FDA Briefing Document

NDA 213972

Drug name: sulopenem etzadroxil/probenecid tablets

Applicant: Iterum Therapeutics US Limited

Antimicrobial Drugs Advisory Committee Meeting

09/09/24

Division of Anti-Infectives /Office of Infectious Diseases

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Glossary

AC	Advisory Committee
AEs	adverse events
ALT	alanine aminotransferase
AMR	antimicrobial resistance
BD	Briefing Document
BRF	Benefit-Risk Framework
cIAI	complicated intra-abdominal infection
CR	complete response
CRE	carbapenem resistant Enterobacterales
cUTI	complicated urinary tract infection
ESBL	extended-spectrum β-lactamase
FDA	Food and Drug Administration
IA	interim analysis
ITT	intent-to-treat
IV	intravenous
MITT	microbiological modified intent-to-treat
micro-MITTS	microbiological modified intent-to-treat-susceptible
micro-MITTR	microbiological modified intent-to-treat-resistant
PTA	probability of target attainment
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
TEAEs	treatment-emergent adverse events
TMP-SMX	trimethoprim-sulfamethoxazole
TOC	test of cure
UTI	urinary tract infection
uUTI	uncomplicated urinary tract infection

1 Executive Summary/Draft Points for Consideration by the Advisory Committee

NDA 213972 for sulopenem etzadroxil/probenecid, a fixed dose oral combination tablet containing 500 mg of sulopenem etzadroxil and 500 mg of probenecid, was resubmitted by the Applicant, Iterum Therapeutics Ltd, on April 25, 2024 for treatment of uncomplicated urinary tract infections (uUTI) caused by designated susceptible bacteria in adult women.

Sulopenem is a penem antibacterial drug with in vitro activity against gram-positive, gram-negative and anaerobic organisms including Enterobacterales species that encode extended-spectrum β-lactamases (ESBLs) and AmpC-type β-lactamases. Sulopenem does not have activity against *Pseudomonas aeruginosa* or methicillin-resistant *Staphylococcus aureus* (MRSA). In nonclinical infection models, the duration of time above a minimum inhibitory concentration ($T_{free} > MIC$) appeared to correlate best with efficacy.

Sulopenem etzadroxil, the oral prodrug, is hydrolyzed immediately after oral administration to the active drug, sulopenem. The Applicant coformulated sulopenem etzadroxil with probenecid, a Food and Drug Administration (FDA)-approved organic ion transport inhibitor, to decrease renal excretion of sulopenem and increase plasma exposure of sulopenem.

1.1 Purpose/Objective of the AC Meeting

The Food and Drug Administration (FDA or the Agency) is convening this Advisory Committee (AC) meeting to discuss a) whether the overall benefit-risk assessment is favorable for the use of sulopenem etzadroxil/probenecid for the treatment of uncomplicated UTI (uUTI) caused by designated susceptible microorganisms in adult women, and b) considerations on the information that would be most important to convey to medical providers to ensure appropriate use of sulopenem etzadroxil/probenecid.

1.2 Context for Issues to Be Discussed at the AC

Uncomplicated urinary tract infections (uUTI) or cystitis are the most common bacterial infections in the ambulatory care setting and affect the majority of women at least once in their lifetimes. uUTI occur in women with normal genitourinary anatomy and are characterized by dysuria, urinary frequency, urinary urgency and suprapubic pain. UTIs that occur in males, immunocompromised individuals, pregnant patients, or those with comorbidities, e.g., renal stones, urinary obstruction or the presence of a urinary catheter, involve the kidneys, or are associated with fevers and other systemic symptoms, bacteremia and sepsis are considered complicated UTIs (cUTI). *E. coli* is the most common cause of uUTI accounting for 75 to 95% of infections (Gupta et al. 2011) and treatment is usually empiric. While there are multiple FDA-approved oral antibacterial drugs for the treatment of uUTI, treatment options can be limited by adverse reactions and increasing antimicrobial resistance (AMR) to first-line antibacterial drugs, including through production of extended-spectrum β-lactamases (ESBL) (Critchley et al. 2019; Dunne et al. 2022). Resistance rates to first-line antibacterial drugs for uUTI treatment are high among ESBL-producers (Critchley et al. 2019). Carbapenem drugs are the mainstay of treatment for infections caused by ESBL-producers, but all approved members of this class require intravenous (IV) administration and are generally reserved for treatment of culture-proven infections. While an oral penem for treatment of resistant bacteria causing uUTI could potentially address an unmet need, its use in an ambulatory setting

where treatment is most commonly empiric raises concern for inappropriate use which may contribute to AMR.

The two phase 3 clinical trials supporting the uUTI indication for sulopenem etzadroxil/probenecid enrolled adult women with uUTI symptoms and subsequent positive urine culture with a prespecified study organism. In Trial 301 which was part of the original NDA submission in 2020, sulopenem etzadroxil/probenecid was inferior to the comparator ciprofloxacin in the microbiological modified intent to treat susceptible (micro-MITTS; ciprofloxacin-susceptible) population but superior to ciprofloxacin in the microbiological modified intent to treat resistant (micro-MITTR; ciprofloxacin-resistant) population. In Trial 310 submitted in the 2024 NDA resubmission, sulopenem etzadroxil/probenecid was noninferior in the overall population and noninferior and superior to the comparator amoxicillin/clavulanate in the microbiological modified intent to treat susceptible (micro-MITTS; amoxicillin/clavulanate-susceptible) population. Insufficient numbers of patients with amoxicillin/clavulanate-resistant organisms in Trial 310 precluded conclusions regarding efficacy in this population. Further, neither trial was designed to enroll patients with uUTI due to resistant bacteria, such as ESBL-producers, or those who failed first-line treatment.

1.3 Brief Description of Issues for Discussion at the AC

On April 25, 2024, Iterum Therapeutics International, Ltd. (Applicant) resubmitted NDA 213972 for oral sulopenem etzadroxil/probenecid for treatment of uUTI caused by designated susceptible bacteria in adult women 18 years of age and older. Sulopenem etzadroxil/probenecid is a fixed-dose bilayer oral tablet containing 500 mg of sulopenem etzadroxil and 500 mg probenecid which was included to decrease renal excretion and increase systemic exposure of sulopenem after hydrolysis of the prodrug, sulopenem etzadroxil. If approved, sulopenem etzadroxil/probenecid would be the first oral penem antibacterial drug marketed in the United States.

NDA 213972 for oral sulopenem etzadroxil/probenecid was first submitted in 2020 for the proposed indication of treatment of adult women with uUTI caused by designated susceptible microorganisms proven or strongly suspected to be nonsusceptible to a quinolone. The uUTI indication was supported by a single uUTI trial (Trial 301). While sulopenem etzadroxil/probenecid demonstrated superiority to ciprofloxacin in Trial 301 for the overall (clinical and microbiological) response rate in the micro-MITTR population with ciprofloxacin-resistant baseline pathogens, it was inferior to ciprofloxacin in the micro-MITTS population with ciprofloxacin-susceptible baseline pathogens. Failure of sulopenem etzadroxil/probenecid in this population was primarily driven by the presence of asymptomatic bacteriuria at the test of cure (TOC) visit.

Additionally, two previously conducted trials, one for cUTI (Trial 302) and another for complicated intra-abdominal infections (cIAI) (Trial 303) failed to meet their primary endpoints. Trial 302 was a phase 3, multicenter, double-blind, randomized trial designed to compare the efficacy, tolerability, and safety of IV sulopenem followed by oral sulopenem etzadroxil/probenecid versus IV ertapenem followed by oral ciprofloxacin or oral amoxicillin/clavulanate for the treatment of cUTI. Participants received IV therapy for at least 5 days followed by oral stepdown therapy to complete 7 to 10 total days of treatment. Trial 302 failed to show noninferiority using a 10% noninferiority margin with sulopenem being inferior to the active comparator based on the primary endpoint of overall (clinical and microbiological) response at test of cure (TOC, Day 21). Failure in the sulopenem arm was primarily driven by the occurrence of asymptomatic bacteriuria at the TOC visit. Trial 303, a phase 3, multicenter, double-blind, randomized trial to compare the efficacy, tolerability and safety of IV sulopenem followed by oral

sulopenem etzadroxil/probenecid versus IV ertapenem followed by oral ciprofloxacin and metronidazole or oral amoxicillin/clavulanate for the treatment of cIAI also failed to meet its primary endpoint of clinical response. Therefore, these trials could not provide supportive evidence of effectiveness. Moreover, the results from Trials 302 and 303 created uncertainty regarding the efficacy of sulopenem in the treatment of bacterial infections caused by pathogens relevant to uUTI.

The NDA received a complete response (CR) on July 23, 2021, due to lack of substantial evidence of effectiveness, and the Applicant was advised to conduct another trial in uUTI. Additionally, further investigation to determine the optimal dosing of sulopenem was recommended. Following the CR, the Applicant decided to stop development of IV sulopenem and focus on development of oral sulopenem etzadroxil/probenecid for treatment of uUTI.

The Applicant subsequently conducted another uUTI trial (Trial 310) with oral sulopenem etzadroxil/probenecid versus amoxicillin/clavulanate – both administered for 5 days – for treatment of uUTI in adult women; this trial is included in the current NDA resubmission. In Trial 310, sulopenem etzadroxil/probenecid achieved its primary endpoint of overall response (clinical and microbiological) and was noninferior to amoxicillin/clavulanate in the microbiologic modified intent-to-treat (micro-MITT) population and noninferior and superior to the comparator in the amoxicillin/clavulanate-susceptible population (micro-MITTS). Trials 301 and 310 appear to be successful, adequate and well-controlled trials in discordant study populations (i.e., the ciprofloxacin-resistant population in Trial 301 and the overall and amoxicillin/clavulanate-susceptible populations in Trial 310). No major safety issues have been identified to date.

The phase 3 trials for uUTI (Trials 301 and 310) studied sulopenem etzadroxil/probenecid for treatment of uUTI in an ambulatory setting and were not designed to evaluate the efficacy of the study drug for the treatment of uUTI caused by resistant bacterial isolates, including those that produce ESBLs, or for treatment of uUTI in patients who failed first-line treatment. Inappropriate use of the drug may contribute to AMR or increase cross-resistance to other carbapenems. Further, because IV sulopenem followed by oral sulopenem etzadroxil/probenecid was found to be inferior to active comparators for cUTI in Trial 302, there is concern that if approved, sulopenem etzadroxil/probenecid as an oral penem may be used off-label in the treatment of cUTI or other infections, as stepdown treatment. There are no data on the effectiveness of oral sulopenem etzadroxil/probenecid as stepdown therapy following IV treatment of cUTI with another β-lactam or carbapenem drug. While antimicrobial stewardship and consideration by guidelines committees, provided that sulopenem etzadroxil/probenecid is approved, may help to determine appropriate positioning of the drug in the hierarchy of uUTI treatment options, a discussion of approaches to inform prescribers of relevant data submitted in this NDA and to ensure the most appropriate use of sulopenem etzadroxil/probenecid is warranted.

1.4 Draft Points for Consideration

- The Applicant is seeking an indication for sulopenem etzadroxil/probenecid in adult women ≥18 years of age for the treatment of uncomplicated UTI caused by designated susceptible microorganisms. Is the overall benefit-risk assessment favorable for the use of sulopenem etzadroxil/probenecid for this indication?
- Considering the totality of the evidence in this application, what are considerations that would be important to convey to medical providers to ensure appropriate use of sulopenem etzadroxil/probenecid.

2 Introduction and Background

2.1 Background of the Condition/Standard of Clinical Care

Uncomplicated UTI (uUTI) or acute cystitis is an acute infection of the bladder that occurs most often in women with normal anatomy of the urinary tract. Uncomplicated UTI are caused when pathogenic bacteria from the gut contaminate the urethra and ascend into the bladder, and occur much more commonly in women compared to men. Signs and symptoms of uUTI include dysuria, urinary frequency, urinary urgency and suprapubic pain. cUTI encompasses UTI occurring in males, immunocompromised individuals or pregnant patients, involving the kidneys, and those associated with fevers and other systemic symptoms, sepsis, and urinary obstruction. Comorbidities such as diabetes, renal stones, urologic surgery, and presence of a urinary catheter may predispose to cUTI with progression of infection to the kidney (pyelonephritis) associated with systemic signs or symptoms such as fever, flank pain, bacteremia and sepsis.

In the United States, uUTI are the most common bacterial infections in the ambulatory setting. Approximately 50 to 60% of adult women will have at least one uUTI during their lifetime (Medina and Castillo-Pino 2019) and 10 to 12% of adult women have at least one uUTI per year, with 20 to 30% of those being recurrent (Kaye et al. 2021). The incidence of uUTI peaks in young, sexually active women aged 15 to 24 years and again in postmenopausal women (Kaye et al. 2021). Risk factors include sexual intercourse, spermicide use, prior UTI, new sexual partner within the past year, and history of UTI in a first-degree female relative (Hooton 2012). In clinical practice, uUTIs are often diagnosed based on symptoms and a dipstick urinalysis positive for leukocyte esterase or nitrite. Therapy for uUTI is often empiric, as baseline or post-treatment urine cultures are not typically recommended for the first incidence of uUTI (Kaye et al. 2021).

The goal of uUTI treatment is to resolve acute symptoms and reduce the risk of infection progression to the upper urinary tract (e.g., pyelonephritis). In two randomized studies of antibacterial drugs compared with nonsteroidal anti-inflammatory drugs (NSAIDs) for uUTI treatment, the rate of pyelonephritis in patients with uUTI who were not treated with antibacterial drugs was between 2 and 5% compared to 0 to 0.4% in patients treated with antibacterial drugs (Gagyor et al. 2015; Kronenberg et al. 2017). The association between asymptomatic bacteriuria and pyelonephritis has been clearly shown in pregnant women (Kazemier et al. 2015; Nicolle 2015) while an association between asymptomatic bacteriuria and bacteremia was shown in renal transplant patients (Lee et al. 2013). Also, discordant clinical and microbiological outcomes have been shown to be associated with late clinical relapse in clinical trials for cUTI (Kadry et al. 2023). While these findings cannot be fully extrapolated to uUTI, microbiological response in patients with UTI seems important. Consequently, FDA includes microbiologic response as part of the primary efficacy endpoint for clinical trials in uUTI and cUTI (see the FDA guidance for industry, *Uncomplicated Urinary Tract Infections: Developing Drugs for Treatment* (August 2019)).

The most common bacterial cause of uUTI is *Escherichia coli* (75 to 95%); less common pathogens include other species of Enterobacterales (e.g., *Klebsiella pneumoniae*, *Proteus mirabilis*) and S*taphylococcus saprophyticus* (Gupta et al. 2011). There is increasing antimicrobial resistance among *E. coli* isolates at the U.S.-community level, including increasing antimicrobial resistance to ciprofloxacin and trimethoprim-sulfamethoxazole (TMP-SMX) and increasing prevalence of ESBL-producing *E.coli.* In a retrospective study, Kaye et al. (2021) evaluated 1,513,882 *E.coli* urinary isolates from female (age ≥12 years) outpatients in the United States from January 2011 to December 2019 and found that the

overall prevalence of isolates nonsusceptible to nitrofurantoin, fluoroquinolones, or TMP-SMX was 3.8%, 21.1%, and 25.4%, respectively. Of the isolates, 6.4% were ESBL producers, 14.4% were resistant to ≥2 antimicrobials (fluoroquinolone, nitrofurantoin, TMP-SMX or were ESBL producers), and 3.8% were resistant to ≥3 antimicrobials (fluoroquinolone, nitrofurantoin, TMP-SMX or were ESBL producers). Over the nine-year study period, the rate of ESBL positivity rose from 4.1% to 7.3%.

In another study (Critchley et al. 2019), resistance to levofloxacin and ciprofloxacin was noted in 24.3% and 25.8% of 1831 *E. coli* isolates collected from patients with UTI, while 32.1% of isolates were resistant to TMP-SMX. ESBL phenotypes were found in 287 (15.7%) of *E. coli* isolates from all U.S. census regions and ranged from 10.5% in the West North Central region to 29.6% in the mid-Atlantic region. Among the 287 ESBL-producing *E. coli* isolates, resistance rates to ciprofloxacin, levofloxacin and TMP-SMX were very high at 71.8%, 67.9% and 56.1%, respectively. The CTX-M-15 ESBL accounted for 59% of ESBL phenotypes, while OXA-1/30 was the next most prevalent although in most isolates, it was coexpressed with CTX-M-15. Further, the TMP-SMX-resistant isolates of *E. coli* exhibited high coresistance (≥30%) to fluoroquinolones and cefuroxime, while fluoroquinolone-resistant isolates of *E. coli* exhibited high coresistance (≥45%) to TMP-SMX and ceforuxime.

First-line treatment options for uUTI include oral nitrofurantoin, TMP-SMX, fosfomycin, and pivmecillinam. Fluoroquinolones, including ciprofloxacin, are no longer considered first-line treatment for uUTI due to adverse reactions such as tendinopathies, QT prolongation, central nervous system effects and peripheral neuropathy as well as increasing rates of fluoroquinolone resistance (Gupta 2024). Other than pivmecillinam, beta-lactam agents including amoxicillin/clavulanate, are considered alternative agents for uUTI as in general, beta-lactams are less effective and have more potential adverse reactions than first-line antibacterials (Gupta et al. 2011).

While there are many FDA-approved antibacterial drugs for the treatment of uUTI, treatment options for some patients may be limited by adverse reactions, such as hypersensitivity reactions, and by increasing antibacterial drug resistance. The Infectious Diseases Society of America (IDSA) recommends that if resistance to an antibacterial drug is >20% in a given region, that drug should not be used for empiric treatment (Gupta et al. 2011). Given the increase in AMR in urinary isolates of *E. coli* around the country and especially the increased prevalence of ESBL-producing strains of Enterobacterales, carbapenem antibacterials may become increasingly important for treatment of these resistant infections. However, carbapenem antibacterial drugs currently marketed in the United States all require intravenous (IV) administration, necessitating placement of an IV catheter and possibly hospitalization. Thus, oral drugs with the spectrum and potency of the intravenous carbapenems would address an unmet need for new options to treat multidrug-resistant pathogens implicated in uncomplicated UTIs.

2.2 Pertinent Drug Development and Regulatory History

Investigational new drug (IND) application 129834 for IV sulopenem and IND 129849 for oral sulopenem etzadroxil/probenecid were opened on March 2, 2016. Sulopenem was granted Qualified Infectious Disease Product designation for uUTI, cUTI, and cIAI on July 29, 2016, and Fast Track designation for these same indications on March 15, 2019.

FDA and the Applicant met in July 2017 to discuss the clinical trial design for Trial 301 for the treatment of uUTI. FDA emphasized that the clinical response component of the overall response endpoint (combined clinical and microbiological responses) should be defined as the resolution of all UTI symptoms that were present at baseline. FDA also noted that for a noninferiority trial it was essential

that only patients with pathogens susceptible to the comparator (ciprofloxacin) be included in the efficacy analysis. The Applicant was concerned that excluding patients with a ciprofloxacin-resistant pathogen would remove a clinically important population from their study. In November 2017, the Applicant submitted a proposal for statistical hypothesis testing for the uUTI trial in which there would be two analysis populations, one for participants with a ciprofloxacin-susceptible pathogen at baseline (microbiological modified intent-to-treat susceptible [micro-MITTS]) and another for participants with a ciprofloxacin-nonsusceptible pathogen at baseline (microbiological modified intent-to-treat resistant [micro-MITTR]). Superiority testing would be used in the micro-MITTR population while noninferiority testing using a 10% margin would be used in the micro-MITTS population. The study protocol was reviewed under a special protocol assessment. FDA communicated to the Applicant that discordant results in the two primary analyses could be problematic and could have significant labeling implications, such as limited use language, and/or limitations of use/warnings regarding empiric use. FDA noted that the utility of a product for which efficacy is not demonstrated in the micro-MITTS population could be limited as therapy for uUTI is generally empiric.

A pre-NDA meeting was held on September 28, 2020. FDA expressed concern regarding discordant results between the micro-MITTS and micro-MITTR populations as sulopenem etzadroxil/probenecid failed to show noninferiority to ciprofloxacin in the micro-MITTS population but was superior to ciprofloxacin in the micro-MITTR population. FDA noted that the results did not support the use of sulopenem etzadroxil/probenecid for uUTI caused by ciprofloxacin-susceptible isolates. In addition, FDA noted that the data from Trial 302 for cUTI did not support a labeled indication for cUTI.

On November 25, 2020, the Applicant submitted NDA 213972 for oral sulopenem etzadroxil/probenecid for the proposed indication of treatment of uUTI caused by designated susceptible microorganisms proven or strongly suspected to be nonsusceptible to a quinolone. The basis for the NDA submission was the single uUTI trial, Trial 301, while the failed Trials 302 (for cUTI) and 303 (for cIAI) were submitted as supportive evidence. The NDA received a CR on July 23, 2021, due to lack of substantial evidence of effectiveness—sulopenem etzadroxil/probenecid demonstrated superiority to ciprofloxacin for the overall (clinical and microbiological) response rate only in the micro-MITTR population but was inferior in the micro-MITTS population. Because the trials of sulopenem (IV sulopenem followed by PO sulopenem etzadroxil/probenecid for stepdown therapy) in the related indications of cUTI (Trial 302) and cIAI (Trial 303) failed to meet their primary endpoints of noninferiority to the comparator, they were not considered to provide supportive evidence of effectiveness. FDA recommended that the Applicant conduct an additional trial for uUTI with a different comparator.

