Sulopenem Etzadroxil/Probenecid

New Drug Application 213972

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Food and Drug Administration
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Purpose of the Advisory Committee Meeting

- Discuss the overall benefits and risks of sulopenem etzadroxil/probenecid (oral sulopenem) for the treatment of uncomplicated UTI caused by designated susceptible microorganisms in adult women ≥18 years of age.
- Considering the totality of the evidence in this application, discuss considerations that would be important to convey to medical providers to ensure appropriate use of oral sulopenem.

Clinical Context

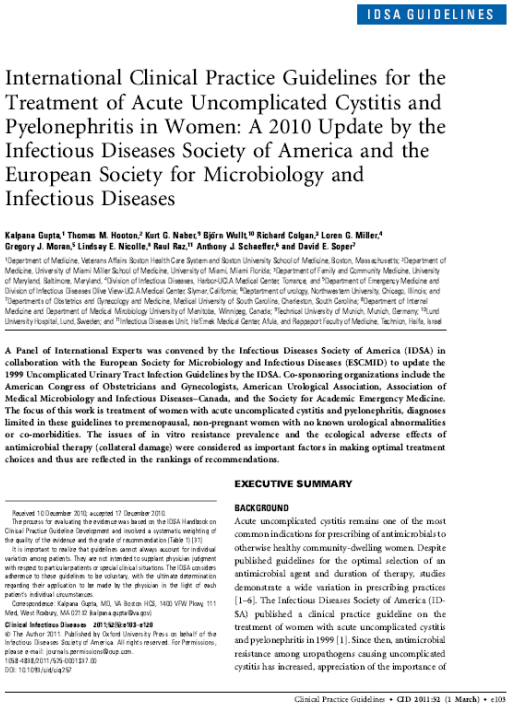
- Approximately 50 to 60% of adult women will have at least one uUTI during their lifetime[1] and 10 to 12% of adult women have at least one uUTI per year, with 20 to 30% of those being recurrent[2]
- For regulatory purposes, uUTIs are considered to occur in women with normal genitourinary anatomy and are characterized by dysuria, urinary frequency, urinary urgency and suprapubic pain[3]
- In clinical practice, uUTIs are often diagnosed based on symptoms and a dipstick urinalysis positive for leukocyte esterase or nitrite

Clinical Context

- Therapy for uUTI is often empiric, as baseline or post-treatment urine cultures are not typically recommended for the first incidence of uUTI.[2]
- *E. coli* are the most common cause of uUTIs accounting for 75% to 95% of infections[4]
- Currently recommended treatment options follow on the next slide

Recommended Treatment Options for uUTIs[4]

- First line therapy:
  - Nitrofurantoin
  - Trimethoprim-sulfamethoxazole
  - Fosfomycin trometamol
  - Pivmecillinam
- Alternative options:
  - Fluoroquinolones
  - Beta-lactam agents other than pivmecillinam



IDSA GUIDELINES

International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases

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A Panel of International Experts was convened by the Infectious Diseases Society of America (IDSA) in collaboration with the European Society for Microbiology and Infectious Diseases (ESCMID) to update the 1999 Uncomplicated Urinary Tract Infection Guidelines by the IDSA. Co-sponsoring organizations include the American Congress of Obstetricians and Gynecologists, American Urological Association, Association of Medical Microbiology and Infectious Diseases–Canada, and the Society for Academic Emergency Medicine. The focus of this work is treatment of women with acute uncomplicated cystitis and pyelonephritis, diagnoses limited in these guidelines to premenopausal, non-pregnant women with no known urological abnormalities or co-morbidities. The issues of in vitro resistance prevalence and the ecological adverse effects of antimicrobial therapy (collateral damage) were considered as important factors in making optimal treatment choices and thus are reflected in the rankings of recommendations.

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The process for evaluating the evidence was based on the IDSA Handbook on Clinical Practice Guideline Development and involved a systematic weighting of the quality of the evidence and the grade of recommendation (Table 1) [11].

It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. The IDSA considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.

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EXECUTIVE SUMMARY

BACKGROUND

Acute uncomplicated cystitis remains one of the most common indications for prescribing of antimicrobials to otherwise healthy community-dwelling women. Despite published guidelines for the optimal selection of an antimicrobial agent and duration of therapy, studies demonstrate a wide variation in prescribing practices [1–6]. The Infectious Diseases Society of America (IDSA) published a clinical practice guideline on the treatment of women with acute uncomplicated cystitis and pyelonephritis in 1999 [1]. Since then, antimicrobial resistance among uropathogens causing uncomplicated cystitis has increased, appreciation of the importance of

Clinical Context

- 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)[5,6]
- 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

Clinical Context

- While an oral penem could potentially address an unmet need for treatment of uUTI caused by resistant bacteria, its use in an ambulatory setting where treatment is most commonly empiric raises concern for inappropriate use which may contribute to AMR.

Considerations From FDA's uUTI Guidance[3]

- Active-controlled trials designed for findings of superiority or noninferiority are potential options to evaluate antibacterial drugs for the treatment of uUTI.
- For a non-inferiority (NI) trial, it is important that the analysis population (micro-ITT or micro-mITT) includes only patients in whom the baseline bacterial pathogen is fully susceptible to the active control drug on in vitro susceptibility testing.
  - The Applicant performed NI hypothesis testing in some populations that included patients with isolates that were not susceptible to the comparator; FDA finds this testing uninterpretable for regulatory purposes.
- A treatment delay, placebo-controlled trial design is acceptable in uUTI trials and allows for a finding of superiority of the study drug versus placebo.

Considerations From FDA's uUTI Guidance[3]

- Primary efficacy endpoint based on overall response, a composite outcome of clinical and microbiologic responses
- Microbiologic outcomes are an important component of the composite endpoint.
  - In analysis of complicated urinary tract infection (cUTI) trials, discordant clinical and microbiologic outcomes at the test of cure (TOC) visit were associated with late clinical failure and this risk increased with time.[7]

Asymptomatic Bacteriuria Versus Microbiologic Persistence

- We note that the term asymptomatic bacteriuria (ASB) is typically used to indicate the presence of bacteria in a urine sample collected in a patient without any symptoms of a UTI.
- This term may not be applicable to a patient who, following the diagnosis and treatment of UTI, has symptom resolution but whose treatment failed to eradicate the causative uropathogen(s) (microbiologic persistence).[7]
- Therefore, FDA considers patients in uUTI and cUTI clinical trials with post-treatment microbiologic persistence as microbiologic failures.

Efficacy Findings in Phase 3 uUTI Trials

- In uUTI Trial 301:
  - Efficacy was established in the ciprofloxacin-resistant population
  - Efficacy was not established in the ciprofloxacin-susceptible population, primarily due to microbiologic failure
- In uUTI Trial 310:
  - Efficacy was established in the amoxicillin/clavulanate-susceptible population
  - Inconclusive results in the amoxicillin/clavulanate-resistant population due to small sample size

Phase 3 Trials in cUTI and cIAI

- Trial 302 enrolled patients with complicated urinary tract infections (cUTI)
  - IV to oral sulopenem did not demonstrate noninferiority versus comparator IV to oral regimen in overall (clinical + microbiologic) response, using a 10% NI margin
  - Differences were driven by microbiologic failure
- Trial 303 enrolled patients with complicated intra-abdominal infections (cIAI)
  - IV to oral sulopenem did not demonstrate noninferiority versus comparator IV to oral regimen in clinical response, using a 10% NI margin

Safety

- Adequate safety database
- Diarrhea was the most common adverse event (AE) in the phase 3 uUTI safety population, but was generally mild and did not lead to treatment discontinuations
- Mild alanine aminotransferase (ALT) elevations that were not treatment-limiting occurred in a small proportion of sulopenem-treated patients
- Identified safety risks could potentially be mitigated through labeling

Considerations

- The two phase 3 trials for uUTI (Trials 301 and 310) studied oral sulopenem for the treatment of uUTI in an ambulatory setting and were not designed to evaluate the efficacy of oral sulopenem for the treatment of uUTI caused by resistant bacterial isolates, or for the treatment of uUTI in patients who failed first-line treatment
- If approved, sulopenem etzadroxil/probenecid would be the first oral penem antibacterial drug marketed in the United States, and inappropriate use may contribute to AMR or increase cross-resistance to other penem drugs

Considerations

- Because IV sulopenem followed by oral sulopenem was found to be inferior to the active comparator regimen for cUTI in Trial 302, there is concern that if approved, oral sulopenem may be used off-label for the treatment of cUTI or other infections, as stepdown treatment
- There are no data on the effectiveness of oral sulopenem as stepdown therapy following IV treatment of cUTI with another antibacterial drug.

