
Min, max	125, 180	142, 185	125, 185	
Weight (kg)				0.974
N	480	442	922	
Mean (SD)	75.76 (16.975)	76.36 (18.136)	76.05 (17.534)	
Median	73.00	74.00	73.40	
Min, max	39.0, 192.7	40.8, 163.6	39.0, 192.7	
BMI (kg/m^2)				0.844
N	480	442	922	
Mean (SD)	29.007 (6.323)	29.120 (6.707)	29.061 (6.507)	
Median	27.986	27.884	27.957	
Min, max	15.547, 67.470	17.604, 59.800	15.547, 67.470	
Categorized BMI (kg/m^2), n (%)				0.172
<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)	
Creatinine clearance (mL/min)				0.540
N1	477	435	912	
Mean (SD)	83.822 (27.756)	85.068 (29.347)	84.417 (28.517)	
Median	82.266	83.837	83.351	
Min, max	8.156, 155.844	16.380, 181.951	8.156, 181.951	
Categorized creatinine clearance (mL/min), n (%)				0.325
<60	104 (21.7)	83 (18.8)	187 (20.3)	
≥60	373 (77.7)	352 (79.6)	725 (78.6)	

Source: Table 14.1.4.4
% = 100 x n/N

Micro-MITTS = Microbiological Modified Intent-to-Treat Susceptible; EMA = European Medicines Agency; FDA = US Food and Drug Administration; NA = Not applicable; N = Number of patients in the Micro-MITTS population; N1 = Number of patients in the Micro-MITTS population with creatinine clearance value; BMI = Body mass index; cm = centimeter; kg = kilogram; SD = Standard deviation; Min = Minimum value; Max = Maximum value; Central lab data are used for Creatinine Clearance results.

Fisher's exact test p-values comparing frequencies in two treatment arms and Wilcoxon Rank Sum test p-values comparing means are reported.

7.5.2.2.2 Baseline Pathogens

Pathogens cultured from urine, and those that qualified patients for the micro-MITTS population, are presented in Table 86. The most commonly identified pathogens in both groups were *E. coli* (83.9%), *K. pneumoniae* (11.6%), and *P. mirabilis* (2.8%).

Table 86 Study 310 Pathogens from Urine at Baseline – micro-MITTS Population

Organism	Sulopenem n (%) N=480	Amoxicillin/ clavulanate n (%) N=422	Total n (%) N=922
Number of Patients with at least one study uropathogen in the urine at baseline	480 (100.0)	442 (100.0)	922 (100.0)
Escherichia coli	400 (83.3)	374 (84.6)	774 (83.9)
Klebsiella pneumoniae	57 (11.9)	50 (11.3)	107 (11.6)
Proteus mirabilis	13 (2.7)	13 (2.9)	26 (2.8)
Klebsiella variicola	5 (1.0)	1 (0.2)	6 (0.7)
Citrobacter koseri	3 (0.6)	2 (0.5)	5 (0.5)
Klebsiella oxytoca	0 (0.0)	2 (0.5)	2 (0.2)
Klebsiella spp	1 (0.2)	1 (0.2)	2 (0.2)
Providencia stuartii	1 (0.2)	1 (0.2)	2 (0.2)
Citrobacter freundii	1 (0.2)	0 (0.0)	1 (0.1)
Enterobacter hormaechei	1 (0.2)	0 (0.0)	1 (0.1)
Escherichia spp	1 (0.2)	0 (0.0)	1 (0.1)
Pantoea spp	1 (0.2)	0 (0.0)	1 (0.1)

Source: Table 14.1.9.2

Note: percentages are calculated as 100 × (n/N). Abbreviations: micro-MITTS = microbiologic modified intent-to-treat susceptible; n = number of patients; N = number of patients in the micro-MITTS population.

7.5.2.2.2.1 Distribution of Baseline Study Uropathogens by Antibiotic Resistance

As shown in Table 87 below, a total of 82 patients, just under 9% of micro-MITTS patients, had at least 1 baseline Enterobacterales pathogen that was ESBL-positive, as determined by having a ceftriaxone MIC of >1 µg/mL. A total of 283 (30.7%) and 248 (26.9%) of micro-MITTS patients overall had at least 1 baseline Enterobacterales pathogen that was non-susceptible to trimethoprim-sulfamethoxazole and quinolones, respectively. Notably, 7.9% had a baseline organism ESBL-positive and quinolone non-susceptible, 5.7% had a baseline organism ESBL-positive, and also quinolone and trimethoprim-sulfamethoxazole non-susceptible, 0.5% had a baseline organism ESBL-positive, and also quinolone, trimethoprim-sulfamethoxazole, and nitrofurantoin non-susceptible, and 1.1% of micro-MITTS patients had a baseline organism non-susceptible to all orally available classes of antibiotics tested (β-lactams, quinolones, trimethoprim-sulfamethoxazole, and nitrofurantoin).

Table 87 Study 310 Distribution of Pathogens by ESBL status and Amoxicillin/clavulanate, Quinolone, Trimethoprim-Sulfamethoxazole and Nitrofurantoin Susceptibility – micro-MITTS Population

Parameter	Sulopenem n (%) N=480	Amoxicillin/ clavulanate n (%) N=442	Total n (%) N=922
ESBL Status			
Negative	443 (92.3)	397 (89.8)	840 (91.1)
Positive	37 (7.7)	45 (10.2)	82 (8.9)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Amoxicillin/clavulanate			
Susceptible	480 (100.0)	442 (100.0)	922 (100.0)
Non-susceptible	0 (0.0)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Nitrofurantoin			
Susceptible	416 (86.7)	386 (87.3)	802 (87.0)
Non-susceptible	64 (13.3)	56 (12.7)	120 (13.0)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Trimethoprim-sulfamethoxazole			
Susceptible	331 (69.0)	308 (69.7)	639 (69.3)
Non-susceptible	149 (31.0)	134 (30.3)	283 (30.7)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Quinolone			
Susceptible	360 (75.0)	314 (71.0)	674 (73.1)
Non-susceptible	120 (25.0)	128 (29.0)	248 (26.9)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
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)
ESBL Positive, Quinolone Non-susceptible, Trimethoprim-sulfamethoxazole Non-susceptible, and Nitrofurantoin Non-susceptible	4 (0.8)	1 (0.2)	5 (0.5)
β-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 14.1.11.2, post hoc Table 7

Note: percentages are calculated as 100 × (n/N). Patients were considered ESBL-positive if they had a baseline urine specimen positive for at least 1 Enterobacterales with a ceftriaxone MIC of >1 µg/mL.

Abbreviations: MIC = minimum inhibitory concentration; micro-MITTS = microbiologic modified intent-to-treat susceptible; ESBL = extended spectrum beta-lactamase; n = number of patients with respective pathogen as baseline pathogen; N = number of patients in the micro-MITTS population.

7.5.2.2.2.2 Susceptibility of Baseline Pathogens

For patients in the micro-MITTS populations, susceptibility data for the sulopenem treatment group, for baseline pathogens isolated in at least 10 patients total, are presented in Table 88. Baseline isolates non-susceptible to carbapenems and/or amoxicillin/clavulanate are included in these tables. There was one patient (subject (b) (6)) in the micro-MITTS population assigned to the amoxicillin/clavulanate treatment group with a baseline *Escherichia coli* isolate with intermediate susceptibility (MIC 1 µg/mL) to ertapenem.

Table 88 Study 310 Activity of Sulopenem and Amoxicillin/clavulanate Against Baseline Pathogens in the micro-MITTS Population – Sulopenem Treatment Group

Organism/Antibiotic	N	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	CLSI %S/%I/%R
Escherichia coli	400			
Sulopenem		0.03	0.03	NA
Amoxicillin/clavulanate		4/2	4/2	100.0/0.0/0.0
Klebsiella pneumoniae	57			
Sulopenem		0.03	0.06	NA
Amoxicillin/clavulanate		1/0.5	4/2	100.0/0.0/0.0
Proteus mirabilis	13			
Sulopenem		0.12	0.5	NA
Amoxicillin/clavulanate		0.5/0.25	4/2	100.0/0.0/0.0

Source: Table 14.1.16.2
Note: percentages are calculated as 100 × (n/N) where N is number of patients in the micro-MITTS population with respective study uropathogen at baseline with valid MIC values; for the %S/%I/%R columns there is no breakpoint for CLSI when NA appears. Abbreviations: CLSI = Clinical and Laboratory Standards Institute; MIC_{50} = minimum inhibitory concentration required to inhibit the growth of 50% of organism; MIC_{90} = minimum inhibitory concentration required to inhibit the growth of 90% of organism; micro-MITTS = microbiologic modified intent-to-treat susceptible; S = susceptible; I = intermediate; R = resistant.

7.5.2.2.3 Overall Response

The primary efficacy endpoint was overall response at the Day 12 (TOC) visit in each of the micro-MITT, micro-MITTS and micro-MITTR populations. The table below (Table 89) presents the overall, clinical and microbiologic responses at TOC in the micro-MITTS population. Overall response of success was seen in 61.7% of patients in the sulopenem group and 55.0% of patients in the amoxicillin/clavulanate group (treatment difference 6.7%, 95% CI [0.3, 13.0]). In addition to demonstrating non-inferiority, sulopenem was also found to be superior to amoxicillin/clavulanate for the treatment of uUTI in the micro-MITTS population.

Clinical success rates at TOC were similar across treatment groups (77.3% in the sulopenem group and 76.7% in the amoxicillin/clavulanate group, treatment difference 0.6%, 95% CI [-4.8, 6.1]).

Microbiologic success rates at TOC were statistically significantly higher in the sulopenem group relative to the amoxicillin/clavulanate group (75.2% in the sulopenem group and 66.7% in the amoxicillin/clavulanate group, treatment difference 8.5%, 95% CI [2.6, 14.3]).

Table 89 Study 310 Overall Response, Clinical Response and Microbiologic Response at TOC – micro-MITTS Population

Outcome	Sulopenem n (%) N=480	Amoxicillin/ clavulanate n (%) N=442	Difference % (95% CI)
Overall response at TOC	296 (61.7)	243 (55.0)	6.7 (0.3, 13.0)
Overall nonresponse	160 (33.3)	177 (40.0)	
Indeterminate	24 (5.0)	22 (5.0)	
Clinical success at TOC	371 (77.3)	339 (76.7)	0.6 (-4.8, 6.1)
Microbiologic success at TOC	361 (75.2)	295 (66.7)	8.5 (2.6, 14.3)

Source: Table 14.2.1.2, Table 14.2.12.1.5, Table 14.2.6.2.1

% = 100 x n/N

micro-MITTS = microbiological modified intent-to-treat susceptible; CI = confidence interval; TOC = test of cure; N = number of patients in the micro-MITTS population

Indeterminate responses are considered failures for CI calculation. CI computed using the method proposed without stratification by Miettinen and Nurminen.

The reasons for overall failure at TOC in the micro-MITTS population are shown in Table 90 below. As was seen in the micro-MITT population, the most common reasons for overall failure in both treatment groups were that the urine culture at TOC demonstrated $\geq 10^3$ CFU/mL of the baseline uropathogen, followed by no resolution/worsening of baseline uUTI symptoms and/or new uUTI symptoms at TOC. Receipt of non-study antibacterial therapy for uUTI occurred in 1.7% and 0.9% of patients in the sulopenem arm and amoxicillin/clavulanate arm, respectively.

Table 90 Study 310 Reasons for Overall Nonresponse at TOC in the micro-MITTS Population

Number of Non-responders/ Reasons for Overall Non-response at TOC	Sulopenem n (%) N=480	Amoxicillin/ clavulanate n (%) N=442
Number of non-responders	160 (33.3)	177 (40.0)
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)
Death due to uUTI	0 (0.0)	0 (0.0)
Receipt of non-study antibacterial therapy for uUTI	8 (1.7)	4 (0.9)

Source: Table 14.2.2.14.2

Abbreviations: uUTI = uncomplicated urinary tract infection; micro-MITT = microbiologic modified intent-to-treat; the percentages are calculated as 100 x (n/N); TOC = test of cure.

7.5.2.2.4 Clinical Response

The clinical response at TOC for the micro-MITTS population and reasons for clinical non-response as determined by the patient and the investigator at TOC for the micro-MITTS population is provided in the following two tables (Table 91, Table 92), respectively. Both patient-determined and investigator-assessed clinical success rates were similar across treatment groups.

Table 91 Study 310 Clinical Response (Patient-Determined) at TOC and Reasons for Clinical Non-response at TOC in the micro-MITTS Population

Clinical Response	Sulopenem n (%) N=480	Amoxicillin/ clavulanate n (%) N=442	Difference % (95% CI)
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)	
Reasons for Clinical Non-response			
uUTI symptoms not resolved/developed new symptoms	89 (18.5)	82 (18.6)	
Rescue therapy received	8 (1.7)	4 (0.9)	
Death	0 (0.0)	0 (0.0)	

Source: Table 14.2.12.1.5, Table 14.2.12.7.5

% = 100 x n/N

micro-MITTS = Microbiological Modified Intent-to-treat Susceptible; TOC = Test of Cure; CI = Confidence Interval; uUTI = Uncomplicated Urinary Tract Infection; N = Number of patients in the micro-MITTS population.

Indeterminate responses are considered failures for CI calculation.

CI computed using the method proposed without stratification by Miettinen and Nurminen.

Patient might have more than one reason for failure.

Table 92 Study 310 Clinical Response at TOC and Reasons for Clinical Non-response as Determined by the Investigator at TOC in the micro-MITTS Population

Investigator's Assessment of Clinical Response	Sulopenem n (%) N=480	Amoxicillin/ clavulanate n (%) N=442	Difference % (95% CI)
Clinical success	421 (87.7)	386 (87.3)	0.4 (-3.9, 4.7)
Clinical failure	43 (9.0)	42 (9.5)	
Indeterminate*	16 (3.3)	14 (3.2)	
Reasons for Clinical Non-response			
Persistence/progression of any pre-therapy uUTI signs/symptoms	40 (8.3)	34 (7.7)	
Use of additional antibiotics for the current infection	8 (1.7)	13 (2.9)	

Investigator's Assessment of Clinical Response	Sulopenem n (%) N=480	Amoxicillin/ clavulanate n (%) N=442	Difference % (95% CI)
Previously met criteria for failure and received rescue antibiotics	5 (1.0)	2 (0.5)	
Death related to uUTI prior to EOT	0 (0.0)	0 (0.0)	

Source: Table 14.2.15.1.5, Table 14.2.15.4.5

Note: *'Indeterminate' represents an investigator's actual selection from choices provided on the case report form; missing investigator assessments are not included as failures in this table; patients may have more than one reason for non-response.