FDA met with the Applicant several times following the CR to discuss a path forward for sulopenem etzadroxil/probenecid for uUTI. The Applicant proposed a noninferiority study using amoxicillin/clavulanate as the comparator. FDA noted that a first-line treatment, such as nitrofurantoin, would be a better choice for the comparator to assess the efficacy of sulopenem etzadroxil/probenecid. The Applicant was informed on May 2, 2022, that if amoxicillin/clavulanate was used as the comparator, the specifics of product labeling would be a review issue.

The Applicant subsequently conducted a second uUTI trial (Trial 310) with oral sulopenem etzadroxil/probenecid versus amoxicillin/clavulanate – both administered for five days – for treatment of uUTI in adult women. The study protocol was reviewed under a special protocol assessment. On April 25, 2024, the Applicant resubmitted NDA 213972 for the proposed indication of treatment of uUTI caused by designated susceptible microorganisms in adult women.

3 Summary of Issues for the AC

3.1 Efficacy Issues

- Trial 301 in uUTI: In this phase 3, randomized, double-blind trial, oral sulopenem etzadroxil/probenecid was superior to oral ciprofloxacin for achieving overall clinical and microbiological response at the TOC visit on Day 12 in subjects with ciprofloxacin-resistant baseline pathogens (micro-MITTR), but was inferior in subjects with ciprofloxacin-susceptible baseline pathogens (micro-MITTS).
- Trial 310 in uUTI: In this phase 3, randomized, double-blind trial, oral sulopenem etzadroxil/probenecid was superior to oral amoxicillin/clavulanate for achieving overall clinical and microbiological response at the TOC visit on Day 12 in subjects with baseline pathogens susceptible to the amoxicillin/clavulanate comparator (micro-MITTS). There were insufficient subjects with baseline pathogens resistant to the amoxicillin/clavulanate comparator to draw conclusions in this population (micro-MITTR). Clinical response rates were similar between the two treatment arms.
- Trial 302 in cUTI: In this phase 3, randomized, double-blind trial, intravenous sulopenem followed by oral sulopenem etzadroxil/probenecid did not demonstrate noninferiority compared to intravenous ertapenem followed by oral ciprofloxacin or oral amoxicillin/clavulanate.
- Trial 303 in cIAI: In this phase 3, randomized, double-blind trial, intravenous sulopenem followed by oral sulopenem etzadroxil/probenecid did not demonstrate noninferiority compared to intravenous ertapenem followed by oral ciprofloxacin and metronidazole or oral amoxicillin/clavulanate.

3.1.1 Sources of Data for Efficacy

Data submitted to demonstrate efficacy are from two randomized clinical trials in uUTI (Trials 301 and 310) conducted by the Applicant. In addition, one trial in cUTI (Trial 302) and one trial in cIAI (Trial 303) will be briefly discussed.

3.1.1.1 Study Design

Table 1 summarizes the study design, treatment, main inclusion/exclusion criteria, study visits, primary efficacy endpoint, analysis populations, and statistical methods for Trials 301 and 310.

Table 1. Summary of Study Design for Trials 301 and 310

	Trial 301	**Trial 310**
Study design	Phase 3, multicenter, double-blind, double-dummy, randomized, controlled study to compare the efficacy, tolerability, and safety of oral sulopenem etzadroxil/probenecid with that of oral ciprofloxacin for the treatment of uUTI in adult women.	Phase 3, multicenter, double-blind, double-dummy, randomized, controlled study to compare the efficacy, tolerability, and safety of oral sulopenem etzadroxil/probenecid to oral amoxicillin/clavulanate for the treatment of uUTI in adult women.
Treatment	Eligible women were randomized 1:1 to receive either: • Oral sulopenem etzadroxil 500 mg/probenecid 500 mg twice daily for 5 days and placebo ciprofloxacin capsules twice daily for 3 days or	Eligible adult women were randomized 1:1 to receive either: • Oral sulopenem etzadroxil/probenecid 500 mg/500 mg twice daily for 5 days or • Oral amoxicillin/clavulanate 875 mg/125 mg twice daily for 5 days.

	Trial 301	Trial 310
	• Oral ciprofloxacin 250 mg capsules twice daily for 3 days and placebo sulopenem etzadroxil/probenecid tablets twice daily for 5 days.	
Main Inclusion/ Exclusion criteria	**Main Inclusion Criteria** • Female patients ≥18 years of age with ≥24 h and ≤96 h of urinary symptoms attributable to a UTI • Two or more of the following signs and symptoms of uUTI: urinary frequency, urinary urgency, pain or burning on micturition, suprapubic pain • A midstream urine specimen with: a) a machine-read dipstick positive for nitrite AND from the same specimen b) evidence of pyuria as defined as either: – A machine-read dipstick positive for leukocyte esterase OR – At least 10 white blood cells (WBCs)/mL on microscopic analysis of unspun urine OR – WBC count ≥10 cells/HPF in the sediment of a spun urine	**Main Inclusion Criteria** • Female patients ≥18 years of age with ≥24 h and ≤96 h of urinary symptoms attributable to a UTI • Two of the following signs and symptoms of uUTI: urinary frequency, urinary urgency, pain or burning on micturition, suprapubic pain • A mid-stream urine specimen with: (a) a machine-read dipstick positive for nitrate AND any positive leukocyte esterase OR (b) evidence of pyuria alone defined by (i) a machine-read dipstick positive for large leukocyte esterase OR (ii) at least 10 WBCs per cubic millimeter on microscopic analysis of unspun urine OR (iii) WBC count ≥10 cells/HPF in the sediment of a spun urine
	Main Exclusion Criteria • 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 uUTI within the prior 7 days • Patients requiring concurrent use of nonstudy 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 vesico-ureteral reflux) • Any history of trauma to the pelvis or urinary tract • Patient's urine culture results, if available at study entry, identify more than two	**Main Exclusion Criteria** • 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 uUTI within the prior 7 days • Concurrent use of nonstudy 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. • Note: Patients could be included if these medications were previously taken and had ceased at the time of screening onward. • Any anatomical abnormality of the urinary tract, including surgically modified urinary tract anatomy, and obstructive uropathy due to nephrolithiasis, stricture, tumor, or fibrosis • Ongoing urinary retention • Neurogenic bladder • Current resident of a long-term care facility

	Trial 301	Trial 310
	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	• Instrumentation of urinary tract in the previous 30 days • An indwelling urinary catheter, ureteral stent or other foreign material in the urinary tract • Any history of trauma to the pelvis or urinary tract • Current urine culture, if available while evaluating eligibility, that was positive for more than two microorganisms regardless of colony count (contaminated), or confirmed a fungal UTI • Receiving hemodialysis, hemofiltration, peritoneal dialysis, or had a renal transplant
Study visits	Days 1, 3 (for Trial 301 only), End of Therapy (Day 5), Test of Cure (Day 12), and Final Visit (Day 28).	
Analysis populations	**Modified Intent-to-Treat (MITT):** randomized patients who received at least a single dose of study medication and had the disease under study, defined as having two of the four baseline uUTI symptoms and pyuria in the baseline urinalysis. **Microbiological MITT (Micro-MITT)**: all MITT patients with a positive study entry urine culture within 48 h prior to first dose, defined as $\geq 10^5$ colony-forming units (CFU)/mL of a uropathogen (Enterobacteriaceae or *Staphylococcus saprophyticus* only) and no more than two species of microorganisms with $\geq 10^5$ CFU/mL. **Susceptible Micro-MITT (Micro-MITTS):** all micro-MITT patients with a baseline uropathogen susceptible to the comparator drug, ciprofloxacin (ciprofloxacin MIC $\leq$1 mg/L), and no baseline pathogen nonsusceptible to ciprofloxacin. **Resistant Micro-MITT (Micro-MITTR):** all micro-MITT patients with a baseline uropathogen nonsusceptible (defined as MIC ≥2 mg/L) to ciprofloxacin. There was uncertainty regarding the extent to which the ciprofloxacin comparator would be more effective than a placebo in this population.	**MITT**: randomized patients who received at least a single dose of study medication. **Micro-MITT**: all MITT patients with a positive study entry urine culture defined as $\geq 10^5$ CFU/mL of a uropathogen (Enterobacterales or *Staphylococcus saprophyticus* only) and no more than two species of microorganisms identified in the study entry urine culture, regardless of colony count. **Micro-MITTS**: the subset of micro-MITT patients whose baseline pathogens are determined to be susceptible (MIC ≤8/4 mg/L) to amoxicillin/clavulanate. **Micro-MITTR**: the subset of micro-MITT patients whose baseline pathogen is determined to be nonsusceptible [intermediate (MIC 16/8 mg/L) or resistant (MIC ≥32/16 mg/L)] to amoxicillin/clavulanate.
Primary efficacy endpoint	**Overall Response** A patient was defined as an overall success if the following criteria were met: 1. The patient was alive 2. The patient had received no nonstudy antibacterial therapy for uUTI (excluding linezolid, daptomycin, vancomycin, azithromycin, metronidazole, josamycin,	**Overall Response** A patient was defined as an overall success if the following criteria were met: • The patient was alive • The patient received no rescue therapy for uUTI – If an antibiotic active against the urinary tract pathogen was given for

	Trial 301	Trial 310
	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 antibacterial drug active against the urinary tract pathogen was given for non-uUTI reasons, then the patient was to be considered indeterminate. 3. 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] as follows). The PSAQ symptom components were reported as no symptom, mild, moderate, or severe. – Pain (uncomfortable pressure) in the lower abdomen/pelvic area – Burning (dysuria) when passing urine – Frequency of urination or going to the toilet very often – Urgency of urination or a strong and uncontrollable urge to pass urine – Missing PSAQ responses were to be treated as missing thus the outcome was indeterminate. 4. Urine culture collected at the follow-up visit demonstrated $<10^3$ CFU/mL of the baseline uropathogen.	other reasons, then the patient would be considered indeterminate • The patient had resolution of the symptoms of uUTI present at trial entry and no new uUTI symptoms (based on the Patient Symptom Assessment Questionnaire) • Urine culture taken on Day 12 (±1 day)/TOC demonstrated $<10^3$ CFU/mL of the baseline uropathogen
Planned Analysis Method for Primary Efficacy Endpoint	For the micro-MITTS population, the Miettinen and Nurminen method was used with an NI margin of -10%. For the micro-MITTR population, the Miettinen and Nurminen method was used for superiority testing. The two analysis populations were considered to address separate questions that for logistical reasons were included in the same study, so no multiplicity adjustment was applied.	To control for inflation of the overall type I error rate, hierarchical testing was used to test the hypotheses of the primary efficacy endpoint in these populations in the sequential order described below. Testing would proceed to the next comparison, only in the case where the null hypothesis in the previous comparison was rejected. For pre-specified sequential hypothesis testing, no adjustment to the Type I error was required. 1. Noninferiority (NI) in the micro-MITT population. 2. NI in the micro-MITTS population or superiority in the micro-MITTR population. 3. Superiority test of overall success in the micro-MITT population Two-sided 95% confidence intervals (CIs) for the treatment difference in success proportions (Sulopenem-active control) was determined using the method of Miettinen and Nurminen.

	Trial 301	Trial 310
		NI was established if the lower bound of the CI was greater than the NI margin of -10% and superiority was established if the lower bound of the CI was greater than 0. The FDA had communicated the following comment regarding the planned analysis: "We strongly recommend testing NI in the micro-MITTS population as the primary endpoint. An alternative is hierarchical testing for (i) NI in the micro-MITTS population followed by (ii) superiority in the micro-MITT population. It would be an important review issue if the trial is unable to demonstrate noninferiority in the micro-MITTS population, which is not currently assessed in the first level of the planned hierarchical testing. We note that the trial is adequately powered for the analysis of noninferiority in the micro-MITTS population."
Interim analysis	Two interim analyses for sample size re-estimation were planned when response data at TOC were available for approximately 33% and 66% of the patients (approximately 450 and 900 patients, respectively). For the susceptible population, the sample size re-estimation was based on the blinded overall outcome and evaluability rate (i.e., percentage of the ITT population in the micro-MITT population). In the micro-MITTR population, a conditional power analysis for the superiority hypothesis was conducted when 66% of patients had been enrolled (unblinded interim analysis). If the conditional power was <40% or ≥80%, no change to the sample size would be made. If the conditional power was 40% to <80%, the sample size would be calculated based on the observed overall success rates in each treatment group and increased to a maximum number. However, the maximum number was not specified. No adjustment to the overall alpha level was needed.	An interim analysis for sample size re-estimation was to be performed when clinical and microbiologic response data at Day 12 (±1 day)/TOC were available for approximately 50% of the patients (approximately 983 patients). The sample size of the study would be computed to ensure that there was sufficient power for overall response in the micro-MITTS population.

Source: NDA submission.
Abbreviations: CFU, colony-forming unit; HPF, high-power field; ITT, intent to treat; MIC, minimum inhibitory concentration; NI, noninferiority; TOC, test of cure; uUTI, uncomplicated urinary tract infection

In the original SAP, microbiological persistence was defined as growth of the baseline pathogen at ≥ 10^3 CFU/mL at TOC, regardless of susceptibility (Table 48). After the interim analysis of Trial 301, the Applicant revised the SAP and utilized the updated SAP for their primary efficacy analysis. FDA did not agree with the Applicant's analysis of efficacy using the updated SAP for the following reasons. The updated SAP changed the definition of microbiological persistence by stating that susceptibility profiles

of pathogens in the baseline and TOC cultures needed to match, and additional molecular testing by pulsed field electrophoresis (PFGE), PCR, or whole genome sequencing (WGS) would be performed to confirm that pathogens at the two time points were the same. FDA did not agree with the revised definition and maintained that assessment of microbiological failure/persistence should be based only on the presence of TOC pathogens with same genus/species. Hetero-resistant subpopulations of the same bacterial pathogen may be present at baseline, and these subpopulations may not be identified because only a single colony was selected for analysis by molecular testing. Further, PCR for the gyrase mutation conferring quinolone resistance may overlook other chromosomal (*parC, parE*) or plasmid-mediated quinolone resistance (PMQR) genes. Additionally, some other aspects of the statistical analysis plan (SAP) were changed by the Applicant following the unblinded interim analysis. FDA's concerns with the Applicant's analysis using the updated SAP were communicated to the Applicant during the first review cycle and re-analysis was requested using the original SAP. Thus, FDA's analyses in this briefing document use the original SAP. Further details of the differences in the FDA's and the Applicant's analysis populations are provided in section 3.1.1.2.2. The timeline and specifics of the SAP alterations are provided in Table 50.

3.1.1.2 Results

3.1.1.2.1 Populations and Baseline Characteristics In Trials 301 and 310

Trial 301

Trial 301 was conducted between August 23, 2018, and January 20, 2020. A total of 1802 subjects from 114 study sites in three countries (United States, Russia, and Ukraine) were screened for enrollment and 1671 subjects were randomized. The endpoints and planned analysis methodology are outlined in the section above. The original study report from the Applicant included results based on the updated SAP with late exclusion of two study sites (Sites 202 and 218). The Applicant considered the data from these two sites unreliable and excluded subjects enrolled at the sites from analysis populations for the following reasons: in Site 202, PFGE analysis found some urinary isolates from different subjects indistinguishable or very similar, a reportedly high rate of contamination of urine cultures and possible intentional nonadherence by subjects, while in Site 218, study-related source records were missing in their entirety. FDA did not agree with exclusion of Site 202 because it was felt that pathogen clonal relationships may exist in UTIs arising in the community, and that the artificial intelligence software used to monitor subject adherence may have been misinterpreted as the adherence of many of those subjects was documented in source records. FDA also questioned the Applicant's decision to exclude site 202 seven months after the unblinded interim analysis and four months after study completion. FDA agreed with the removal of Site 218 due to the missing source documentation. Subsequently, at the FDA's request, the Applicant provided additional analyses using the original SAP and including Site 202.

Table 2 shows the analysis populations defined in the original SAP according to FDA's requested approach to the statistical analysis. Approximately 95% of randomized subjects were included in MITT population; 66% were included in the micro-MITT population; 19% were included in the micro-MITTR population and 48% were included in the micro-MITTS population.

Table 2. Trial 301: Analysis Populations Using the Original SAP, ITT Population

Population	Sulopenem (N=835)	Ciprofloxacin (N=836)	Total (N=1671)
MITT	785 (94.0)	795 (95.1)	1580 (94.6)
Micro-MITT	538 (64.4)	567 (67.8)	1105 (66.1)
Micro-MITTR	162 (19.4)	149 (17.8)	311 (18.6)
Micro-MITTS	376 (45.0)	418 (50.0)	794 (47.5)

Source: Statistical Reviewer's analysis.

Abbreviations: ITT, intent-to-treat; MITT, modified intent-to-treat; micro-MITT, microbiological MITT; micro-MITTR, micro-MITT-resistant; micro-MITTS, micro-MITT-susceptible; SAP, statistical analysis plan; sulopenem, sulopenem etzadroxil/probenecid

Further results below are also based on the original SAP, with the exclusion of Site 218.

In the micro-MITTR population, the mean age was 55 years, with a range of 18 to 89 years (Table 3). The majority of subjects was of white race and not Hispanic or Latino in ethnicity. About 59% were from the United States, followed by Russia (29%) and Ukraine (12%). A total of 64% of the subjects had creatinine clearance >60 mL/min and 16% of the subjects were diabetic. Compared with subjects in the micro-MITTR population, subjects in the micro-MITTS population were younger (37% versus 45% were ≥60 years old), less likely to be Hispanic or Latino (25.2% versus 41.5%), more likely to be from Ukraine (21.8% versus 12.2%), and more likely to have creatinine clearance >60 mL/min.

Table 3. Trial 301: Demographics and Baseline Characteristics, Micro-MITTR and Micro-MITTS Populations

	Micro-MITTR			Micro-MITTS		
Variable	Sulopenem (N=162)	Ciprofloxacin (N=149)	Total (N=311)	Sulopenem (N=376)	Ciprofloxacin (N=418)	Total (N=794)
Age (years)						
Mean (SD)	53.6 (19.53)	55.8 (20.03)	54.7 (19.77)	51.0 (18.90)	49.9 (18.53)	50.5 (18.70)
Median	55.5	57.0	57.0	52.0	51.0	51.5
Min, max	18.0, 89.0	18.0, 87.0	18.0, 89.0	18.0, 89.0	18.0, 96.0	18.0, 96.0
Age (years), n (%)						
<30	25 (15.4)	21 (14.1)	46 (14.8)	71 (18.9)	83 (19.9)	154 (19.4)
30-<60	67 (41.4)	59 (39.6)	126 (40.5)	162 (43.1)	181 (43.3)	343 (43.2)
≥60	70 (43.2)	69 (46.3)	139 (44.7)	143 (38.0)	154 (36.8)	297 (37.4)
Race, n (%)						
American Indian or Alaska Native	0	0	0	4 (1.1)	0	4 (<1)
Asian	2 (1.2)	0	2 (<1)	3 (<1)	3 (<1)	6 (<1)
Black or African American	15 (9.3)	12 (8.1)	27 (8.7)	35 (9.3)	34 (8.1)	69 (8.7)
Other	1 (<1)	1 (<1)	2 (<1)	0	2 (<1)	2 (<1)
White	144 (88.9)	136 (91.3)	280 (90.0)	334 (88.8)	379 (90.7)	713 (89.8)
Ethnicity, n (%)						
Hispanic or Latino	70 (43.2)	59 (39.6)	129 (41.5)	92 (24.5)	108 (25.8)	200 (25.2)
Not Hispanic or Latino	92 (56.8)	89 (59.7)	181 (58.2)	281 (74.7)	310 (74.2)	591 (74.4)
Not reported	0	1 (<1)	1 (<1)	2 (<1)	0	2 (<1)

Variable	Micro-MITTR			Micro-MITTS		
	Sulopenem (N=162)	Ciprofloxacin (N=149)	Total (N=311)	Sulopenem (N=376)	Ciprofloxacin (N=418)	Total (N=794)
Country, n (%)						
Russia	43 (26.5)	46 (30.9)	89 (28.6)	93 (24.7)	109 (26.1)	202 (25.4)
Ukraine	24 (14.8)	14 (9.4)	38 (12.2)	88 (23.4)	85 (20.3)	173 (21.8)
United States	95 (58.6)	89 (59.7)	184 (59.2)	195 (51.9)	224 (53.6)	419 (52.8)
Creatinine clearance (mL/min), n (%)						
<30	4 (2.5)	6 (4.0)	10 (3.2)	9 (2.4)	2 (<1)	11 (1.4)
30-60	50 (30.9)	52 (34.9)	102 (32.8)	106 (28.2)	100 (23.9)	206 (25.9)
>60	108 (66.7)	91 (61.1)	199 (64.0)	261 (69.4)	316 (75.6)	577 (72.7)
Diabetes, n (%)	30 (18.5)	27 (18.1)	57 (18.3)	45 (12.0)	50 (12.0)	95 (12.0)

Source: Statistical Reviewer's analysis.

Abbreviations: Micro-MITTR, microbiological modified intent-to-treat-resistant; micro-MITTS, microbiological modified intent-to-treat-susceptible; SD, standard deviation; sulopenem, sulopenem etzadroxil/probenecid

In the micro-MITTR population, 3.5% of subjects discontinued the study. About 2% of the subjects discontinued treatment, mainly due to adverse events (AEs) (1%). The two treatment groups were comparable in study discontinuation and treatment discontinuation. In the micro-MITTS population, a slightly higher proportion of subjects discontinued the study and discontinued study drug (Table 4).