Considerations

- While antimicrobial stewardship and consideration by guidelines committees may help to determine appropriate positioning of oral sulopenem, if approved, in the hierarchy of uUTI treatment options, a discussion of approaches to inform prescribers of relevant data submitted in this NDA to ensure the most appropriate use of oral sulopenem is warranted.

References

1. Medina, M and E Castillo-Pino, 2019, An introduction to the epidemiology and burden of urinary tract infections, Ther Adv Urol, 11:1756287219832172.
2. Kaye, KS, V Gupta, A Mulgirigama, AV Joshi, NE Scangarella-Oman, K Yu, G Ye, and FS Mitrani-Gold, 2021, Antimicrobial Resistance Trends in Urine *Escherichia coli* Isolates From Adult and Adolescent Females in the United States From 2011 to 2019: Rising ESBL Strains and Impact on Patient Management, Clin Infect Dis, 73(11):1992-1999.
3. FDA, 2019, Guidance for Industry; Uncomplicated Urinary Tract Infections: Developing Drugs for Treatment. Link: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/uncomplicated-urinary-tract-infections-developing-drugs-treatment-guidance-industry
4. Gupta, K, TM Hooton, KG Naber, B Wullt, R Colgan, LG Miller, GJ Moran, LE Nicolle, R Raz, AJ Schaeffer, DE Soper, A Infectious Diseases Society of, M European Society for, and D Infectious, 2011, International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases, Clin Infect Dis, 52(5):e103-120.
5. Critchley, IA, N Cotroneo, MJ Pucci, and R Mendes, 2019, The burden of antimicrobial resistance among urinary tract isolates of Escherichia coli in the United States in 2017, PLoS One, 14(12):e0220265.
6. Dunne, MW, SI Aronin, KC Yu, JA Watts, and V Gupta, 2022, A multicenter analysis of trends in resistance in urinary Enterobacterales isolates from ambulatory patients in the United States: 2011-2020, BMC Infect Dis, 22(1):194.
7. Kadry, N, M Natarajan, E Bein, P Kim, and J Farley, 2023, Discordant Clinical and Microbiological Outcomes Are Associated With Late Clinical Relapse in Clinical Trials for Complicated Urinary Tract Infections, Clin Infect Dis, 76(10):1768-1775.

Thank You

Efficacy and Safety Assessments

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September 9, 2024

Outline

- **Brief Regulatory History**
- **Highlights of Trial Design and Analysis of Trials 301 and 310**
- Efficacy of sulopenem for uUTI
- Efficacy of sulopenem for cUTI and cIAI
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NDA 213972 – Brief Regulatory History

11/25/2020: NDA submitted for treatment of uUTI in adult women caused by designated organisms nonsusceptible to a quinolone.

Trials: 301 (uUTI); 302 (cUTI); 303 (cIAI)

7/23/2021: Complete Response due to lack of SEE.

Trial 301: sulopenem superior to ciprofloxacin in micro-MITTR, inferior in micro-MITTS populations.

Trial 302: failed

Trial 303: failed

4/25/2024: NDA resubmitted for treatment of uUTI in adult women caused by designated organisms susceptible to sulopenem.

Trial 310 (uUTI)

Design of Trials 301 and 310

	Trial 301	Trial 310
Design	Phase 3, randomized, multicenter, double-blind, double-dummy controlled study in women aged ≥ 18 years	
Sulopenem	Sulopenem etzadroxil/probenecid 500 mg/500 mg, BID, 5 days	
Active control	Ciprofloxacin 250 mg, BID, 3 days	Amoxicillin/clavulanate 875 mg/125 mg, BID, 5 days
Primary endpoint	Overall response (clinical & microbiological response) on Day 12 (±1 day)/test of cure (TOC) in 3 analysis populations • Clinical success: resolution of baseline UTI symptoms & no new UTI symptoms • Microbiological success: TOC urine culture results of $<10^3$ CFU/mL of the baseline pathogen	

Trials 301 and 310 Analysis Populations

	Trial 301	Trial 310
Micro-MITT	All randomized patients who received at least 1 dose of study drug and had ≥10^5 CFU/mL of a baseline pathogen	
Micro-MITTS	Subjects with baseline pathogens susceptible (MIC≤ 1 mg/L) to ciprofloxacin (NI, 10% margin)	Susceptible (MIC≤ 8/4 mg/L) to amoxicillin/clavulanate (NI, 10% margin)
Micro-MITTR	Non-susceptible [MIC ≥2 mg/L)] to ciprofloxacin (superiority)	Non-susceptible [intermediate (MIC 16/8 mg/L) or resistant (MIC ≥ 32/16 mg/L)] to amoxicillin/clavulanate (superiority)

Trials 301 and 310 Analysis Methods

	Trial 301	Trial 310
Overall type I error control	Micro-MITTR and micro-MITTS populations were separate and considered as two studies. Hierarchical testing was used to control overall Type I error among three analysis populations.	
	Hierarchical testing (first step) 1) NI in micro-MITTS or superiority in micro-MITTR	Hierarchical testing 1) NI in micro-MITT 2) NI in micro-MITTS or superiority in micro-MITTR 3) Superiority in micro-MITT

Trials 301 and 310 Analysis Methods

	Trial 301	Trial 310
Interim analysis (IA) for sample size re-estimation	2 blinded IAs (33%, 66%) for micro-MITTS population; 1 unblinded IA (66%) for micro-MITTR population	1 blinded IA (50%)
Protocol change after IA	Definitions for susceptibility & microbiologic persistence changed by addition of whole genome sequencing (WGS) & PCR; Sites 202 and 218 excluded	No
Analysis method	95% confidence interval approach (Miettinen and Nurminen)	

For Trial 301, FDA used the original statistical analysis plan (SAP) and included Site 202 for all analyses due to disagreement with protocol changes made after the unblinded IA and with exclusion of Site 202

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Trials 301 and 310: Study Populations

Trial 301	Sulopenem (N=835)	Cipro (N=836)	Total (N=1671)
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)
Trial 310	**Sulopenem (N=1111)**	**A/C (N=1111)**	**Total (N=2222)**
Micro-MITT	522 (47.0)	468 (42.1)	990 (44.6)
Micro-MITTR*	42 (3.8)	25 (2.3)	67 (3.0)
Micro-MITTS	480 (43.2)	442 (39.8)	922 (41.5)

Source: Tables 15 & 21 of the study report and statistical reviewer's analysis including Site 202 and using original SAP. *Planned sample size: 134 per arm.

Trials 301 and 310: Age Distribution

Age (years), n (%)	Sulopenem	Control	Total
Trial 301 Micro-MITTR	**N=162**	**N=149**	**N=311**
<30	25 (15.4)	21 (14.1)	46 (14.8)
30-<60	67 (41.4)	59 (39.6)	126 (40.5)
≥60	70 (43.2)	69 (46.3)	139 (44.7)
Trial 301 Micro-MITTS	**N=376**	**N=418**	**N=794**
<30	71 (18.9)	83 (19.9)	154 (19.4)
30-<60	162 (43.1)	181 (43.3)	343 (43.2)
≥60	143 (38.0)	154 (36.8)	297 (37.4)
Trial 310 Micro-MITT	**N=522**	**N=468**	**N=990**
<65	400 (76.6)	372 (79.5)	772 (78.0)
≥65	122 (23.4)	96 (20.5)	218 (22.0)

Source: Statistical reviewer's analysis and Table 22 of the study report of Trial 310

Trials 301 and 310: Race Distribution

Age (years), n (%)	Sulopenem	Control	Total
Trial 301 Micro-MITTR	N=162	N=149	N=311
Black or African American	15 (9.3)	12 (8.1)	27 (8.7)
White	144 (88.9)	136 (91.3)	280 (90.0)
Other	3 (1.9)	1 (0.7)	4 (1.3)
Trial 301 Micro-MITTS	**N=376**	**N=418**	**N=794**
Black or African American	35 (9.3)	34 (8.1)	69 (8.7)
White	334 (88.8)	379 (90.7)	713 (89.8)
Other	7 (1.9)	5 (1.2)	12 (1.5)
Trial 310 Micro-MITT	**N=522**	**N=468**	**N=990**
Black or African American	84 (16.1)	84 (17.9)	168 (17.0)
White	419 (80.3)	370 (79.1)	789 (79.7)
Other	19 (3.6)	13 (2.8)	32 (3.2)

