

# Sulopenem for the Treatment of Complicated and Uncomplicated Bacterial Urinary Tract Infection (UTI)

Aiyi Ivy Chen, Thanh-Liem Vu, Daniel J Yang, Landon Olsen, PharmD Candidates, and H Stephen Lee, PharmD, MSc, BSc (Honors)  
College of Pharmacy, Roseman University of Health Sciences, South Jordan, UT



## Urinary Tract Infections (UTIs)

- E. coli* and *K. pneumoniae* are the leading causes of UTIs, and the increased use of antibiotics has conferred increasing drug resistance<sup>1</sup>, such as extended spectrum beta-lactamase (ESBL), fluoroquinolone (FQ), and trimethoprim-sulfamethoxazole (TMP-SMX) resistance.
- UTIs may be classified as complicated due to a variety of factors like treatment failure, pregnancy, renal failure, diabetes, immunosuppression, or symptoms of UTI lasting  $\geq 7$  days.<sup>2</sup>

## Common Therapeutic Options

ESBL	Complicated	Uncomplicated
Absence (Negative)	<ul style="list-style-type: none"> <li>3rd Generation cephalosporins (e.g. ceftriaxone)</li> <li>Fluoroquinolones (e.g. ciprofloxacin, levofloxacin)</li> </ul>	<ul style="list-style-type: none"> <li>TMP/SMX</li> <li>Fosfomycin</li> <li>Nitrofurantoin</li> <li>Ciprofloxacin, Levofloxacin</li> </ul>
Presence (Positive)	Carbapenem (e.g. ertapenem) Fluoroquinolones	

## ESBLs and the Need for an Oral Carbapenem

- E. coli* and *K. pneumoniae* have extended spectrum  $\beta$ -lactamase (ESBL) that confers their multidrug resistance
- Incidences of ESBL in uropathogens are on the rise.<sup>3</sup>
- Current recommended therapy for ESBL-producing isolates includes carbapenems, fluoroquinolones and ceftolozane/tazobactam.
- Carbapenems are especially effective against ESBLs, but they are currently FDA-approved only as IV formulation.
- An oral carbapenem would, therefore, be an excellent addition for UTI therapy for individuals with ESBL-positive uropathogens.

## Sulopenem

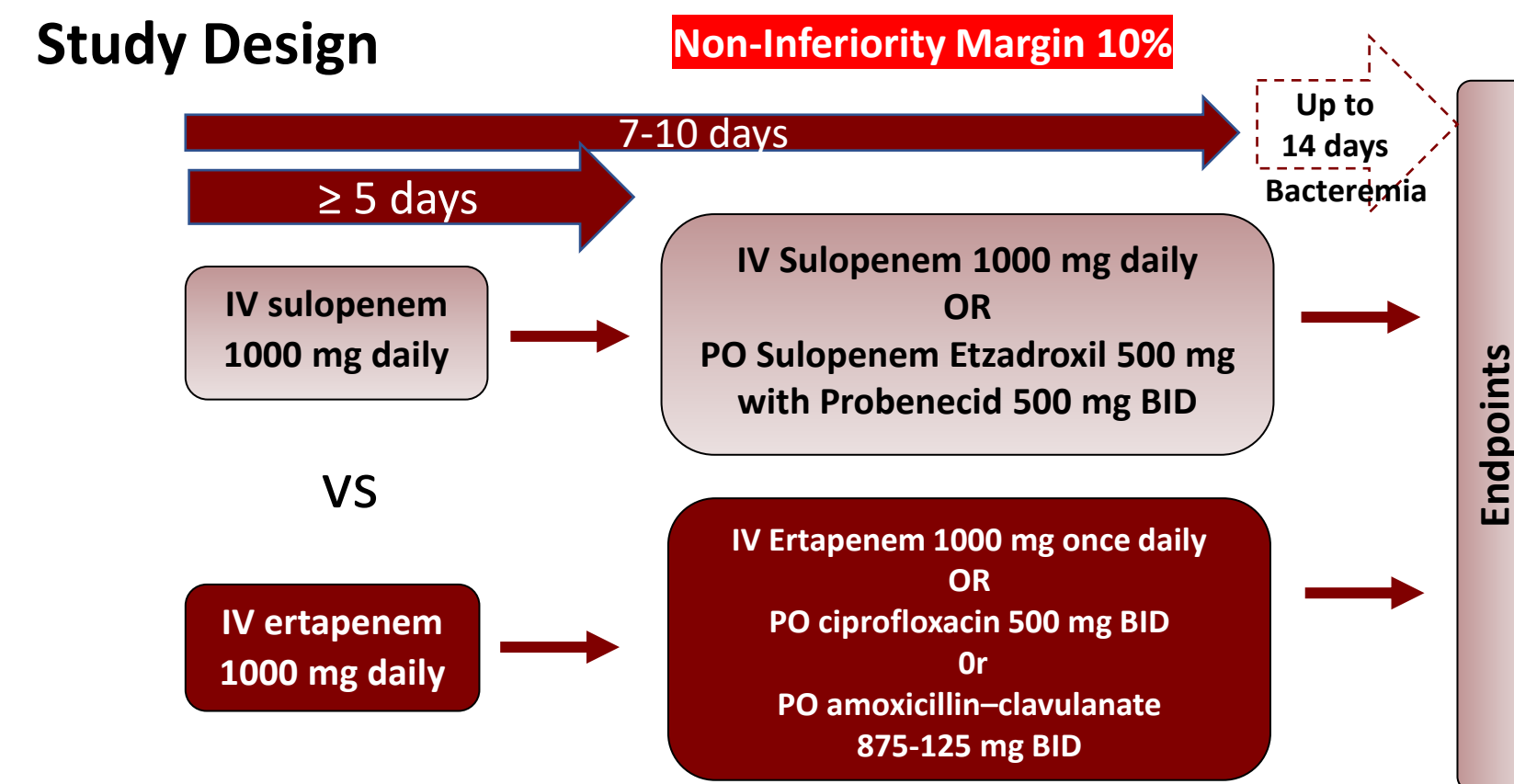
- A novel carbapenem (beta lactam) that is given by oral or intravenous routes.
- Sulopenem etzadroxil is a oral prodrug that is metabolized to the active form sulopenem.
- Oral bioavailability =  $\sim 25\%$  (without probenecid or food); With probenecid-  $\uparrow$ AUC by 63% and  $\uparrow$ bioavailability by 60%; in fed state-  $\uparrow$ AUC by 24%.<sup>4</sup>
- Serum half-life =  $\sim 1$  hour;  $V_D = \sim 22$  L.<sup>4</sup>