Table 4. Trial 301: Subject Disposition, Micro-MITTR and Micro-MITTS Populations

Variable	Micro-MITTR			Micro-MITTS		
	Sulopenem (N=162)	Ciprofloxacin (N=149)	Total (N=311)	Sulopenem (N=376	Ciprofloxacin (N=418)	Total (N=794)
Study discontinuation, n (%)	4 (2.5)	7 (4.7)	11 (3.5)	18 (4.8)	20 (4.8)	38 (4.8)
Adverse event	0	1 (<1)	1 (<1)	3 (<1)	1 (<1)	4 (<1)
Loss to follow-up	1 (<1)	1 (<1)	2 (<1)	3 (<1)	6 (1.4)	9 (1.1)
Noncompliance with study drug	0	0	0	3 (<1)	1 (<1)	4 (<1)
Physician decision	1 (<1)	1 (<1)	2 (<1)	0	0	0
Withdrawal by subject	2 (1.2)	4 (2.7)	6 (1.9)	8 (<1)	10 (2.4)	18 (2.3)
Other	0	0	0	1 (<1)	2 (<1)	3 (<1)
Treatment discontinuation, n(%)	4 (2.5)	2 (1.3)	6 (1.9)	14 (3.7)	12 (2.9)	26 (3.7)
Adverse event	2 (1.2)	1 (<1)	3 (1.0)	8 (2.1)	5 (1.2)	13 (1.6)
Loss to follow-up	0	0	0	1 (<1)	2 (<1)	3 (<1)
Physician decision	1 (<1)	0	1 (<1)	0	0	0
Need for concomitant system antibacterial therapy	0	0	0	1 (<1)	0	1 (<1)
Withdrawal by subject	1 (<1)	1 (<1)	2 (<1)	4 (1.0)	4 (<1)	8 (1.0)
Other	0	0	0	0	1 (<1)	1 (<1)

Source: Statistical Reviewer's analysis.

Abbreviations: Micro-MITTR, microbiological modified intent-to-treat resistant; micro-MITTS, microbiological modified intent-to-treat-susceptible; sulopenem, sulopenem etzadroxil/probenecid

Trial 310

The trial was conducted between October 18, 2022 and November 21, 2023. All subjects were enrolled in the United States, in contrast to Trial 301 in which a substantial fraction was enrolled in Russia and Ukraine. Demographic characteristics in the micro-MITTS population in Trial 310 are summarized in Table 5. The mean age was 49.3 years and mean BMI was 29.1 kg/m^2. Ethnicity was primarily Hispanic or Latino (63.1%), and race was predominantly white (79.5%). Of these subjects, 78.6% had a creatinine clearance ≥60 mL/min and 15.8% had diabetes (data are not shown in Table 5). In general, baseline characteristics were balanced between the two treatment groups.

Table 5. Trial 310: Demographic Characteristics, Micro-MITTS Population

Variable	Sulopenem (N=480)	Amoxicillin/Clavulanate (N=442)	Total (N=922)
Age (years)			
Mean (SD)	50.1 (17.54)	48.5 (17.32)	49.3 (17.45)
Median	51.0	49.0	50.0
Min, max	18.0, 91.0	18.0, 93.0	18.0, 93.0
Age (years), n (%)			
<65	367 (76.5)	350 (79.2)	717 (77.8)
≥65	113 (23.5)	92 (20.8)	205 (22.2)
Sex, n (%)			
Female	480 (100.0)	442 (100.0)	922 (100.0)
Race, n (%)			
American Indian or Alaska Native	1 (<1)	1 (<1)	2 (<1)
Asian	10 (2.1)	8 (1.8)	18 (2.0)
Black or African American	78 (16.3)	78 (17.6)	156 (16.9)
Native Hawaiian or other Pacific Islander	0	1 (<1)	1 (<1)
Other	8 (1.7)	4 (<1)	12 (1.3)
White	383 (79.8)	350 (79.2)	733 (79.5)
Ethnicity, n (%)			
Hispanic or Latino	304 (63.3)	278 (62.9)	582 (63.1)
Not Hispanic or Latino	176 (36.7)	163 (36.9)	339 (36.8)
Not reported	0	1 (<1)	1 (<1)
Height (cm)			
Mean (SD)	161.7 (7.27)	162.0 (7.00)	161.8 (7.14)
Median	162.0	162.0	162.0
Min, max	125.0, 180.0	142.0, 185.0	125.0, 185.0
Weight (kg)			
Mean (SD)	75.8 (16.97)	76.4 (18.14)	76.0 (17.53)
Median	73.0	74.0	73.4
Min, max	39.0, 192.7	40.8, 163.6	39.0, 192.7
Body mass index (kg/m^2)			
Mean (SD)	29.0 (6.32)	29.1 (6.71)	29.1 (6.51)
Median	28.0	27.9	28.0
Min, max	15.5, 67.5	17.6, 59.8	15.5, 67.5
Body mass index (kg/m^2), n (%)			
25-30	178 (37.1)	144 (32.6)	322 (34.9)
<25	124 (25.8)	137 (31.0)	261 (28.3)
>30	178 (37.1)	161 (36.4)	339 (36.8)

Source: Table 31 of the Study Report and Statistical Reviewer's analysis.

Abbreviations: Micro-MITTS, microbiological modified intent-to-treat-susceptible; SD, standard deviation; sulopenem, sulopenem etzadroxil/probenecid

Table 6 summarizes the disposition of all randomized subjects in Trial 310. A total of 2222 subjects were randomized and included in the ITT population. Four subjects in each arm were excluded from the MITT population for not receiving study drug. A total of 44.5% of the ITT subjects were included in the micro-MITT population. A total of 922 (42%) and 67 (3%) subjects were included in the micro-MITTS population and micro-MITTR population, respectively. The number of subjects in the micro-MITTR was much lower than the planned sample size of 125 per arm to achieve the desired statistical power.

Overall, approximately 95% of the ITT subjects completed study drug treatment, while 4% discontinued treatment prematurely (Table 6). The primary reasons for discontinuation of treatment were noncompliance with study drug and withdrawal by subject. Approximately 95% of ITT subjects completed the study. The primary reasons for study discontinuation were loss to follow-up (1.8%) and withdrawal by subject (3.0%). The two treatment groups were comparable regarding the reasons for treatment or study discontinuation.

Table 6. Trial 310: Disposition of All Randomized Subjects (ITT Population)

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

Variable	Sulopenem (N=1111) n (%)	Amoxicillin/ Clavulanate (N=1111) n (%)	Total (N=2222) n (%)
Completed study	1056 (95.0)	1050 (94.5)	2106 (94.8)
Reason for discontinuation from study			
Adverse event	4 (<1)	1 (<1)	5 (<1)
Loss to follow-up	17 (1.5)	23 (2.1)	40 (1.8)
Other	1 (<1)	2 (<1)	3 (<1)
Physician decision	1 (<1)	0	1 (<1)
Withdrawal by subject	32 (2.9)	35 (3.2)	67 (3.0)

Source: Tables 15 and 21 of the Study Report and Statistical Reviewer's analysis.
Abbreviations: CFU, colony-forming units; ITT, intent-to-treat; micro-MITT: microbiological modified intent-to-treat; micro-MITTR: microbiological modified intent-to-treat-resistant; micro-MITTS: microbiological modified intent-to-treat-susceptible; sulopenem, sulopenem etzadroxil/probenecid

Baseline Pathogens in Trials 301 and 310

In Trial 301, baseline urine pathogens from the micro-MITTR and micro-MITTS populations are shown in Table 7. In the micro-MITTR population, about 88% of the subjects had *E. coli*. The next most common pathogens were *K. pneumoniae* and *P. mirabilis*. In the micro-MITTS population, about 84% of the subjects had *E. coli*. The next most common pathogens were *K. pneumoniae* and *P. mirabilis*. The two treatment groups were comparable in occurrence of baseline pathogens (Table 7).

Table 7. Trial 301: Pathogens From Urine at Baseline by Resistant Population

Organism	Sulopenem	Ciprofloxacin	Total
Micro-MITTR	**N=162**	**N=149**	**N=311**
Escherichia coli	141 (87.0)	131 (87.9)	272 (87.5)
Klebsiella pneumoniae	15 (9.3)	14 (9.4)	29 (9.3)
Proteus mirabilis	9 (5.6)	6 (4.0)	15 (4.8)
Morganella morganii	3 (1.9)	1 (0.7)	4 (1.3)
Enterobacter cloacae complex	1 (0.6)	0 (0.0)	1 (0.3)
Providencia stuartii	0 (0.0)	1 (0.7)	1 (0.3)
Micro-MITTS	**N=376**	**N=418**	**N=794**
Escherichia coli	316 (84.0)	348 (83.3)	664 (83.6)
Klebsiella pneumoniae	37 (9.8)	35 (8.4)	72 (9.1)
Proteus mirabilis	9 (2.4)	11 (2.6)	20 (2.5)
Staphylococcus saprophyticus	5 (1.3)	8 (1.9)	13 (1.6)
Klebsiella aerogenes	4 (1.1)	6 (1.4)	10 (1.3)
Klebsiella variicola	5 (1.3)	2 (0.5)	7 (0.9)
Citrobacter freundii	0 (0.0)	6 (1.4)	6 (0.8)
Klebsiella oxytoca	2 (0.5)	4 (1.0)	6 (0.8)
Citrobacter koseri	4 (1.1)	1 (0.2)	5 (0.6)
Other*	2 (0.5)	8 (1.9)	10(1.3)

Source: Statistical Reviewer's analysis.
*Including *Enterobacter aerogenes* (1), *Lelliottia amnigena* (4), *Pantoea septica* (1), *Providencia rettgeri* (1), *Raoultella planticola* (2), and *Serratia marcescens* (1).
Abbreviations: Micro-MITTR, microbiological modified intent-to-treat-resistant; micro-MITTS, microbiological modified intent-to-treat-susceptible; sulopenem, sulopenem etzadroxil/probenecid

In the micro-MITTS population of Trial 310, similar baseline urine pathogens were reported, as shown in Table 8. The two treatment groups were generally balanced with regard to the pathogens isolated at baseline.

Table 8. Trial 310: Pathogens From Urine at Baseline, Micro-MITTS Population

Pathogen	Sulopenem (N=480) n (%)	Amoxicillin/ Clavulanate (N=442) n (%)	Total (N=922) n (%)
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)
Other*			5 (0.5)

Source: Table 33 of the Study Report and Statistical Reviewer's analysis.

* Including 0 to 1 isolates each in the sulopenem and amoxicillin/clavulanate arms of *Providencia stuartii, Pantoea sp., Klebsiella sp., Klebsiella oxytoca, Escherichia* sp*., Enterobacter hormaechei*, and *Citrobacter freundii*

Abbreviations: Micro-MITTS, microbiological modified intent-to-treat-susceptible; sulopenem, sulopenem etzadroxil/probenecid

Due to the small number of subjects in the micro-MTTR population (67/2222, 3%) of Trial 310, data for this population are not presented.

Table 9 shows the distribution of baseline pathogens in the two trials by antibacterial drug resistance characteristics. The micro-MITTS populations of Trials 301 and 310 had comparable occurrence of phenotypic ESBL-producing organisms while the incidence of these organisms in the micro-MITTR population of Trial 301 was more than four-fold higher than in the micro-MITTS populations.

Table 9. Distribution of Baseline Pathogens by Antibacterial Resistance in Trials 301 and 310

Resistance Class of Baseline Pathogens	Trial 301*				Trial 310			
	Micro-MITTR		Micro-MITTS		Micro-MITTS		Micro-MITT	
	Sulo N=147 n (%)	Cipro N=139 n (%)	Sulo N=370 n (%)	Cipro N=415 n (%)	Sulo N=480 n(%)	Amox-Clav N=442 n(%)	Sulo N=522 n (%)	Amox-Clav N=468 n (%)
ESBL-positive (phenotypic)	50 (34)	41 (29.5)	23 (6.2)	31 (7.5)	37 (7.7)	45 (10.2)	52 (10)	46 (9.8)
Quinolone-resistant	145 (98.6)	137 (98.6)	5 (1.4)	6 (1.4)	120 (25)	128 (29)	130 (24.9)	131 (28.0)
TMP-SMX resistant	94 (63.9)	78 (56.1)	77 (20.8)	89 (21.4)	149 (31)	134 (30.3)	161 (30.8)	139 (29.7)
Nitrofurantoin resistant	39 (26.5)	38 (27.3)	58 (15.7)	57 (13.7)	64 (13.3)	56 (12.7)	83 (15.9)	69 (14.7)
Beta-lactam resistant	129 (87.8)	121 (83.5)	201 (54.3)	224 (53.9)	ND	ND	ND	ND

Source: NDA submission

* The numbers of baseline isolates in Trial 301 are according to the initial submission and differ from those in the revised analyses presented in other tables; however, this did not significantly change the proportions of different resistant types.

Abbreviations: amox-clav, amoxicillin-clavulanate; cipro, ciprofloxacin; micro-MITTR, microbiological modified intent-to-treat resistant; micro-MITTS, microbiological modified intent-to-treat susceptible; micro-MITT, microbiological modified intent-to-treat; ND, not determined; SMX, sulfamethoxazole; sulo, sulopenem etzadroxil/probenecid; TMP, trimethoprim

3.1.1.2.2 Efficacy Outcomes

Trial 301 Micro-MITTR Population

In the initial NDA submission, the Applicant provided the primary efficacy analysis results using the updated SAP with a sample size of 147 and 139 subjects in the sulopenem etzadroxil/probenecid and ciprofloxacin treatment groups, respectively. The FDA did not agree with this analysis using the updated SAP, as discussed in Section 3.1.1.1. This was communicated to the Applicant on March 18, 2021; at FDA's request, the Applicant submitted an updated clinical study report using the original SAP and with inclusion of site 202 on April 27, 2021.

Table 10 shows the Applicant's analysis results using the updated SAP and excluding Site 202, the Applicant's FDA-requested analysis using the original SAP and including Site 202, and FDA's analysis results using the original SAP with inclusion of Site 202.

With the inclusion of Site 202 and analysis using the original SAP and its corresponding definition of susceptibility, the sample sizes increased to 162 and 149 in the sulopenem etzadroxil/probenecid and ciprofloxacin groups, respectively. The overall response rates were 48.1% and 32.9% in the sulopenem etzadroxil/probenecid and ciprofloxacin groups, respectively, with a difference of 15.3% (95% CI: [4.3%, 25.8]). There was a significant treatment effect favoring sulopenem etzadroxil/probenecid in this analysis with a p-value of 0.0062. There was a minimal sample size difference between the FDA's and Applicant's analysis populations when using the original SAP and including Site 202 (three subjects excluded and one subject included in the sulopenem etzadroxil/probenecid group, compared with the Applicant-defined analysis population); this document subsequently uses the Applicant's population unless stated otherwise.

As shown in Table 10, superiority of sulopenem etzadroxil/probenecid over ciprofloxacin was demonstrated for the primary endpoint overall response at TOC in the micro-MITTR population irrespective of definitions in the original or updated SAP or handling of Site 202. It is noted, however, that there was uncertainty regarding the extent to which the ciprofloxacin comparator would be more effective than a placebo in this micro-MITTR population.

Table 10. Trial 301: Applicant's and FDA's Analyses of Overall Response at TOC, Micro-MITTR Population

Outcome	Sulopenem	Ciprofloxacin	Difference (%) 95% CI	P-Value
Applicant's results using updated SAP, excluding Site 202	92/147 (62.6)	50/139 (36.0)	26.6 (15.1, 37.4)	<0.001
Results using original SAP, including Site 202				
Applicant's results	78/162 (48.1)	49/149 (32.9)	15.3 (4.3, 25.8)	0.0062
FDA's results	77/160 (48.1)	49/149 (32.9)	15.2 (4.4, 26.1)	0.0065

Source: Tables 52 and 84, updated Study Report and Statistical Reviewer's analysis.
Abbreviations: CI, confidence interval; micro-MITTR, microbiological modified intent-to-treat-resistant; SAP, statistical analysis plan; sulopenem, sulopenem etzadroxil/probenecid

As Table 11 shows, the main reasons for overall nonresponse at TOC in the sulopenem etzadroxil/probenecid group were microbiologic failure only (32.7%), followed by clinical failure only (8.6%) and both clinical and microbiologic failure (5.6%). The main reasons for overall nonresponse in

the ciprofloxacin group were microbiologic failure only (32.9%), followed by both clinical and microbiologic failure (18.1%) and clinical failure only (8.1%).

Table 11. Trial 301: Reasons for Overall Nonresponse at TOC, Micro-MITTR Population

Number of Nonresponders/Reasons for Overall Nonresponse at TOC	Sulopenem (N=162) n (%)	Ciprofloxacin (N=149) n (%)
Total number of nonresponders	76 (46.9)	95 (63.8)
Urine culture at TOC visit demonstrates ≥10^3 CFU/mL of the baseline uropathogen (microbiologic failure only)	53 (32.7)	49 (32.9)
No resolution or worsening of symptoms of uUTI present at trial entry and/or new uUTI symptoms (clinical failure only)	14 (8.6)	12 (8.1)
Urine culture ≥10^3 and at least one symptom not resolved (both clinical and microbiologic failure)	9 (5.6)	27 (18.1)
Receipt of nonstudy antibacterial therapy for uUTI	0 (0.0)	10 (6.7)
Failure only for rescue therapy	0 (0.0)	7 (4.7)

Source: Table 88 of the Updated Study Report.

Abbreviations: CFU, colony forming unit; cUTI, complicated urinary tract infection; micro-MITTR, microbiological modified intent-to-treat-resistant; sulopenem, sulopenem etzadroxil/probenecid; TOC, test of cure; uUTI, uncomplicated urinary tract infection;

Overall response by visit is shown in Table 12. At EOT, the difference in response rates was highest, then dropped to 15.3% at TOC, and then increased to 21% at the final visit. At all visits, the differences were statistically significant.

Table 12. Trial 301: Overall Response by Visit, Micro-MITTR Population

Outcome	Sulopenem (N=162)	Ciprofloxacin (N=149)	Difference (%) (95% CI)	P-Value
Overall response at EOT	98 (60.5)	38 (25.5)	35.0 (24.3, 44.8)	<0.001
Overall nonresponse	58 (35.8)	108 (72.5)		
Indeterminate	6 (3.7)	3 (2.0)		
Overall response at TOC	78 (48.1)	49 (32.9)	15.3 (4.3, 25.8)	0.0062
Overall nonresponse	76 (46.9)	95 (63.8)		
Indeterminate	8 (4.9)	5 (3.4)		
Overall response at FV	97 (59.9)	58 (38.9)	21.0 (9.9, 31.5)	<0.001
Overall nonresponse	57 (35.2)	77 (51.7)		
Indeterminate	8 (4.9)	14 (9.4)		

Source: Table 84, updated Study Report.

Abbreviations: CI, confidence interval; EOT, end of therapy; TOC, test of cure; FV, final visit; micro-MITTR, microbiological modified intent-to-treat-resistant; sulopenem, sulopenem etzadroxil/probenecid

Sensitivity Analyses in Trial 301 – Micro-MITTR Population

In the Applicant's primary efficacy analysis, contaminated urine cultures were considered to be successes for the microbiological outcome. As a sensitivity analysis, FDA identified three subjects in the sulopenem etzadroxil/probenecid arm and one subject in the ciprofloxacin arm who were considered to be overall responders in the primary efficacy analysis despite their cultures at TOC growing ≥3 organisms and recalculated results after classifying these subjects as microbiological failures (Table 13). The treatment effect remained statistically significant.

Table 13. Trial 301: FDA's Analysis of Overall Response at TOC, Counting Contaminated Urine Culture as Failure in the Definition of Microbiological Success, Micro-MITTR Population

Outcome	Sulopenem (N=160)	Ciprofloxacin (N=149)	Difference (%) 95% CI	P-Value
Overall response	74 (46.3)	48 (32.3)	14.0 (3.1, 24.6)	0.012

Source: Reviewer's analysis.
Abbreviations: CI, confidence interval; Micro-MITTR, microbiological modified intent-to-treat-resistant; sulopenem, sulopenem etzadroxil/probenecid; TOC, test of cure

FDA's analysis of overall response using complete eradication of baseline pathogens at TOC (defined as $<10^2$ CFU/mL) is displayed in Table 14. Compared with FDA's primary analysis, eight additional sulopenem etzadroxil/probenecid subjects and four additional ciprofloxacin subjects were found to have baseline pathogen counts between 10^2 and 10^3 CFU/mL at TOC and were considered nonresponders. The treatment effect remained statistically significant.

Table 14. Trial 301: FDA's Analysis of Overall Response at TOC Using Complete Eradication as Definition of Microbiological Success, Micro-MITTR Population

Outcome	Sulopenem (N=160)	Ciprofloxacin (N=149)	Difference (%) 95% CI	P-Value
Overall response	69 (43.1)	44 (29.5)	13.6 (2.9, 24.1)	0.013

Source: Reviewer's analysis
Abbreviations: CI, confidence interval; micro-MITTR, microbiological modified intent-to-treat-resistant; sulopenem, sulopenem etzadroxil/probenecid; TOC, test of cure

Trial 301 Micro-MITTS Population

Table 15 shows overall response based on the original SAP and including Site 202 in the micro-MITTS population. Noninferiority was not demonstrated using the predefined -10% noninferiority margin, as the 95% CI lower limit for the difference in response rates was lower than -10%. Further, sulopenem etzadroxil/probenecid had a significantly lower overall response rate compared to ciprofloxacin.

Table 15. Trial 301: Overall Response at TOC, Micro-MITTS Population

Variable	Sulopenem (N=376) n (%)	Ciprofloxacin (N=418) n (%)	Difference (%) (95% CI)
Overall response	227 (60.4)	300 (71.8)	-11.4 (-17.9, -4.8)
Overall nonresponse	130 (34.6)	91 (21.8)	
Indeterminate	19 (5.1)	27 (6.5)	

Source: Table 122, updated Study Report.
Abbreviations: CI, confidence interval; micro-MITTS, microbiological modified intent-to-treat-susceptible; sulopenem, sulopenem etzadroxil/probenecid; TOC, test of cure

The reasons for nonresponse at TOC in the micro-MITTS population are listed in Table 16. The main reason was microbiologic failure only, followed by clinical failure only, and both clinical and microbiologic failure.