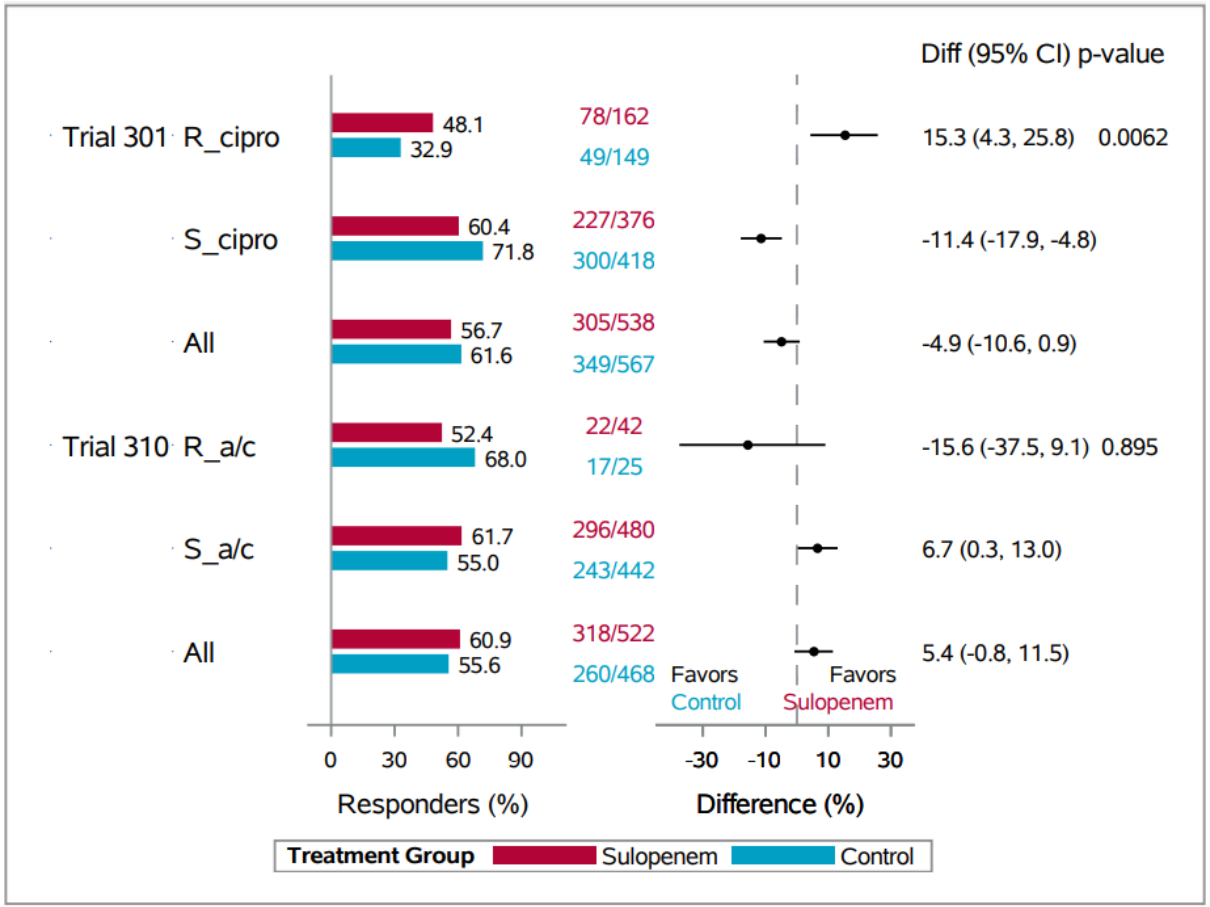
Source: Statistical reviewer's analysis and Table 22 of the study report for Trial 310

Trial 301: Overall Response at TOC, Micro-MITTR Population

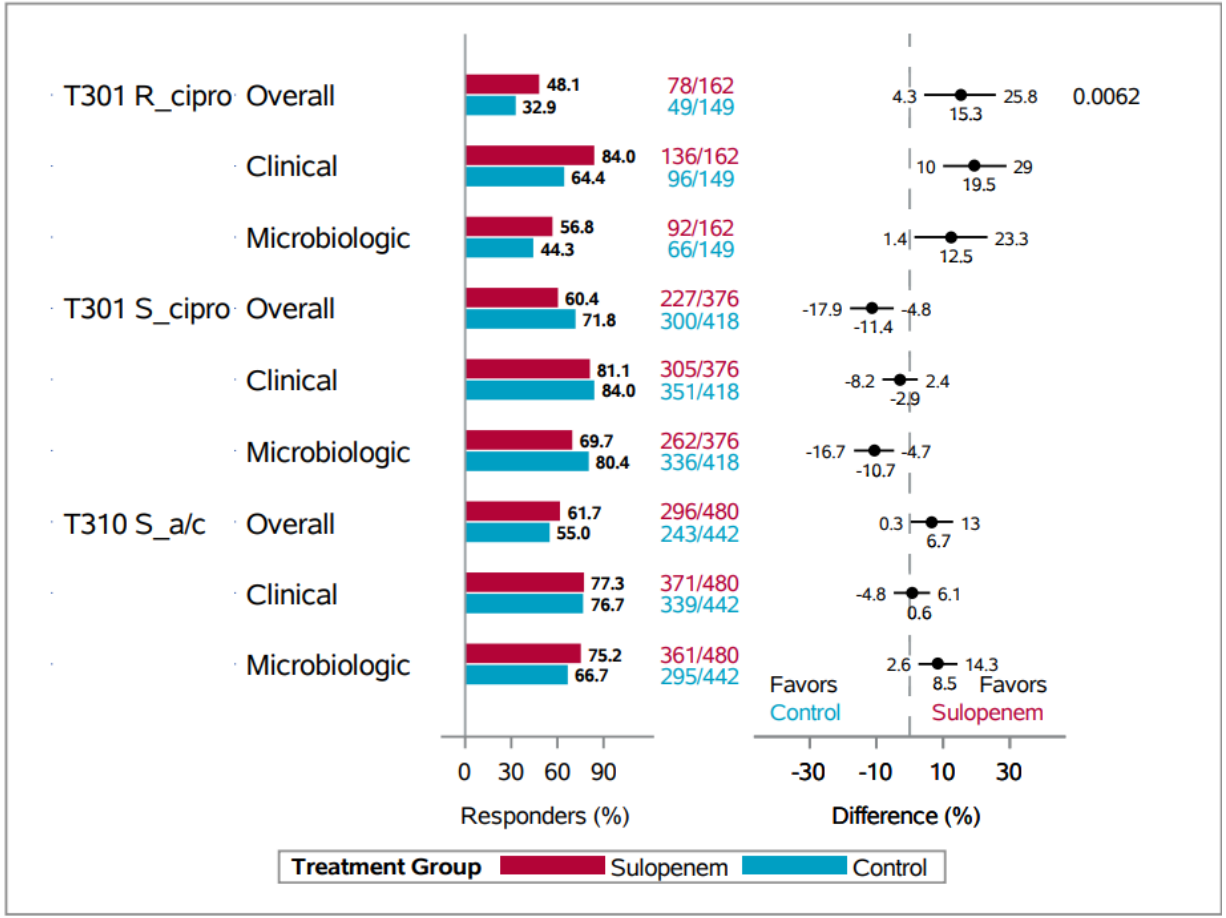
Response	Sulopenem	Ciprofloxacin	Diff (95% CI) p-Value
Applicant: Updated SAP, excluding Site 202	92/147 (62.6)	50/139 (36.0)	26.6 (15.1, 37.4) <0.001
FDA: Original SAP, including Site 202	78/162 (48.1)	49/149 (32.9)	15.3 (4.4, 26.1) 0.0062