7.5.2.2.5 Microbiologic Response

The microbiologic response per patient at TOC for the micro-MITTS population is provided in Table 93. As was seen for the entire micro-MITT population, the microbiologic response rates were statistically significantly higher for patients receiving sulopenem.

Table 93 Study 310 Microbiologic Response Per Patient at TOC in the micro-MITTS Population

Microbiologic Response per Patient / Reason for Overall Non-response	Sulopenem n (%) N=480	Amoxicillin/ clavulanate n (%) N=442	Difference % (95% CI)
Microbiologic success	361 (75.2)	295 (66.7)	8.5 (2.6, 14.3)
Microbiologic failure	96 (20.0)	126 (28.5)	
Persistence	96 (20.0)	126 (28.5)	
Persistence with increasing MIC	0 (0.0)	0 (0.0)	
Indeterminate	23 (4.8)	21 (4.8)	

Source: Table 14.2.6.2.1

Note: CI = confidence interval; MIC = minimum inhibitory concentration; TOC = test of cure; the percentages are calculated as 100 x (n/N); persistence with increasing MIC means a ≥ 4-dilution higher MIC from baseline visit; microbiologically evaluable patients are both clinically evaluable and micro-MITT.

7.5.2.2.6 Additional Analyses of Primary Endpoint

7.5.2.2.6.1 Covariate Analysis of the Overall Response in the microMITT-S Population

A covariate analysis of the overall response at TOC in the micro-MITTS population is provided in Table 94. The pre-specified covariate analysis identified 4 statistically significant variables related to overall response at the TOC visit. Age was the most significant variable affecting outcome, with younger age resulting in a higher likelihood of overall response. Having Diabetes and lower albumin levels were associated with relatively lower overall response at the TOC visit.

Table 94 Study 310 Significant Covariates from Stepwise Selection Associated with Overall Response at Test of Cure in the micro-MITTS Population

Covariate	Odds Ratio (95% CI)	p-value
Treatment (Sulopenem vs Amoxicillin/clavulanate)	1.320 (1.008, 1.728)	0.044
Age	0.988 (0.980, 0.996)	0.005
Albumin	1.059 (1.010, 1.109)	0.017
Diabetes	0.649 (0.443, 0.953)	0.027

Source: Table 14.2.2.11.2

CI = Confidence interval; micro-MITTS = Microbiological Modified Intent-to-treat susceptible; TOC = Test of Cure; Logistic regression with the stepwise selection method was performed using the following covariates: study drug, continuous variable age, race, *E. coli* at baseline (Y vs N), creatinine clearance, albumin, comorbidities (diabetes (Y vs N)). Study drug is included in the model regardless of significance. The alpha level for both entering and removing a covariate was 0.10.

7.5.2.2.6.2 Impact of Asymptomatic Bacteriuria on Clinical Outcomes at Subsequent Visits

In the previous trial of uUTI where sulopenem was compared to ciprofloxacin (IT001-301), asymptomatic bacteriuria was identified as the primary reason non-inferiority was not achieved in the comparison of sulopenem and ciprofloxacin in patients with quinolone susceptible pathogens. In the current study, asymptomatic bacteriuria at TOC was prespecified as an additional efficacy endpoint to be assessed for the micro-MITT and ME populations. In addition, as shown in the following two tables (Table 95 and Table 96), the presence of asymptomatic bacteriuria at the EOT and TOC visit was evaluated to see if it impacted clinical response at the TOC and FV visit, respectively. As shown, for both treatment arms, microbiologic failure alone (asymptomatic bacteriuria) did not lead to clinical failure at the following visit in the micro-MITTS population.

Table 95 Study 310 Association of Asymptomatic Bacteriuria at the End of Treatment and Clinical Response at the Test of Cure – micro-MITTS Population

Sulopenem			Amoxicillin/clavulanate		
Overall Response at EOT (D5)	Clinical Success at TOC (D12) n/N (%)	p-value	Overall Response at EOT (D5)	Clinical Success at TOC (D12) n/N (%)	p-value
Success	241/252 (95.6)	0.872	Success	210/226 (92.9)	0.538
Fail: ASB	26/27 (96.3)		Fail: ASB	42/44 (95.5)	

Source: Post hoc Table 13.2, post hoc Table 14.2, post hoc Table 16

Note: micro-MITTS = microbiologic modified intent-to-treat susceptible; EOT = end of treatment; TOC = test of cure; ASB = asymptomatic bacteriuria

Table 96 Study 310 Association of Asymptomatic Bacteriuria at the Test of Cure and Clinical Response at the Final Visit – micro-MITTS Population

Sulopenem			Amoxicillin/clavulanate		
Overall Response at TOC (D12)	**Clinical Success at FV (D28) n/N (%)**	**p-value**	**Overall Response at TOC (D12)**	**Clinical Success at FV (D28) n/N (%)**	**p-value**
Success	274/296 (92.6)	0.634	Success	231/243 (95.1)	0.186
Fail: ASB	65/69 (94.2)		Fail: ASB	83/91 (91.2)	

Source: Post hoc Table 13.2, post hoc Table 14.2, post hoc Table 16

Note: micro-MITTS = microbiologic modified intent-to-treat susceptible; TOC = test of cure; FV = final visit; ASB = asymptomatic bacteriuria

7.5.2.3 MicroMITT-R Population

Per the prespecified hierarchical testing plan, non-inferiority in the microMITT-S population or superiority in the microMITT-R population would be assessed if noninferiority had been established in the microMITT population. Due to the small sample size in the micro-MITTR population (only 25% of planned sample size was achieved) and the imbalance in randomization to the treatment groups, there was insufficient power (approximately 20%) in the micro-MITTR population to draw any conclusions about treatment effect.

7.5.2.3.1 Baseline Demographics

Demographic and other baseline characteristics are summarized by treatment for patients in the micro-MITTR population in Table 97 below. The mean age was 51.8 years and mean BMI was 29.913 kg/m^2. Ethnicity was primarily Hispanic (68.7%), race was predominantly White (82.1%), and Diabetes was present in a minority (11.9%) of the patients. While there were no statistically significant differences between the sulopenem and amoxicillin/clavulanate treatment groups, sulopenem patients trended toward being older, diabetic, heavier, and with worse renal function.

Table 97 Study 310 Demographics and Baseline Characteristics in micro-MITTR Population

Parameter	Sulopenem	Amoxicillin/ clavulanate	Total	p-value
Age (years)				0.811
N	42	25	67	
Mean (SD)	52.2 (14.43)	51.1 (14.56)	51.8 (14.38)	
Median	53.0	53.0	53.0	
Min, max	25, 79	24, 77	24, 79	
Age group (FDA), n (%)				0.753
<65 years	33 (78.6)	21 (84.0)	54 (80.6)	
≥65 years	**9 (21.4)**	4 (16.0)	13 (19.4)	
Age group (EMA), n (%)				0.893

<65 years	33 (78.6)	21 (84.0)	54 (80.6)	
65-74 years	6 (14.3)	2 (8.0)	8 (11.9)	
75-84 years	3 (7.1)	2 (8.0)	5 (7.5)	
≥85 years	0 (0.0)	0 (0.0)	0 (0.0)	
Gender, n (%)				NA
Female	42 (100.0)	25 (100.0)	67 (100.0)	
Ethnicity, n (%)				1.000
N	42	25	67	
Hispanic or Latina	29 (69.0)	17 (68.0)	46 (68.7)	
Not Hispanic or Latina	13 (31.0)	8 (32.0)	21 (31.3)	
Not Reported	0 (0.0)	0 (0.0)	0 (0.0)	
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	
Race, n (%)				0.341
N	42	25	67	
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)	
Asian	0 (0.0)	0 (0.0)	0 (0.0)	
Black or African American	6 (14.3)	6 (24.0)	12 (17.9)	
Native Hawaiian or Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)	
White	36 (85.7)	19 (76.0)	55 (82.1)	
Other	0 (0.0)	0 (0.0)	0 (0.0)	
Diabetes at Baseline, n (%)				0.700
N	42	25	67	
Present	**6 (14.3)**	2 (8.0)	8 (11.9)	
Absent	36 (85.7)	23 (92.0)	59 (88.1)	
Height (cm)				0.664
N	42	25	67	
Mean (SD)	162.2 (6.99)	162.7 (7.70)	162.4 (7.21)	
Median	161.5	165.0	163.0	
Min, max	147, 175	144, 173	144, 175	
Weight (kg)				0.703
N	42	25	67	
Mean (SD)	79.76 (16.958)	77.63 (14.154)	78.97 (15.893)	

Median	**78.15**	73.00	75.00	
Min, max	53.1, 117.8	59.6, 119.0	53.1, 119.0	
BMI (kg/m^2)				0.666
N	42	25	67	
Mean (SD)	30.234 (5.717)	29.374 (5.058)	29.913 (5.457)	
Median	**30.189**	27.852	29.333	
Min, max	21.454, 43.599	21.117, 41.176	21.117, 43.599	
Categorized BMI (kg/m^2), n (%)				0.274
<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)	
Creatinine clearance (mL/min)				0.995
N1	42	25	67	
Mean (SD)	84.278 (30.107)	85.361 (28.643)	84.682 (29.355)	
Median	85.316	76.720	84.633	
Min, max	19.408, 178.065	39.044, 165.764	19.408, 178.065	
Categorized creatinine clearance (mL/min), n (%)				0.189
<60	**9 (21.4)**	2 (8.0)	11 (16.4)	
≥60	33 (78.6)	23 (92.0)	56 (83.6)	

Source: Table 14.1.4.5

% = 100 x n/N.

Micro-MITTR = Microbiological Modified Intent-to-Treat Resistant; EMA = European Medicines Agency; FDA = US Food and Drug Administration; NA = Not applicable; N = Number of patients in the Micro-MITTR population; N1= Number of patients in the Micro-MITTR population with creatinine clearance value; BMI = Body mass index; cm = centimeter; kg = kilogram; SD = Standard deviation; Min = Minimum value; Max = Maximum value; Central lab data are used for Creatinine Clearance results.

Fisher's exact test p-values comparing frequencies in two treatment arms and Wilcoxon Rank Sum test p-values comparing means are reported.

7.5.2.3.2 Baseline Pathogens

Pathogens cultured from urine that qualified patients for the micro-MITTR population are presented in Table 98. The most commonly identified pathogens in both groups were *E. coli* (52.2%), *Enterobacter hormaechei* (16.4%), and *K. aerogenes* (10.4%). *E. hormaechei* was identified more often in patients treated with amoxicillin/clavulanate than sulopenem (32.0% vs 7.1%).

Table 98 Study 310 Pathogens from Urine at Baseline – micro-MITTR Population

Organism	Sulopenem n (%) N=42	Amoxicillin/ clavulanate n (%) N=25	Total n (%) N=67
Number of Patients with at least one study uropathogen in the urine at baseline	42 (100.0)	25 (100.0)	67 (100.0)
Escherichia coli	23 (54.8)	12 (48.0)	35 (52.2)
Enterobacter hormaechei	3 (7.1)	8 (32.0)	11 (16.4)
Klebsiella aerogenes	4 (9.5)	3 (12.0)	7 (10.4)
Citrobacter freundii	4 (9.5)	0 (0.0)	4 (6.0)
Serratia marcescens	3 (7.1)	1 (4.0)	4 (6.0)
Morganella morganii	2 (4.8)	1 (4.0)	3 (4.5)
Enterobacter bugandensis	0 (0.0)	1 (4.0)	1 (1.5)
Enterobacter cloacae	1 (2.4)	0 (0.0)	1 (1.5)
Enterobacter kobei	1 (2.4)	0 (0.0)	1 (1.5)
Klebsiella pneumoniae	1 (2.4)	0 (0.0)	1 (1.5)
Proteus mirabilis	1 (2.4)	0 (0.0)	1 (1.5)
Providencia stuartii	1 (2.4)	0 (0.0)	1 (1.5)

Source: Table 14.1.9.3

Note: percentages are calculated as 100 × (n/N). Abbreviations: micro-MITTR = microbiologic modified intent-to-treat resistant; n = number of patients; N = number of patients in the micro-MITTR population.

7.5.2.3.2.1 Distribution of Baseline Study Uropathogens by Antibiotic Resistance

As shown in Table 99 below, a total of 16 patients, just under 24% of micro-MITTR patients, had at least 1 baseline Enterobacterales pathogen that was ESBL-positive, as determined by having a ceftriaxone MIC of >1 µg/mL, with 15 of these patients being in the sulopenem arm. A total of 17 (25.4%) and 13 (19.4%) study patients overall had at least 1 baseline Enterobacterales pathogen that was non-susceptible to trimethoprim-sulfamethoxazole and quinolones, respectively. Notably, 9.0% had a baseline organism ESBL-positive and quinolone non-susceptible, 6.0% had a baseline organism ESBL-positive, and also quinolone and trimethoprim-sulfamethoxazole non-susceptible, and 1.5% had a baseline organism ESBL-positive, and also quinolone, trimethoprim-sulfamethoxazole, and nitrofurantoin non-susceptible, and 3% of micro-MITTR patients had a baseline organism non-susceptible to all orally available classes of antibiotics tested (β-lactams, quinolones, trimethoprim-sulfamethoxazole, and nitrofurantoin).