Table 16. Trial 301: Reasons for Overall Nonresponse at TOC, Micro-MITTS Population

Number of Nonresponders Reasons for Overall Nonresponse at TOC	Sulopenem (N=376) n (%)	Ciprofloxacin (N=418) n (%)
Total number of nonresponders	130 (34.6)	91 (21.8)
Urine culture at TOC visit demonstrates ≥10^3 CFU/mL of the baseline uropathogen (microbiologic failure only)	72 (19.1)	41 (9.8)
No resolution or worsening of symptoms of uUTI present at trial entry and/or new uUTI symptoms (clinical failure only)	33 (8.8)	35 (8.4)
Urine culture ≥10^3 and at least one symptom not resolved (both clinical and microbiologic failure)	23 (6.1)	12 (2.9)
Receipt of nonstudy antibacterial therapy for uUTI	4 (1.1)	6 (1.4)
Failure only for rescue therapy	2 (0.5)	3 (0.7)

Source: Table 124 of the updated Study Report.

Abbreviations: CFU, colony forming unit; cUTI, complicated urinary tract infection; micro-MITTR, microbiological modified intent-to-treat-resistant; sulopenem, sulopenem etzadroxil/probenecid; TOC, test of cure; uUTI, uncomplicated urinary tract infection

Overall response by visit is shown in Table 17. At EOT, there was no difference between the two groups. From TOC to FV, sulopenem was significantly worse than ciprofloxacin.

Table 17. Trial 301: Overall Response by Visit, Micro-MITTS Population

Outcome	Sulopenem (N=376) n (%)	Ciprofloxacin (N=418) n (%)	Difference (%) (95% CI)
Overall response at EOT	242 (64.4)	254 (60.8)	3.6 (-3.2, 10.3)
Overall nonresponse	116 (30.9)	142 (34.0)	
Indeterminate	18 (4.8)	22 (5.3)	
Overall response at TOC	227 (60.4)	300 (71.8)	-11.4 (-17.9, -4.8)
Overall nonresponse	130 (34.6)	91 (21.8)	
Indeterminate	19 (5.1)	27 (6.5)	
Overall response at FV	224 (59.6)	288 (68.9)	-9.3 (-16.0, -2.6)
Overall nonresponse	126 (33.5)	107 (25.6)	
Indeterminate	26 (6.9)	23 (5.5)	

Source: Table 122, updated Study Report.

Abbreviations: CI, confidence interval; EOT, end of therapy; FV, final visit; micro-MITTS, microbiological modified intent-to-treat-susceptible; sulopenem, sulopenem etzadroxil/probenecid; TOC, test of cure

Trial 310 Micro-MITTS Population

Table 18 shows the overall response at TOC in the micro-MITTS population in Trial 310. There was a statistically significant difference in overall response and both noninferiority (using a -10% margin) and superiority were demonstrated in the overall response between the two treatment groups.

Table 18. Trial 310: Overall Response at TOC, Micro-MITTS Population

Outcome	Sulopenem (N=480) n (%)	Amoxicillin/ Clavulanate (N=442) n (%)	Difference (%) (95% CI)
Overall response	296 (61.7)	243 (55.0)	6.7 (0.3, 13.0) Two-sided p-value for superiority =0.040
Overall nonresponse	160 (33.3)	177 (40.0)	
Indeterminate	24 (5.0)	22 (5.0)	

Source: Table 86 of the Study Report and Statistical Reviewer's analysis.
Abbreviations: micro-MITTS, microbiological modified intent-to-treat-susceptible; sulopenem, sulopenem etzadroxil/probenecid; TOC, test of cure

As Table 19 shows, the main reason for overall nonresponse was microbiologic failure only, followed by clinical failure only and both clinical and microbiologic failure.

Table 19. Trial 310: Reasons for Overall Nonresponse at TOC, Micro-MITTS Population

Number of Nonresponders/Reasons for Overall Nonresponse at TOC	Sulopenem (N=480) n (%)	Amoxicillin/Clavulanate (N=442) n (%)
Number of nonresponders	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)
Receipt of nonstudy antibacterial therapy for uUTI	8 (1.7)	4 (0.9)
Failure only for rescue therapy	1 (0.2)	4 (0.9)

Source: Table 87 of the Study Report and Statistical Reviewer's analysis.
A subject may be classified into multiple categories.
Abbreviations: micro-MITTS, microbiological modified intent-to-treat-susceptible; sulopenem, sulopenem etzadroxil/probenecid; TOC, test of cure; uUTI, uncomplicated urinary tract infection

Sensitivity Analyses of Primary Efficacy Endpoint in Trial 310 (Micro-MITTS Population)

Contaminated Urine Sample Treated as Failure

At TOC in the micro-MITTS population, there were 23 and 24 subjects coded by the Applicant as "Eradication" with ≥3 organisms present (indicating contamination at collection) in the sulopenem and active control groups, respectively, and 13 and 18 of these subjects were coded as success in the overall response. If these successes were changed to failures, then the treatment effect was slightly higher, as shown in Table 20.

Complete Eradication (<100 CFU/mL)

The overall response at TOC when using complete eradication (<100 CFU/mL) as the definition of microbiologic success was lower in both groups, but the treatment effect was similar to that observed in the primary analysis (6.5% versus 6.7%) (Table 20).

Table 20. Trial 310: Sensitivity Analysis of Overall Response, Micro-MITTS Population

Variable	Sulopenem (N=480) n (%)	Amoxicillin/Clavulanate (N=442) n (%)	Difference (%) [95% CI] Two-Sided p-Value
Primary analysis (contamination as success)	296 (61.7)	243 (55.0)	6.7 (0.3, 13.0) 0.040
Contamination as failure	283 (59.0)	225 (50.9)	8.1 (1.6, 14.4) 0.014
Complete eradication (<100 CFU/mL)	280/480 (58.3)	229/442 (51.8)	6.5 (0.1, 12.9) 0.047

Source: Table 103 of the Study Report and Statistical Reviewer's analysis.
Abbreviations: CI, confidence interval; CFU, colony-forming unit; micro-MITTS: microbiological modified intent-to-treat-susceptible; sulopenem, sulopenem etzadroxil/probenecid

Overall Response by Visit in the Study 310 Micro-MITTS Population

The overall success proportions were 52.5% and 51.1% in the two treatment groups at Day 5, then increased slightly to 61.7% and 55.0% in the two treatment groups, respectively, at Day 12 (TOC) and stabilized at Day 28 (Table 21).

Table 21. Trial 310: Overall Response by Visit, Micro-MITTS Population

Timepoint/Response	Sulopenem (N=480) n (%)	Amoxicillin/ Clavulanate (N=442) n (%)
End of treatment (Day 5)		
Overall responder	252 (52.5)	226 (51.1)
Overall nonresponder	214 (44.6)	200 (45.2)
Indeterminate	14 (2.9)	16 (3.6)
Test of cure (Day 12)		
Overall responder	296 (61.7)	243 (55.0)
Overall nonresponder	160 (33.3)	177 (40.0)
Indeterminate	24 (5.0)	22 (5.0)
Final visit (Day 28)		
Overall responder	295 (61.5)	247 (55.9)
Overall nonresponder	143 (29.8)	157 (35.5)
Indeterminate	42 (8.8)	38 (8.6)

Source: Table 100 of the Study Report and Statistical Reviewer's analysis.
Abbreviations: Micro-MITTS, microbiologic modified intent-to-treat-susceptible; sulopenem, sulopenem etzadroxil/probenecid

3.1.1.2.3 Subgroup Analyses of the Primary Efficacy Endpoint of Overall Response

Trial 301 MITTR Population

In Trial 301, subgroup analysis results by age, race, and country per the original SAP are shown in Table 22. As age increased, the treatment effect of sulopenem etzadroxil/probenecid compared to ciprofloxacin increased. In White subjects there was a nominally significant difference between the two treatment groups. It is difficult to make any conclusions regarding other races due to the small sample sizes. In the United States, the treatment effect was consistent with the overall effect, while in Russia and Ukraine the observed treatment effect was numerically lower and higher than the overall effect, respectively.

Table 22. Trial 301: Subgroup Analyses of the Overall Response by Age, Race, and Country, Micro-MITTR Population

Variable	Sulopenem (N=162) n/N (%)	Ciprofloxacin (N=149) n/N (%)	Difference (%) (95% CI)
Age (years)			
<30	17/25 (68.0)	12/21 (57.1)	10.9 (-17.0, 37.7)
30-<60	38/67 (56.7)	26/59 (44.1)	12.7 (-4.9, 29.4)
60 or above	23/70 (32.9)	11/69 (15.9)	16.9 (2.6, 30.8)
Race			
Asian	0/2 (0)	0	
Black or African American	9/15 (60.0)	6/12 (50.0)	10.0 (-26.7, 44.7)
White	69/144 (47.9)	42/136 (30.9)	17.0 (5.6, 28.0)
Other	0/1 (0)	1/1 (100)	
Country			
Russia	17/46 (37.0)	18/43 (41.9)	-4.9 (-24.8, 15.3)
Ukraine	14/24 (58.3)	4/14 (28.6)	29.8 (-3.6, 56.2)
United States	46/95 (48.4)	28/89 (31.5)	17.0 (2.8, 30.5)

Source: Statistical Reviewer's analysis. CI for Ukraine was an exact CI.
Abbreviations: CI, confidence interval; Micro-MITTR, microbiological modified intent-to-treat-resistant; sulopenem, sulopenem etzadroxil/probenecid

Table 23 shows the FDA's analysis of overall response by baseline creatinine clearance and ESBL-producing pathogens. The treatment response was higher in sulopenem-treated subjects in the >60 mL/min subgroup and was similar in other creatinine clearance subgroups, though the number of subjects with a creatinine clearance <30 mL/min was too small to make a reliable estimation of the treatment effect. The treatment response rate was higher in the sulopenem etzadroxil/probenecid group as compared to the ciprofloxacin group regardless of phenotypic ESBL-resistance with a nominally significant treatment effect observed in the ESBL-negative subgroup.

Table 23. Trial 301: Subgroup Analysis of Overall Response by Creatinine Clearance and ESBL Pathogens, Micro-MITTR Population

Variable	Sulopenem (N=162) n/N (%)	Ciprofloxacin (N=149) n/N (%)	Difference (%) (95% CI)
Creatinine clearance (mL/min)			
>60	62/108 (57.4)	40/91 (44.0)	13.5 (-0.5, 26.9)
30-60	14/50 (28.0)	9/52 (17.3)	10.7 (-5.7, 27.7)
<30	2/4 (50.0)	0/6 (0)	
ESBL			
Positive	25/52 (48.1)	14/44 (31.8)	16.3 (-3.6, 34.7)
Negative	53/110 (48.2)	35/105 (33.3)	14.9 (1.7, 27.5)

Source: Statistical Reviewer's analysis.
Abbreviations: CI, confidence interval; ESBL, extended spectrum β-lactamase; micro-MITTR, microbiological modified intent-to-treat resistant; sulopenem, sulopenem etzadroxil/probenecid

Trial 301 Micro-MITTS Population

Subgroup analysis of the overall response indicated nominally significantly lower results in the <30 and 30 to <60-year age groups, and white race, 30 to 60 mL/min creatinine clearance and ESBL-negative subgroups (Table 24 and Table 25).

Table 24. Trial 301: Subgroup Analysis of Overall Response by Age, Race, Country, Micro-MITTS Population

Variable	Sulopenem (N=376)	Ciprofloxacin (N=418)	Difference (%) (95% CI)
Age (years)			
<30	49/71 (69.0)	70/83 (84.3)	-15.3 (-28.8, -2.0)
30-<60	101/162 (62.3)	133/181 (73.5)	-11.1 (-20.9, -1.3)
60 or above	77/143 (53.8)	97/154 (63.0)	-9.1 (-20.2, 2.1)
Race			
American Indian or Alaska Native	2/4	0	
Asian	1/3 (33.3)	1/3 (33.3)	
Black or African American	27/35 (77.1)	30/34 (88.2)	-11.1 (-29.5, 7.4)
White	197/334 (59.0)	267/379 (70.4)	-11.5 (-18.4, -4.5)
Other	0	2/2 (100)	
Country			
Russia	54/93 (58.1)	74/109 (67.9)	-9.8 (-23.0, 3.5)
Ukraine	58/88 (65.9)	69/85 (81.2)	-15.3 (-28.1, -2.1)
United States	115/195 (59.0)	157/224 (70.1)	-11.1 (-20.2, -1.9)

Source: Statistical Reviewer's analysis.
Abbreviations: CI, confidence interval; micro-MITTS, microbiological modified intent-to-treat susceptible population; sulopenem, sulopenem etzadroxil/probenecid

Table 25. Trial 301: Subgroup Analysis of Overall Response by Creatinine Clearance and ESBL, Micro-MITTS Population

Variable	Sulopenem (N=376)	Ciprofloxacin (N=418)	Difference (%) (95% CI)
Creatinine clearance (mL/min)			
≥60	173/261 (66.3)	233/316 (73.7)	-7.5 (-15.0, 0.0)
30-60	50/106 (47.2)	65/100 (65.0)	-17.8 (-30.8, -4.3)
<30	4/9 (44.4)	2/2 (100)	
ESBL			
Positive	9/21 (42.9)	17/28 (60.7)	-17.9 (-43.6, 10.5)
Negative/missing	218/355 (61.4)	283/390 (72.6)	-11.1 (-17.9, -4.4)

Source: Statistical Reviewer's analysis.
Abbreviations: CI, confidence interval; ESBL, extended-spectrum β-lactamase; micro-MITTS, microbiological modified intent-to-treat susceptible population; sulopenem, sulopenem etzadroxil/probenecid

Trial 310 Micro-MITTS Population

In the Trial 310 micro-MITTS population, subgroup analyses were performed to assess the treatment response among subgroups defined by age, race, ethnicity, body mass index and diabetes. Breslow-Day tests did not suggest any heterogeneity of odds ratios in the primary efficacy endpoint. When the sample size was greater than 90 in each group, the lower limits of the 95% CIs were larger than -10%, suggesting noninferiority in these groups with a -10% noninferiority margin. In a few subgroups (age >65 years, Hispanic or Latino ethnicity, and nondiabetes), a nominally statistically significant difference was seen. Of note, multiple subgroup analyses were conducted without multiplicity adjustment which could result in spurious findings due to chance (Table 26).

Table 26. Trial 310: Subgroup Analysis of the Overall Response, Micro-MITTS Population

Variable	Sulopenem (N=480) n (%)	Amoxicillin/Clavulanate (N=442) n (%)	Difference (%) [95% CI]
Age (years)			
≤65	231/367 (62.9)	205/350 (58.6)	4.4 (-2.8, 11.5)
>65	65/113 (57.5)	38/92 (41.3)	16.2 (2.4, 29.4)
Race			
American Indian or Alaska Native	1/1 (100)	0/1 (0)	
Asian	8/10 (80.0)	7/8 (87.5)	-7.5 (-43.2, 32.9)
Black or African American	45/78 (57.7)	39/78 (50.0)	7.7 (-7.9, 23.3)
Native Hawaiian or other Pacific Islander	0	0/1 (0)	
Other	6/8 (75.0)	1/4 (25.0)	50.0 (-10.9, 83.3)
Ethnicity			
Hispanic or Latino	201/304 (66.1)	160/278 (57.6)	8.6 (0.7, 16.4)
Not Hispanic or Latino	95/176 (54.0)	83/163 (50.9)	3.1 (-7.6, 13.6)
Not reported		0/1	
Body mass index (kg/m^2)			
<25	81/124 (65.3)	82/137 (59.9)	5.5 (-6.3, 17.1)
25-30	118/178 (66.3)	85/144 (59.0)	7.3 (-3.3, 17.8)
>30	97/178 (54.5)	76/161 (47.2)	7.3 (-3.4, 17.8)
Diabetes			
Yes	37/80 (46.3)	28/66 (42.4)	3.8 (-12.4, 19.7)
No	259/400 (64.8)	215/376 (57.2)	7.6 (0.3, 14.4)
Creatinine clearance (mL/min)			
<60	63/104 (60.6)	37/83 (44.6)	16.0 (1.6, 29.8)
≥60	231/373 (61.9)	204/352 (58.0)	4.0 (-3.2, 11.1)
Missing	2/3 (66.7)	2/7 (28.6)	
Quinolone susceptibility			
Susceptibility	234/360 (65.0)	180/314 (57.3)	7.7 (0.3, 15.0)
Resistant/nonsusceptible	62/120 (51.7)	63/128 (49.2)	2.5 (-10.0, 14.8)
Extended-spectrum β-lactamase			
Positive	22/37 (59.5)	20/45 (44.4)	15.0 (-6.8, 35.4)
Negative	274/443 (61.9)	223/397 (56.2)	5.7 (-1.0, 12.3)
Baseline pathogen			
E. coli	251/400 (62.8)	210/74 (56.1)	6.6 (-0.3, 13.5)
K. pneumoniae	31/57 (54.4)	22/50 (44.0)	10.4 (-8.6, 28.7)
P. mirabilis	5/13 (38.5)	6/13 (46.2)	-7.7 (-42.84, 29.45)
Other	11/14 (78.6)	6/7 (85.7)	-7.1 (-38.69, 34.99)

Source: Tables 93, 96, and 99 of the Study Report and Statistical Reviewer's analysis.
CIs were calculated using the Miettinen-Nurminen method.
Abbreviations: CI, confidence interval; micro-MITTS, microbiological modified intent-to-treat susceptible population; sulopenem, sulopenem etzadroxil/probenecid

Subgroup analyses for Trial 310 micro-MITTR population are not reported, as the number of subjects was small.

3.1.1.2.4 Secondary Efficacy Endpoints

Trial 301 Micro-MITTR Population

In the Trial 301 micro-MITTR population, clinical and microbiological response per patient at TOC based on the original SAP as assessed by the Applicant are displayed in Table 27, where microbiological success

was defined as TOC urine culture results of $<10^3$ CFU/mL of the baseline pathogen(s) regardless of susceptibility. Clinical response was based on patient-determined clinical response defined as resolution of baseline uUTI symptoms and no new uUTI symptoms at TOC. There were significant treatment effects for clinical success (resolution of baseline symptoms) and microbiological response between the two treatment groups.

Table 27. Trial 301: Clinical Response, Microbiological Response Per Patient at TOC, Micro-MITTR Population

Response	Sulopenem (N=162) n (%)	Ciprofloxacin (N=149) n (%)	Difference (%) (95% CI)	P-Value
Clinical response				
Success	136 (84.0)	96 (64.4)	**19.5 (10.0, 29.0)**	**<0.0001**
Failure	23 (14.2)	47 (31.5)		
Indeterminate	3 (1.9)	6 (4.0)		
Microbiological response by patient				
Success	92 (56.8)	66 (44.3)	**12.5 (1.4, 23.3)**	**0.028**
Failure	62 (38.3)	76 (51.0)		
Indeterminate	8 (4.9)	7 (4.7)		

Source: Statistical Reviewer's analysis based on updated data set.
Abbreviations: CI, confidence interval; micro-MITTR, microbiological modified intent-to-treat resistant; sulopenem, sulopenem etzadroxil/probenecid; TOC, test of cure

Trial 301 Micro-MITTS Population

In the Trial 301 micro-MITTS population, there was no observed difference in clinical response between the two treatment groups at the TOC visit; however, a significantly lower microbiological response rate was observed in the sulopenem etzadroxil/probenecid group (Table 28).

Table 28. Trial 301: Clinical and Microbiological Response Using the Original Definitions of Microbiologic Response at TOC in Micro-MITTS Population

Response Type	Sulopenem (N=376) n (%)	Ciprofloxacin (N=418) n (%)	Difference(%) (95% CI)
Clinical response	305 (81.1)	351 (84.0)	-2.9 (-8.2, 2.4)
Microbiologic response	262 (69.7)	336 (80.4)	-10.7 (-16.7, -4.7)

Source: Statistical Reviewer's analysis.
Abbreviations: CI, confidence interval; Micro-MITTS, microbiological modified intent-to-treat-susceptible; sulopenem, sulopenem etzadroxil/probenecid; TOC, test-of-cure

Trial 310 Micro-MITTS Population

Table 29 shows results for clinical response and microbiologic response at TOC in the micro-MITTS population in Trial 310. There was a nominally statistically significant difference in microbiologic response favoring sulopenem etzadroxil/probenecid over amoxicillin/clavulanate.

Table 29. Trial 310: Patient-Determined Clinical Response, and Microbiologic Response at TOC, Micro-MITTS Population

Outcome	Sulopenem (N=480) n (%)	Amoxicillin/Clavulanate (N=442) n (%)	Difference (%) (95% CI)
Patient-determined clinical success	371 (77.3)	339 (76.7)	0.6 (-4.8, 6.1)
Investigator-determined clinical success	421 (87.7)	386 (87.3)	0.4 (-3.9, 4.7)
Microbiologic success	361 (75.2)	295 (66.7)	8.5 (2.6, 14.3)

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

Abbreviations: CI, confidence interval; micro-MITT: microbiological modified intent-to-treat; sulopenem, sulopenem etzadroxil/probenecid; TOC, test of cure

Trial 310 Micro-MITTR Population

The analyses of the clinical and microbiologic responses in the micro-MITTR population are summarized in Table 30. Due to the small sample size, there remained considerable statistical uncertainty about the treatment effect in this population.