Source: Tables 52 and 84 of updated study report

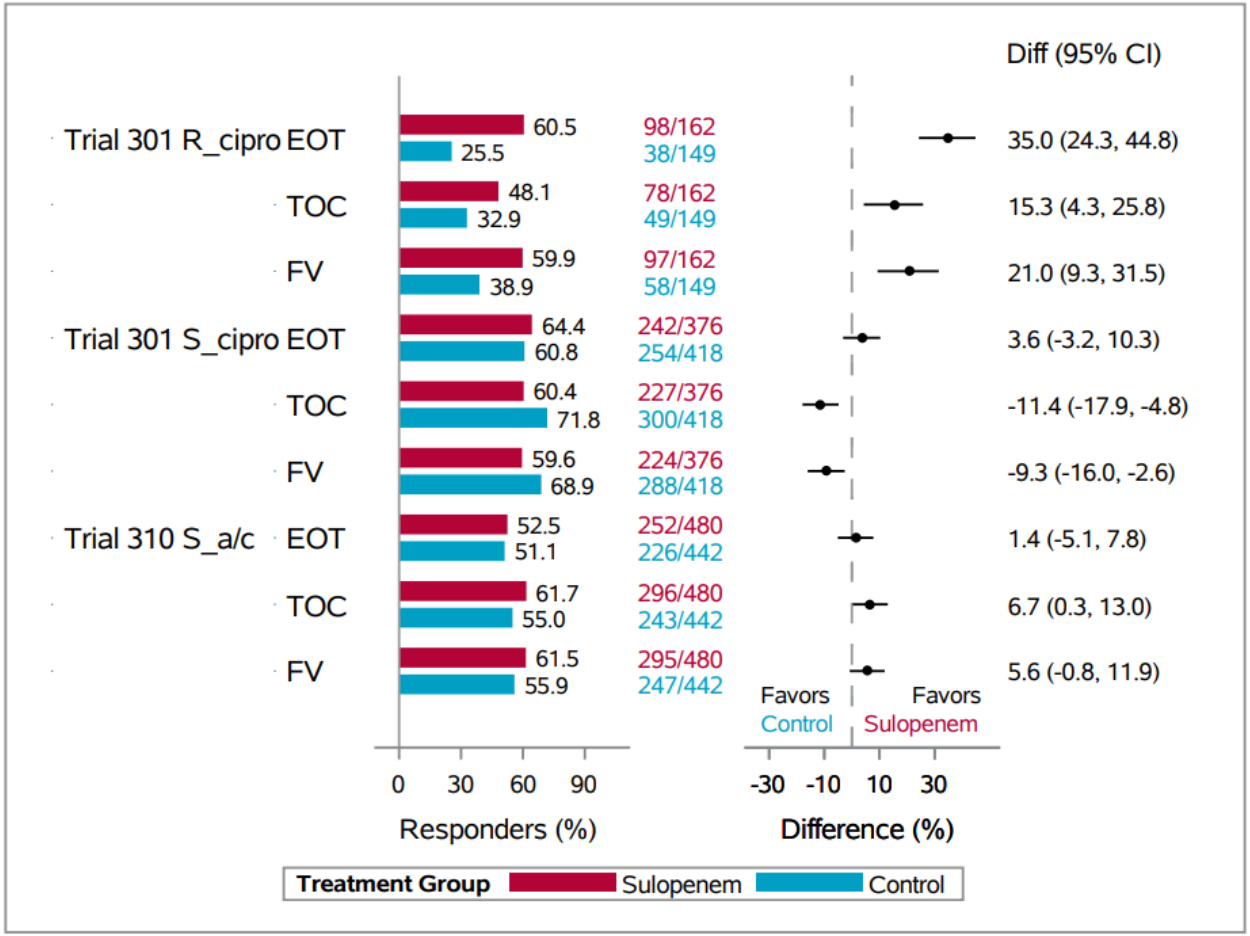
Overall Response by Susceptibility to Comparator in Trials 301 and 310



Clinical and Microbiological Responses in Trials 301 and 310

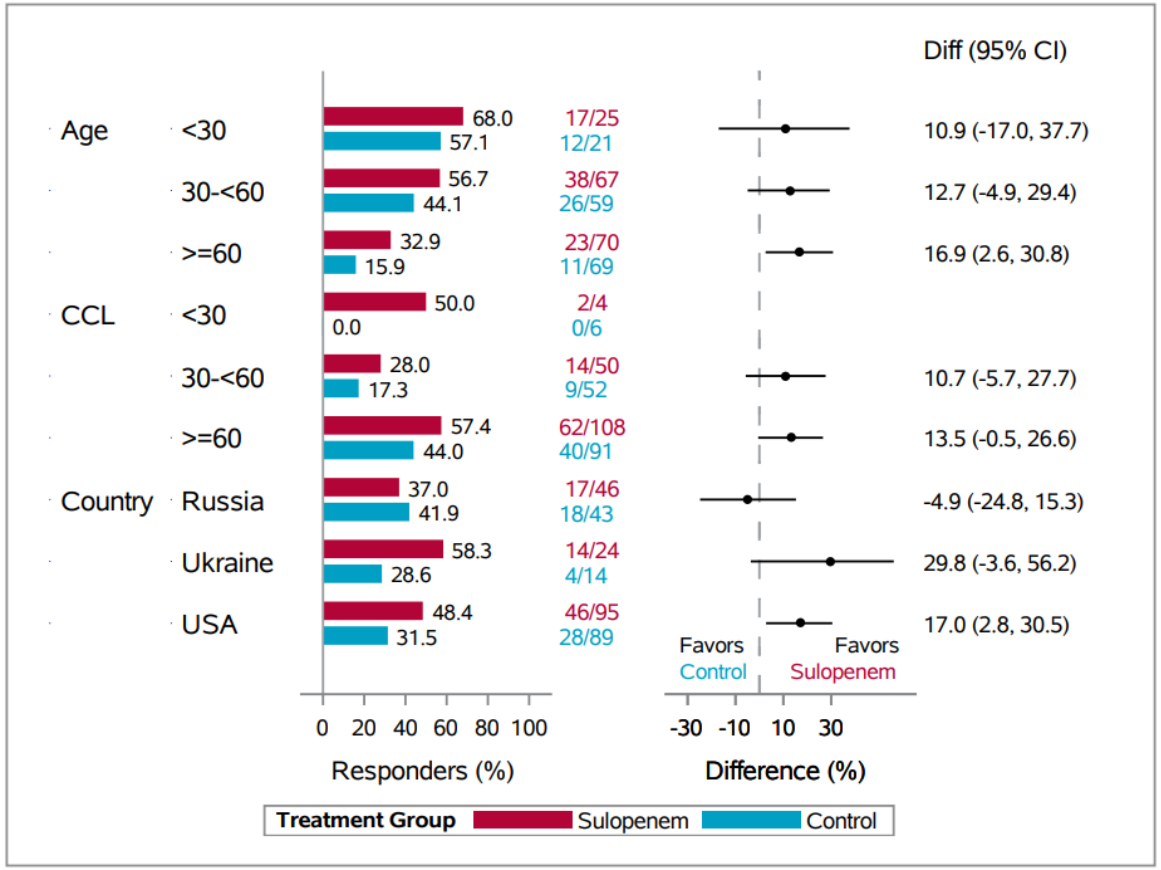


Overall Response by Visit in Trials 301 and 310



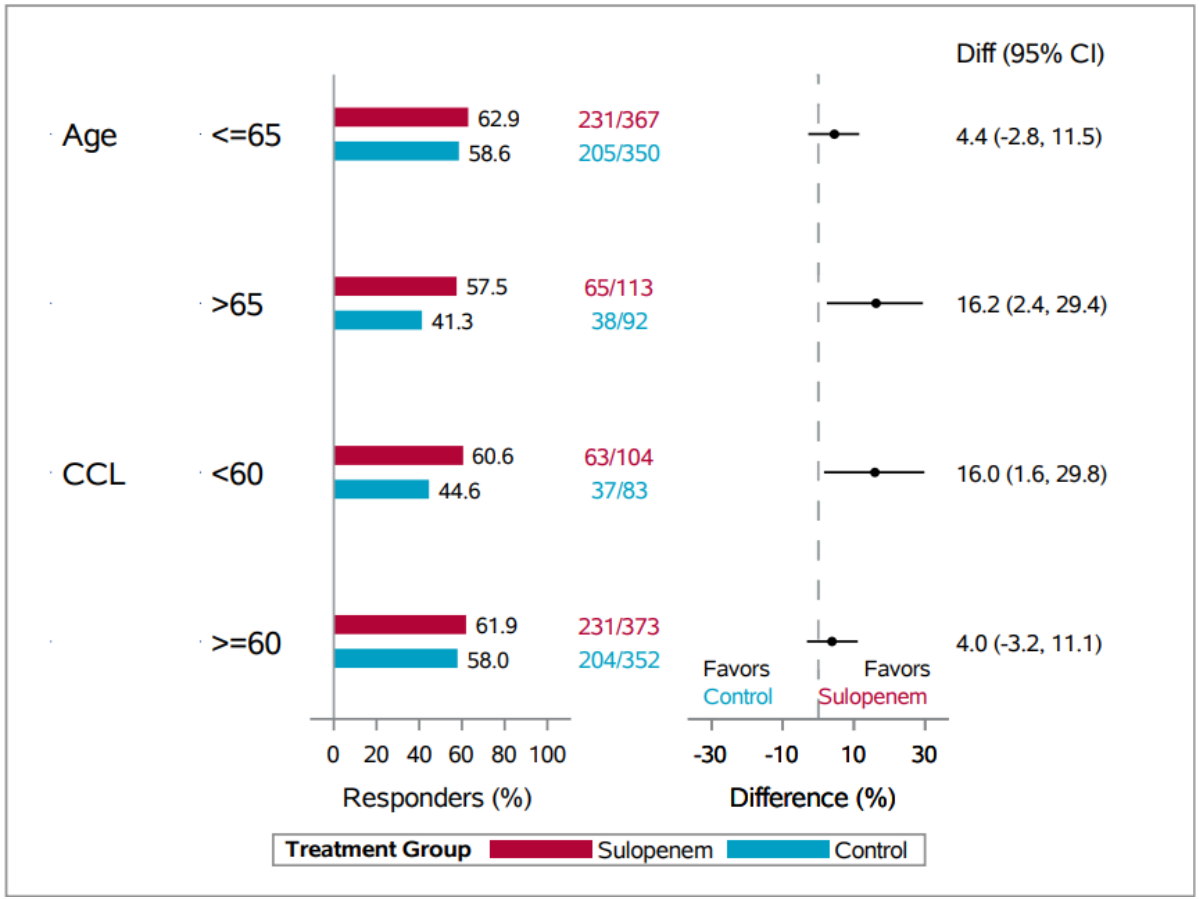
EOT: end of therapy; TOC: test of cure; FV: final visit