Table 99 Study 310 Distribution of Pathogens by ESBL status and Amoxicillin/clavulanate, Quinolone, Trimethoprim-Sulfamethoxazole and Nitrofurantoin Susceptibility – micro-MITTR Population

Parameter	Sulopenem n (%) N=42	Amoxicillin/ clavulanate n (%) N=25	Total n (%) N=67
ESBL Status			
Negative	27 (64.3)	24 (96.0)	51 (76.1)
Positive	15 (35.7)	1 (4.0)	16 (23.9)
Amoxicillin/clavulanate			
Susceptible	0 (0.0)	0 (0.0)	0 (0.0)
Non-susceptible	42 (100.0)	25 (100.0)	67 (100.0)
Nitrofurantoin			
Susceptible	23 (54.8)	12 (48.0)	35 (52.2)
Non-susceptible	19 (45.2)	13 (52.0)	32 (47.8)
Trimethoprim-sulfamethoxazole			
Susceptible	30 (71.4)	20 (80.0)	50 (74.6)
Non-susceptible	12 (28.6)	5 (20.0)	17 (25.4)
Quinolone			
Susceptible	32 (76.2)	22 (88.0)	54 (80.6)
Non-susceptible	10 (23.8)	3 (12.0)	13 (19.4)
ESBL Positive and Quinolone Non-susceptible	6 (14.3)	0 (0.0)	6 (9.0)
ESBL Positive, Quinolone Non-susceptible, and Trimethoprim-sulfamethoxazole non-susceptible	4 (9.5)	0 (0.0)	4 (6.0)
ESBL Positive, Quinolone Non-susceptible, Trimethoprim-sulfamethoxazole Non-susceptible, and Nitrofurantoin Non-susceptible	1 (2.4)	0 (0.0)	1 (1.5)
β-lactam Non-susceptible, Quinolone Non-susceptible, Trimethoprim-sulfamethoxazole Non-susceptible, and Nitrofurantoin Non-susceptible	2 (4.8)	0 (0.0)	2 (3.0)

Source: Table 14.1.11.3, post hoc Table 7

Note: percentages are calculated as 100 × (n/N). Patients were considered ESBL-positive if they had a baseline urine specimen positive for at least 1 Enterobacterales with a ceftriaxone MIC of >1 µg/mL.

Abbreviations: MIC = minimum inhibitory concentration; micro-MITTR = microbiologic modified intent-to-treat resistant; ESBL = extended spectrum beta-lactamase; n = number of patients with respective pathogen as baseline pathogen; N = number of patients in the micro-MITTR population.

7.5.2.3.2.2 Susceptibility of Baseline Pathogens

Susceptibility data for the sulopenem treatment group, for baseline pathogens isolated in at least 10 patients total, are presented in Table 100. Baseline isolates non-susceptible to carbapenems and/or amoxicillin/clavulanate are included in these tables. There was one patient (subject (b) (6) (b) (6)) in the micro-MITTR population assigned to the sulopenem treatment group with a baseline *Enterobacter hormaechei* isolate with intermediate susceptibility (MIC 1 µg/mL) to ertapenem.

Table 100 Study 310 Activity of Sulopenem and Amoxicillin/clavulanate Against Baseline Pathogens in the micro-MITTR Population – Sulopenem Treatment Group

Organism/Antibiotic	N	MIC_{50} (µg/mL)	MIC_{90} (µg/mL)	CLSI %S/%I/%R
Escherichia coli	23			
Sulopenem		0.06	0.12	NA
Amoxicillin/clavulanate		16/8	32/16	0.0/56.5/43.5

Source: Table 14.1.16.3
Note: percentages are calculated as 100 × (n/N) where N is number of patients in the micro-MITTR population with respective study uropathogen at baseline with valid MIC values; for the %S/%I/%R columns there is no breakpoint for CLSI when NA appears. Abbreviations: CLSI = Clinical and Laboratory Standards Institute; MIC_{50} = minimum inhibitory concentration required to inhibit the growth of 50% of organism; MIC_{90} = 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; S = susceptible; I = intermediate; R = resistant.

7.5.2.3.3 Overall Response

The primary efficacy endpoint was overall response at the Day 12 (TOC) visit in each of the micro-MITT, micro-MITTS and micro-MITTR populations. Table 101 presents the overall response at TOC in the micro-MITTR population. Overall response of success was seen in 52.4% of patients in the sulopenem group and 68% of patients in the amoxicillin/clavulanate group (treatment difference -15.6%, 95% CI [-37.5, 9.1]). Due to the small sample size in the micro-MITTR population (only 25% of planned sample size was achieved) and the imbalance in randomization to the treatment groups, there was insufficient power (approximately 20%) in the micro-MITTR population to draw any conclusions about treatment effect.

Table 101 Study 310 Overall Response at TOC – micro-MITTR Population

Outcome	Sulopenem n (%) N=42	Amoxicillin/ clavulanate n (%) N=25	Difference (95% CI)	p-value
Overall response at TOC	22 (52.4)	17 (68.0)	-15.6 (-37.5, 9.1)	0.895
Overall non-response	17 (40.5)	7 (28.0)		
Indeterminate	3 (7.1)	1 (4.0)		

Source: Table 14.2.1.3
% = 100 x n/N
micro-MITTR = microbiological modified intent-to-treat resistant; CI = confidence interval; TOC = test of cure; N = number of patients in the micro-MITTR population.
Success is defined as combined clinical and microbiologic success at TOC. Indeterminate responses are considered failures for CIcalculation. CI computed using the method proposed without stratification by Miettinen and Nurminen.
One-sided p-value corresponding to the lower bound of the 95% confidence interval is reported.

The reasons for overall failure at TOC in the micro-MITTR population are shown in Table 102 below. The most common reasons for overall failure in both treatment groups were no resolution/worsening of baseline uUTI symptoms and/or new uUTI symptoms at TOC (clinical failure alone), followed by both clinical failure plus the urine culture at TOC demonstrated $\geq 10^3$ CFU/mL of the baseline uropathogen (clinical and microbiologic failure).

Table 102 Study 310 Reasons for Overall Non-response at TOC in the micro-MITTR Population

Number of Non-responders/Reasons for Overall Non-response at TOC	Sulopenem n (%) N=42	Amoxicillin/ clavulanate n (%) N=25
Number of non-responders	17 (40.5)	7 (28.0)
Urine culture at the TOC visit demonstrates $\geq 10^3$ CFU/mL of the baseline uropathogen (**microbiologic failure only**)	4 (9.5)	1 (4.0)
No resolution or worsening of symptoms of uUTI present at trial entry and/or new uUTI symptoms (**clinical failure only**)	7 (16.7)	3 (12.0)
Urine culture $\geq 10^3$ CFU/mL and at least one symptom not resolved (**both clinical and microbiologic failure**)	6 (14.3)	3 (12.0)
Antibacterial therapy alone	0 (0.0)	0 (0.0)
Death due to uUTI	0 (0.0)	0 (0.0)
Receipt of non-study antibacterial therapy for uUTI*	2 (4.8)	0 (0.0)

Source: Table 14.2.2.14.3

Abbreviations: uUTI = uncomplicated urinary tract infection; micro-MITTR = microbiologic modified intent-to-treat resistant; the percentages are calculated as 100 x (n/N); TOC = test of cure; CFU = colony forming units. *Patients may have had an additional reason for failure

7.5.2.3.4 Clinical Response

The clinical response at TOC for the micro-MITTR population and reasons for clinical non-response as determined by the patient and the investigator at TOC for the micro-MITTR population is provided in Table 103 and Table 104, respectively. Patient-determined clinical response rates appear higher for patients receiving amoxicillin/clavulanate (61.9% in the sulopenem group and 72.0% in the amoxicillin/clavulanate group, treatment difference -10.1%, 95% CI [-31.5, 14.0]), while investigator-assessed clinical response rates were higher for patients receiving sulopenem (83.3% in the sulopenem group and 72.0% in the amoxicillin/clavulanate group, treatment difference 11.3%, 95% CI [-8.6, 33.4]). Additionally, there was a slight imbalance between treatment groups in the number of patients with indeterminate patient-determined and investigator-determined clinical response assessment. If patients with indeterminate responses are excluded from the analysis, clinical response outcomes in the two treatment groups are similar (patient-determined clinical success rate 26/39 [66.7%] in the sulopenem group and 18/24 [75.0%] in the amoxicillin/clavulanate group; investigator-determined clinical success rate 35/39 [89.7%] in the sulopenem group and is 18/24 [75.0%] in the amoxicillin/clavulanate group). These findings highlight the difficulty in interpreting outcomes in a population with a small number of patients.

Table 103 Study 310 Clinical Response (Patient-Determined) at TOC and Reasons for Clinical Non-response at TOC in the micro-MITTR Population

Clinical Response	Sulopenem n (%) N=42	Amoxicillin/ clavulanate n (%) N=25	Difference (95% CI)
Clinical success	26 (61.9)	18 (72.0)	-10.1 (-31.5, 14.0)
Clinical failure	13 (31.0)	6 (24.0)	
Indeterminate	3 (7.1)	1 (4.0)	
Reasons for Clinical Non-response			
uUTI symptoms not resolved/developed new symptoms	13 (31.0)	6 (24.0)	
Rescue therapy received	2 (4.8)	0 (0.0)	
Death	0 (0.0)	0 (0.0)	

Source: Table 14.2.12.1.6, Table 14.2.12.7.6

Table 104 Study 310 Clinical Response at TOC and Reasons for Clinical Non-response as Determined by the Investigator at TOC in the micro-MITTR Population

Investigator's Assessment of Clinical Response	Sulopenem n (%) N=42	Amoxicillin/ clavulanate n (%) N=25	Difference (95% CI)
Clinical success	35 (83.3)	18 (72.0)	11.3 (-8.6, 33.4)
Clinical failure	4 (9.5)	6 (24.0)	
Indeterminate*	3 (7.1)	1 (4.0)	
Reasons for Clinical Non-response			
Persistence/progression of any pre-therapy uUTI signs/symptoms	4 (9.5)	6 (24.0)	
Use of additional antibiotics for the current infection	2 (4.8)	1 (4.0)	
Previously met criteria for failure and received rescue antibiotics	1 (2.4)	0 (0.0)	
Death related to uUTI prior to EOT	0 (0.0)	0 (0.0)	

Source: Table 14.2.15.1.6, Table 14.2.15.4.6

Note: *'Indeterminate' represents an investigator's actual selection from choices provided on the case report form; missing investigator assessments are not included in this table as failures; patients may have more than one reason for non-response.

7.5.2.3.5 Microbiologic Response

The microbiologic response per patient at TOC for the micro-MITTR population is provided in Table 105. Microbiologic response rates were comparable in the two treatment groups at TOC.

Additionally, there was a slight imbalance between treatment groups in the number of patients with indeterminate microbiologic response at TOC. If these patients are excluded from the analysis, microbiologic response outcomes in the two treatment groups remain similar (microbiologic success rate 29/39 [74.4%] in the sulopenem group and 20/24 [83.3%] in the amoxicillin/clavulanate group). These findings highlight the difficulty in interpreting outcomes in a population with a small number of patients.

Table 105 Study 310 Microbiologic Response Per Patient at TOC – micro-MITTR Population

Microbiologic Response per Patient / Reasons for Microbiologic Non-response	Sulopenem n (%) N=42	Amoxicillin/ clavulanate n (%) N=25	Difference (95% CI)
Microbiologic success	29 (69.0)	20 (80.0)	-11.0 (-30.7, 12.0)
Microbiologic failure	10 (23.8)	4 (16.0)	
Persistence	10 (23.8)	4 (16.0)	
Persistence with increasing MIC	0 (0.0)	0 (0.0)	
Indeterminate	3 (7.1)	1 (4.0)	

Source: Table 14.2.6.3.1

Note: CI = confidence interval; MIC = minimum inhibitory concentration; TOC = test of cure; the percentages are calculated as 100 x (n/N); persistence with increasing MIC means a ≥ 4-dilutions higher MIC from baseline visit; microbiologically evaluable patients are both clinically evaluable and micro-MITT.

7.5.2.3.6 Additional Analyses of Primary Endpoint

7.5.2.3.6.1 Overall Response at TOC by Infection Type

Overall response at TOC for patients with monomicrobial or polymicrobial infections is presented in Table 106.

Table 106 Study 310 Overall Response at TOC by Infection Type – micro-MITTR Population

Parameter/Overall Response	Sulopenem n (%) N=42	Amoxicillin/ clavulanate n (%) N=25
Monomicrobial infection	33	24
Overall success	18 (54.5)	16 (66.7)
Overall failure	13 (39.4)	7 (29.2)
Indeterminate	2 (6.1)	1 (4.2)
Polymicrobial infection	9	1
Overall success	4 (44.4)	1 (100.0)
Overall failure	4 (44.4)	0 (0.0)

Parameter/Overall Response	Sulopenem n (%) N=42	Amoxicillin/ clavulanate n (%) N=25
Indeterminate	1 (11.1)	0 (0.0)

Source: Post hoc Table 6

7.5.2.3.6.2 Random Imbalances that Likely Contributed to Results Seen in microMITT-R Population

The micro-MITTR population included a total of 67 patients (42 assigned to sulopenem and 25 assigned to amoxicillin/clavulanate), much fewer than the 268 patients planned for when the study was designed. The analyses performed for the micro-MITTR population are the same as were performed for the micro-MITT and micro-MITTS populations. The low number of patients in the population and the 1.7 to 1 ratio for sulopenem to amoxicillin/clavulanate treatment assignment, however, makes it difficult to draw conclusions from these analyses. Notably, as shown in the three tables below (Table 107, Table 108, Table 109), there are some random imbalances which likely contributed to the results seen in this population. First, among the micro-MITTR patients, there were differences in baseline isolates in terms of MIC to amoxicillin/clavulanate. As shown in the table below, the infecting study pathogen had intermediate susceptibility to amoxicillin/clavulanate for 40.5% and 64.0% of patients in the sulopenem and amoxicillin/clavulanate arm, respectively. The infecting study pathogen was fully resistant to amoxicillin/clavulanate for 59.5% and 36.0% of patients in the sulopenem and amoxicillin/clavulanate arm, respectively. Second, patients assigned to sulopenem were significantly more likely to have a polymicrobial baseline infection than those assigned to amoxicillin/clavulanate. Third, patients assigned to sulopenem were more likely to have a multidrug resistant baseline study pathogen than those assigned to amoxicillin/clavulanate. All three of these criteria, resistance to amoxicillin/clavulanate, polymicrobial infections at baseline and multidrug resistant baseline pathogens can be markers of failure. As shown in Table 108 below, overall success rate for patients with infections due to amoxicillin/clavulanate resistant isolates (MIC ≥32 µg/mL) is much lower than those with infections caused by pathogens with intermediate susceptibility to amoxicillin/clavulanate (55.6% vs 75.0%, respectively) in the amoxicillin/clavulanate arm, and lower than the success rate seen in the same group in the sulopenem arm (64.0%).