Table 30. Trial 310: Clinical and Microbiologic Response, Micro-MITTR Population

Outcome	Sulopenem (N=42) n (%)	Amoxicillin/ Clavulanate (N=25) n (%)	Difference (%) (95% CI)
Clinical success at TOC	26 (61.9)	18 (72.0)	-10.1 (-31.5, 14.0)
Microbiologic success at TOC	29 (69.0)	20 (80.0)	-11.0 (-30.7, 12.0)

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

Abbreviations: CI, confidence interval; micro-MITTR, microbiological modified intent-to-treat resistant; sulopenem, sulopenem etzadroxil/probenecid; TOC, test of cure

Trial 310 Micro-MITT Population

In the micro-MITT population, the difference in overall success rates was driven by the difference in microbiological success between the two treatment groups, as the clinical success proportions were similar (Table 31).

Table 31. Trial 310: Clinical and Microbiologic Response at TOC, Micro-MITT Population

Outcome	Sulopenem (N=522) n (%)	Amoxicillin/Clavulanate (N=468) n (%)	Difference (%) (95% CI)
Clinical success	397 (76.1)	358 (76.5)	-0.4 (-5.7, 4.9)
Microbiologic success	390 (74.7)	315 (67.3)	7.4 (1.8, 13.1)

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

Abbreviations: Micro-MITT, microbiological modified intent-to-treat; sulopenem, sulopenem etzadroxil/probenecid; TOC, test of cure

3.1.1.3 302-cUTI and Trial 303-cIAI Results

The Applicant conducted two additional phase 3 trials, one in cUTI and one in cIAI. These trials were submitted as part of the data package in the original NDA submission but were not proposed as treatment indications since both trials failed to meet their primary objectives of demonstrating noninferiority to active comparators. These trials are summarized here for a comprehensive assessment of the efficacy and safety of sulopenem.

3.1.1.3.1 Trial 302 for cUTI

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

Subjects were randomized 1:1 to receive either IV sulopenem 1000 mg once daily for at least 5 days (five doses) followed by oral sulopenem etzadroxil 500 mg co-administered with oral probenecid 500 mg twice daily to complete 7 to 10 total days of treatment versus ertapenem IV 1000 mg once daily for at least 5 days (five doses) followed by oral ciprofloxacin 500 mg or amoxicillin/clavulanate 875 mg twice daily to complete 7 to 10 total days of therapy. Duration of treatment could be extended up to a total of 14 days for patients with bacteremia at baseline.

The primary efficacy endpoint was overall response (resolution of symptoms and clearance of the baseline uropathogen) at Day 21 (TOC). The primary analysis population was the micro-MITT, defined as subjects who received at least a single dose of study medication, had the disease under study (with two of the five baseline cUTI symptoms), and a positive study entry urine culture within 48 h prior to the first dose. The study entry urine culture had to have no more than two species of uropathogens (Enterobacterales only, susceptible to sulopenem [MIC ≤1] and ertapenem [MIC ≤0.5]) at $\geq 10^5$ CFU/mL, except in the situation where one of the organisms cultured from the urine was also isolated from blood cultures drawn at baseline. Patients with a study pathogen isolated from baseline blood cultures were included in the micro-MITT population regardless of the patient's baseline urine culture result.

The Applicant's efficacy results were based on definitions of microbiological responses using the same definition for "persistence" as in Trial 301, i.e., a uropathogen present in baseline urine culture which grew at $\geq 10^3$ CFU/mL at TOC with further specification as follows: "The genus/species and susceptibility profiles need to match. For the Baseline and TOC visits, additional molecular testing by pulsed field gel electrophoresis or whole-genome sequencing (WGS) may be performed for confirmation." FDA requested reanalysis of the data for Trials 301, 302, and 303 (for cIAI), based on definitions of microbiological response without using additional molecular testing. The results from the two analyses from the initial and updated reports were consistent, but only the results using the initial SAP are reported here.

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

As shown in the following table, Trial 302 failed to show noninferiority using a -10% noninferiority margin. IV sulopenem followed by PO sulopenem etzadroxil/probenecid was significantly worse than the active comparator, IV ertapenem followed by PO ciprofloxacin or amoxicillin/clavulanate (Table 32).

Table 32. Trial 302: Overall Response at TOC, Micro-MITT Population

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

Source: Table 62, updated Study Report.
Abbreviations: CI, confidence interval; ertapenem, IV ertapenem/PO ciprofloxacin or amoxicillin/clavulanate; micro-MITT, microbiological modified intent-to-treat; sulopenem, IV sulopenem/PO sulopenem etzadroxil/probenecid; TOC, test of cure

Table 33 shows the overall response by visit using the original SAP to determine microbiologic response in the micro-MITT population. At Day 5, the response rates were approximately 44% in both treatment groups and then increased to 85% in the sulopenem group and 88% in the ertapenem group at EOT.

Table 33. Trial 302: Overall Response at Day 5 and EOT, Micro-MITT Population

Outcome	Sulopenem (N=444) n (%)	Ertapenem (N=440) n (%)	Difference (%) (95% CI)
Overall response at Day 5	198 (44.6)	191 (43.4)	1.2 (-5.4, 7.7)
Overall nonresponse	243 (54.7)	240 (54.5)	
Indeterminate	3 (0.7)	9 (2.0)	
Overall response at EOT	379 (85.4)	387 (88.0)	-2.6 (-7.1, 1.9)
Overall nonresponse	54 (12.2)	38 (8.6)	
Indeterminate	11 (2.5)	15 (3.4)	

Source: Table 62 of the updated Study Report submitted on April 28, 2021 and Statistical Reviewer's analysis.
Abbreviations: EOT, end of therapy; ertapenem, IV ertapenem/PO ciprofloxacin or amoxicillin/clavulanate; micro-MITT, microbiological modified intent-to-treat; sulopenem, IV sulopenem/PO sulopenem etzadroxil/probenecid; TOC, test of cure

In the sulopenem group, 87% of all subjects in the micro-MITT population stepped down from IV sulopenem to PO sulopenem etzadroxil/probenecid and the overall response rate in these subjects was 61.2% [i.e., (154+26+53+5)/(248+55+80+6)]; the response rates by ciprofloxacin and amoxicillin/clavulanate susceptibility are shown in Table 34. In the ertapenem group, 67.5% (297/440) of subjects stepped down to oral therapy with either ciprofloxacin or amoxicillin/clavulanate; of these subjects, 50% (220/440) stepped down to ciprofloxacin PO with an overall response rate of 82.3% (181/220) while 17.5% (77/440) of subjects stepped down to amoxicillin/clavulanate with an overall response rate of 54.5% (42/77). Comparisons of outcomes between subjects who stepped down to oral therapy in the two groups are limited by being postrandomization subgroup analyses. The fact that more subjects stepped down to oral therapy in the sulopenem group suggested that subjects receiving oral sulopenem etzadroxil/probenecid were not necessarily comparable to subjects receiving oral ciprofloxacin or oral amoxicillin/clavulanate at the time of stepdown. Nevertheless, the results in Table 34 suggest that an efficacy decrement of stepdown sulopenem etzadroxil/probenecid compared to stepdown ciprofloxacin in the subgroup with ciprofloxacin-susceptible pathogens may have contributed to the disfavorable trial conclusions. Such an efficacy decrement would be consistent with the Trial 301 results seen for uUTI.

Table 34. Trial 302: Overall Response at TOC by Stepdown Category, Sulopenem IV to PO Sulopenem Etzadroxil/Probenecid, Ertapenem IV to PO Ciprofloxacin, and Ertapenem IV to PO Amoxicillin/Clavulanate, Micro-MITT Population

Overall Response	Ciprofloxacin Susceptible n/N (%)	Ciprofloxacin Resistant, Amoxicillin/Clavulanate Susceptible n/N (%)	Ciprofloxacin Resistant, Amoxicillin/Clavulanate Resistant n/N (%)
Sulopenem IV to PO sulopenem etzadroxil/probenecid			
Overall responder	154/248 (62.1)	26/55 (47.3)	53/80 (66.3)
Overall nonresponder	86/248 (34.7)	28/55 (50.9)	27/80 (33.8)
Indeterminate	8/248 (3.2)	1/55 (1.8)	0/80 (0.0)
Ertapenem IV to PO ciprofloxacin			
Overall responder	179/215 (83.3)	0	2/5 (40.0)
Overall nonresponder	27/215 (12.6)	0	3/5 (60.0)
Indeterminate	9/215 (4.2)	0	0/5 (0)
Ertapenem IV to PO amoxicillin/clavulanate			
Overall responder	4/6 (66.7)	37/66 (56.1)	0/2 (0.0)
Overall nonresponder	2/6 (33.3)	27/66 (40.9)	2/2 (100.0)
Indeterminate	0/6 (0)	2/66 (3.0)	0/2 (0.0)

Source: Tables 40 and 42 submitted July 29, 2024 and Statistical Reviewer's analysis.
Five of six subjects with missing resistance data were responders.
Abbreviations: IV, intravenous; micro-mITT, microbiological modified intent-to-treat; PO, oral; TOC, test of cure

Patients who remained on IV sulopenem were either not able to tolerate oral therapy or did not have sufficient resolution of their infection for the investigator to recommend stepdown treatment; the overall response in these patients by ciprofloxacin or amoxicillin/clavulanate susceptibility is shown in Table 35. Twenty-seven (49%) of fifty-five subjects who received only sulopenem IV were overall responders.

Table 35. Trial 302: Overall Response at TOC by Stepdown Category, Sulopenem Group (IV Only), Micro-MITT Population

Overall Response	Ciprofloxacin Susceptible n/N (%)	Ciprofloxacin Resistant, Amoxicillin/Clavulanate Susceptible n/N (%)	Ciprofloxacin Resistant, Amoxicillin/Clavulanate Resistant n/N (%)
Overall responder	18/34 (52.9)	3/5 (60.0)	6/15 (40.0)
Overall nonresponder	10/34 (29.4)	2/5 (40.0)	7/15 (46.7)
Indeterminate	6/34 (17.6)	0/5 (0.0)	2/15 (13.3)

Source: Table 41 submitted July 29, 2024 and Statistical Reviewer's analysis. One subject with missing resistance data were a nonresponder.
Abbreviations: IV, intravenous; micro-mITT, microbiological modified intent-to-treat; TOC, test of cure

As shown in Table 36 for the ertapenem group, 32.0% [(106+35)/440)] received IV only and 51.8% [(58+15)/(106+35)] of these subjects were overall responders.

Table 36. Trial 302: Overall Response at TOC at TOC by Stepdown Category, Ertapenem Arm (IV Only), Micro-MITT Population

Overall Response	CIP R/I and AMO/CLAV R/I n/N (%)	CIP R/I and AMO/CLAV R/I As Only Reason For Staying on IV ERT n/N (%)	CIP R/I and AMO/CLAV R/I Plus Another Reason For Staying on IV ERT n/N (%)	NOT CIP R/I and AMO/CLAV R/I n/N (%)
Overall responder	58/106 (54.7)	45/84 (53.6)	13/22 (59.1)	15/35 (42.9)
Overall Nonresponder	45/106 (42.5)	38/84 (45.2)	7/22 (31.8)	12/35 (34.3)
Indeterminate	3/106 (2.8)	1/84 (1.2)	2/22 (9.1)	8/35 (22.9)

Source: Table 43 submitted July 29, 2024 and Statistical Reviewer's analysis.
Abbreviations: AMO, amoxicillin; CIP, ciprofloxacin; CLAV, clavulanate; ERT, ertapenem; I, intermediate; IV, intravenous; micro-mITT, microbiological modified intent-to-treat; R, resistant; TOC, test of cure

Table 37 shows the microbiologic and clinical responses by visit. At the Day 5 and EOT visits, the two treatment groups had similar microbiologic response rates. Only at the TOC visit did a significantly lower treatment effect emerge in the sulopenem group. At each visit, clinical response rates were similar between the two treatment groups.

Table 37. Trial 302: Microbiologic Response and Clinical Response at Day 5, EOT, and TOC, Micro-MITT Population

Outcome	Sulopenem (N=444) n (%)	Ertapenem (N=440) n (%)	Difference (%) (95% CI)
Microbiologic response			
Day 5	429 (96.6)	419 (95.2)	1.4 (-1.3, 4.2)
EOT	413 (93.0)	417 (94.8)	-1.8 (-5.0, 1.4)
TOC	275 (61.9)	308 (70.0)	-8.1 (-14.3, -1.8)
Clinical response			
Day 5	203 (45.7)	196 (44.5)	1.2 (-5.4, 7.7)
EOT	398 (89.6)	399 (90.7)	-1.0 (-5.0, 2.9)
TOC	397 (89.4)	389 (88.4)	1.0 (-3.2, 5.2)

Source: Statistical Reviewer's analysis.
Abbreviations: CI, confidence interval; EOT, end of therapy; ertapenem, IV ertapenem/PO ciprofloxacin or amoxicillin/clavulanate; micro-MITT, microbiological modified intent-to-treat; sulopenem, IV sulopenem/PO sulopenem etzadroxil/probenecid; TOC, test of cure

Efficacy Conclusions From Trial 302

Trial 302 did not provide evidence for the efficacy of IV sulopenem followed by oral sulopenem etzadroxil/probenecid for the treatment of cUTI. In the primary efficacy analysis of overall clinical and microbiological response at the TOC visit, IV sulopenem followed by oral sulopenem etzadroxil/probenecid did not demonstrate noninferiority compared to the control group treated with IV ertapenem followed by oral ciprofloxacin or oral amoxicillin/clavulanate. Further, the sulopenem group was statistically inferior to the control group. Results for overall response in the two treatment groups were similar at Day 5 (the minimum duration of IV therapy) and the EOT but differed by the TOC visit on Day 21. The efficacy decrement was driven by a difference in microbiologic response rates, as clinical response rates were similar between the sulopenem and ertapenem treatment groups. There was remaining uncertainty regarding whether any efficacy decrements were due to the intravenous or oral sulopenem because while the randomized comparisons were designed to evaluate intravenous-to-oral regimens, results were suggestive of an efficacy decrement of stepdown sulopenem

etzadroxil/probenecid compared to stepdown ciprofloxacin in subjects with ciprofloxacin-susceptible pathogens. Such an efficacy decrement is consistent with the Trial 301 results seen for uUTI where the noninferiority of oral sulopenem etzadroxil/probenecid to oral ciprofloxacin in ciprofloxacin-susceptible isolates was not demonstrated.

3.1.1.3.2 Trial 303 for cIAI

Trial 303 was a phase 3, multicenter, double-blind, randomized trial designed to compare the efficacy, tolerability, and safety of IV sulopenem followed by oral sulopenem etzadroxil/probenecid with that of IV ertapenem followed by oral ciprofloxacin and metronidazole or amoxicillin/clavulanate for the treatment of cIAI.

A total of 674 subjects were randomized (1:1) to receive either IV sulopenem 1000 mg once daily for at least 5 days (five doses) followed by sulopenem etzadroxil 500 mg coadministered with oral probenecid 500 mg twice daily to complete 7 to 10 total days of treatment or ertapenem IV 1000 mg once daily for at least 5 days (five doses) followed by oral ciprofloxacin 500 mg twice daily and metronidazole 500 mg four times a day or amoxicillin/clavulanate 875 mg twice daily to complete 7 to 10 total days of therapy. Duration of treatment could be extended up to a total of 14 days. The results are shown in Table 38. After initial unblinding of the study, imbalances in outcome by treatment were identified by the Applicant. Subsequently, the Applicant conducted a post hoc analysis by re-examining and re-analyzing the data. FDA did not agree with the Applicant's post hoc analysis after the study data were unblinded. Trial 303 failed to show noninferiority using a -10% margin, either based on the primary analysis or the post hoc analysis.

Table 38. Study 303: Applicant's Analysis of Primary and Post Hoc Results—Clinical Response at TOC, Micro-MITT Population

Clinical Success	Sulopenem (N=249)	Ertapenem (N=266)	Difference (%) [95% CI]
Primary	204 (81.9)	233 (87.9)	-6.0 (-12.2, 0.2)
Post hoc	213 (85.5)	240 (90.2)	-4.7 (-10.3, 1.0)

Source: Study Report.

Abbreviations: CI, confidence interval; ertapenem, IV ertapenem/PO ciprofloxacin and metronidazole or amoxicillin/clavulanate; micro-MITT, microbiological modified intent-to-treat; sulopenem, IV sulopenem/PO sulopenem etzadroxil/probenecid; TOC, test of cure

3.1.2 Efficacy Summary

Trial 301 and Trial 310 were designed to be two adequate and well-controlled trials to provide evidence of efficacy for sulopenem etzadroxil/probenecid for the treatment of adult women with uUTI due to designated susceptible microorganisms. Although sulopenem etzadroxil/probenecid demonstrated superiority to ciprofloxacin in a primary analysis of subjects with ciprofloxacin-resistant baseline pathogens (micro-MITTR) in Trial 301, the Applicant received a CR on their initial NDA submission. There were uncertainties regarding efficacy given the disfavorable results in a primary analysis of subjects with ciprofloxacin-susceptible baseline pathogens (micro-MITTS), and the lack of supportive evidence from Trial 302 in cUTI and Trial 303 in cIAI. Under 20% of randomized subjects in Trial 301 were in the micro-MITTR population in which results favored sulopenem etzadroxil/probenecid. There was uncertainty regarding the extent to which the ciprofloxacin comparator would be more effective than a placebo in this micro-MITTR population. In the CR letter, the FDA recommended that the Applicant conduct at least one additional adequate and well-controlled study in uUTI. Following this recommendation, Trial 310 in

uUTI was conducted and sulopenem etzadroxil/probenecid demonstrated efficacy compared to amoxicillin/clavulanate in the susceptible population (micro-MITTS).

In Trial 302 for cUTI, there was remaining uncertainty regarding whether any efficacy decrements were due to intravenous sulopenem or oral sulopenem etzadroxil/probenecid because the trial was designed to evaluate intravenous-to-oral regimens. However, results were suggestive of an efficacy decrement of stepdown oral sulopenem etzadroxil/probenecid compared to stepdown oral ciprofloxacin in subjects with ciprofloxacin-susceptible pathogens.

3.1.3 Microbiology Assessment

Nonclinical Summary

Sulopenem is a penem antibacterial drug that inhibits bacterial cell-wall synthesis by binding to penicillin-binding proteins (PBPs) resulting in cell death. The relative order of binding affinity towards PBPs was PBP2>PBP1A>PBP1B>PBP4>PBP3>PBP5/6 and was demonstrated in *E. coli* (Gootz et al. 1989). Similar to other carbapenems, sulopenem showed bactericidal killing by time-kill assay at concentrations ≥4× the MIC against tested isolates of *E. coli* and *K. pneumoniae* (*Project Report Uppsala 2018-10-11; 17-ITR-01 Part 2*).

Sulopenem's spontaneous mutation frequency was determined in vitro as 1×10^{-8} with a ≤2-fold minimum inhibitory concentration (MIC) increase using two *E. cloacae* isolates[1]. Sulopenem demonstrated in vitro activity against certain Enterobacterales isolates genetically confirmed to contain AmpC and certain extended-spectrum β-lactamases (e.g., CTX-M, TEM, and SHV), however, carbapenem resistance occurs primarily due to enzymatic inactivation by carbapenemases, β-lactamase production, efflux pump expression, and changes in porins and/or PBPs.

Sulopenem shows in vitro activity against both aerobic and anaerobic gram-positive and gram-negative bacteria. In vitro $MIC_{50/90}$ values (inhibits the growth of ≥50% and ≥90% of isolates) were determined for sulopenem against isolates of uUTI relevant pathogens from recent surveillance studies (North American and European isolates) and from completed clinical studies. In general, against *E. coli* isolates, sulopenem had $MIC_{50/90}$ values of 0.03/0.03 to 0.06 mcg/mL; against *K. pneumoniae* isolates, sulopenem had $MIC_{50/90}$ values of 0.03 to 0.06/0.06 to 0.12 mcg/mL; and against *P. mirabilis* isolates, sulopenem had $MIC_{50/90}$ values of 0.12 to 0.25/0.25 to 0.5 mcg/mL.

Against *E. coli* isolates, sulopenem had similar activity to meropenem, lower activity than imipenem, and slightly lower activity than ertapenem. Against *K. pneumoniae* isolates, sulopenem had similar activity to meropenem, lower than imipenem and similar to ertapenem. Against *P. mirabilis* isolates, the MIC distribution for sulopenem and the comparator carbapenems shows that sulopenem was less active than ertapenem and slightly less active than meropenem; however, sulopenem, meropenem and ertapenem were all more active than imipenem.