Trial 301: Subgroup Analyses Of Overall Response, Micro-MITTR Population



CCL: Creatinine clearance

Trial 310: Subgroup Analyses of Overall Response, Micro-MITTS Population



CCL: Creatinine clearance

Efficacy Conclusions for Trials 301 and 310

- Trial 301
  - In Micro-MITTR population (cipro-resistant), superiority was established
  - In Micro-MITTS population (cipro-susceptible), NI (using a 10% margin) was not established. Sulopenem was similar to ciprofloxacin for clinical response but worse than ciprofloxacin for microbiologic response.
- Trial 310
  - In Micro-MITTS population (Amoxicillin/clavulanate [A/C]-susceptible), NI (using a 10% margin) and superiority were established
  - In Micro-MITTR population (A/C-resistant), trial did not enroll the planned sample size, so conclusions could not be drawn
  - Differences between arms were driven by microbiologic success rather than clinical success rates

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Trial 302 – cUTI

Design	Phase 3, randomized, multicenter, double-blind, double-dummy controlled study in men and women aged 18 years or older
Sulopenem	Sulopenem 1000 mg IV daily for at least 5 days followed by oral sulopenem etzadroxil 500 mg/probenecid 500 mg BID to complete 7-10 days of total treatment
Active Control	Ertapenem 1000 mg IV daily for at least 5 days followed by oral ciprofloxacin 500 mg BID or amoxicillin/clavulanate 875 mg BID to complete 7-10 days of total treatment
Primary Endpoint	Overall response (clinical & microbiologic response) on Day 21/TOC in the micro-MITT population (NI, 10% margin)

Trial 302: Overall Response at TOC (Day 21)

	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)	

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)

Trial 302: Overall Response at TOC by Stepdown Category and Pathogen Susceptibility

Overall Response	Cipro Susceptible n/N (%)	Cipro Resistant, Amox/Clav Susceptible n/N (%)	Cipro Resistant, Amox/Clav Resistant n/N (%)
IV sulopenem to oral sulopenem	154/248 (62.1)	26/55 (47.3)	53/80 (66.3)
IV ertapenem to oral ciprofloxacin	179/215 (83.3)	0	2/5 (40.0)
IV ertapenem to oral amoxicillin/clavulanate	4/6 (66.7)	37/66 (56.1)	0/2 (0.0)

Source: Tables 40 and 42 of updated study report, and statistical reviewer; Cipro: ciprofloxacin; Amox/Clav: amoxicillin/clavulanate

Note: 106 subjects remained on IV ertapenem because their baseline pathogen was resistant to both cipro and amox/clav

Efficacy Conclusions for Trial 302

- Sulopenem did not establish noninferiority to comparator in overall response, using a NI margin of 10%
- Differences were driven by microbiologic response rather than clinical response
- Results suggested that differences were driven by inferior overall response in subjects with ciprofloxacin-susceptible pathogens who stepped down to oral therapy

Trial 303 – cIAI

- 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

Clinical Response at TOC (Day 28)

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)

- **Efficacy Conclusion**: Sulopenem did not demonstrate non-inferiority to ertapenem in clinical response, using a non-inferiority margin of 10%.

Overall Efficacy Conclusions

- Trial 301 in uUTI
  - Efficacy was established in the ciprofloxacin-resistant population
  - Efficacy was not established in the ciprofloxacin-susceptible population
- Trial 310 in uUTI
  - Efficacy was established in the amoxicillin/clavulanate-susceptible population
  - Inconclusive results in the amoxicillin/clavulanate-resistant population due to small sample size
- Efficacy was not established in cUTI (Trials 302) and cIAI (Trial 303)

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Clinical Safety Database for Sulopenem

Clinical Studies	Number of Subjects	Formulation	Median Duration (Days)
Phase 1 and 2 (24 studies)	2006	IV and oral	
Phase 3 uUTI trials (Trials 301 and 310)	1932*	oral	5
Phase 3 cUTI trial (Trial 302)	695	IV and oral	10 (IV + oral) 4 (oral)
Phase 3 cIAI trial (Trial 303)	335	IV and oral	9 (IV + oral) 3 (oral)
Total	4968		

Source: Reviewer table

Abbreviations: cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; IV, intravenous; uUTI, uncomplicated urinary tract infection

* Eight subjects in the sulopenem etzadroxil/probenecid arm from Site 218 in Trial 301 were excluded from the clinical safety database

Deaths, Sulopenem Phase 3 Safety Population

Trial	Age (Yrs)/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

None of the deaths were attributable to sulopenem

Overview of Adverse Events (AE), Trials 301 and 310

Event Category	Sulopenem N=1932 n (%)	Amox/Clav N=1107 n (%)	Cipro N=822 n (%)
Serious adverse event (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.

Adverse Events Occurring at > 1% Frequency in Subjects Receiving Sulopenem Etzadroxil/Probenecid, 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)

Source: adae.xpt; software, R. 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.

* Most cases were mild in severity and did not lead to sulopenem discontinuation. There were no cases of *Clostridioides difficile* infection in the sulopenem arm.

ALT Elevations in the Sulopenem Phase 3 Trials

- Significant hepatotoxicity was not noted in the phase 3 trials
- Hy's Law (Trial 302): 1 subject met laboratory criteria for Hy's Law but LFTs improved while on sulopenem
- **Trials 301 and 310**: Slightly more subjects (6, 0.3%) in the sulopenem group had ALT ≥ 3x to <5x upper limit of normal (ULN) compared to ciprofloxacin (1, 0.1%) and amoxicillin/clavulanate (1, 0.1%)
  - 1 subject (Trial 301) had >5x ULN ALT elevation at TOC which was asymptomatic and resolved 5 days later
- **All phase 3 trials (301, 302, 303 and 310)**: In the sulopenem group, 31 (1.1%) subjects had at least 1 postbaseline ALT elevation > 3x ULN vs. 19 (0.7%) in the comparator groups
  - Of these, 9 sulopenem subjects (1 in 301 (noted above), 8 in 302 and 303) had ALT > 5x ULN and one had ALT > 10x ULN
  - Attribution of causality to sulopenem was confounded by the subjects' underlying medical conditions and/or concomitant medications

Safety Conclusions

- Adequate safety database
- Diarrhea was the most common AE in the phase 3 uUTI safety population, but was generally mild and did not lead to treatment discontinuations
- Mild ALT elevations that were not treatment-limiting occurred in a small proportion of sulopenem-treated subjects
- Reasonable safety profile, identified safety risks may be mitigated through labeling

Summary and Conclusions

- Although Trials 301 and 310 had different comparators and efficacy was shown in discordant populations, they provide evidence of benefit of oral sulopenem for the treatment of uUTI caused by susceptible organisms in adult women
- The efficacy of oral sulopenem as stepdown therapy following IV therapy for cUTI has not been established. If approved, communication to medical providers of the lack of efficacy of sulopenem etzadroxil/probenecid as stepdown therapy for cUTI will be important