7.5.2.3.6.2.1 Imbalance in Baseline Pathogen's MIC to Amoxicillin/clavulanate

Table 107 Study 310 Baseline Pathogen by Amoxicillin/clavulanate MIC – micro-MITTR Population

Baseline Study Pathogen Parameter	Sulopenem n (%) N=42	Amoxicillin/ clavulanate n (%) N=25
Amoxicillin/clavulanate MIC (µg/mL)		

Baseline Study Pathogen Parameter	Sulopenem n (%) N=42	Amoxicillin/ clavulanate n (%) N=25
16 (intermediate)	17 (40.5)	16 (64.0)
≥32 (resistant)	25 (59.5)	9 (36.0)
Polymicrobial infection*	9 (21.4)	1 (4.0)
Multidrug resistant pathogen**	15 (35.7)	2 (8.0)

Source: Post hoc Table 5, post hoc Table 6, Listing 16.2.6.8

*Polymicrobial infection: ≥100,000 CFU/mL in baseline specimen of any 2 Enterobacterales.

**Multidrug resistant pathogen: non-susceptible to three or more classes of antibiotics tested.

7.5.2.3.6.2.2 Overall Response at TOC by Amoxicillin/clavulanate MIC

Table 108 Study 310 Overall Response at TOC by Amoxicillin/clavulanate MIC – micro-MITTR Population

Parameter/Overall Response	Sulopenem n (%) N=42	Amoxicillin/ clavulanate n (%) N=25
Amoxicillin/clavulanate MIC 16 µg/mL	17	16
Overall success	6 (35.3)	12 (75.0)
Overall failure	8 (47.1)	3 (18.8)
Indeterminate	3 (17.6)	1 (6.3)
Amoxicillin/clavulanate MIC ≥32 µg/mL	25	9
Overall success	16 (64.0)	5 (55.6)
Overall failure	9 (36.0)	4 (44.4)
Indeterminate	0 (0.0)	0 (0.0)

Source: Post hoc Table 5

7.5.2.3.6.2.3 Overall Response at TOC by Infection Type

Overall response at TOC for patients with monomicrobial or polymicrobial infections is presented in table below.

Table 109 Study 310 Overall Response at TOC by Infection Type – micro-MITTR Population

Parameter/Overall Response	Sulopenem n (%) N=42	Amoxicillin/ clavulanate n (%) N=25
Monomicrobial infection	33	24
Overall success	18 (54.5)	16 (66.7)
Overall failure	13 (39.4)	7 (29.2)
Indeterminate	2 (6.1)	1 (4.2)
Polymicrobial infection	9	1
Overall success	4 (44.4)	1 (100.0)
Overall failure	4 (44.4)	0 (0.0)
Indeterminate	1 (11.1)	0 (0.0)

Source: Post hoc Table 6

7.5.3 Additional Clinical Data Supporting the Claim

Two other studies generated data supportive of the findings in the superiority assessment of oral sulopenem and ciprofloxacin.

7.5.3.1 Study 302 (Complicated Urinary Tract Infections)

Study 302 was a double-blinded (pharmacist unblinded), randomized, controlled trial comparing once daily sulopenem IV for five days followed by oral sulopenem with once daily ertapenem IV for five days followed by either ciprofloxacin if the baseline pathogen was susceptible to quinolones or amoxicillin-clavulanate if resistant to quinolones; patients resistant to both classes of antibiotics had to remain on IV ertapenem. Non-inferiority was to be declared if the lower limit of the confidence interval for the treatment difference for overall success between sulopenem and ertapenem was greater than -10%.

Sulopenem was not non-inferior to ertapenem in this study [sulopenem: 301/444 (67.8%), ertapenem: 325/440 (73.9%): difference, (95%CI); -6.1, (-12.0, -0.1)], again driven primarily by a lower rate of asymptomatic bacteriuria seen in patients randomized to the ertapenem regimen and, as in the uncomplicated UTI study, specifically in that subset of patients who received ciprofloxacin as step-down therapy (Table 110).

Importantly, within the microMITT population, for those patients for whom a quinolone was not a step-down therapy option because of resistance of their uropathogen, oral sulopenem appears to be a reasonable alternative treatment option, accepting the limitations of drawing any statistical inference in subpopulations where the primary comparison was not met [sulopenem: 114/162 (70.4%), ertapenem: 122/193 (63.2%); difference (95%CI): 7.2 (-2.7, 16.8)].

Table 110 Study 302 Overall Response at TOC microMITT Population

Outcome	Sulopenem n (%)	Ertapenem n (%)	Difference (%) (95% CI)
All patients			
Overall Success, n/N (%)	301/444 (67.8)	325/440 (73.9)	-6.1 (-12.0, -0.1)
Reason for failure: Asymptomatic bacteriuria	93 (20.9)	59 (13.4)	
Patients with ciprofloxacin susceptible isolates by treatment regimen			
	IV sulopenem followed by oral sulopenem etzadroxil plus probenecid	**IV ertapenem followed by oral ciprofloxacin**	
Overall Success, n/N (%)	168/248 (67.7)	186/215 (86.5)	-18.8 (-26.1, -11.0)
Reason for failure: Asymptomatic bacteriuria	54 (21.8)	10 (4.7)	
	IV sulopenem	**IV ertapenem only (n=26) or IV ertapenem followed by oral amoxicillin-clavulanate (n=6)**	
Overall Success, n/N (%)	19/34 (55.9)	17/32 (53.1)	2.8 (-20.9, 26.2)
Reason for failure: Asymptomatic bacteriuria	7 (20.6)	7 (21.9)	
Patients with ciprofloxacin non-susceptible isolates by treatment regimen			
	IV sulopenem only or IV sulopenem followed by oral sulopenem etzadroxil plus probenecid	**IV ertapenem only or IV ertapenem followed by oral amoxicillin-clavulanate**	
Overall Success, n/N (%)	114/162 (70.4)	122/193 (63.2)	7.2 (-2.7, 16.8)
Reason for failure: Asymptomatic bacteriuria	32 (19.8)	42 (21.8)	

Source: Table 14.2.1.1.1, Table 14.2.1.2.1, Table 14.2.8.1.1, Table 14.2.4.1.1, Post-hoc Table 2, Post-hoc Table 3, Post-hoc Table 4, Post-hoc Table 5, Post-hoc Table 14, Post-hoc Table 15
Note: microMITT = microbiologic modified intent-to-treat; CI = confidence interval

The clinical response to treatment at TOC was similar [sulopenem 397/444 (89.4%), ertapenem 389/440 (88.4%); difference (95%CI): 1.0% (-3.1, 5.1)], as expected if asymptomatic bacteriuria was the reason for the difference in overall response (Table 111). Importantly, the 7.5% higher rate of asymptomatic bacteriuria at the Test of Cure did not result in an 7.5% increase in clinical failure relative to ertapenem at the subsequent follow up visit one week later, further evidence that asymptomatic bacteriuria does not predict subsequent treatment failure or relapse and should not contribute to the primary endpoint analysis of treatment outcome in urinary tract infection studies.

Table 111: Study 302 Clinical Response at the End of Treatment, Test of Cure and Follow up Visit microMITT Population

Timepoint/ Clinical Response	Sulopenem n (%) N=444	Ertapenem n (%) N=440	Difference % (95% CI)
End of Treatment (D10)	399 (89.9)	399 (90.7)	-0.8 (-4.7, 3.1)
Test of Cure (D21)	397 (89.4)	389 (88.4)	1.0 (-3.1, 5.1)
Final Visit (D28)	386 (86.9)	383 (87.0)	-0.1 (-4.5, 4.3)

Source: IT001-302, Table 14.2.8.1.1, 14.2.11.1.1, 14.2.10.1.1

The finding from these patients with a serious complicated urinary tract infection with quinolone non-susceptible organisms provide additional support for the activity of oral sulopenem in the treatment of uncomplicated UTI.

7.6 EFFICACY CONCLUSIONS

Evidence for the effectiveness of sulopenem in the treatment of uUTI is based on the results of two double-blind, double dummy, multicenter, randomized, comparative and controlled studies, IT001-301, in which oral sulopenem was superior to ciprofloxacin in the treatment of uUTI in patients with quinolone non-susceptible pathogens with a clinically meaningful difference in the treatment effect that was highly statistically significant, and Study IT001-310, in which oral sulopenem demonstrated non-inferiority and was found to be superior to amoxicillin/clavulanate in the treatment of uUTI in patients with amoxicillin/clavulanate susceptible pathogens, despite using a higher dose of amoxicillin/clavulanate than the dose listed in its USPI for uUTI.

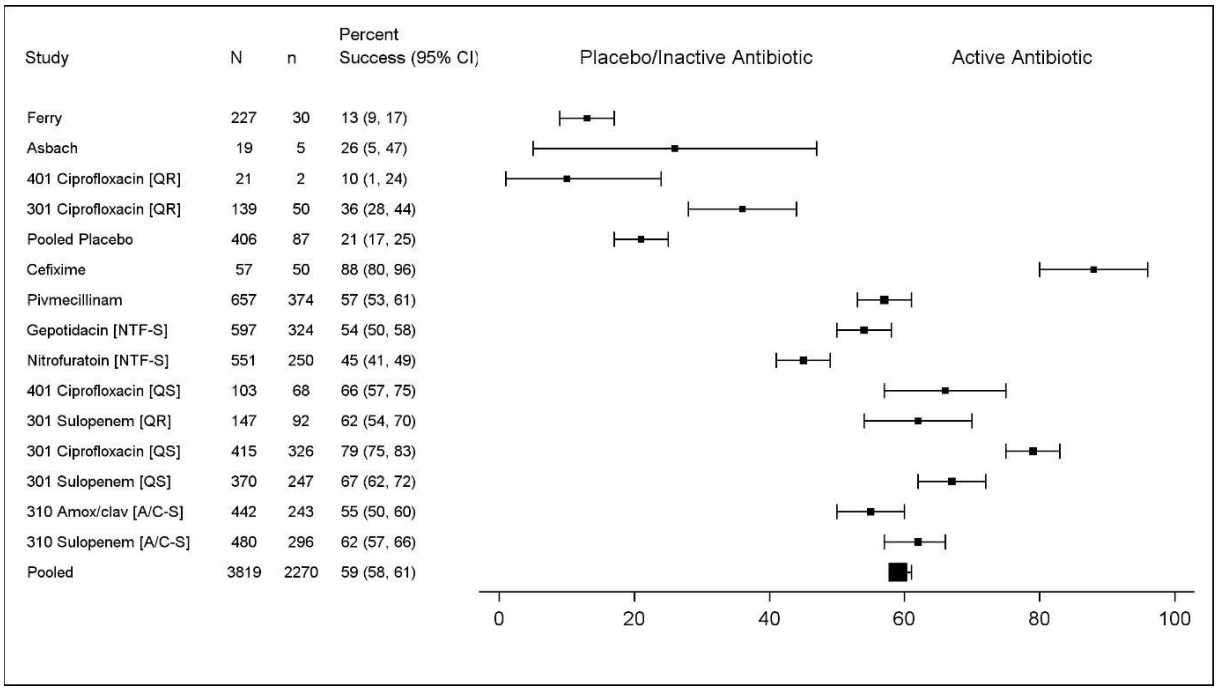
As discussed above, the patient population in both pivotal trials was diverse, there was a high degree of compliance with treatment and follow up visits, the analysis plans were prespecified prior to breaking the blind following accepted conventions for handling of missing data, and the findings of the primary endpoint comparison were consistently observed across important secondary endpoints and subset analyses. The data derived from these two clinical trials are further supported by *in vitro* susceptibility data of sulopenem against a wide variety of Enterobacterales relevant to uUTI, pharmacokinetic-pharmacodynamic analyses which build on the pharmacokinetics of sulopenem in the urinary tract from Phase 1 and Phase 3 studies and relevant animal models. Taken together, these two studies provide data consistent with the *FDA Guidance for Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* and provide substantial evidence of effectiveness for the intended indication of treatment of uUTIs in women known or suspected to be caused by susceptible pathogens.

Figure 18 presents a Forest plot of the point estimates of clinical success in treatment of an uUTI with either placebo/inactive agent or an active antibiotic, respectively. The design and conduct of these studies varied in size, complexity and analysis methodology however they do provide support for the role of antibiotics over placebo in treatment of uncomplicated UTI and some useful background towards support of the outcomes in the micro-MITTR population of IT001-301.

The point estimates of success for ciprofloxacin treated patients who had a quinolone non-susceptible isolate in IT001-301 are higher than those of a true placebo, strengthening the likelihood that oral sulopenem would be superior to a true placebo. The point estimate of

success for oral sulopenem patients with a quinolone non-susceptible pathogen is similar to that in patients with a quinolone susceptible isolate and fall between the outcomes seen with pivmecillinam and cefixime.

Figure 18 Forest plot of Treatment Success (95%CI) in Uncomplicated UTI



Source: Data on file

8 CLINICAL SAFETY

The safety discussion in this briefing document will address the Phase 3 program, with a focus on Study 301 and Study 310.

8.1 DEMOGRAPHIC AND BASELINE CHARACTERISTICS OF STUDY POPULATION

8.1.1 Study Drug Exposure

8.1.1.1 Phase 3 Program

Study drug exposure for sulopenem, oral sulopenem, or comparator during the treatment period was summarized for all Phase 3 studies and Phase 3 uUTI studies separately. Total study drug dosage during the study per subject, frequency distributions of the number of calendar days on study drug (last dose date minus first dose date +1), and descriptive summaries of durations of dosing are presented by treatment group for all study groups' analysis sets. Exposure to sulopenem, oral sulopenem and comparator agents are provided below for patients in the Phase 3 program (Table 112) as well as those in the Phase 3 uUTI studies, Study 301 and Study 310 (Table 113).