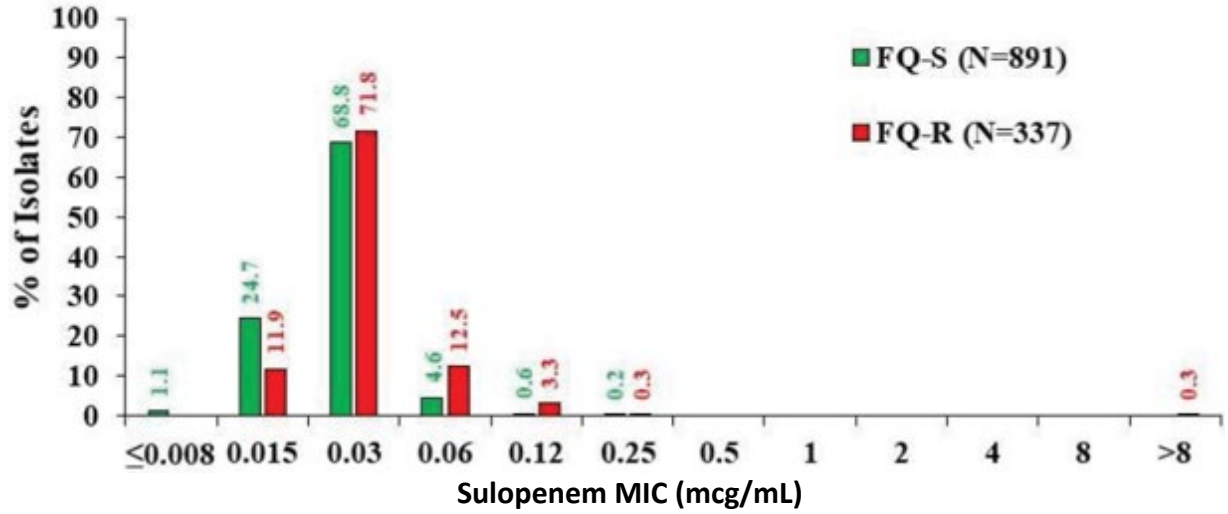
Sulopenem Activity Against Organisms With Key Resistance Phenotypes

Sulopenem activity was also studied against a subset of organisms with key resistance phenotypes. Sulopenem had an MIC_{50}/90 value of 0.03/0.03 mcg/mL against fluroquinolone-susceptible (FQ-S) isolates compared to 0.03/0.06 mcg/mL for fluroquinolone-resistant (FQ-R) isolates of *E. coli*. The MIC_{90}

[1] Gootz TD. 1986. Preclinical Summary CP-65,207. A Broad-Spectrum Penem Antibiotic. Department of Immunology and Infectious Diseases. Pfizer Inc.

values are one doubling dilution higher for FQ-R isolates compared to FQ-S isolates. The sulopenem MIC distribution is shown in Figure 1.

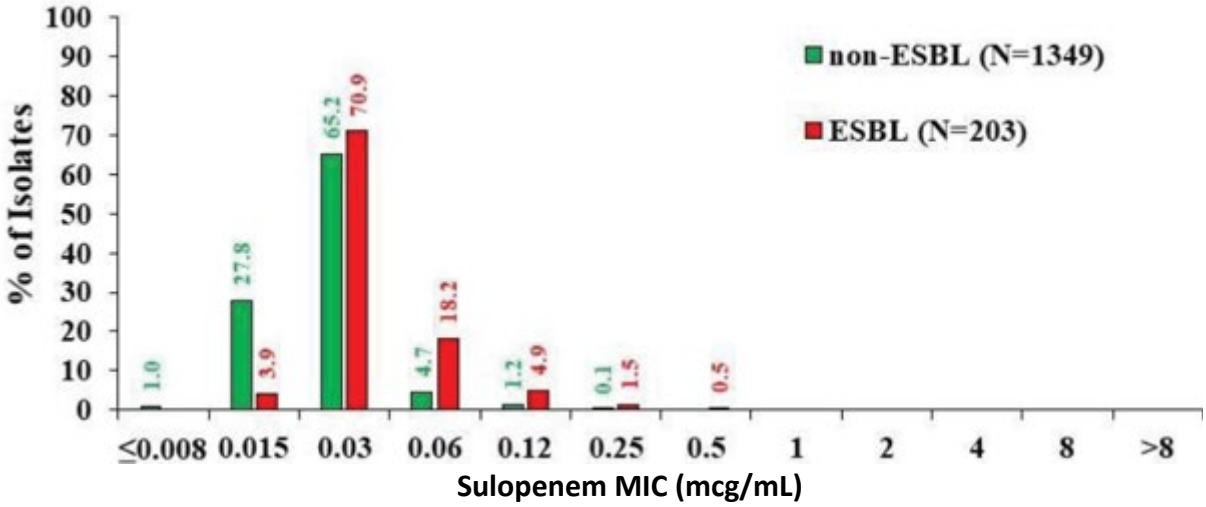
Figure 1. Sulopenem MIC Distribution Against FQ-S and FQ-R *E. coli*



Source: NDA submission.
Abbreviations: FQ-S, fluoroquinolone-susceptible, FQ-R, fluoroquinolone-resistant; MIC, minimum inhibitory concentration

Based on phenotypic ESBL screening (ceftriaxone MIC values ≥2 mcg/mL), sulopenem MIC distribution against non-ESBL and ESBL isolates of *E. coli* were similar (Figure 2). Sulopenem had an $MIC_{50}/_{90}$ value of 0.03/0.03 mcg/mL against non-ESBL isolates compared to 0.03/0.06 mcg/mL for ESBL isolates.

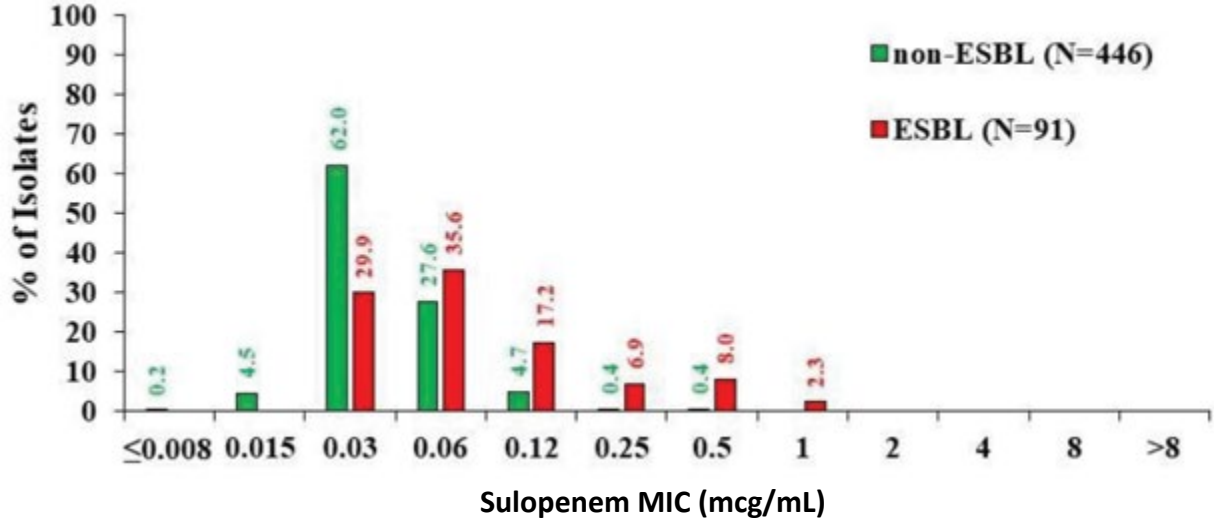
Figure 2. Sulopenem MIC Distribution Against Non-ESBL and ESBL *E. coli*



Source: NDA submission.
Abbreviations: ESBL, extended spectrum beta-lactamase screen-positive by ceftriaxone MIC; non-ESBL, ESBL screen-negative by ceftriaxone MIC; MIC, minimum inhibitory concentration

Against non-ESBL *K. pneumoniae* isolates (N=446), sulopenem had $MIC_{50/90}$ values of 0.03/0.06 mcg/mL compared to 0.06/0.5 mcg/mL for ESBL isolates (N=91). The sulopenem MIC distribution against non-ESBL and ESBL isolates is shown in Figure 3.

Figure 3. Sulopenem MIC Distribution Against Non-ESBL and ESBL *K. pneumoniae*



Source: NDA submission.
Abbreviations: ESBL, extended spectrum beta-lactamase screen-positive by ceftriaxone MIC; non-ESBL, ESBL screen-negative by ceftriaxone MIC; MIC, minimum inhibitory concentration

Sulopenem had very poor to no activity against carbapenem-resistant Enterobacterales (CRE) isolates with known carbapenemases. Sulopenem $MIC_{50/90}$ value of ≥16/>16 mcg/mL was observed for CRE isolates expressing carbapenemases such as IMP (N=50), KPC (N=50), NDM (N=50), VIM (N=50), and OXA (N=50), compared to 1.0/4.0 mcg/mL for non-carbapenemase-producing CRE isolates (N=50).

Sulopenem Activity Against AmpC and ESBL Isolates With Known β-Lactamase (*bla*) Genes

A total of 336 phenotypically resistant baseline uUTI isolates from Trials 301 and 310 were further analyzed by multiplex PCR to screen for *bla* genes encoding ESBLs, AmpC β-lactamases, and carbapenemases. Table 39 and Table 40 summarize the clinical and microbiological response to sulopenem in AmpC- and predominant ESBL-producing isolates in Trials 301 and 310, respectively. Against 208 AmpC and ESBL isolates in Trial 301, sulopenem had $MIC_{50/90}$ values of 0.06/0.12, 0.03/0.06, and 0.03/0.06 mcg/mL against predominant AmpC (n=12), CTX-M (n=105), and TEM-OSBL (n=38) genotypes, respectively. The clinical responses were 33.3%, 66.7%, and 63.2% and microbiological responses were 50%, 49.5%, and 50% against AmpC, CTX-M, and TEM-OSBL, respectively. Similarly, against 128 AmpC- and ESBL-producing isolates in Trial 310, sulopenem $MIC_{50/90}$ values were 0.06/0.12, 0.03/0.06, 0.03/0.06 mcg/mL against predominant AmpC (n=14), CTX-M (n=78), and TEM-OSBL (n=22) genotypes, respectively. Against AmpC, CTX-M, and TEM-OSBL, the clinical responses were 71.4%, 84.6%, and 72.7% and the microbiological responses were 85.7%, 62.8%, and 50%, respectively. Among all ESBL genotypes, CTX-M-15 was the most frequently identified from 107/336 (31.8%) baseline ESBL-producing isolates.

Table 39. Clinical and Microbiological Response to Sulopenem in AmpC and Predominant ESBL-Producing Isolates at TOC (Micro-MITT population; Trial 301)

Pathogen	*bla* Type	Total Isolates	MIC Range (mcg/mL)	MIC_{50}/MIC_{90} (mcg/mL)	Clinical Response n/N (%)	Microbiological Response n/N (%)
E. coli	AmpC	12	0.03-1.0	0.06/0.12	4/12 (33.3)	6/12 (50)
	CTX-M	105	≤0.008-1.0	0.03/0.06	70/105 (66.7)	52/105 (49.5)
	TEM-OSBL	38	0.015-0.25	0.03/0.06	24/38 (63.2)	19/38 (50)
K. pneumoniae	CTX-M	14	0.03-0.5	0.12/0.5	12/14 (85.7)	9/14 (64.3)
	OXA-48	3	4-8		2/3 (66.7)	2/3 (66.7)
	SHV	19	0.03-8	0.12/4	16/19 (84.2)	13/19 (68.4)
	TEM-OSBL	11	0.03-0.5	0.06/0.5	10/11 (90.9)	7/11 (63.6)

Source: NDA submission.

Table 40. Clinical and Microbiological Response to Sulopenem in AmpC and Predominant ESBL-Producing Isolates at TOC (Micro-MITT Population; Trial 310)

Pathogen	*bla* Type	Total Isolates	MIC Range (mcg/mL)	MIC_{50}/MIC_{90} (mcg/mL)	Clinical Response n/N (%)	Microbiological Response n/N (%)
E. coli	AmpC	14	0.03-0.25	0.06/0.12	10/14 (71.4)	12/14 (85.7)
	CTX-M	78	0.015-0.25	0.03/0.06	66/78 (84.6)	49/78 (62.8)
	TEM-OSBL	22	0.015-0.12	0.03/0.06	16/22 (72.7)	11/22 (50)
K. pneumoniae	AmpC	1	0.06-0.06		0/1 (0)	1/1 (100)
	CTX-M	2	0.06-0.25		1/2 (50)	1/2 (50)
	SHV-OSBL	3	0.06-0.25		1/3 (33.3)	2/3 (66.7)
	TEM-OSBL	1	0.06-0.06		1/1 (100)	1/1 (100)
P. mirabilis	CTX-M	2	0.25-0.5		2/2 (100)	2/2 (100)
	TEM-OSBL	2	0.25-0.5		2/2 (100)	2/2 (100)

Source: NDA submission.

3.1.4 Clinical Pharmacology Assessment

Studies and Analyses to Support a uUTI Indication

PK/PD Index and Target Determination Based on Nonclinical Studies and Probability of Target Attainment (PTA) Analyses

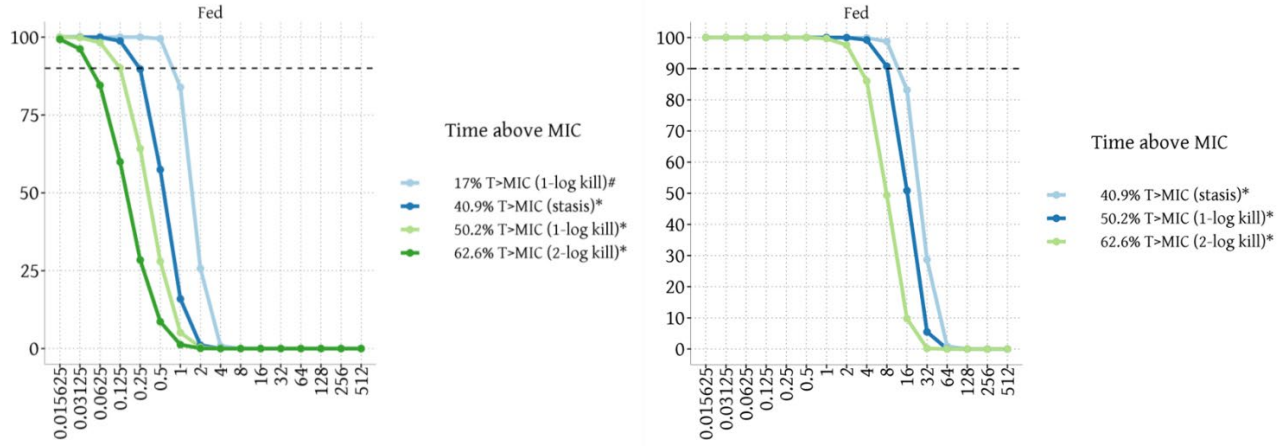
In antibacterial drug development, PTA analyses are conducted to evaluate the probability of achieving the PK/PD target (determined in nonclinical infection models) relevant to efficacy based on: 1) the exposures associated with a drug's dosing regimen, and 2) microbiology data (i.e., MIC distribution for relevant pathogens). For uUTI, the lack of an established nonclinical model leads to uncertainties regarding the relevance of traditional PK/PD indices and the bacteriologic endpoint that best correlates with efficacy. Furthermore, while urinary drug concentrations are important to the successful treatment of uUTIs, the role of plasma drug concentrations in supporting efficacy is unclear. Given these uncertainties, the role of PTA analysis in predicting clinical efficacy is limited.

The Applicant conducted PTA analyses for both plasma and urinary drug concentrations using PK/PD targets derived from a murine thigh infection model and in vitro 1-compartment infection model to support the proposed dosage of 500 mg sulopenem etzadroxil/500 mg probenecid twice daily, and to support a cutoff value of 0.5 mcg/mL for Enterobacterales susceptibility. Studies in the murine thigh

infection model were unable to delineate the PK/PD index that best correlates with sulopenem's antibacterial activity. In the in vitro infection model, the percentage of the dosing interval that free-drug concentrations exceed the MIC (i.e., % *f*T > MIC) best correlated with sulopenem's activity based on a coefficient of determination (r^2) of 0.90, followed closely by the ratio of free sulopenem peak concentration to MIC (i.e., fC_{max}/MIC), which had an r^2 value of 0.89. Given that traditionally, % *f*T > MIC is the PK/PD index that best correlates with the efficacy of beta-lactams, subsequent studies focused on determining % *f*T > MIC targets for PTA analyses. Due to deficiencies in the murine thigh infection model study design and limited interpretability of the findings, the resulting targets (i.e., 16.6 and 20.3 for stasis and 1-log kill, respectively) were unreliable to guide dose selection. The in vitro 1-compartment model did not account for bladder tissue architecture or the complexities of urodynamics, thus it is unclear whether the derived targets are reasonable surrogates for the relevant infection site. Nonetheless, PTA based on the in vitro targets of 39.6, 50.4, and 65.9 for stasis, 1-log kill, and 2-log kill, respectively, which numerically offered a more conservative appraisal of efficacy than those determined in the murine thigh infection model, were prioritized by the FDA review team.

The proposed dosage is to be administered with food to improve the bioavailability and tolerability of the 500 mg sulopenem etzadroxil/500 mg probenecid bilayer tablet, therefore discussion of PTA is limited to the findings under fed conditions. Nonetheless, in all instances, results were either comparable or a single-fold dilution lower under fasted conditions. PTA results showed that the free plasma concentrations associated with the Applicant's proposed dose regimen resulted in achievement of the in vitro targets in ≥90% of simulated subjects at MICs ranging from 0.031 to 0.25 mcg/mL (Figure 4). The Applicant also evaluated the probability of achieving PK/PD targets in urine by simulating 1 h and 2 h bladder voiding patterns. Given that the outcome of the analyses for the different voiding patterns were either comparable or within a single-fold dilution, only the results for a 2 h voiding pattern are provided in Figure 4. Using the urine concentrations associated with the Applicant's proposed dose regimen, PTA showed achievement of the in vitro targets in ≥90% of simulated subjects at MICs ranging from 2 to 8 mcg/mL.

Figure 4. Results of Probability of Target Attainment Analyses for Plasma (Left) and Urine (Right)

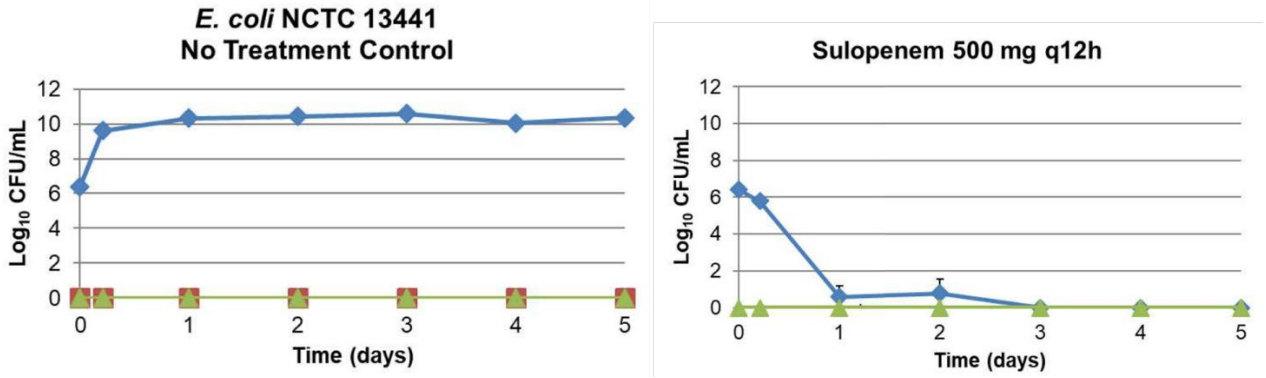


Source: Adapted from Figures 32 and 34 of Applicant's Population PK Report.
Abbreviations: MIC, minimum inhibitory concentration; PK, pharmacokinetics

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

To further support the proposed dosage of 500 mg sulopenem etzadroxil/500 mg probenecid twice daily for the treatment of uUTI, the Applicant evaluated the bactericidal activity of urinary concentrations associated with the proposed dosage regimen. The simulated urinary concentrations were demonstrated to suppress the growth of four *E. coli* isolates (with sulopenem MIC values ranging from 0.03 to 0.5 mcg/mL) and prevent the development of resistance for the entire duration of a 5-day study in a hollow-fiber infection model (Figure 5).

Figure 5. Results of Hollow-Fiber Infection Model Studies for No-Treatment Control (Left) and Sulopenem (Right)



Source: Figure 22 of Applicant's ICPD 00671 Report In Vitro Pharmacokinetics and Pharmacodynamics of Sulopenem.
Abbreviations: 4×MEM MIC, drug-resistant population grown on drug plates containing 4× the meropenem MIC; 4×SLP MIC, drug-resistant population grown on drug plates containing 4× the sulopenem MIC; MIC, minimum inhibitory concentration; q12h, every 12 h

Despite the aforementioned limitations (i.e., uncertainties regarding the relevant bacteriologic endpoint for an uUTI indication and the complexities of sulopenem's PK/PD behavior), collectively, information from the nonclinical PK/PD studies and PTA analyses lend supportive evidence for the efficacy of the proposed dosage for the treatment of uUTI. The results of these studies alone cannot discern whether the proposed dosage of sulopenem etzadroxil is fully optimized nor predict sulopenem's performance against different comparators in an efficacy trial. Differences in PK/PD attributes between sulopenem and different comparators such as antibacterial killing mechanism, elimination half-life, post antibiotic effect, and tissue penetration may also provide context for the observed uUTI trial outcomes. For example, sulopenem etzadroxil was noninferior to amoxicillin/clavulanate (which shares a similarly short plasma half-life of ~1 h with sulopenem). In contrast, it achieved mixed results when compared against ciprofloxacin, which has a longer plasma half-life of 4 h and thus potentially a longer duration of target engagement at the infection site.

Effects of Probenecid and Renal Impairment on Efficacy

There is a theoretical concern for loss of clinical efficacy in the treatment of uUTI due to the reduction in sulopenem urine excretion observed with the use of probenecid and in the setting of renal impairment. It was observed that 500 mg probenecid increased sulopenem plasma AUC_{τ} by 1.8-fold with a corresponding 1.9-fold reduction in renal clearance as summarized in Table 41. Nonetheless, the cumulative amount of sulopenem recovered in urine over a 24 h period was comparable in the presence and absence of probenecid. Given the existing uncertainties regarding the PK/PD parameters that best characterize sulopenem's bactericidal activity in urine, the impact of probenecid on efficacy is inconclusive.