Thank You

Microbiology Assessment

NDA 213972

Jalal Sheikh, PhD
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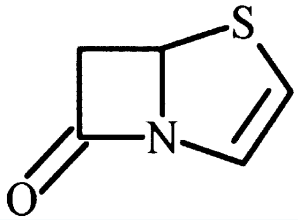
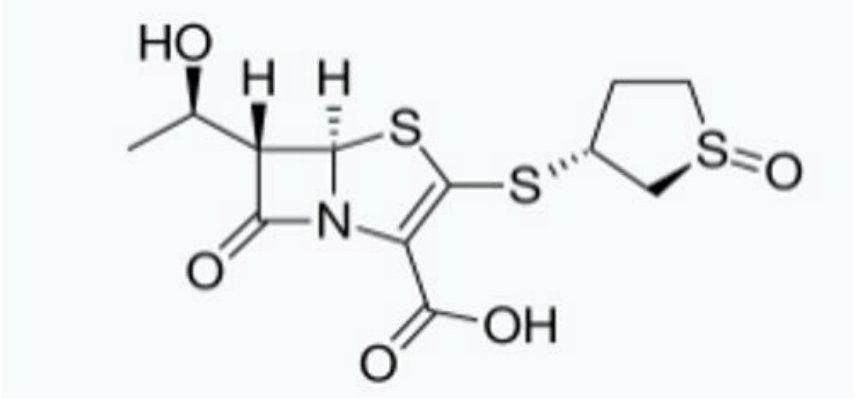
Structural Difference Between Penems and Carbapenems

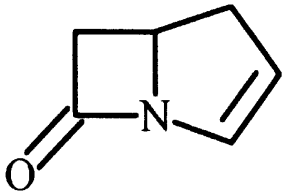
Penems: Sulfur-Containing Rings

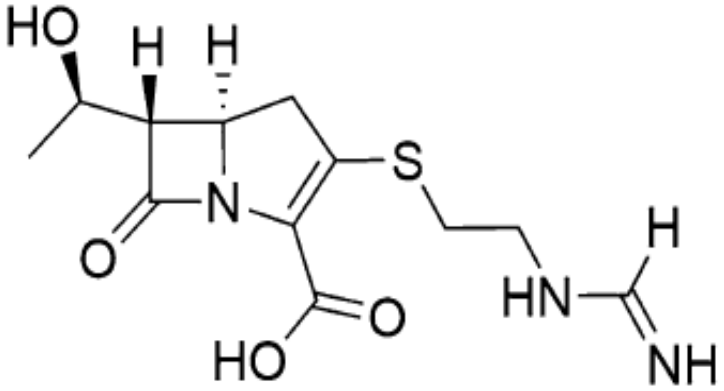




e.g., Sulopenem

Carbapenems: Carbon-Containing Rings





e.g., Imipenem

Mechanisms of Action (MOA)

- The bactericidal activity of sulopenem is the result of inhibiting the transpeptidase enzymes (penicillin binding protein [PBPs]) from cross-linking peptidoglycan that induces cell lysis
- Sulopenem preferentially binds to PBPs in the following order of affinity: PBP2> PBP1A> PBP1B> PBP4> PBP3> PBP5 or PBP6
- The ionization and low molecular weight of penems, allow them to easily diffuse through outer membrane proteins in gram-negative bacteria, e.g., OmpK in *K. pneumoniae* and OmpF in *E. coli*

Mechanisms of Resistance

Resistance conferred by one of four well-described mechanisms and in some cases a combination of these

1. Alteration in PBPs results in reduced efficacy
2. Expression of ß-lactamases may facilitate the hydrolysis of the ß-lactam ring of the antibacterial drug
3. Modification of outer membrane proteins (OMPs), limits or prevents access to the periplasmic space
4. The expression of efflux pumps actively expel the antimicrobial drug

Data From Other In Vitro Studies

- Sulopenem showed bactericidal activity (99.9% reduction in the number of viable colony-forming units) at concentrations of ≥4X the MIC against isolates of *E. coli* and *K. pneumoniae*
- The 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
- Sulopenem has poor activity against *P. aeruginosa* and *A. baumannii* isolates

In Vitro Activity Against UTI Pathogens: Sulopenem and FDA-Approved Carbapenems

Minimum Inhibitory Concentrations (MIC) 50/90 values (mcg/mL) of major uUTI pathogens from various surveillance studies

Penem/ Carbapenem Drugs	*E. coli*	*K. pneumoniae*	*P. mirabilis*	*E. cloacae* Complex	*S. saprophyticus*
Sulopenem	0.03/ 0.03 to 0.06	0.03 to 0.06/ 0.06 to 0.12	0.06 to 0.25/ 0.12 to 0.5	0.06 to 0.25/ 0.25 to 1	0.12 to 0.5/ 0.25 to 0.5
Meropenem	≤0.015 to 0.03/ ≤0.03 to 0.03	≤0.03 to 0.03/ 0.03 to 0.06	0.06/ 0.06 to 0.12	≤0.03 to 0.06/ 0.06 to 0.25	0.25/ 0.25 to 0.5
Ertapenem	≤0.008 to ≤0.03/ ≤0.03 to 0.03	≤0.008 to ≤0.03/ 0.06 to 0.25	≤0.008 to ≤0.03/ ≤0.03 to 0.03	0.03 to 0.12/ 0.5 to 2	1/2
Imipenem	≤0.12 to 0.12/ ≤0.12 to 0.25	≤0.12 to 0.25/ 0.25 to 0.5	1 to 2/ 2 to 4	0.25 to 0.5/ 0.5 to 1.0	0.03/0.06

Source: IHMA_2757, 17-ITR-05, CANWARD 2016, 18-ITR-03, CANWARD 2014-2021, 23-ITR-03

Sulopenem Activity Against Organisms With Key Resistance Phenotypes

In vitro MIC50/90 (mcg/mL)						
Major UTI pathogens	**FQ-S**	**FQ-R**	**ESBL-Negative**	**ESBL-Positive**	**CSE**	**CRE**
E. coli	0.03/0.03 (N=891)	0.03/0.06 (N=337)	0.03/0.03 (N=1349)	0.03/0.06 (N=203)	Not Available	Not Available
K. pneumoniae	Not Available	Not Available	0.03/0.06 (N=446)	0.06/0.5 (N=91)	0.03/0.06 (N=445)	>8/>8 (N=46)

Source: ad hoc analyses of CANWARD 2016, 17-ITR-05, and IHMA_2757

In Vivo Activity of Sulopenem and Its Oral Prodrug, Sulopenem Etzadroxil

- The in vivo activity of sulopenem and sulopenem etzadroxil was demonstrated by determining 50% Protective Doses (PD50) compared to other drugs in animal infection models:
  - the mouse systemic infection model against *S. pneumoniae* and *K. pneumoniae*;
  - the mouse pulmonary infection model against S. *pneumoniae*; and
  - the Mongolian gerbil otitis media model against *H. influenzae*

Clinical Microbiology Highlights in the Sulopenem uUTI Clinical Program

- In clinical trials, the primary efficacy endpoint was the outcome of Overall Response (combined clinical and microbiological) at TOC visit (Day 12)
- **Microbiological success or eradication** was defined when a urine culture, obtained at TOC, demonstrated $<10^3$ CFU/mL of the baseline uropathogen
- **Microbiological failure or persistence** was defined when a urine culture, obtained at TOC, grew $\geq 10^3$ CFU/mL of the same genus/species as the baseline regardless of antimicrobial susceptibility, or genetic dissimilarity as determined by molecular testing

Baseline Predominant uUTI Pathogens in the micro-MITTR/Trial 301 and micro-MITTS/Trial 310 Populations

	Trial 301 (micro-MITTR)		Trial 310 (micro-MITTS)	
Predominant uUTI Pathogens	**Sulopenem Etzadroxil/ Probenecid n/N (%)**	**Ciprofloxacin n/N (%)**	**Sulopenem Etzadroxil/ Probenecid n/N (%)**	**Amoxicillin/ Clavulanate n/N (%)**
E. coli	141/162 (87)	131/149 (87.9)	400/480 (83.3)	374/442 (84.6)
K. pneumoniae	15/162 (9.3)	14/149 (9.4)	57/480 (11.9)	50/442 (11.3)
P. mirabilis	9/162 (5.6)	6/149 (4.0)	13/480 (2.7)	13/442 (2.9)