Phase 3 Program

Table 112: Study Drug Exposure – Phase 3 Safety Population

Parameter	Sulopenem	Comparators
Total dosing		
Duration of exposure (days)		
N	1863	1857
Mean (SD)	7.5 (2.5)	6.5 (3.2)
Median	7.00	7.00
Min, max	1.0, 15.0	1.0, 14.0
IV dosing		
Duration of exposure (days)		
N	1030	1030
Mean (SD)	6.2 (1.7)	6.7 (2.1)
Median	5.0	6.0
Min, max	1.0, 14.0	1.0, 14.0
Oral Dosing		
Duration of exposure (days)		
N	1716	1520
Mean (SD)	4.4 (1.3)	3.5 (1.0)
Median	5.00	3.00
Min, max	0.5, 8.0	0.0, 9.0

Note: N = number of patients in the Safety population; SD = standard deviation; Min = minimum value; Max = maximum value. The percentages are calculated as 100 x (n/N).

8.1.1.2 Phase 3 uUTI Studies Combined

Table 113: Extent of Exposure to Active Study Drug Phase 3 uUTI Studies Safety Population

Parameter	Oral Sulopenem	Comparator*
N	1940	1934
Duration of exposure (days)		
Mean (SD)	5.2 (0.75)	4.4 (1.20)
Median	5.0	5.0
Min, max	1, 8	1, 10
Duration of exposure n (%)		
≥ 1 day	1940 (100)	1934 (100)
≥ 2 days	1911 (98.5)	1904 (98.4)
≥3 days	1900 (97.9)	1892 (97.8)
≥4 days	1892 (97.5)	1296 (67.0)
≥5 days	1884 (97.1)	1077 (55.7)
≥6 days	525 (27.1)	336 (17.4)
≥7 days	7 (0.4)	5 (0.3)
≥8 days	2 (0.1)	1 (<0.1)
≥9 days	0	1 (<0.1)
≥10 days	0	1 (<0.1)

Post hoc Table 4.3.39.1a N = number of patients in the safety population with non-missing data; SD = standard deviation; Min = minimum value; Max = maximum value. The percentages are calculated as 100 x (n/N). Number of days on therapy is the elapsed time from start of therapy to end of therapy (i.e., calendar days), not the number of days the subject took treatment; duration of exposure does not include the placebo used to maintain the blinding. *NOTE: duration of active treatment for the comparator was 3 days in Study 301 and 5 days in Study 310.

8.1.2 Disposition and Completion Status

Study disposition and completion status for sulopenem, oral sulopenem, or comparator during the treatment period was summarized for all Phase 3 studies and Phase 3 uUTI studies separately.

8.1.2.1 Phase 3 Program

In the entire Phase 3 program, the majority of patients completed both the study drug and the study. The percentage of patients who prematurely discontinued from study drug and/or the study, as well as the reasons for doing so, were similar in the sulopenem and comparator groups (Table 114).

Table 114: Patient Completion Status – Phase 3 ITT Population

Parameter	Sulopenem N = 2981 n (%)	Comparator N = 2981 n (%)
Completed study drug	**2855 (95.8)**	**2857 (95.8)**
Patients who did not receive study drug	11 (0.4)	17 (0.6)
Prematurely discontinued from study drug	115 (3.9)	107 (3.6)
Primary reason for premature treatment discontinuation		
Adverse event	29 (1.0)	23 (0.8)
Death	3 (0.1)	4 (0.1)
Insufficient therapeutic effect	2 (< 0.1)	3 (0.1)
Non-compliance with study drug	16 (0.5)	12 (0.4)
Carbapenem-resistant pathogen[1]	3 (0.1)	1 (<0.1)
Need for concomitant systemic antibacterial therapy	1 (<0.1)	1 (<0.1)
Lost to follow-up	13 (0.4)	19 (0.6)
Patient request	31 (1.0)	34 (1.1)
Sponsor decision	0	0
Investigator decision	7 (0.2)	2 (< 0.1)
Other	10 (0.3)	8 (0.3)
Completed the study	**2847 (95.5)**	**2830 (94.9)**
Prematurely discontinued from study	134 (4.5)	151 (5.1)
Primary reason for early study termination		
Adverse event	9 (0.3)	6 (0.2)
Death	3 (0.1)	0
Insufficient therapeutic effect	0	0
Non-compliance with study drug[2]	3 (0.1)	1 (<0.1)
Subject noncompliance[1]	0	0
Need for concomitant systemic antibacterial therapy	0	0
Lost to follow-up	26 (0.9)	39 (1.3)
Patient request	58 (1.9)	66 (2.2)
Sponsor decision	0	0
Investigator decision	4 (0.1)	3 (0.1)
Other	6 (0.2)	5 (0.2)
Missing	25 (0.8)	31 (1.0)

Source: Table 4.3.1.6
Abbreviations: N=All patients with non-missing treatment; ITT=Intent-to-treat.
For some patients who were lost to follow-up, no specific reason was provided for their discontinuation; thus, the number of patients who completed the study and who discontinued from the study do not add up to the denominator.[1] Applies to Study IT001-303; [2] Applies to Studies IT001-301, -302 and -310.

8.1.2.2 Phase 3 uUTI Studies

8.1.2.2.1 Study 301

The disposition of all patients in the ITT population is summarized in Table 115.

Overall, approximately 97% of the patients completed study drug treatment, while 3% discontinued treatment prematurely. The primary reasons for discontinuation of treatment were adverse events and 'patient request'; gastrointestinal disorders accounted for most of the discontinuations due to AEs among sulopenem-treated patients.

Overall, approximately 98% of patients completed the study through the TOC Visit, and approximately 2% terminated early. The primary reasons for early study termination were 'patient request' and patients who were lost to follow-up.

Table 115: Study 301 Disposition of Patients by Treatment – ITT Population*

Parameter	Sulopenem n (%) N=787	Ciprofloxacin n (%) N=803
Safety population		
Completed study drug	764 (97.1)	776 (96.6)
Patients who did not receive study drug	2 (0.3)	9 (1.1)
Prematurely discontinued from study drug	21 (2.7)	18 (2.2)
Primary reason for premature treatment discontinuation		
AE	12 (1.5)	7 (0.9)
Death	0 (0.0)	0 (0.0)
Insufficient therapeutic effect	0 (0.0)	0 (0.0)
Need for concomitant systemic antibacterial therapy	1 (0.1)	0 (0.0)
Non-compliance with study drug	0 (0.0)	0 (0.0)
Lost to follow-up	1 (0.1)	3 (0.4)
Patient request	5 (0.6)	7 (0.9)
Sponsor decision	0 (0.0)	0 (0.0)
Investigator decision	1 (0.1)	0 (0.0)
Other	1 (0.1)	1 (0.1)
Completed the study	755 (97.9)	761 (97.4)
Prematurely discontinued from study	16 (2.1)	20 (2.6)
Primary reason for early study termination		
AE	0 (0.0)	1 (0.1)
Death	0 (0.0)	0 (0.0)
Insufficient therapeutic effect	0 (0.0)	0 (0.0)
Need for concomitant systemic antibacterial therapy	0 (0.0)	0 (0.0)
Non-compliance with study drug	2 (0.3)	1 (0.1)
Lost to follow-up	3 (0.4)	7 (0.9)
Patient request	11 (1.4)	8 (1.0)
Sponsor decision	0 (0.0)	0 (0.0)
Investigator decision	0 (0.0)	1 (0.1)
Other	0 (0.0)	2 (0.3)

Source: Table 14.1.3.3.2, Listing 16.2.9.12; *excludes patients from sites 202 and 218
Abbreviation: AE=adverse events

8.1.2.2.2 Study 310

The disposition of all patients in the ITT population is summarized below (Table 116). There were a total of 2222 randomized patients (2459 potential patients minus 237 screen failures). The 2222 patients enrolled in the study were randomly assigned in a 1:1 ratio to the sulopenem group (N = 1111) or the amoxicillin/clavulanate group (N = 1111). There were 8 patients who did not receive study drug, leaving 2214 patients in the safety population. Overall, approximately 95% of the patients completed study drug treatment, while 4% discontinued treatment prematurely. The primary reasons for discontinuation of treatment were 'non-compliance with study drug' and 'withdrawal by subject'.

Overall, approximately 95% of patients completed the study through the TOC Visit, and approximately 5% terminated early. The primary reasons for early study termination were 'withdrawal by subject' and 'lost to follow-up'. Disposition of patients by treatment in the micro-MITTS population and micro-MITTR population is similar to what is shown for the ITT population except in the micro-MITTR population, the primary reasons for discontinuation of treatment were 'lost to follow-up' and 'withdrawal by subject'.

Table 116: Study 310 Disposition of Patients by Treatment – ITT Population

Parameter	Sulopenem n (%) N=1111	Amoxicillin/ clavulanate n (%) N=1111	Total n (%) N=2222	p-value
Completed study drug	1057 (95.1)	1063 (95.7)	2120 (95.4)	0.6125
Patients who did not receive study drug	4 (0.4)	4 (0.4)	8 (0.4)	1.0000
Prematurely discontinued from study drug	50 (4.5)	44 (4.0)	94 (4.2)	0.5984
Primary reason for premature treatment discontinuation				
AE	8 (0.7)	4 (0.4)	12 (0.5)	
Death	0 (0.0)	0 (0.0)	0 (0.0)	
Non-compliance with study drug	16 (1.4)	12 (1.1)	28 (1.3)	
Lost to follow-up	6 (0.5)	11 (1.0)	17 (0.8)	
Withdrawal by subject	14 (1.3)	12 (1.1)	26 (1.2)	
Sponsor decision	0 (0.0)	0 (0.0)	0 (0.0)	
Physician decision	1 (0.1)	0 (0.0)	1 (0.0)	
Other	5 (0.5)	5 (0.5)	10 (0.5)	
Completed the study	1056 (95.0)	1050 (94.5)	2106 (94.8)	0.6336
Prematurely discontinued from study	52 (4.7)	57 (5.1)	109 (4.9)	0.6945
Primary reason for early study termination				
AE	4 (0.4)	1 (0.1)	5 (0.2)	
Death	0 (0.0)	0 (0.0)	0 (0.0)	
Non-compliance with study drug	0 (0.0)	0 (0.0)	0 (0.0)	
Lost to follow-up	17 (1.5)	23 (2.1)	40 (1.8)	

Withdrawal by subject	31 (2.8)	32 (2.9)	63 (2.8)	
Sponsor decision	0 (0.0)	0 (0.0)	0 (0.0)	
Physician decision	0 (0.0)	0 (0.0)	0 (0.0)	
Other	0 (0.0)	1 (0.1)	1 (0.0)	

Source: Table 14.1.3.1

8.2 ADVERSE EVENTS

8.2.1 Overall Summary

8.2.1.1 Phase 3 Program

In the Phase 3 integrated analysis set, TEAEs (20.4% vs. 14.9%) and treatment-related TEAEs (12.1% vs. 7.4%) were more common among sulopenem-treated subjects than comparator-treated subjects, while the premature discontinuation rates due to TEAEs were comparable in the two groups (Table 117).

There were no SAEs in the sulopenem group in Study IT001-310. Overall, more sulopenem-treated subjects than comparator-treated subjects experienced at least one SAE (45 vs. 25). Only three SAEs, all in the sulopenem group, were considered drug-related; all three occurred in subjects receiving sulopenem etzadroxil.

There were seven deaths among those receiving sulopenem, four among those receiving comparator.

Table 117: Overall Summary of Adverse Events – Phase 3 Safety Population

Preferred Term	**Sulopenem (N=2970)** **n (%)**	**Comparator (N=2964)** **n (%)**
Number of patients who experienced at least one:		
AE	614 (20.7)	446 (15.0)
TEAE	606 (20.4)	441 (14.9)
Drug-related TEAE	359 (12.1)	218 (7.4)
IV drug-related TEAE	45 (1.5)	70 (2.4)
Oral drug-related TEAE	323 (10.9)	158 (5.3)
TEAE leading to premature discontinuation of study drug	30 (1.0)	25 (0.8)
TEAE leading to premature discontinuation from study	9 (0.3)	6 (0.2)
SAE	45 (1.5)	25 (0.8)

Treatment emergent SAE	45 (1.5)	25 (0.8)
Drug-related SAE	3 (0.1)	0
IV drug-related SAE	1 (<0.1)	0
Oral drug-related SAE	3 (0.1)	0
SAE leading to death	7 (0.2)	4 (0.1)
SAE leading to premature discontinuation of study drug	5 (0.2)	7 (0.2)

Source: Table 4.3.3.1

AE = Adverse Events; TEAE = Treatment-Emergent Adverse Events; SAE = Serious Adverse Events;IT001-302 and IT001-303 collected relationship to oral and IV as two distinct variables; therefore, it's possible that a TEAE can be attributed to both oral and IV if it occurred shortly after IV dosing was completed and oral dosing started;Version 26.1 of MedDRA is used to code adverse events except Loose stools. Comparator: IT001-301 -

Ciprofloxacin, IT001-302 – Ertapenem followed by either ciprofloxacin or amoxicillin/clavulanate, IT001-303 – Ertapenem followed by either ciprofloxacin plus metronidazole or amoxicillin/clavulanate, IT001-310 – Amoxicillin/clavulanate

8.2.1.2 Phase 3 uUTI Studies Combined

The Phase 3 uUTI integrated analysis set includes 1940 oral sulopenem-treated subjects from Studies 310 and 301.

An overview of safety in the Phase 3 uUTI integrated analysis set is presented in Table 118; TEAEs (21.4% vs. 13.0%) were more common among oral sulopenem-treated subjects than comparator-treated subjects, while the premature discontinuation rates due to TEAEs were comparable in the two groups.

In the integrated Phase 3 uUTI set, there was one death among those receiving sulopenem and none among those receiving comparator. The one death was a patient with poorly differentiated adenocarcinoma of the lung that occurred more than 5 months after study completion and was not considered related to study drug.