Table 41. Effect of Probenecid on the Pharmacokinetics of Sulopenem

Agent(s)	Mean±SD Plasma AUC_τ (mcg/mL)	Mean±SD Renal Clearance (L/h)	Mean±SD Cumulative Urinary Recovery (mcg)
Sulopenem etzadroxil	3.80±0.90	18.98±3.04	68.23±17.61
Sulopenem etzadroxil with probenecid	6.83±1.9	9.91±2.53	64.76±10.41

Source: Adapted from Tables 14.2.3.2, 14.2.4.1 and 14.2.4.2 of Applicant's Individual Study Report IT001-101.
Abbreviations: AUC, area under the curve; SD, standard deviation

In a similar fashion, mild (CrCL 60 to <90 mL/min), moderate (CrCL 30 to <60 mL/min) and severe renal impairment (CrCL <30 mL/min to 15 mL/min) decreased sulopenem renal clearance while maintaining a similar 24 h urinary recovery as subjects with normal renal function (Table 42). In Trial 301, overall response at the TOC visit was lower in subjects with CrCL <60 mL/min compared to those with CrCL ≥60 mL/min. However, in Trial 310, overall response was comparable for subjects with CrCL above and below this threshold (Table 42). Of note, CrCL <60 mL/min was not a pre-specified criterion for treatment group randomization, and thus, other confounders may have contributed to the observed outcomes in Trial 301. Therefore, the totality of information is inconclusive on the effect of renal impairment on sulopenem's efficacy in the treatment of uUTI.

Table 42. Overall Response at TOC by CrCL in the Micro-MITT Population

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

Source: Table 60 of the Applicant's Individual Study Report IT001-310 and Statistical Reviewer's analysis.
Abbreviations: CrCL, creatinine clearance; micro-MITT, microbiological modified intent-to-treat; TOC, test of cure

Safety of Sulopenem in Subjects With Renal Impairment

Compared to subjects with normal renal function, sulopenem plasma AUC_{inf} increased 2.0-, 3.0- and 7.4-fold in subjects with mild, moderate and severe renal impairment, respectively, following administration of 1000 mg dose of sulopenem etzadroxil. Given that sulopenem exhibits dose proportionality within the dose range of 400 to 2000 mg, similar fold increases in AUC are anticipated for the Applicant's proposed 500 mg dose of sulopenem etzadroxil. According to the probenecid prescribing information (USPI), its activity as an OAT3 inhibitor diminishes with declining renal function. Consequently, concomitant administration of probenecid and sulopenem extazdroxil is not expected to increase sulopenem exposure to a significant extent in the setting of renal impairment, especially in the setting of severe impairment. In the dedicated renal impairment study as well as in Trials 301 and 310, renal impairment was not associated with an increased incidence of treatment-emergent adverse events. Given these observations, sulopenem's short plasma half-life of 1.2 h and the 5-day proposed duration of therapy, 500 mg sulopenem etzadroxil/500 mg probenecid twice daily for 5 days is expected to be safe in patients with mild, moderate and severe renal impairment. However, the drug's use is not recommended in patients with CrCL <15 mL/min or those on hemodialysis due to the lack of pharmacokinetic data and established safety in this subpopulation.

Studies and Analyses to Support the cUTI Indication

The dosage selected for the cUTI trial (Trial 302), i.e., 1000 mg sulopenem administered as a 3 h IV infusion for at least 5 days, with the option for oral stepdown therapy with 500 mg sulopenem etzadroxil/500 mg probenecid twice daily for a total of 7 to 10 days of treatment was informed by the results of the Applicant's PTA analysis. The PK/PD targets used in this analysis were the same targets derived from the murine thigh infection model described under the discussion of nonclinical studies conducted to support an uUTI indication. Given that deficiencies in the murine thigh infection model study design and limited interpretability of the study findings precluded their use to guide dose selection for the treatment of uUTI, the FDA review team also concluded that the results of these studies could not reliably inform dose selection for the treatment of cUTI. Nonetheless, there is uncertainty regarding the adequacy of the sulopenem etzadroxil/probenecid oral stepdown regimen used in Trial 302. Specifically, the sulopenem etzadroxil/probenecid bilayer tablet has an absolute bioavailability of 40% to 63% and thus the 500 mg sulopenem etzadroxil/500 mg probenecid twice daily regimen provides lower systemic exposures than the 1000 mg IV sulopenem daily dosage.

3.2 Safety Issues

3.2.1 Sources of Data for Safety

During the course of the development program, a total of 4968 subjects received sulopenem including 1932 subjects who received oral sulopenem etzadroxil/probenecid in two uUTI trials and 1030 subjects who received IV sulopenem followed by the oral formulation in the phase 3 cUTI (695 subjects) and cIAI trials (335 subjects). The Applicant and Pfizer (the original owner) conducted 24 phase 1 and 2 studies with IV and oral formulations of sulopenem in which a total of 2006 subjects were exposed to sulopenem.

During the initial review cycle for NDA 213972, the primary safety analysis was conducted on data derived from Trial 301 with additional analyses conducted on the combined phase 3 study population which included safety data from Trials 301, 302, and 303. The phase 1 and 2 studies were evaluated at that time and did not provide significant additional safety data.

During the current review cycle, safety analyses were conducted on data derived from Trial 310 and the combined phase 3 uUTI study population which included safety data from Trials 301 and 310. This integrated safety dataset consisting of 1932 subjects will be the primary focus of the safety analysis discussed below. Eight subjects from the sulopenem etzadroxil/probenecid arm and five subjects from the ciprofloxacin arm of Trial 301 were removed from the Agency's safety database as source records from Site 218 could not be confirmed.

As shown in Table 43, the median duration of sulopenem etzadroxil/probenecid treatment in Trials 301 and 310 was 5 days.

Table 43. Duration of Treatment, Safety Population, Trials 301 and 310

Parameter	Sulopenem N=1932	Amox/Clav N=1107	Cipro N=822
Duration of treatment, days			
Mean (SD)	5.2 (0.8)	5.2 (0.8)	3.2 (0.5)
Median (Q1, Q3)	5 (5, 6)	5 (5, 6)	3 (3, 4)
Min, max	1, 8	1, 10	1, 6
Total exposure (person years)	27	16	7

Parameter	Sulopenem N=1932	Amox/Clav N=1107	Cipro N=822
Patients treated, by duration, n (%)			
<1 days	0	0	0
≥1 to <4 days	48 (2.5)	27 (2.4)	606 (73.7)
≥4 to <7 days	1877 (97.2)	1075 (97.1)	216 (26.3)
≥7 days	7 (0.4)	5 (0.5)	0

Source: adsl.xpt; software, R.

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

Abbreviations: Amox, amoxicillin; cipro, ciprofloxacin; clav, clavulanate; N, number of subjects in treatment arm; n, number of subjects with given treatment duration; Q1, first quartile; Q3, third quartile; SD, standard deviation; sulopenem, sulopenem etzadroxil/probenecid

In Trial 302, the median total duration of treatment (IV and oral) was 10 days in each treatment arm of which the median duration of oral treatment was 4 days. In Trial 303, the median total duration of treatment (IV and oral) was 9 days in each treatment arm of which the median duration of oral treatment was 3 days.

3.2.2 Safety Summary

As described in Section 3.2.1, the safety database is considered adequate. There were no unexpected safety signals identified in the sulopenem development program. AEs identified in the phase 1 studies included diarrhea, nausea, abdominal pain, headache, dizziness, rash, and abnormal urine odor. Additionally, one subject in phase 1 who received oral sulopenem etzadroxil/probenecid experienced angioedema of the face and lips and discontinued study drug. Treatment-emergent adverse events (TEAEs) from Trials 301, 302, and 303 during the initial review cycle of NDA 213972 included angioedema in one subject in Trial 301, elevated alanine aminotransferase (ALT) (generally less than 5× the upper limit of normal [ULN]), and gastrointestinal adverse reactions. There was one death in the sulopenem etzadroxil/probenecid arm of Trial 301 and six deaths in the sulopenem arms of Trials 302 and 303 (Table 44); none was considered to be related to sulopenem.

Table 44. Deaths in the Sulopenem Safety Population of Trials 301, 302, and 303

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

Source: Reviewer table.

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

The review team concluded that the known risks of sulopenem etzadroxil/probenecid could likely be managed by appropriate labeling.

With the NDA resubmission, an additional 1107 subjects from Trial 310 were added to the safety database for the proposed sulopenem etzadroxil/probenecid dose and indication. There were no deaths and no SAEs in Trial 310 and the most common TEAEs included diarrhea, nausea, vomiting, vulvovaginal

mycotic infection headache, and gastroesophageal reflux disease, mostly of mild to moderate severity consistent with prior studies.

Probenecid has been in use since the 1950s and is generally well-tolerated with a favorable safety profile. Labeled warnings and precautions for probenecid include exacerbation of gout, increased plasma concentration of methotrexate with concomitant use, severe allergic reactions including anaphylaxis, hematuria, renal colic, costovertebral pain, formation of uric acid stones, and antagonism of the uricosuric action of probenecid with use of salicylates. Adverse reactions observed with probenecid include headache, dizziness, precipitation of acute gouty arthritis, hepatic necrosis, nausea, vomiting, anorexia, sore gums, genitourinary adverse events including uric acid stones and nephrotic syndrome, hypersensitivity reactions, aplastic anemia, leukopenia, hemolytic anemia, dermatitis, alopecia, and flushing. No adverse event in Trial 301 or 310 was specifically attributable to probenecid.

Overview of Treatment-Emergent Adverse Events

The single death in the phase 3 uUTI trials (Trials 301 and 310) occurred in a patient with underlying lung cancer in Trial 301 and was not related to study drug. Serious adverse events (SAE) occurred in six (0.3%) subjects in the combined sulopenem etzadroxil/probenecid arm, and all were from Trial 301. One SAE, angioedema, was judged to be related to sulopenem etzadroxil/probenecid and led to treatment discontinuation. The other SAEs included pyelonephritis, chest pain, small intestinal obstruction, lung adenocarcinoma and presyncope—all (except lung adenocarcinoma) started on or after Day 15 from initial receipt of sulopenem etzadroxil/probenecid and were thought to be unrelated to study drug. TEAEs resulting in treatment discontinuation were reported in 21 (1.1%) subjects in the combined sulopenem etzadroxil/probenecid group with the majority being gastrointestinal AEs, including diarrhea, nausea, vomiting, abdominal pain, and gastroesophageal reflux disease. No TEAE necessitated dose modification of either study drug or comparator. The overall incidence of TEAEs was higher (21.5%) in the sulopenem etzadroxil/probenecid group than in the comparator groups (amoxicillin/clavulanate, 12.3%; ciprofloxacin, 14.0%). In all three treatment groups, the majority of TEAEs were mild or moderate (Table 45).

Table 45. Overview of Adverse Events, Safety Population, Trials 301 and 310

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

Source: adae.xpt; software, R.

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

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

Severity as assessed by the investigator.

Abbreviations: AE, adverse event; amox, amoxicillin; cipro, ciprofloxacin; clav, clavulanate; N, number of patients in treatment arm; n, number of patients with at least one event; SAE, serious adverse event; sulopenem, sulopenem etzadroxil/probenecid

In both Trial 301 and Trial 310, diarrhea was the most common AE, occurring in 10% of subjects in the combined sulopenem etzadroxil/probenecid arm, and was the largest contributor to the imbalance in AE occurrence between the sulopenem etzadroxil/probenecid and comparator arms. Diarrhea was monitored as an adverse event of special interest (AESI) during the clinical development program. While most diarrhea events were mild in severity, there were three cases of severe diarrhea in Trial 310, though none resulted in discontinuation of study treatment nor required specific therapy. Discontinuations of sulopenem etzadroxil/probenecid due to diarrhea were rare, occurring in 0.3% of sulopenem-treated subjects in Trials 301 and 310 combined. No SAEs were attributed to diarrhea in either trial, and there were no cases of *Clostridiodes difficile* infection in the sulopenem etzadroxil/probenecid arms of Trials 301 and 310.

The most common AEs occurring in more than 0.5% of subjects receiving sulopenem etzadroxil/probenecid are shown in Table 46; aside from diarrhea, these AEs include nausea (4.1%), vulvovaginal mycotic infection (2.4%), headache (2.2%), vomiting (1.5%) and abdominal pain (1.1%). Other common AEs in subjects treated with sulopenem etzadroxil/probenecid included gastroesophageal reflux disease (0.7%), abnormal urine odor (0.6%), and dizziness (0.6%).

Table 46. Adverse Events Occurring at >0.5% Frequency in Subjects Receiving Sulopenem Etzadroxil/Probenecid, Safety Population, Trials 301 and 310

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

Source: adae.xpt; software, R.

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

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

Coded as MedDRA preferred terms.

The PT diarrhea includes the PTs of diarrhea and loose stools; the PT vulvovaginal mycotic infection includes vulvovaginal mycotic infection, vulvovaginal candidiasis, vaginal infection, fungal infection, genital infection fungal and *Candida* infection; the PT abdominal pain includes abdominal pain, abdominal pain lower, abdominal pain upper and abdominal discomfort.

Abbreviations: AE, adverse event; amox, amoxicillin; cipro, ciprofloxacin; clav, clavulanate; MedDRA, Medical Dictionary for Regulatory Activities; N, number of patients in treatment arm; n, number of patients with adverse event; PT, preferred term; sulopenem, sulopenem etzadroxil/probenecid

Elevations in ALT

During the initial review cycle, an imbalance was noted in peak postbaseline elevations of ALT (generally less than 5× ULN) in Trials 301, 302, and 303, with more subjects in the sulopenem arm having an elevated ALT compared to the comparator arms. A similar imbalance was not seen for aspartate aminotransferase (AST) values.

Table 47 shows the number of subjects with peak postbaseline ALT elevations in the integrated phase 3 uUTI trial dataset. Slightly more subjects in the sulopenem etzadroxil/probenecid arm had ALT elevations between ≥2× ULN to <5× ULN. There were no Hy's Law cases in the sulopenem etzadroxil/probenecid arm of either Trial 301 or Trial 310. Three (0.3%) subjects in the amoxicillin/clavulanate arm compared to one (0.1%) subject in the sulopenem etzadroxil/probenecid arm had ALT elevations between 5× ULN to <10× ULN.

Table 47. Peak Postbaseline ALT Elevations, Safety Population, Trials 301 and 310

ALT Postbaseline	Sulopenem N=1932 n/N_w (%)	Amox/Clav N=1107 n/N_w (%)	Cipro N=822 n/N_w (%)
≤ULN	1799/1867 (96.4)	1032/1060 (97.4)	769/797 (96.5)
>ULN to <2× ULN	52/1867 (2.8)	22/1060 (2.1)	27/797 (3.4)
≥2× ULN to <3× ULN	9/1867 (0.5)	2/1060 (0.2)	0/797 (0)
≥3× ULN to <5× ULN	6/1867 (0.3)	1/1060 (0.1)	1/797 (0.1)
≥5× ULN to <10× ULN	1/1867 (0.1)	3/1060 (0.3)	0/797 (0)

Source: adlb.xpt; software, R.

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

Abbreviations: ALT, alanine aminotransferase, amox, amoxicillin; ALT, alanine aminotransferase; cipro, ciprofloxacin; clav, clavulanate; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w number of patients with data; sulopenem, sulopenem etzadroxil/probenecid ULN, upper limit of normal

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

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

In the integrated analysis of the entire phase 3 population (Trials 301, 302, 303, and 310), 31 (1.1%) subjects in the sulopenem group had at least one postbaseline ALT elevation >3× ULN compared to 19 (0.7%) subjects in the comparator group. In the sulopenem group, nine (0.3%) subjects and one (<0.1) subject had ALT levels of >5× ULN and >10× ULN, respectively. Of these subjects, one was in Trial 301 as described above and eight subjects were in Trials 302 and 303.

On review of the narratives of these eight subjects, attribution of causality to sulopenem is confounded by the subjects' underlying medical conditions and/or concomitant medications. One subject in Trial 302 with schizoaffective disorder on valproic acid had normal AST, ALT and bilirubin values at baseline but met criteria for Hy's Law after completing 5 days of IV sulopenem with an ALT of 269 U/L, AST of 313 U/L and total bilirubin of 2.8 mg/dL. However, study drug was continued and the subject was switched to oral sulopenem etzadroxil/probenecid on Days 6 and 7 with normalization in liver enzymes by Day 10. Penem antibacterial drugs are known to be associated with decreased valproic acid levels (which were noted in this subject). While IV sulopenem may have caused elevated liver enzymes in this patient, the abnormalities resolved while on study drug.

3.3 Risk Mitigation

Based on the safety review to date, it appears that the identified safety risks for sulopenem etzadroxil/probenecid may be adequately mitigated through labeling and further evaluated during routine pharmacovigilance. Because there is concern that oral sulopenem etzadroxil/probenecid may be used off-label for treatment of cUTI or as stepdown therapy after IV antibacterial treatment of cUTI, the review team anticipates language in the labeling to mitigate the risk of off-label use. No additional risk mitigation strategies are anticipated at this time.

4 Benefit-Risk Framework

Benefit-Risk Framework

Disclaimer: This predecisional Benefit-Risk Framework does not represent the FDA's final benefit-risk assessment or regulatory decision.

	Evidence and Uncertainties	Comments to the Advisory Committee
Analysis of Condition	uUTI are the most common bacterial infections in the ambulatory setting in the United States and occur most commonly in women with an anatomically normal urinary tract and no risk factors for cUTI. Common symptoms include urinary frequency, urinary urgency, burning on micturition and suprapubic pain. *E. coli* accounts for 75-95% of uUTI. Treatment is often empiric, and a urine culture is not recommended unless there are complicating factors. AMR among urinary isolates is increasing across the U.S., including production of ESBL.	uUTIs are very common, especially in women and treatment is often empiric though AMR among urinary isolates is increasing in the United States.
Current Treatment Options	First-line treatment includes nitrofurantoin, TMP-SMX, fosfomycin and pivmecillinam. Alternative drugs include β-lactams such as amoxicillin, amoxicillin/clavulanate or oral cephalosporins. Quinolones are no longer recommended as first-line treatment for uUTI due to safety concerns. uUTI due to resistant organisms, such as ESBL-producers, may require intravenous carbapenem treatment necessitating IV line placement and potentially hospitalization.	Several oral antibacterial drugs are FDA-approved for treatment of uUTI, but their use can be limited by adverse events or increasing antimicrobial resistance. uUTI due to resistant strains of Enterobacterales may require treatment with IV antibacterial drug therapy.
Benefits	In Trial 301, sulopenem etzadroxil/probenecid was superior to ciprofloxacin in the micro-MITTR (ciprofloxacin-resistant) population but inferior in the MITT and micro-MITTS (ciprofloxacin-susceptible) populations. In Trial 310, sulopenem etzadroxil/probenecid was noninferior to amoxicillin/clavulanate in the MITT and noninferior and superior in the micro-MITTS populations; however, the sample size in the micro-MITTR population in Trial 310 was too small (N=67) to allow definitive conclusions.	Although the two phase 3 uUTI trials had different comparators and efficacy was shown in discordant populations, they provide evidence of benefit. **Point to consider:** Is the overall benefit-risk assessment favorable for the use of sulopenem etzadroxil/probenecid for the treatment of adult woman with uUTI?
Risks and Risk Management	Trial 302 for IV/PO sulopenem for cUTI failed to meet its primary endpoint. Data from this trial do not support the use of sulopenem as stepdown therapy following IV treatment with a different drug. A total of 4968 subjects have been exposed to sulopenem IV and/or sulopenem etzadroxil/probenecid across its development with 1932 subjects exposed to sulopenem etzadroxil/probenecid for the uUTI indication. No serious and unexpected safety signals were observed, although hypersensitivity and mild elevation of liver enzymes were seen in a small	**Point to consider**: The efficacy of oral sulopenem etzadroxil/probenecid as stepdown therapy following IV therapy of cUTI has not been established. If approved, communication to medical providers of the lack of efficacy of oral sulopenem etzadroxil/probenecid as stepdown therapy for cUTI will be important.

	Evidence and Uncertainties	Comments to the Advisory Committee
	proportion of patients. Common adverse events occurring in more than 1% of subjects in the uUTI trials included diarrhea (10.0%), nausea (4.1%), vulvovaginal mycotic infection (2.4%), headache (2.2%), vomiting (1.5%), and abdominal pain (1.1%). Empiric use of sulopenem etzadroxil/probenecid, an oral penem, could result in inappropriate and/or extensive use and consequently contribute to AMR via cross-resistance with carbapenems.	Sulopenem etzadroxil/probenecid appears to have a reasonable safety profile with adverse effects that can be mitigated through labeling. Careful antimicrobial stewardship and consideration by guidelines committees are needed to ensure appropriate positioning of sulopenem etzadroxil/probenecid in the hierarchy of treatment options for uUTI.