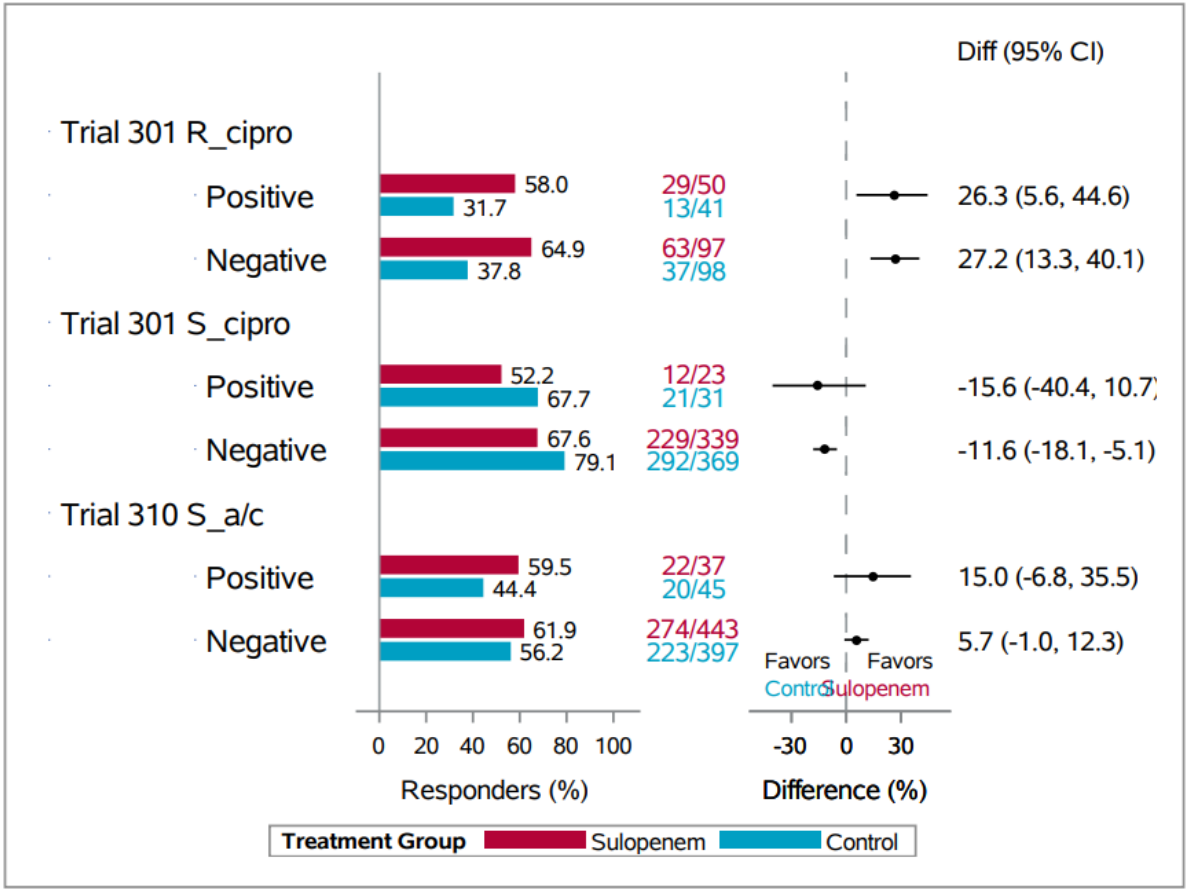
E. coli was isolated at the highest frequency at baseline followed by *K. pneumoniae, and P. mirabilis* in both arms of the clinical trials

Distribution of Baseline uUTI Pathogens by Antibacterial Resistance in Trials 301 and 310

Antibacterial Resistance Parameter	Trial 301				Trial 310			
	micro-MITTR		micro-MITTS		micro-MITTS		micro-MITTR	
	Sulo. n/N (%)	Cipro. n/N (%)	Sulo. n/N (%)	Cipro. n/N (%)	Sulo. n/N (%)	Amox.-Clav. n/N (%)	Sulo. n/N (%)	Amox.-Clav. n/N (%)
ESBL-positive (phenotypic)	50/147 (34)	41/139 (29.5)	23/370 (6.2)	31/415 (7.5)	37/480 (7.7)	45/442 (10.2)	15/42 (35.7)	1/25 (4.0)
Quinolone-resistant	145/147 (98.6)	137/139 (98.6)	5/370 (1.4)	6/415 (1.4)	120/480 (25.0)	10/42 (23.8)	3/25 (12.0)	131/468 (28.0)
TMP-SMX resistant	94/147 (63.9)	78/139 (56.1)	77/370 (20.8)	89/415 (21.4)	149/480 (31.0)	12/42 (28.6)	5/25 (20.0)	139/468 (29.7)
Nitrofurantoin resistant	39/147 (26.5)	38/139 (27.3)	58/370 (15.7)	57/415 (13.7)	64/480 (13.3)	19/42 (45.2)	13/25 (52.0)	69/468 (14.7)

Source: NDA submission
Sulo. = Sulopenem-arm; Cipro. = Ciprofloxacin-arm; Amox.-Clav. = Amoxicillin-Clavulanate-arm

Subgroup Analyses of Overall Response by ESBL Status in Trials 301 and 310



Sulopenem Activity Among AmpC and Predominant ESBL-Producing Isolates (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.

Sulopenem Activity Among AmpC and Predominant ESBL-Producing Isolates (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.

Clinical Microbiology Summary and Conclusions

- Overall, sulopenem demonstrated similar in vitro activity against most targeted species compared to meropenem and ertapenem; this activity appeared better than imipenem
- Sulopenem had no discernible activity against *P. aeruginosa* and *A. baumannii* isolates
- The in vivo activity of sulopenem was demonstrated in animal therapeutic infection models
- Sulopenem demonstrated similar activity against fluoroquinolone-resistant and –susceptible isolates
- Sulopenem demonstrated activity against certain beta-lactamase containing isolates (e.g., AmpC, CTX-M, TEM, SHV), both in vitro and in clinical infections

Thank You

Clinical Pharmacology Assessment

NDA 213972

Sulopenem Etzadroxil/Probenecid

Henrietta Abodakpi, Pharm.D., Ph.D.
Clinical Pharmacology Reviewer
Division of Infectious Disease Pharmacology
Office of Clinical Pharmacology/CDER/FDA

Pharmacokinetic (PK) Highlights

<table>
<tr><th>PK Properties</th><th>Oral Sulopenem</th></tr>
<tr><td>Absolute Bioavailability</td><td>
<table>
<tr><td>Fasted</td><td>Fed</td></tr>
<tr><td>40%</td><td>64%</td></tr>
</table>
</td></tr>
<tr><td>Distribution</td><td>Plasma-protein binding: 11%</td></tr>
<tr><td>Metabolism</td><td>Oral tablet formulation as prodrug sulopenem etzadroxil that is hydrolyzed by esterases to active sulopenem</td></tr>
<tr><td>Elimination</td><td>$t_{1/2}$: ~1 hour
Excretion: primarily excreted in urine, 26.9% as unchanged sulopenem
<table>
<tr><th>CrCL (mL/min)</th><th>Fold-increase in AUC Compared to Subjects with CrCL ≥ 90 mL/min</th></tr>
<tr><td>≥ 60 to < 90</td><td>2.0</td></tr>
<tr><td>≥ 30 to < 60</td><td>3.0</td></tr>
<tr><td>≥ 15 to < 30</td><td>7.4</td></tr>
</table>
</td></tr>
<tr><td>Drug-drug Interactions</td><td>• Drug-drug interaction liabilities are driven by probenecid, an OAT1/3 inhibitor
• Coformulated with sulopenem (an OAT3 substrate) to increase plasma exposures</td></tr>
</table>

Abbreviations: $t_{1/2}$: half-life; CrCL: creatinine clearance; AUC: area under the concentration-time curve; OAT1/3: organic anion transporter 1 and 3

Clinical Pharmacology Considerations

1. Adequacy of dosages evaluated for the treatment of uUTI and cUTI:
   a. Strength of supportive evidence from probability of target attainment (PTA) analyses
   b. Pharmacokinetic/pharmacodynamic (PK/PD) perspectives on clinical trial efficacy outcomes
2. Clinical pharmacology perspective on the contribution of probenecid
3. Recommendations for use in the setting of renal impairment

Utility of PTA Analysis Based on Nonclinical PK/PD in the Setting of uUTI

- For most antibacterial indications:
  - Dose selection is informed by the probability of achieving the PK/PD target determined in a nonclinical infection model relevant to clinical efficacy
- However, for uUTIs:
  - Lack of an established nonclinical model and,
  - Knowledge gaps about urine-specific PK/PD parameters, the appropriate bacteriologic endpoint and relative importance of urinary versus plasma drug exposures in PTA analyses
- Therefore, there are limitations to the use of PTA analyses to assess the adequacy of a proposed drug dosage for the treatment of uUTI. Nonetheless, PTA analyses were conducted in support of oral sulopenem dosage selection

PK/PD Index Selection

- Dose fractionation studies were conducted in a murine thigh and in vitro 1-compartment infection models
- Concerns with the design of the murine thigh infection model studies limited their utility
- In vitro studies suggested that sulopenem exhibits both time and concentration-dependent killing. Nonetheless, *f*T>MIC was selected based on:
  - The highest observed r^2 amongst the 3 traditional PK/PD indices
  - Mechanism of bacterial killing attributed to the β-lactam class