Table 118: Overall Summary of Adverse Events – Phase 3 uUTI Studies Safety Population

Preferred Term	Sulopenem (N=1940) n (%)	Comparator (N=1934) n (%)
Number of patients who experienced at least one:		
AE	419 (21.6)	252 (13.0)
TEAE	416 (21.4)	251 (13.0)
Drug-related TEAE	297 (15.3)	136 (7.0)

TEAE leading to premature discontinuation of study drug	21 (1.1)	12 (0.6)
TEAE leading to premature discontinuation from study	7 (0.4)	4 (0.2)
SAE	6 (0.3)	7 (0.4)
Treatment emergent SAE	6 (0.3)	7 (0.4)
Drug-related SAE	1 (0.1)	0
SAE leading to death	1 (0.1)	0
SAE leading to premature discontinuation of study drug	1 (0.1)	2 (0.1)

Post hoc Table 4.3.3.1a, post hoc Table 4.3.17.1a, post hoc Table 4.3.25.1a

8.2.2 All Causality Adverse Events

From this point on, the safety data presented will be from the Phase 3 uUTI studies, Study 301 and Study 310 combined.

8.2.2.1 Phase 3 uUTI Studies Combined

TEAEs appearing in ≥1% of patients in either treatment group are presented in Table 119. The incidence of nausea, headache and vomiting was comparable in the two groups. Diarrhea, loose stool and vulvovaginal mycotic infection were reported more frequently by patients in the sulopenem arm.

Table 119: Treatment-Emergent Adverse Events Occurring in ≥1% of Patients in Either Treatment Group – Phase 3 uUTI Studies Safety Population

Preferred Term	Sulopenem N=1940 n (%)	Comparator N=1934 n (%)
Diarrhea	172 (8.9)	59 (3.1)
Nausea	80 (4.1)	62 (3.2)
Headache	42 (2.2)	35 (1.8)
Vomiting	29 (1.5)	15 (0.8)
Loose stools	26 (1.3)	8 (0.4)
Vulvovaginal mycotic infection	20 (1.0)	6 (0.3)

Source: post hoc Table 4.3.18.1a
Notes: N = Number of patients in the Safety population. The percentages are calculated as 100 * (n/N). Version 26.1 of MedDRA is used to code adverse events.

8.2.3 Severity of Adverse Events

8.2.3.1 Phase 3 uUTI Studies Combined

Most TEAEs were mild to moderate in severity (Table 120).

Table 120: Severity of TEAEs – Phase 3 uUTI Studies Safety Population

Parameter	Sulopenem N=1940 n (%)	Comparator N=1934 n (%)
Number of patients who experienced at least one:		
TEAE	416* (21.4)	251 (13.0)
TEAE by maximum severity		
Mild	293 (15.1)	183 (9.4)
Moderate	110 (5.7)	64 (3.3)
Severe	12 (0.6)	4 (0.2)

Source: Study 301 Table 14.3.3.1.3, Study 310 Table 14.3.1.1

Notes: TEAE = Treatment-Emergent Adverse Events; *One patient had missing severity information for the AE.

No patient in Study 310 experienced a severe treatment-related TEAE. Three patients in Study 301 experienced what were considered severe treatment-related TEAEs.

- One patient experienced severe dizziness approximately three hours after taking her third dose of oral sulopenem; the dizziness resolved after discontinuation of study therapy.
- A second patient developed signs and symptoms of angioedema approximately twenty minutes after taking her first dose of oral sulopenem; the event was reported as an SAE (important medical event). This patient is described in Section 8.4.5.
- A third patient experienced severe abdominal pain from Days 2 to 4 of oral sulopenem treatment; this occurred in the setting of mild to moderate treatment-related diarrhea. No changes to study therapy were made and the abdominal pain resolved.

8.2.4 Discontinuations Due to Adverse Events

8.2.4.1 Phase 3 uUTI Studies Combined

Seventeen (0.9%) patients in the oral sulopenem arm and 9 (0.5%) patients in the comparator arm discontinued study drug treatment prematurely due to TEAEs (Table 121); in the sulopenem arm one of the events leading to discontinuation, angioedema, was serious. In both treatment groups, gastrointestinal disorders were the most common reason for discontinuation of study drug.

Table 121: Incidence of TEAEs Leading to Premature Discontinuation of Study Drug – Phase 3 uUTI Studies Safety Population

Parameter MedDRA SOC MedDRA PT	Sulopenem N=1940 n (%)	Comparator N=1934 n (%)
Number of patients with at least 1 TEAE Leading to Premature Discontinuation of Study Drug	17 (0.9)	9 (0.5)
Diarrhea	4 (0.2)	3 (0.2)
Dizziness	3 (0.2)	1 (0.1)
Abdominal discomfort	0 (0.0)	1 (0.1)
Abdominal pain	2 (0.1)	1 (0.1)
Dyspepsia	1 (0.1)	0 (0.0)
Constipation	1 (0.1)	0 (0.0)
Dysgeusia	1 (0.1)	0 (0.0)
Dyspnea	1 (0.1)	0 (0.0)
Angioedema	1 (0.1)	0 (0.0)
Eructation	1 (0.1)	0 (0.0)
Fatigue	1 (0.1)	0 (0.0)

Source: post hoc Table 4.3.16.1a
Notes: TEAE = Treatment-Emergent Adverse Events; SOC = System Organ Class; PT = Preferred Term; N = Number of patients in the Safety population. The percentages are calculated as 100 * (n/N). Version 26.1 of MedDRA is used to code adverse events.

8.2.5 Serious Adverse Events

8.2.5.1 Phase 3 uUTI Studies Combined

A total of 13 patients (6 sulopenem, 7 comparator) experienced a total of 16 SAEs (Table 122).

Table 122: Incidence of Treatment-Emergent Serious Adverse Events by MedDRA System Organ Class and Preferred Term – Phase 3 uUTI Studies Safety Population

MedDRA SOC MedDRA PT	Sulopenem N=1940 n (%)	Comparator N=1934 n (%)
Number of patients with at least one serious TEAE	6 (0.3)	7 (0.4)
Gastrointestinal disorders	2 (0.1)	2 (0.1)
Abdominal pain upper	1 (0.1)	0 (0.0)
Diarrhea	0 (0.0)	1 (0.1)
Diverticulum	0 (0.0)	1 (0.1)
Small intestine obstruction	1 (0.1)	0 (0.0)
General disorders and administration site conditions	1 (0.1)	1 (0.1)
Chest pain	1 (0.1)	1 (0.1)
Hepatobiliary disorders	0 (0.0)	1 (0.1)
Bile duct stone	0 (0.0)	1 (0.1)
Infections and infestations	1 (0.1)	2 (0.1)
Genital herpes	0 (0.0)	1 (0.1)
Pneumonia	0 (0.0)	1 (0.1)
Pyelonephritis acute	1 (0.1)	0 (0.0)
Urosepsis	1 (0.1)	0 (0.0)
Metabolism and nutrition disorders	0 (0.0)	1 (0.1)
Dehydration	0 (0.0)	1 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.1)	0 (0.0)
Lung adenocarcinoma	1 (0.1)	0 (0.0)
Nervous system disorders	1 (0.1)	0 (0.0)
Presyncope	1 (0.1)	0 (0.0)
Renal and urinary disorders	0 (0.0)	1 (0.1)
Ureterolithiasis	0 (0.0)	1 (0.1)
Skin and subcutaneous tissue disorders	1 (0.1)	0 (0.0)
Angioedema	1 (0.1)	0 (0.0)

Source: post hoc Table 4.3.10.1a
Notes: TEAE = Treatment-Emergent Adverse Events; N = Number of patients in the Safety population; SOC = System Organ Class; PT = Preferred Term. The percentages are calculated as 100 * (n/N). Version 26.1 of MedDRA is used to code adverse events.

Only one SAE, angioedema in a patient receiving sulopenem, was considered treatment-related. The patient was a 54 y/o female with an unremarkable PMH. On 29 July 2019, ~20 minutes following the first dose of oral sulopenem, she developed swelling of the tongue, lips and nasolabial fold; ten minutes later, she became dyspneic. The patient then traveled by bus to a local pharmacy and was advised by the pharmacist to take an OTC antihistamine. Her symptoms resolved withing three hours of taking a single dose of desloratadine. The patient informed the site of this event 2.5 hours later. The investigator

considered the event an SAE that was probably related to study therapy, categorizing it as an important medical event. The event was considered resolved on 31 July 2019.

8.2.6 Deaths

8.2.6.1 Phase 3 uUTI Studies Combined

There were no deaths in Study 310 in either treatment group. There was one death in Study 301. A 71 y/o female completed treatment with oral sulopenem for her uUTI on 22 July 2019 and was diagnosed with poorly differentiated adenocarcinoma of the lung on 1 August 2019. She died of the cancer on (b) (6).

8.2.7 Adverse Events of Special Interest

8.2.7.1 Diarrhea

8.2.7.1.1 Phase 3 uUTI Studies Combined

A summary of treatment-emergent diarrhea is presented in Table 123. Most diarrhea was considered treatment-related, and most was judged to be mild.

The median duration of diarrhea among sulopenem-treated patients was 3 days, with a maximum duration of 15 days. The median duration among comparator-treated patients was 2 days, with a maximum duration of 10 days.

Table 123: Treatment-Emergent Diarrhea by Maximum Intensity and Relationship to Study Drug – Phase uUTI Studies Safety Population

Parameter	Sulopenem (N = 1940)	Comparator (N =1934)
Total number of patients with treatment-emergent diarrhea, n (%)	172 (8.9)	59 (3.1)
Intensity[1], n (%)		
Mild	128 (6.6)	49 (2.5)
Moderate	41 (2.1)	9 (0.5)
Severe	3 (0.2)	1 (0.1)
Drug relationship[2], n (%)		
Related	156 (8.0)	46 (2.4)
Not related	16 (0.8)	13 (0.7)
Duration of treatment-emergent diarrhea (days)		
N*	172	59
Mean (SD)	3.9 (2.8)	2.8 (1.7)
Median	3.0	2.0

Min, max	1, 15	1, 10
Duration of study drug related treatment-emergent diarrhea (days)		
N*	156	46
Mean (SD)	4.1 (2.8)	2.9 (1.8)
Median	3.5	2.0
Min, max	1, 15	1, 10

Source: post hoc Table 4.3.22.1a

TEAE = Treatment-Emergent Adverse Events; N* =Number of Patients with Diarrhea (NOTE: there was one patient for whom the duration of diarrhea could not be determined). Subjects are only counted once at each level of summarization. [1] Worst intensity per patient. [2] Drug-related if at least one AE of diarrhea is drug-related. Version 26.1 of MedDRA is used to code adverse events except Loose stools. Comparator: IT001-301 - Ciprofloxacin, IT001-310 – Amoxicillin/clavulanate

The effect of fed/fasted status on the incidence of diarrhea among uUTI patients receiving oral study therapy is presented in Table 124. Fed/fasted status did not appear to affect the overall incidence of diarrhea among sulopenem-treated patients.

Table 124: Treatment-Emergent Diarrhea By Maximum Intensity and Relationship to Study Drug – Oral by Fed/Fasted Status –Phase 3 uUTI Studies Safety Population

Parameter	Sulopenem (N = 1920)		Comparator (N = 1908)	
	Fasted	Fed	Fasted	Fed
Total number of patients with treatment-emergent diarrhea, n/N (%)	61/655 (9.3)	110/1265 (8.7)	20/624 (3.2)	39/1284 (3.0)
Intensity[1], n/N (%)				
Mild	48/655 (7.3)	79/1265 (6.2)	17/624 (2.7)	32/1284 (2.5)
Moderate	13/655 (2.0)	28/1265 (2.2)	2/624 (0.3)	7/1284 (0.5)
Severe	0	3/1265 (0.2)	1/624 (0.2)	0
Drug relationship[2], n/N (%)				
Related	57/655 (8.7)	98/1265 (7.7)	12/624 (1.9)	34/1284 (2.6)
Not related	4/655 (0.6)	12/1265 (0.9)	8/624 (1.3)	5/1284 (0.4)
Duration of treatment-emergent diarrhea (days)				
N*	61	110	20	39
Mean (SD)	3.9 (2.8)	3.9 (2.8)	2.6 (1.4)	2.9 (1.9)
Median	3.0	3.0	2.5	2.0

Min, max	1, 15	1, 13	1, 6	1, 10
Duration of study drug related treatment-emergent diarrhea (days)				
N*	57	98	12	34
Mean (SD)	4.0 (2.9)	4.1 (2.7)	2.6 (1.3)	3.0 (1.9)
Median	3.0	3.5	2.5	2.0
Min, max	1, 15	1, 13	1,5	1, 10

Source: post hoc Table 4.3.22.9a

TEAE = Treatment-Emergent Adverse Events; N* =Number of Patients with Diarrhea (NOTE: there was one patient for whom the duration of diarrhea could not be determined). Subjects are only counted once at each level of summarization. [1] Worst intensity per patient. [2] Drug-related if at least one AE of diarrhea is drug-related. Version 26.1 of MedDRA is used to code adverse events except Loose stools. Comparator: IT001-301 - Ciprofloxacin, IT001-310 – Amoxicillin/clavulanate

8.2.7.2 Hepatic Adverse Events and Liver Function Abnormalities

8.2.7.2.1 Phase 3 uUTI Studies

An overview of the transaminase and bilirubin elevations seen in the Phase 3 uUTI studies safety population is presented in Table 125.

Table 125: Incidence of Elevated Transaminases and Bilirubin – Phase 3 uUTI Studies Safety Population

Parameter	Sulopenem n/N (%)	Comparators n/N (%)
Patients with an elevated ALT level		
> 3x ULN	7/1875 (0.4)	5/1862 (0.3)
> 5x ULN	1/1875 (<0.1)	3/1862 (0.2)
> 10x ULN	0/1875 (0.0)	0/1862 (0.0)
Patients with an elevated AST level		
> 3x ULN	4/1873 (0.2)	4/1861 (0.2)
> 5x ULN	2/1873 (0.1)	1/1861 (<0.1)
> 10x ULN	0/1873 (0.0)	0/1861 (0.0)
Patients with an elevated bilirubin level		
> 1.5x ULN	4/1876 (0.2)	10/1862 (0.5)
> 2x ULN	1/1876 (<0.1)	5/1862 (0.3)

Source: post hoc Table 4.3.32.1a

N = Number of patients in the Safety population with at least one post-baseline value of a given lab parameter; n = number of patients; ALT= Alanine Aminotransferase; AST= Aspartate Aminotransferase; ULN = Upper Limit of Normal. The percentages are calculated as 100 * (n/N). The worst post-baseline values are summarized in the table. Comparator: IT001-301 - Ciprofloxacin, IT001-310 – Amoxicillin/clavulanate

The proportions of subjects who had any elevation in ALT or AST > ULN were comparable in the sulopenem and comparator groups, as were the proportions of subjects who had elevations in either ALT or AST > ULN up to 10x ULN.