Abbreviations: AMR, antimicrobial resistance; uUTI, uncomplicated urinary tract infection; cUTI, complicated urinary tract infection; TMP-SMX, trimethoprim-sulfamethoxazole; ESBL, extended-spectrum β-lactamase; IV, intravenous; micro-MITTR, microbiological modified intent-to-treat resistant; micro-MITTS, microbiological modified intent-to-treat susceptible; MITT, modified intent-to-treat; PO, per oral

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6 Appendix

6.1 Efficacy

6.1.1 Trial 301 and Trial 310

Trial 301 Inclusion and Exclusion Criteria

Inclusion criteria were as follows:

1. Female patients ≥18 years of age with ≥24 h and ≤96 h of urinary symptoms attributable to a urinary tract infection
2. Two or more of the following signs and symptoms of uUTI: urinary frequency, urinary urgency, pain or burning on micturition, suprapubic pain
3. A midstream urine specimen with:
   a. A machine-read dipstick positive for nitrite AND from the same specimen
   b. Evidence of pyuria as defined as either:
      i. A machine-read dipstick positive for leukocyte esterase OR
      ii. At least 10 white blood cells (WBC)/mL on microscopic analysis of unspun urine OR
      iii. WBC count ≥10 cells/HPF in the sediment of a spun urine
4. Patient or the patient's legally acceptable representative able to provide a signed written informed consent prior to study enrollment

Exclusion criteria were as follows:

1. 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
2. Receipt of antibacterial drug therapy potentially effective as treatment of uUTI within the prior 7 days
3. Causative uropathogen for the presenting illness known to be resistant to a carbapenem
4. 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
5. Patients with ileal loops or urinary stoma
6. Patients with an indwelling urinary catheter in the previous 30 days
7. Patients with paraplegia
8. Patients who are likely to receive ongoing antibacterial drug prophylaxis after treatment of uUTI (e.g., patients with vesico-ureteral reflux)
9. Any history of trauma to the pelvis or urinary tract
10. Patient's urine culture results, if available at study entry, identify more than two microorganisms regardless of colony count or patient has a confirmed fungal UTI
11. Patient is receiving hemodialysis, hemofiltration, peritoneal dialysis, or had a renal transplant
12. Known history of creatinine clearance <50 mL/min as calculated by Cockcroft and Gault equation
13. Patient known to be immunocompromised as evidenced by any of the following:
    c. 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
    d. Neutropenia (defined as an absolute neutrophil count <1000 cells/mm^3)

e. Systemic or hematological malignancy requiring chemotherapeutic or radiation/immunologic interventions within 6 weeks prior to randomization or anticipated to begin prior to completion of the study
f. Immunosuppressive therapy, including maintenance corticosteroid therapy (>40 mg/day equivalent prednisolone for 5 days or more in the 30 days prior to randomization)

14. Patients known to have a history of liver disease as defined by the following laboratory criteria:
    a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3× upper limit of normal (ULN)
    b. Total bilirubin >2× ULN
15. Females of child-bearing potential who are unable to take adequate contraceptive precautions, have a positive pregnancy test result within 24 h prior to study entry, are otherwise known to be pregnant, or are currently breastfeeding
16. 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)
17. History of seizures
18. Patients with a history of blood dyscrasias
19. Patients with a history of uric acid kidney stones
20. Patients with acute gouty attack
21. Patients on chronic methotrexate therapy
22. Patients with a known history of myasthenia gravis
23. Patients who require concomitant administration of tizanidine or valproic acid
24. Patients with a history of allergy or hypersensitivity to carbapenems, β-lactams, quinolones, or probenecid, as formulated with their excipients
25. 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
26. The use of any other investigational drug in the 30 days prior to the first dose of study drug, or prior participation in any sulopenem clinical trial

Trial 310 Inclusion and Exclusion Criteria

Inclusion Criteria

Each patient had to meet the following criteria to be eligible for the study:

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

Exclusion Criteria

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

1. 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
2. Receipt of antibacterial drug therapy potentially effective as treatment of uUTI within the prior 7 days
3. 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.
4. Note: Patients could be included if these medications were previously taken and had ceased at the time of Screening onward.
5. Any anatomical abnormality of the urinary tract, including surgically modified urinary tract anatomy, and obstructive uropathy due to nephrolithiasis, stricture, tumor, or fibrosis
6. Ongoing urinary retention
7. Neurogenic bladder
8. Current resident of a long-term care facility
9. Instrumentation of urinary tract in the previous 30 days
10. An indwelling urinary catheter, ureteral stent or other foreign material in the urinary tract
11. Any history of trauma to the pelvis or urinary tract
12. Current urine culture, if available while evaluating eligibility, that was positive for more than two microorganisms regardless of colony count (contaminated), or confirmed a fungal UTI
13. Receiving hemodialysis, hemofiltration, peritoneal dialysis, or had a renal transplant
14. Immunocompromised as evidenced by any of the following:
    a. Known HIV positive, with either a recent (in the past 6 months) AIDS-defining condition or a $CD4^+$ T lymphocyte count <200/mm^3
    b. Known neutropenia (defined as absolute neutrophil count <1000 cells/mm^3)
    c. 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
    d. Immunosuppressive therapy, including maintenance corticosteroid therapy (>40 mg/day equivalent prednisolone for 5 days or more in the 30 days prior to randomization)
15. Known liver function abnormalities as defined by the following laboratory criteria:
    e. ALT or AST >3× ULN, and/or
    f. Total bilirubin >2× ULN
16. Females of child-bearing potential who were unable to take adequate contraceptive precautions (refer to IT001-310 Protocol Sections 4.4 and 4.5), had a positive pregnancy test result within 24 h of study entry, were otherwise known to be pregnant, or were currently breastfeeding
17. Poorly controlled diabetes mellitus, including the presence of ketoacidosis and hyperosmolar hyperglycemia
18. History of seizures
19. History of blood dyscrasias
20. History of uric acid kidney stones
21. Acute (current) gouty arthritis

22. Concomitant administration of valproic acid
23. History of allergy or hypersensitivity to carbapenems, β-lactams, or probenecid, as formulated with their excipients
24. Unlikely to survive the 4-week study period or had a rapidly progressive or terminal illness, including septic shock, associated with a high risk of mortality
25. The use of any other investigational drug in the 30 days prior to the first dose of study drug, or prior participation in any sulopenem clinical trial
26. Urine samples, including results from urine tests, collected as part of routine standard of care, prior to obtaining informed consent, may have been used to assess eligibility for enrollment into study and/or for baseline urine culture.

Trials 301 and 310: Secondary Efficacy Endpoints

Microbiologic Response

In the protocol, microbiological response was assessed using the definitions in Table 48.

Table 48. Definitions of Microbiological Response

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

Source: NDA submission.
For Trial 301, the definition was from the protocol before unblinded analysis.
Abbreviations: CFU, colony-forming unit; MIC, minimum inhibitory concentration

A per-pathogen microbiological success was defined as “eradication.” A pathogen microbiological failure was defined as “persistence” or “persistence with increasing minimum inhibitory concentration (MIC).”

A per-patient microbiological success was defined as “eradication” if all pathogens for a patient were eradicated. A per-patient microbiological failure of “persistence” or “persistence with increasing MIC” was based on the presence of one or more pathogens at that visit. Otherwise, the patient was considered “indeterminate.”

Patient-Determined Clinical Response

A patient was considered a clinical success at a given timepoint if the first three conditions in the definition of overall response were met. All other patients not meeting the success criteria were to be considered as failures unless data were unavailable to determine a success or failure. In this case, an indeterminate response was assigned. Deaths due to reasons other than the uUTI would also be considered as indeterminate responses.

- The patient received no rescue therapy for uUTI
  - If an antibiotic active against the urinary tract pathogen was given for other reasons, then the patient would be considered indeterminate

- The patient had resolution of the symptoms of uUTI present at trial entry and no new uUTI symptoms (based on the Patient Symptom Assessment Questionnaire)
    - Baseline symptoms associated with another known condition (e.g., overactive bladder) did not need to be resolved

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

Investigator Assessment of Clinical Response

In Trial 310, investigators used the definitions in Table 49 to document clinical response, irrespective of microbiologic findings.

Table 49. Definitions of Clinical Response

Response	Definition
Success	All pretherapy signs and symptoms of the index infection had resolved such that no additional antibiotics were required
Failure	Patients who met any one of the criteria below to be considered as failure: • Death related to uUTI prior to visit • Persistence or progression of any pre-therapy uUTI signs and symptoms or use of additional antibiotics for the current infection • Patient previously met criteria for failure and received rescue antibiotics
Indeterminate	Data not available for evaluation of efficacy for any reason, including but not limited to: • Patient lost to follow-up or assessment not undertaken such that a determination of clinical response could not be made at the visit • Death prior to study visit, where uUTI was clearly noncontributory

Source: NDA submission.
Abbreviation: uUTI, uncomplicated urinary tract infection

Trial 301 Timeline of Statistical Analysis Changes

The timeline of changes in the protocol and SAP, including changes after the unblinded interim analysis, are highlighted in Table 50.

Table 50. Timeline of Changes in Statistical Analysis in Trial 301

Date	Action
September 30, 2019	SAP version 1 submitted with two planned independent primary analyses in the micro-MITTR (superiority) and the micro-MITTS (non-inferiority) populations Definition of microbiological response: Eradication: Urine culture obtained at TOC demonstrates $<10^3$ CFU/mL of the baseline uropathogen. Persistence: The baseline uropathogen regardless of susceptibility grew at $\geq 10^3$ CFU/mL at TOC.

Date	Action
33% of subjects had outcome data	Planned blinded interim analysis (IA) 1 for micro-MITTS.
66% of subjects had outcome data	Planned blinded IA 2 for MMITTS. Applicant conducted a planned unblinded IA for MMITTR using Mehta-Pocock (conditional power). The plan was that if conditional power was <40%, hypothesis testing for superiority would not be conducted in the MMITTR population at the final analysis.
October 10, 2019	Results of the unblinded IA were presented to the Data Monitoring Committee (DMC) by the Applicant's unblinded statistician. Conditional power was 0.345 with the revised sample size due to sample size increase in the micro-MITTS population. FDA was unaware that the unblinded IA had been conducted.
October 29, 2019	The Applicant was informed by the DMC that the conditional power for MMITTR was below 40%. Thus, according to the SAP, the sample size calculation for superiority was not warranted.
December 20, 2019	Enrollment completed
March 25, 2020	SAP version 2 submitted (after the IA) with the following changes: • The statement "If the conditional power is <40%, the superiority hypothesis in the MMITTR population will not be tested at the end of the study" was replaced with "If the conditional power is <40%, no change to the sample size will be made." Microbiologic response criteria were changed by the addition of whole genome sequencing (WGS) so that if the identical pathogen based on WGS was not found at TOC, the baseline pathogen would be considered eradicated. • Addition of PCR for the gyrase mutation to determine assignment of subjects to the MMITTS or MMITTR populations. FDA did not agree with the addition of WGS and PCR to microbiologic response criteria due to the possibility that heteroresistant subpopulations of the same bacterial pathogen may be missed with molecular testing, and PCR for the gyrase mutation conferring quinolone resistance may overlook other chromosomal (*parC, parE*) or plasmid-mediated quinolone resistance genes. Further, there was concern for bias because these amendments were made after the unblinded IA. Thus, FDA's analysis of efficacy results utilized the original SAP and post-baseline growth in urine culture at $\geq 10^3$ CFU/mL of the same bacterial species present at baseline continued to be considered a microbiological failure.
June, 2020	Applicant notified FDA that Site 202 was removed from the efficacy analysis. FDA did not agree with the reasons for removal and included Site 202 in their efficacy analysis. Site 218 was removed from efficacy analysis due to concern for missing source documentation.

Abbreviations: CFU, colony-forming unit; CI, confidence interval; MMITTR: microbiological modified intent-to-treat-resistant; MMITTS: microbiological modified intent-to-treat-susceptible; SAP, statistical analysis plan; TOC, test of cure; IA, interim analysis; DMC, Data Monitoring Committee; WGS, whole genome sequencing; PCR, polymerase chain reaction; PFGE, pulse-field gel electrophoresis

Trial 310 Results

Distribution of Baseline Study Uropathogens by Antibacterial Drug Resistance

Distribution of baseline study uropathogens by antibacterial drug resistance in the micro-MITTS population for Trial 310 is shown in Table 51. A total of 8.9% of micro-MITTS subjects had at least one baseline Enterobacterales pathogen that was ESBL-positive, as determined by having a ceftriaxone MIC of >1 mcg/mL. A total of 13%, 30.7%, and 26.9% of subjects were non-susceptible to nitrofurantoin,

trimethoprim-sulfamethoxazole and quinolones, respectively. The distribution of susceptibility to the abovementioned antibacterial drugs was comparable (not nominally statistically significant) between the two treatment groups.

Table 51. Trial 310: Distribution of Pathogens by ESBL Status and Amoxicillin/Clavulanate, Quinolone, Trimethoprim-Sulfamethoxazole and Nitrofurantoin Susceptibility, Micro-MITTS Population

Parameter	Sulopenem (N=480) n (%)	Amoxicillin/ Clavulanate (N=442) n (%)	Total (N=922) n (%)
ESBL status			
Negative	443 (92.3)	397 (89.8)	840 (91.1)
Positive	37 (7.7)	45 (10.2)	82 (8.9)
Amoxicillin/clavulanate			
Susceptible	480 (100.0)	442 (100.0)	922 (100.0)
Nitrofurantoin			
Susceptible	416 (86.7)	386 (87.3)	802 (87.0)
Nonsusceptible	64 (13.3)	56 (12.7)	120 (13.0)
Trimethoprim-sulfamethoxazole			
Susceptible	331 (69.0)	308 (69.7)	639 (69.3)
Nonsusceptible	149 (31.0)	134 (30.3)	283 (30.7)
Quinolone			
Susceptible	360 (75.0)	314 (71.0)	674 (73.1)
Nonsusceptible	120 (25.0)	128 (29.0)	248 (26.9)
ESBL positive and quinolone nonsusceptible	33 (6.9)	40 (9.0)	73 (7.9)
ESBL positive, quinolone nonsusceptible, and trimethoprim-sulfamethoxazole nonsusceptible	24 (5.0)	29 (6.6)	53 (5.7)
ESBL positive, quinolone nonsusceptible, trimethoprim-sulfamethoxazole nonsusceptible, and nitrofurantoin nonsusceptible	4 (0.8)	1 (0.2)	5 (0.5)
β-Lactam nonsusceptible, quinolone nonsusceptible, trimethoprim-sulfamethoxazole nonsusceptible, and nitrofurantoin nonsusceptible	6 (1.3)	4 (0.9)	10 (1.1)

Source: Table 34 of the Study Report and Statistical Reviewer's analysis.
Abbreviations: ESBL, extended-spectrum β-lactamase; micro-MITTS, microbiological modified intent-to-treat-susceptible; sulopenem, sulopenem etzadroxil/probenecid

Demographic characteristics in the micro-MITT population for Trial 310 are reported in Table 52. The mean age was 49.5 years. White subjects were 80% of the population. Demographic characteristics were generally balanced between treatment groups.

Table 52. Trial 310: Demographic Characteristics, Micro-MITT Population

Variable	Sulopenem (N=522)	Amoxicillin/ Clavulanate (N=468)	Total (N=990)
Age, years			
Mean (SD)	50.3 (17.31)	48.6 (17.18)	49.5 (17.26)
Median	52.0	50.0	51.0
Min, max	18.0, 91.0	18.0, 93.0	18.0, 93.0
Age group (years), n (%)			
<65	400 (76.6)	372 (79.5)	772 (78.0)
≥65	122 (23.4)	96 (20.5)	218 (22.0)
Sex, n (%)			
Female	522 (100.0)	468 (100.0)	990 (100.0)
Race, n (%)			
American Indian or Alaska Native	1 (<1)	1 (<1)	2 (<1)
Asian	10 (1.9)	8 (1.7)	18 (1.8)
Black or African American	84 (16.1)	84 (17.9)	168 (17.0)
Native Hawaiian or other Pacific Islander	0	1 (<1)	1 (<1)
Other	8 (1.5)	4 (<1)	12 (1.2)
White	419 (80.3)	370 (79.1)	789 (79.7)
Ethnicity, n (%)			
Hispanic or Latino	333 (63.8)	296 (63.2)	629 (63.5)
Not Hispanic or Latino	189 (36.2)	171 (36.5)	360 (36.4)
Not reported	0	1 (<1)	1 (<1)
Height (cm)			
Mean (SD)	161.7 (7.25)	162.0 (7.05)	161.8 (7.15)
Median	162.0	162.0	162.0
Min, max	125.0, 180.0	142.0, 185.0	125.0, 185.0
Weight (kg)			
Mean (SD)	76.1 (16.99)	76.4 (17.92)	76.2 (17.43)
Median	73.4	74.0	73.5
Min, max	39.0, 192.7	40.8, 163.6	39.0, 192.7
Body mass index (kg/m^2)			
Mean (SD)	29.1 (6.28)	29.1 (6.62)	29.1 (6.44)
Median	28.1	27.9	28.0
Min, max	15.5, 67.5	17.6, 59.8	15.5, 67.5
Body mass index group (kg/m^2), n (%)			
<25	132 (25.3)	140 (29.9)	272 (27.5)
25-30	190 (36.4)	157 (33.5)	347 (35.1)
>30	200 (38.3)	171 (36.5)	371 (37.5)

Source: Table 22 of the Clinical Study Report and Statistical Reviewer's analysis.
Abbreviations: Micro-MITT, microbiological modified intent-to-treat; min, minimum; max, maximum; SD, standard deviation; sulopenem, sulopenem etzadroxil/probenecid

Baseline disease characteristics are summarized in Table 53. Approximately 16% of the subjects had diabetes. The mean creatinine clearance was 84 mL/min and 20% of the subjects had creatinine clearance of <60 mL/min. The two treatment groups were comparable.

Table 53. Trial 310: Baseline Disease Characteristics, Micro-MITT Population

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

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

Abbreviations: Micro-MITT, microbiological modified intent-to-treat; SD, standard deviation; sulopenem, sulopenem etzadroxil/probenecid

Baseline pathogens for Trial 310 are shown in Table 54. In the micro-MITT population, the most common pathogens were *Escherichia coli* (81.8%), *Klebsiella pneumoniae* (10.9%), and *Proteus mirabilis* (2.7%). The two treatment groups were generally balanced with regard to pathogens isolated at baseline.

Table 54. Trial 310: Baseline Urine Pathogen, Micro-MITT Population

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

Source: Table 24 of the Study Report and Statistical Reviewer's analysis.

Abbreviations: Micro-MITT, microbiological modified intent-to-treat; sulopenem, sulopenem etzadroxil/probenecid

In the micro-MITT population, the overall success rates were 60.9% and 55.6% in the sulopenem and the active control groups, respectively, with a difference of 5.4% and a 95% confidence interval of -0.8%, 11.5%. The results demonstrated noninferiority of sulopenem to the active control, using a -10% noninferiority margin. The difference in overall success rates was driven by microbiological success, as the clinical success proportions were similar between the two treatment groups (see secondary efficacy endpoint) (Table 55).

Table 55.Trial 310: Overall Response (Primary Endpoint), Clinical and Microbiologic Response at TOC, Micro-MITT Population

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

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

Abbreviations: CI, confidence interval; Micro-MITT, microbiological modified intent-to-treat; sulopenem, sulopenem etzadroxil/probenecid TOC, test of cure

In the micro-MITT population, the subgroup analysis results were similar to these in the micro-MITTS population, except for only observing nominally significant differences in age >65 years and creatinine clearance <60 mL/min subgroups (Table 56).

Table 56. Trial 310: Subgroup Analysis of Overall Response at TOC, Micro-MITT Population

Variable	Sulopenem (N=522) n (%)	Amoxicillin/ Clavulanate (N=468) n (%)	Difference (%) [95% CI]
Age, years			
≤65	250/400 (62.5)	221/372 (59.4)	3.1 (-3.8, 10)
>65	68/122 (55.7)	39/96 (40.6)	**15.1 (1.7, 27.9)**
Race			
American Indian or Alaska Native	1/1 (100.0)	0	
Asian	8/10 (80.0)	7/8 (87.5)	-7.5 (-43.2, 32.9)
Black or African American	47/84 (56.0)	43/84 (51.2)	4.8 (-10.3, 19.6)
Native Hawaiian or other Pacific Islander	0	0/1	
Other	6/8 (75.0)	1/4 (25.0)	
Ethnicity			
Hispanic or Latino	220/333 (66.1)	173/296 (58.4)	7.6 (-0.0, 15.2)
Not Hispanic or Latino	98/189 (51.9)	87/171 (50.9)	1.0 (-9.3, 11.3)
Not reported	0	0/1	
Body mass index (kg/m^2)			
<25	86/132 (65.2)	82/140 (58.6)	6.6 (-5.0, 18)
25-30	125/190 (65.8)	95/157 (60.5)	5.3 (-4.9, 15.5)
>30	107/200 (53.5)	83/171 (48.5)	5.0 (-5.2, 15.1)
Diabetes			
Yes	40/86 (46.5)	29/68 (42.6)	3.9 (-11.9, 19.4)
No	278/436 (63.8)	231/400 (57.8)	6.0 (-0.6, 12.6)

Variable	Sulopenem (N=522) n (%)	Amoxicillin/ Clavulanate (N=468) n (%)	Difference (%) [95% CI]
Creatinine clearance (mL/min)			
<60	66/113 (58.4)	37/86 (43.0)	**15.4 (1.3, 28.8)**
≥60	250/406 (61.6)	221/375 (58.9)	2.6 (-4.2, 9.5)
Missing	2/3 (66.7)	2/7 (28.6)	
Quinolone susceptibility			
Susceptibility	250/392 (63.8)	195/336 (58.0)	5.7 (-1.4, 12.8)
Resistant/nonsusceptible	68/130 (52.3)	65/131 (49.6)	2.7 (-9.4, 14.7)
Missing		0/1	
ESBL			
Positive	32/52 (61.5)	21/46 (45.7)	15.9 (-4.0, 34.6)
Negative	286/470 (60.9)	239/421 (56.8)	4.1 (-2.4, 10.5)
Missing		0/1	
Baseline pathogen			
E. coli	263/423 (62.2)	219/387 (56.6)	5.6 (-1.2, 12.3)
K. pneumoniae	31/58 (53.4)	22/50 (44.0)	9.4 (-9.5, 2.8)
P. mirabilis	6/14 (42.9)	6/13 (46.2)	-3.3 (-38.7, 32.8)
Other	21/33 (63.4)	15/21 (71.4)	-7.8 (-31.53, 18.65)

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

CIs were created using the Miettinen-Nurminen method.

Abbreviations: CI, confidence interval; ESBL, extended spectrum β-lactamase; micro-MITT, microbiological modified intent-to-treat; sulopenem, sulopenem etzadroxil/probenecid; TOC, test of cure