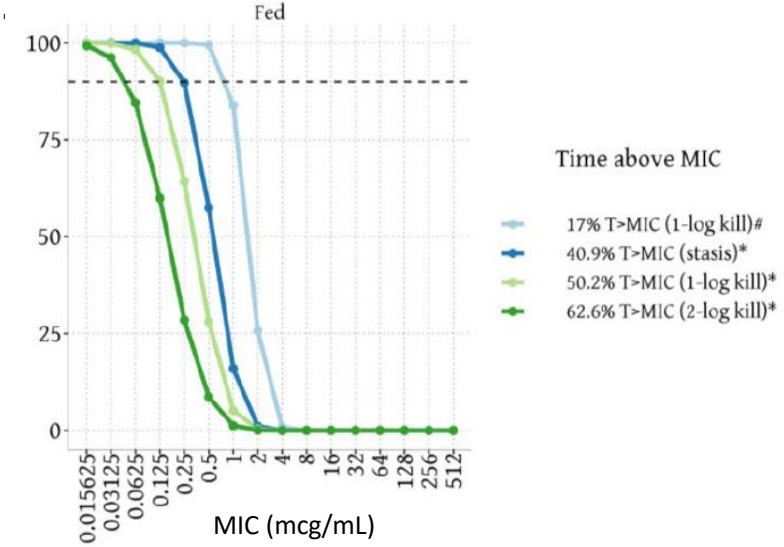
PK/PD Target Determination

- Applicant relied on in vivo targets from the murine thigh infection model for initial dose selection
  - FDA found these targets unreliable due to concerns with study design and limited interpretability of the results
- Subsequent in vitro target determination studies were used to justify retaining the dosage used in uUTI Trial 301 for Trial 310
  - Targets were derived from 10 Enterobacterales isolates (6 *E. coli* and 4 *K. pneumoniae*) with sulopenem MICs ranging from 0.03 – 0.5 mcg/mL
  - Median targets for stasis, 1-$\log_{10}$ kill and 2-$\log_{10}$ kill were 40.9, 50.2 and 62.6% *f*T>MIC, respectively

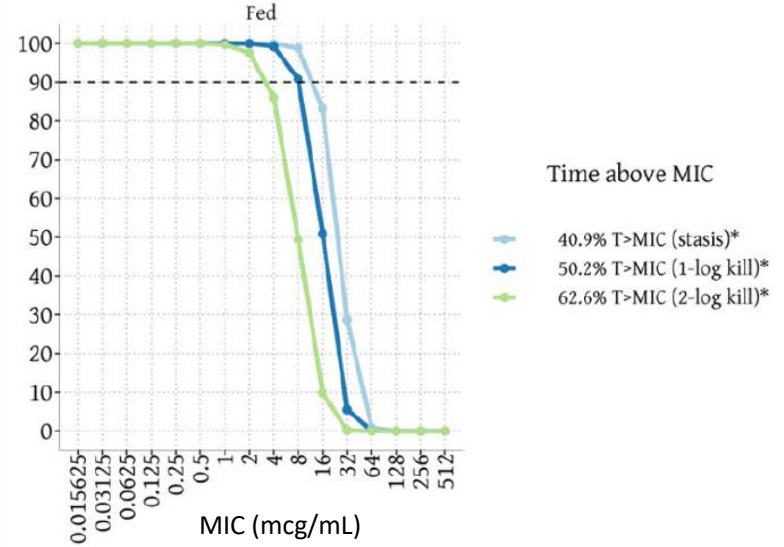
Probability of PK/PD Target Attainment in Plasma Versus Urine

- Probability of achieving the target for stasis is > 90% at MIC = 0.25 mcg/mL in plasma and MIC = 8 mcg/mL in urine
- For 2-log kill, urine-based PTA remains > 90% up to MIC = 2 mcg/mL

Plasma



Urine



Source: NDA submission

Assessment of Proposed Dosage for the Treatment of uUTI

- The results of urine and plasma exposure-based PTA analyses evaluating the probability of achieving the in vitro PK/PD targets support the efficacy of 500 mg sulopenem etzadroxil/500 mg probenecid twice daily
- However, PTA results alone are insufficient to inform dose optimization and there are no clinical dose-ranging studies to ascertain whether the proposed dosage for the treatment of uUTI is fully optimized
- Furthermore, PTA results cannot predict oral sulopenem's performance against different comparators, but differences in PK/PD attributes between drug classes may help contextualize the observed clinical trial outcomes

Assessment of Dosage Used in cUTI Trial

- cUTI Trial 302 evaluated a 1000 mg dose of sulopenem administered as a 3 h IV infusion for at least 5 days, followed by optional stepdown therapy with 500 mg sulopenem etzadroxil/500 mg probenecid twice daily
- Selection of this dosage was informed by the in vivo PK/PD targets deemed unreliable by the FDA to inform dose selection
- Moreover, the bioavailability of oral sulopenem is 40-64% relative to the IV formulation, thus raising concerns about the adequacy of the oral stepdown dosage

Contribution of Probenecid

- Probenecid's mechanism of action as an OAT inhibitor is leveraged to increase plasma drug exposures by decreasing renal clearance (CLr)
- Multiple dose administration of 500 mg probenecid increases sulopenem plasma AUC by 1.8-fold while decreasing CLr by 1.9-fold
  - However, the cumulative amount of sulopenem recovered in urine over a 24-hour period is comparable in the presence and absence of probenecid
- Given the importance of urinary drug concentrations to the effective treatment of uUTIs, the contribution of probenecid to the efficacy of oral sulopenem for uUTI is unclear

Recommendations for Use in the Setting of Renal Impairment

- The Applicant does not propose alternative dosage recommendations for patients with renal impairment
- Similar to probenecid, renal impairment decreases sulopenem CLr but the available data are inconclusive on the efficacy implications
- Increases in sulopenem plasma exposures are observed with decreasing renal function
  - Increases in subjects with mild, moderate and severe renal impairment are not considered clinically significant
- Given sulopenem's short plasma half-life and the 5-day duration of treatment for uUTI, the general oral sulopenem dosage is expected to be safe in patients with mild, moderate and severe renal impairment
- Because the PK and safety of oral sulopenem have not been evaluated in patients with CrCL < 15 mL/min or on hemodialysis, use is not recommended in these subpopulations

Summary

- Limitations notwithstanding, the PTA results support the efficacy of 500 mg oral sulopenem twice daily for the treatment of uUTI
- The available data are inconclusive on the contribution of probenecid to the efficacy of oral sulopenem in the treatment of uUTI
- Use of oral sulopenem is expected to be safe in the setting of mild, moderate or severe renal impairment but is not recommended in patients with CrCL < 15 mL/min and patients on hemodialysis

Thank You

Charge to the Committee

Sulopenem Etzadroxil/Probenecid

NDA 213972

Peter Kim, MD, MS
Director, Division of Anti-Infectives
Office of Infectious Diseases
Center for Drug Evaluation and Research
Food and Drug Administration

September 9, 2024

Considerations

- The two phase 3 trials for uUTI (Trials 301 and 310) studied oral sulopenem for the treatment of uUTI in an ambulatory setting and were not designed to evaluate the efficacy of oral sulopenem for the treatment of uUTI caused by resistant bacterial isolates, or for the treatment of uUTI in patients who failed first-line treatment.
- If approved, sulopenem etzadroxil/probenecid would be the first oral penem antibacterial drug marketed in the United States, and inappropriate use may contribute to AMR or increase cross-resistance to other penem drugs.

Considerations

- Because IV sulopenem followed by oral sulopenem was found to be inferior to the active comparator regimen for cUTI in Trial 302, there is concern that if approved, oral sulopenem may be used off-label for the treatment of cUTI or other infections, as stepdown treatment.
- There are no data on the effectiveness of oral sulopenem as stepdown therapy following IV treatment of cUTI with another antibacterial drug.

Considerations

- While antimicrobial stewardship and consideration by guidelines committees may help to determine appropriate positioning of oral sulopenem, if approved, in the hierarchy of uUTI treatment options, a discussion of approaches to inform prescribers of relevant data submitted in this NDA to ensure the most appropriate use of oral sulopenem is warranted.

Questions for the Advisory Committee

1. **DISCUSSION:** 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. Discuss the overall benefits and risks for the use of sulopenem etzadroxil/probenecid for this indication.
2. **DISCUSSION:** Considering the totality of the evidence in this application, discuss considerations that would be important for medical providers to know to ensure appropriate use of sulopenem etzadroxil/probenecid.