Elevations in ALT and AST at increasing levels of severity (times the upper limit of normal), for patients with normal or abnormal values at baseline are shown in Table 126. There were eight patients who developed ALT values between >3x to 5x ULN, six in the sulopenem arm and two in the comparator arm; six of these eight patients had abnormal ALT values at baseline.

Four patients developed ALT values between >5x to 10 x ULN, one in the sulopenem arm and three in the comparator arm; two of these four patients had abnormal ALT values at baseline. There were no patients in either treatment arm with ALT or AST elevations >10 × ULN and there were no patients in either arm who fulfilled the criteria for Hy's Law (an ALT and/or AST of >3 × ULN associated with an increase in bilirubin >2 × ULN and no evidence of cholestasis (i.e. alkaline phosphatase < 2 × ULN).

Table 126: Elevated ALT and AST Analysis, Normal and Abnormal at Baseline – Phase 3 uUTI Studies Safety Population

		Sulopenem n/N1 (%)		Comparator n/N1 (%)	
Parameter	**Criterion**	**Normal at BL**	**Abnormal at BL**	**Normal at BL**	**Abnormal at BL**
ALT	>ULN	26/1654 (1.6)	40/211 (19.0)	20/1650 (1.2)	36/196 (18.4)
	>ULN to 3 × ULN	23/1654 (1.4)	36/211 (17.1)	19/1650 (1.2)	32/196 (16.3)
	>3 × to 5 × ULN	2/1654 (0.1)	4/211 (1.9)	0/1650 (0.0)	2/196 (1.0)
	>5 × to 10 × ULN	1/1654 (<0.1)	0/211 (0.0)	1/1650 (<0.1)	2/196 (1.0)
	>10 ×to 20 × ULN	0/1654 (0.0)	0/211 (0.0)	0/1650 (0.0)	0/196 (0.0)
	>20 × ULN	0/1654 (0.0)	0/211 (0.0)	0/1650 (0.0)	0/196 (0.0)
AST	>ULN	22/1552 (1.4)	34/311 (10.9)	17/1559 (1.1)	28/285 (9.8)
	>ULN to 3 × ULN	19/1552 (1.2)	33/311 (10.6)	17/1559 (1.1)	24/285 (8.4)
	>3 × to 5 × ULN	1/1552 (<0.1)	1/311 (0.3)	0/1559 (0.0)	3/285 (1.1)
	>5 × to 10 × ULN	2/1552 (0.1)	0/311 (0.0)	0/1559 (0.0)	1/285 (0.4)
	>10 ×to 20 × ULN	0/1552 (0.0)	0/311 (0.0)	0/1559 (0.0)	0/285 (0.0)
	>20 × ULN	0/1552 (0.0)	0/311 (0.0)	0/1559 (0.0)	0/285 (0.0)

Source: post hoc Tables 4.3.35.2a, 4.3.35.3a, 4.3.36.2a, and 4.3.36.3a
Note: the worst postbaseline values are summarized in the table; percentages are calculated as n/N × 100. Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BL=baseline; n= number of patients; N = number of patients in the Safety population; N1 = number of patients in the Safety population with normal or abnormal ALT value at baseline; ULN = upper limit of normal

Serum ALT values are presented by study visit in Table 127. Of the 7 sulopenem patients with ALT values >3 × ULN, one (b) (6)) had a normal value by the time of the

TOC visit, while two others ((b) (6)) had a post-TOC value that returned to normal. Patient (b) (6) had hepatic steatosis and was on two concomitant medications which may have contributed to the elevated ALT level. One patient ((b) (6)) with a known history of fatty liver disease had a baseline ALT that was elevated and was slightly higher at TOC. One patient (b) (6)) with a known history of elevated liver function tests had an elevated baseline ALT that was slightly lower at TOC. One patient, (b) (6), had an elevated ALT at baseline that was higher at TOC; the cause of these elevations was not clear. One patient, (b) (6), had a normal ALT at baseline that had increased at TOC and that could not be explained by the patient's medical history or medication use.

Table 127: ALT by Study Day For Those With ALT Values >3 x ULN – Phase 3 uUTI Studies Safety Population

PID	BL	Unscheduled	TOC	Unscheduled	Unscheduled	Comment
Sulopenem						
(b) (6)	108	--	128	--		Fatty liver disease
	11	--	148	--		Asymptomatic; unclear etiology
	216	137 (D3)	21	--		Returned to normal
	20	--	208	46		Obese (BMI 30.7); Returned to normal
	85	--	125	--		Stable at baseline value; hemolyzed specimen
	15		192	63 (D20)	28 (D28)	Hepatic steatosis, rosuvastatin and metformin; asymptomatic; normalized
	236	221 (D5)	213			Known history elevated liver function tests; asymptomatic; stable below baseline value
Comparator						
(b) (6)	110		149	29		Returned to normal
	60		162	115 (D21)	76 (D27)	Hepatic steatosis; asymptomatic; stable at near baseline value
	206	294 (D5)	233	230 (D28)		Hepatic steatosis; asymptomatic; stable at near baseline value
	307	316 (D7)	181	252 (D28)		Hepatic steatosis; asymptomatic; stable below baseline value

(b) (6)	24		381	59 (D20)		Unclear etiology; asymptomatic; stable at near normal value

Source: Study 301 Listing 16.2.8.2; Study 310 Listing 16.2.8.2, Listing 16.2.8.3
Abbreviations: ALT = alanine aminotransferase; BL = baseline; D = day; PID = patient identification number; TOC = test of cure; ULN = upper limit of normal. Comparator: IT001-301 - Ciprofloxacin, IT001-310 – Amoxicillin/clavulanate

8.2.7.3 Renal Adverse Events and Renal Function Abnormalities

8.2.7.3.1 Phase 3 Program

Renal disorder TEAEs occurring in the Phase 3 uUTI studies are summarized in Table 128. Abnormal urine odor was the most frequently occurring such event in the sulopenem group and accounted for much of the overall difference in renal disorder TEAEs in the two groups.

The sulopenem-treated patient with the TEAE of acute kidney injury was a 46-year-old female who presented with flank and abdominal pain, dysuria, and fever in the setting of an obstructing stone and hydroureteronephrosis, twelve days after completing treatment for uUTI in study IT001-301. Her creatinine was 1.7 on presentation and increased to 2.1. Five days later, following nephrostomy tube placement and antibiotics, the creatinine had decreased to 1.1. A detailed narrative on this patient ((b) (6)) can be found in the CSR for study IT001-301.

Table 128: Renal Disorder Treatment-Emergent Adverse Events – Phase 3 uUTI Studies Safety Population

MedDRA SOC MedDRA PT	Sulopenem (N=1940) n (%)	Comparator (N=1934) n (%)
Total number of TEAE	18	6
Number of patients with at least 1 TEAE	16 (0.8)	6 (0.3)
Acute kidney injury	1 (0.1)	1 (0.1)
Chromaturia	0	1 (0.1)
Hematuria	1 (0.1)	1 (0.1)
Hydronephrosis	1 (0.1)	0
Nephrolithiasis	1 (0.1)	1 (0.1))
Renal pain	1 (0.1)	0
Ureterolithiasis	1 (0.1)	1 (0.1)

Urine odor abnormal	12 (0.6)	1 (0.1)

Source: post hoc Table 4.3.26.1a

TEAE = Treatment-Emergent Adverse Events. A TEAE is any AE that newly appeared, increased in frequency, or worsened in severity following initiation of study drug. Subjects are only counted once at each level of summarization. Events are sorted in alphabetical order. Renal Disorder Adverse Events are AEs which are under the MedDRA system organ class 'Renal and urinary disorders'. Version 26.1 of MedDRA is used to code adverse events except Loose stools. Comparator: IT001-301 – Ciprofloxacin, IT001-310 – Amoxicillin/clavulanate

8.3 OTHER SAFETY EXPLORATIONS

8.3.1 Drug-Demographic Interactions

8.3.1.1 Age

8.3.1.1.1 Phase 3 uUTI Studies

Among sulopenem-treated patients, the overall incidence of TEAEs was comparable in the < 65 and ≥ 65 age groups (Table 129). Within the ≥ 65-year-old group, patients 75 years of age and older had a slightly higher rate of AEs than those in the 65 – 74 age group but similar to patients <65 years old. Among comparator-treated patients, the incidence of TEAEs was higher in the ≥65 age group.

Table 129: Incidence of TEAEs by Age Group – Phase 3 uUTI Studies Safety Population

	Sulopenem (N = 1940)				
	< 65 (N = 1498)	**≥ 65 (N = 442)**	**65 – 74 (N = 276)**	**75 – 84 (N = 142)**	**≥ 85 (N = 24)**
Total number of TEAE	605	155	72	77	6
Number of patients with at least one TEAE, n (%)	326 (21.8)	90 (20.4)	52 (18.8)	33 (23.2)	5 (20.8)
	Comparator (N = 1934)				
	< 65 (N = 1488)	**≥ 65 (N = 446)**	**65 – 74 (N = 284)**	**75 – 84 (N = 140)**	**≥ 85 (N = 22)**
Total number of TEAE	268	101	53	45	3
Number of patients with at least one TEAE, n (%)	179 (12.0)	72 (16.1)	41 (14.4)	30 (21.4)	1 (4.5)

Source: post hoc Table 4.3.4.2a

8.3.1.2 Race

8.3.1.2.1 Phase 3 Program

Though the number of non-White patients is small (335/2970 [11.3%] in the sulopenem group, making meaningful comparisons difficult), the rate of TEAEs is similar among White and African American patients treated with sulopenem.

8.3.1.3 Pediatric Subpopulations

There is no data on the safety and efficacy of sulopenem in children and adolescents (<18 years old) and therefore, the use of sulopenem in this age group is not recommended. Probenecid is approved in children ≥ 2 years of age.

8.3.2 Drug-Drug Interactions

8.3.2.1 Potential Interactions

CYP enzymes

Sulopenem does not inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A in human liver microsomes. Sulopenem is not an inducer of CYP1A2, CYP2B6, or CYP3A4/5 *in vitro*.

The potential of sulopenem etzadroxil to inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP2D6 was not evaluated due to non-quantifiable circulating concentrations of the intact prodrug. However, sulopenem etzadroxil is a weak inhibitor of CYP3A4/5 which is expressed in the GI tract.

Transporter systems

Sulopenem is a substrate for MRP2 and OAT3 transporters. *In vitro* studies indicated that sulopenem does not inhibit human BCRP, MDR1, BSEP, MATE1, MATE2K, OAT1, OAT3, OATP1B1, OATP1B3, OCT1, or OCT2 mediated transport at clinically relevant concentrations.

Sulopenem etzadroxil is a substrate for BCRP and P-gp (MDR1) but not a substrate for OAT1 and OAT3 transporters. Sulopenem etzadroxil inhibited the OAT1 and OAT3 transporters *in vitro* with an IC50 value of 93.6 and 34.8 μM, respectively. Sulopenem etzadroxil also inhibited BCRP and P-gp (MDR1) transporters *in vitro* with an IC50 value of 20.4 and 1.91 μM, respectively.

Sulopenem etzadroxil is hydrolyzed rapidly to sulopenem. Therefore, drug-drug interactions between sulopenem etzadroxil and concomitant medications may occur at the level of the GI tract. Administration of the bilayer tablet may result in a probenecid concentration that exceeds the *in vitro* IC50 for BCRP and a sulopenem etzadroxil concentration that exceeds the *in vitro* IC50 values for CYP3A4/5, P-gp (MDR1), and BCRP. Concomitant administration of the bilayer tablet with oral medications that are

substrates for CYP3A4/5, BCRP, and/or MDR1 may therefore result in enhanced bioavailability and increased systemic exposure of those medications.

8.3.2.2 Contribution of Probenecid to Adverse Events Profile of Sulopenem etzadroxil/probenecid

Probenecid is an inhibitor of the organic ion transporters with clinical utility as a uricosuric and renal tubular transport blocking agent. As combined with sulopenem etzadroxil in the bilayer tablet it prolongs the circulating half-life of sulopenem in the plasma, increasing its antibacterial effect, and may also serve to improve the bioavailability of sulopenem etzadroxil from the gastrointestinal tract. Probenecid was first approved for use in the 1970's and has an established safety and efficacy profile.

A phase 1 study compared the adverse event profile of sulopenem etzadroxil alone and probenecid alone. As can be seen in Table 130, the percent of subjects with an adverse event was similar for patients receiving probenecid and placebo and lower than that receiving sulopenem etzadroxil, confirming that probenecid is well-tolerated.

Table 130: Adverse Events of Probenecid, Sulopenem Etzadroxil and Combined in Phase 1 Volunteers

	Sulopenem etzadroxil n (%)	Placebo n (%)	Sulopenem etzadroxil/ Probenecid n (%)	Placebo + Probenecid n (%)
Fed State (N=16)				
Total TEAEs	47	10	42	27
Number with ≥1 TEAE	10 (62.5)	7 (43.8)	12 (75.0)	6 (37.5)
Fasted State (N=16)				
Total TEAEs	72	9	51	14
Number with ≥1 TEAE	13 (81.3)	6 (37.5)	12 (75.0)	5 (31.3)

Source: IT001-101 Tables: 14.3.1.3, 14.3.1.4

The USPI for probenecid reflects the adverse events that have been observed over the decades that probenecid has been commercially available. Table 131 compares the adverse events as noted in the Probenecid USPI with the adverse events observed in the phase 1 and phase 3 program for sulopenem.

Table 131: Comparison of Adverse Events for Probenecid, Sulopenem Etzadroxil, Sulopenem Etzadroxil/Probenecid and Comparators - Phase 1 and Phase 3 Program

	Probenecid USPI	Sulopenem or sulopenem etzadroxil	Sulopenem etzadroxil/ probenecid	Comparator
Headache	•	•	•	•
Dizziness	•	•	•	•
Acute gouty arthritis	•			
Hepatic necrosis	•			
Vomiting	•	•	•	•
Nausea	•	•	•	•
Anorexia	•	•		
Sore gums	•			
Nephrotic syndrome	•			
Uric acid stones	•	0	Nephrolithiasis/ ureterolithiasis	Ureterolithiasis
Renal colic	•		Pyelonephritis	Pyelonephritis
Costovertebral pain	•			•
Urinary frequency	•		uUTI Sx	uUTI Sx
Anaphylaxis	•			
Fever	•	•	•	•
Urticaria	•		•	•
Pruritis	•		•	•
Aplastic anemia	•			
Leukopenia	•			
Hemolytic anemia	•			
Anemia	•		•	•
Dermatitis	•		Allergic/contact	Exfoliative/contact
Alopecia	•		•	
Flushing	•			

Drug Hypersensitivity	•		Angioedema	•

Source: ISS Phase 1 Tables; ISS Phase 3 Tables; Probenecid (Watson) USPI; sulopenem Investigator Brochure

The duration of treatment with probenecid for gout is much longer than the duration of treatment for an uUTI so many adverse events associated with probenecid may not be seen when used in the bilayer tablet. Symptoms typically associated with gout or the treatment of gout, such as acute gouty arthritis and uric acid stones, were not seen on oral sulopenem, suggesting that some of those adverse events may be related to the underlying disease (gout) and not probenecid itself. As many patients in the sulopenem phase 3 safety database presented with pyelonephritis, overlap of the symptoms associated with an infectious pyelonephritis and a uric acid stone obstruction could be expected and they are most likely related to the disease and not the drug. Hematologic adverse events were also not observed; an association with hemolysis due to G6PD deficiency was initially proposed for probenecid but was subsequently found to be unlikely. Rash and pruritis with β-lactams is not unexpected; both were very uncommon in the Phase 3 program.

Taken together, the addition of probenecid does not add substantially to either the number of adverse events or the type of adverse events when combined in the bilayer tablet with sulopenem etzadroxil.

8.4 SPECIAL SAFETY INVESTIGATIONS

8.4.1 Cardiac Safety

A comparison of plasma sulopenem concentrations across studies demonstrates that the effect of sulopenem on QTcF was investigated at concentrations substantially greater than those anticipated after the recommended dose 500 mg sulopenem etzadroxil plus 500 mg probenecid administered orally twice daily in subjects with normal renal function. Furthermore, concentrations included in the QTcF analysis are much greater than those expected in subjects with renal impairment. Therefore, no clinically relevant increase in QTcF interval is expected after administration of oral sulopenem etzadroxil.

Ten clinical studies with ECG data collected from 228 subjects on sulopenem revealed no evidence of trends of concern for cardiac safety, including consistently normal values of QTcF and dQTcF, and no overall safety concerns.

8.5 OVERDOSE, POTENTIAL FOR DEPENDENCE, REBOUND OR ABUSE

The highest dose of oral prodrug administered in Phase 1 clinical studies was a single dose of 8000 mg. The highest dose administered in the multiple-dose study was 2000 mg BID for 10 days. The dose limiting adverse reaction was diarrhea.

In case of accidental overdosing of sulopenem, vital functions should be monitored carefully in an appropriate health care facility. Special attention should be given to gastrointestinal, cardiovascular, hematological and renal function.

8.6 SAFETY CONCLUSIONS

The percentage of subjects with TEAEs and the AE burden experienced by subjects in the sulopenem treatment group were somewhat higher than the comparator group. That difference was largely accounted for by the higher incidence of diarrhea among those receiving sulopenem. Diarrhea was more common among those receiving oral sulopenem than those receiving IV sulopenem and was mitigated when taking oral treatment with food. The median duration of TEAEs was identical in the two treatment groups. SAEs were reported more frequently among sulopenem-treated subjects, with over half occurring in the cIAI study, which enrolled a sicker population of patients.

Overall, oral sulopenem's safety profile compares favorably to those of other antibacterials that might be used to treat uncomplicated UTIs in women at risk for multidrug resistant pathogens such as nitrofurantoin, fosfomycin, amoxicillin/clavulanate and pivmecillinam.

9 BENEFITS AND RISKS OF SULOPENEM TREATMENT IN UUTI

9.1 CLINICAL EFFICACY

The focus of this NDA is the treatment of uUTIs in women with a susceptible uropathogen. Multiple lines of evidence support the activity of oral sulopenem in the treatment of uUTI.

- In the MITT population for both Study 301 and Study 310 (the population most akin to patients encountered in clinical practice, and defined as patients who were randomized and received study drug and had symptoms consistent with uUTI and a positive urinalysis but not necessarily a positive urine culture at $\geq 10^5$ CFU/mL at baseline), the clinical response was similar across the treatment groups.
- In the micro-MITTR population of IT001-301, a clinically meaningful and highly statistically significant reduction in UTI symptom burden was documented among patients who received oral sulopenem.
    - This superior outcome was seen in numerous sub-analyses, including patients with infections due to multidrug resistant pathogens.
- In the micro-MITTS population of Study IT001-310, oral sulopenem achieved the pre-specified primary endpoint of non-inferiority and demonstrated superiority relative to amoxicillin/clavulanate
    - Results for key secondary endpoints such as patient-and investigator-determined clinical success and microbiologic success at TOC were consistent with results for the primary endpoint
- The robust results for oral sulopenem from the micro-MITTR population in Study IT001-301 and the micro-MITTS population from Study IT001- 310 were supported by data from multiple additional sources, including:

- The micro-MITTS population in Study IT001-301, where sulopenem did not achieve non-inferiority to ciprofloxacin solely due to asymptomatic bacteriuria. Asymptomatic bacteriuria may be antibiotic class dependent with quinolones being associated with a lower rate of ASB than any other class of antibiotics. The ASB rate observed with sulopenem is consistent with that seen in association with other non-quinolone antibiotics (gepotidacin, nitrofurantoin and amoxicillin/clavulanate). Additionally, data from the Phase 3 sulopenem uUTI studies indicates that ASB is not a marker of subsequent clinical failure, and consensus garnered from the FDA public workshop on "Development Considerations of Antimicrobial Drugs for the Treatment of Uncomplicated Urinary Tract Infections (UTI) (Virtual)" conducted on 03 June 2022 as well as IDSA guidelines lend support for removing ASB as a component of the primary endpoint. Notably, clinical success rates at TOC were similar for sulopenem and ciprofloxacin treated patients.
- The results from the subset of patients in the complicated urinary tract infection study, IT001-302 that did not receive quinolones: Sulopenem did not achieve non-inferiority to the comparator for the primary endpoint of overall response at TOC in this cUTI study due again to the imbalance in asymptomatic bacteriuria in the two treatment groups, driven primarily by patients who received ciprofloxacin. In the sub-group of patients who did not step-down to ciprofloxacin, both the ASB rates and clinical success rates at TOC were similar in the two treatment groups.
- A series of uncontrolled studies comparing an active agent with either placebo or mismatched empiric antibiotic therapy.

- Relative to ciprofloxacin or amoxicillin/clavulanate, oral sulopenem demonstrates certain advantages:
  - In the development program for treatment of complicated and uncomplicated urinary tract infection, 1485 patients had $\geq 10^5$ CFU/mL of a uropathogen in their baseline culture and were treated with oral sulopenem. Emergence of an isolate post baseline with a susceptibility to sulopenem that had increased by more than four-fold relative to a baseline isolate of the same genus and species was not observed in these studies.
  - In this development program, ciprofloxacin treatment of ciprofloxacin susceptible pathogens was associated with an increased risk of being colonized with a quinolone resistant uropathogen and amoxicillin/clavulanate treatment of amoxicillin/clavulanate susceptible pathogens was associated with an increased risk of being colonized with an amoxicillin/clavulanate pathogen, respectively, while treatment with oral sulopenem was not associated with selection of resistance. This increase in quinolone resistance and

amoxicillin/clavulanate resistance could increase the likelihood of a future urinary tract infection due to a quinolone-resistant and/or ESBL- producing uropathogen.

The expected labeling for oral sulopenem will target women with infections known or suspected to be caused by susceptible uropathogens. In IT001-301, the overall response to oral sulopenem among patients with susceptible organisms was not non-inferior to that of ciprofloxacin, potentially raising a concern that the inadvertent prescription of sulopenem to those with susceptible organisms could result in adverse outcomes. The following observations from the development program effectively address those concerns:

- An analysis of the overall response to treatment by ciprofloxacin MIC demonstrates a greater likelihood of success after treatment with oral sulopenem if the susceptibility threshold for ciprofloxacin is as low as 0.12 μg/mL, not necessarily limited to 2 μg/mL that defined the micro- MITTR population.
- The prespecified analysis in the combined population of patients with susceptible and non-susceptible pathogens, while not directed at achieving a primary regulatory claim as was originally proposed and has been done for ceftolozane/tazobactam, suggests that empiric therapy with oral sulopenem in a population where quinolone resistance is 20% or higher, will be as effective as ciprofloxacin. Given that the majority of communities in the United States now have quinolone resistance rates at this level or higher, the population level risk of harm is low.
- The risk to the patient, based on the outcome in the micro-MITTS population in IT001-301, is not a higher risk of a subsequent uUTI associated with clinical symptoms but rather a risk of having asymptomatic bacteriuria which, based on IDSA Guideline recommendations, is not a condition, with certain exceptions, warranting treatment and likely reflects the patient's baseline state of bladder colonization.

If providing clinical benefit to patients with a limited impact on colonizing flora is desirable, oral sulopenem may offer an advantage over quinolones and amoxicillin/clavulanate in the treatment of uUTI.

9.2 CLINICAL SAFETY

While the use of any antibiotic is associated with risk, compared to other options available for treatment of uUTI, treatment with oral sulopenem was well tolerated and may avoid some of the risks associated with alternative agents. Specifically:

- The only adverse event noted at a rate greater for sulopenem patients than Phase 3 comparator patients was diarrhea in 6.9% overall. Diarrhea is seen with a number of oral antibiotics, most notably with amoxicillin-clavulanate in

15% of patients treated [Augmentin USPI].

- Though diarrhea was observed in patients treated with sulopenem, no patients had *C. difficile* isolated. While this does not preclude *C. difficile* being identified after broader community use, the fact that no cases were observed in the clinical program is reassuring.
- Laboratory assessments on therapy were similar in the sulopenem and comparator arms, consistent with expectations based on the lack of significant systemic toxicity in animal studies.
- No adjustment in dosing is required in patients with renal insufficiency, given that exposures measured by AUC with oral sulopenem are well below the exposures when the drug is given intravenously.
- No notable differences in either safety or efficacy were observed between the elderly and overall population, an important attribute given that almost 30% of the patients with a uUTI in IT001-301 were over the age of 60 and, because of age-related reductions in creatinine clearance, are not candidates for treatment with nitrofurantoin.
- The incidence of rash in the clinical program was relatively low.
- The concomitant use of penem antibiotics and valproic acid (VPA) is contraindicated potentially due to a metabolic interaction that increases an hepatotoxic metabolite of VPA. A Phase 1 study confirmed such an interaction with sulopenem when given IV; however, based on relatively unchanged VPA levels, such an interaction was not observed when VPA was administered with oral sulopenem. Probenecid may be interfering with the penem/VPA/VPA metabolite process to limit the time that the metabolite is circulating. One patient in the clinical program dosed with IV sulopenem and VPA did develop increases in their liver function tests that fit the criteria of Hy's law, but they resolved 2-3 days after switching to oral therapy.
- No adequate and well controlled trials in pregnancy have been performed; however, no effects on embryo-fetal development were identified in animal studies, consistent with what has been reported for the penem class.
- Coadministration of probenecid did not appear to introduce any adverse events not potentially attributable to sulopenem etzadroxil administered alone.
- After over 50 years of experience, the safety profile of probenecid has been well established. Clinically significant drug interactions due to changes in plasma levels of other drugs based on the competitive effects of probenecid at the OAT receptors have not been observed to date, though physicians should be alert to this possibility. [Probenecid White paper; Probenecid USPI (Watson)].
- Adverse events associated with alternative options for treatment of uUTI are well described:
    - Treatment with a quinolone antibiotic, including ciprofloxacin, has

been associated with an increased risk for 'disabling and potentially irreversible serious adverse reactions …including: tendinitis and tendon rupture, peripheral neuropathy and central nervous system effects,'...and 'risk of aortic aneurysm and dissection.'

- Treatment with nitrofurantoin should be avoided in patients with creatinine clearance under 60 mL per minute or clinically significant elevated serum creatinine including the elderly with age-related decline in renal function, and adverse events have been reported such as acute, subacute, or chronic pulmonary reactions and peripheral neuropathy.
- Treatment with trimethoprim-sulfamethoxazole is associated with hyperkalemia and rash including Stevens-Johnson syndrome and toxic epidermal necrolysis and other adverse hematologic sequelae and is contraindicated in patients with marked hepatic damage or with severe renal insufficiency when renal function status cannot be monitored.
- Treatment with pivmecillinam and other β-lactams are associated with severe cutaneous adverse reactions including acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), Steven-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN). Clinically significant hypocarnitinemia has been observed with pivmecillinam in patients at risk for reductions in serum carnitine; alternative antibacterial therapy should be considered in patients with significant renal impairment or decreased muscle mass and those patients requiring long term antimicrobial treatment; concurrent treatment with pivmecillinam and valproic acid, valproate or other pivalate-generating drugs should be avoided due to increased risk of carnitine depletion. Pivmecillinam is contraindicated in patients with porphyria as it has been associated with acute attacks of porphyria.

10 CONCLUSIONS

Oral sulopenem was effective and well tolerated in the treatment of women with a uUTI due to susceptible uropathogens. The only adverse event seen more frequently on oral sulopenem than the comparator was a self-limited, mild diarrhea, not resulting in premature discontinuation of treatment.

A safe and effective oral antibiotic such as oral sulopenem would provide an important treatment option for the treatment of women with uUTI due to a susceptible uropathogen. Some women who receive initial, inappropriate therapy for their multidrug resistant infection may end up requiring hospitalization for intravenous treatment, a scenario which could be avoided if

the option for treatment with oral sulopenem is available.

Treatment of uncomplicated urinary tract infections with oral sulopenem offers women a significant clinical benefit with easily identifiable, limited and manageable risks.

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