## Phase 3 Clinical Trials Review

### Complicated Urinary Tract Infection (cUTI)

- NCT03357614 Trial (Dunne et al, 2023).<sup>5</sup>
- Multicenter, randomized, comparative, double-blind trial, multicentered, multinational non-inferiority trial.

#### Study Design

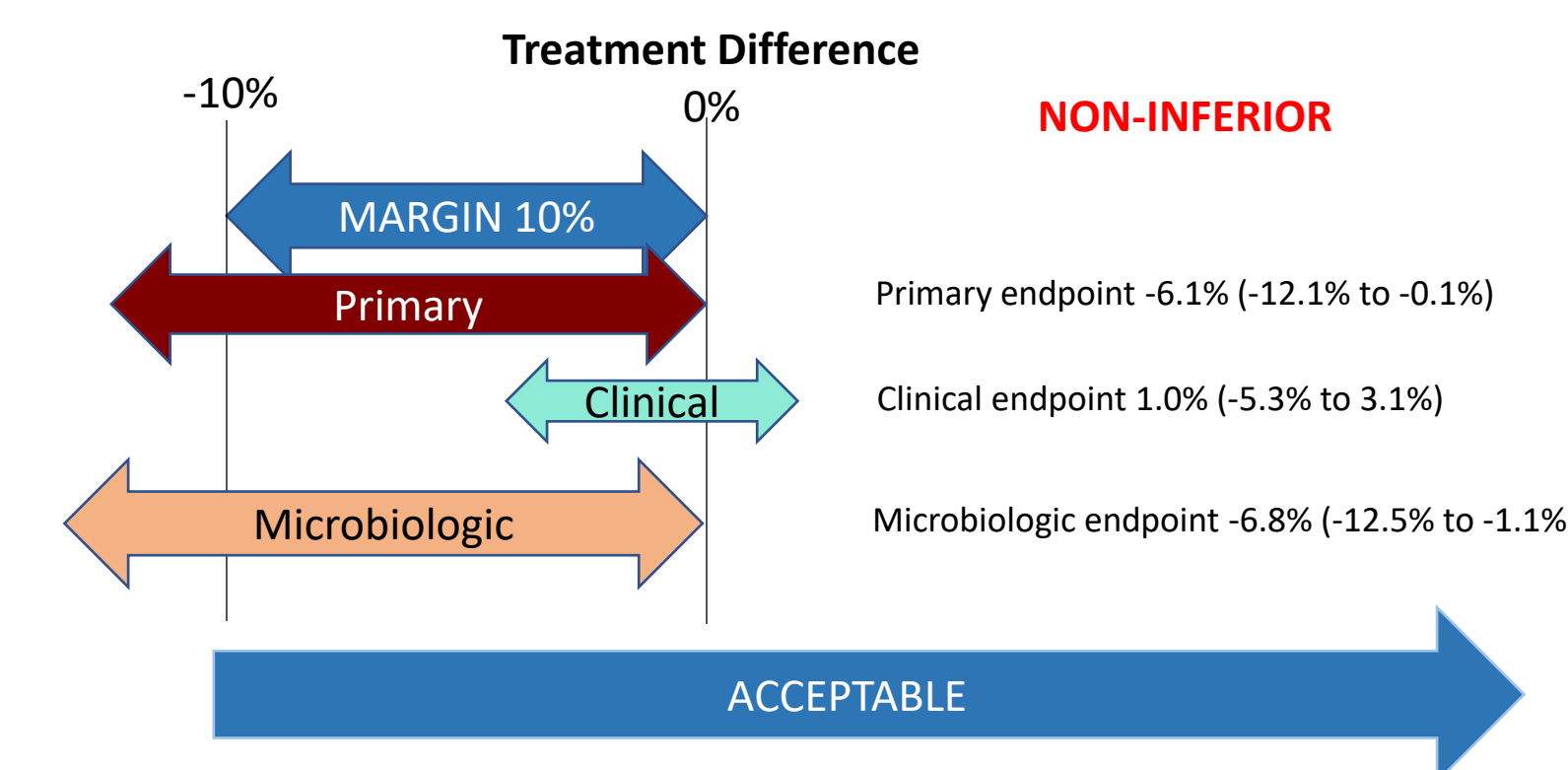


#### Subjects

- Hospitalized adults with pyuria, bacteriuria, and signs and symptoms; average age 58 years, 60% females, 5% from the U.S.
- 90% with CrCl  $> 30$  ml/min, pyelonephritis 58%, cUTI 42%; bacteremia 10%

#### Pathogen Isolates

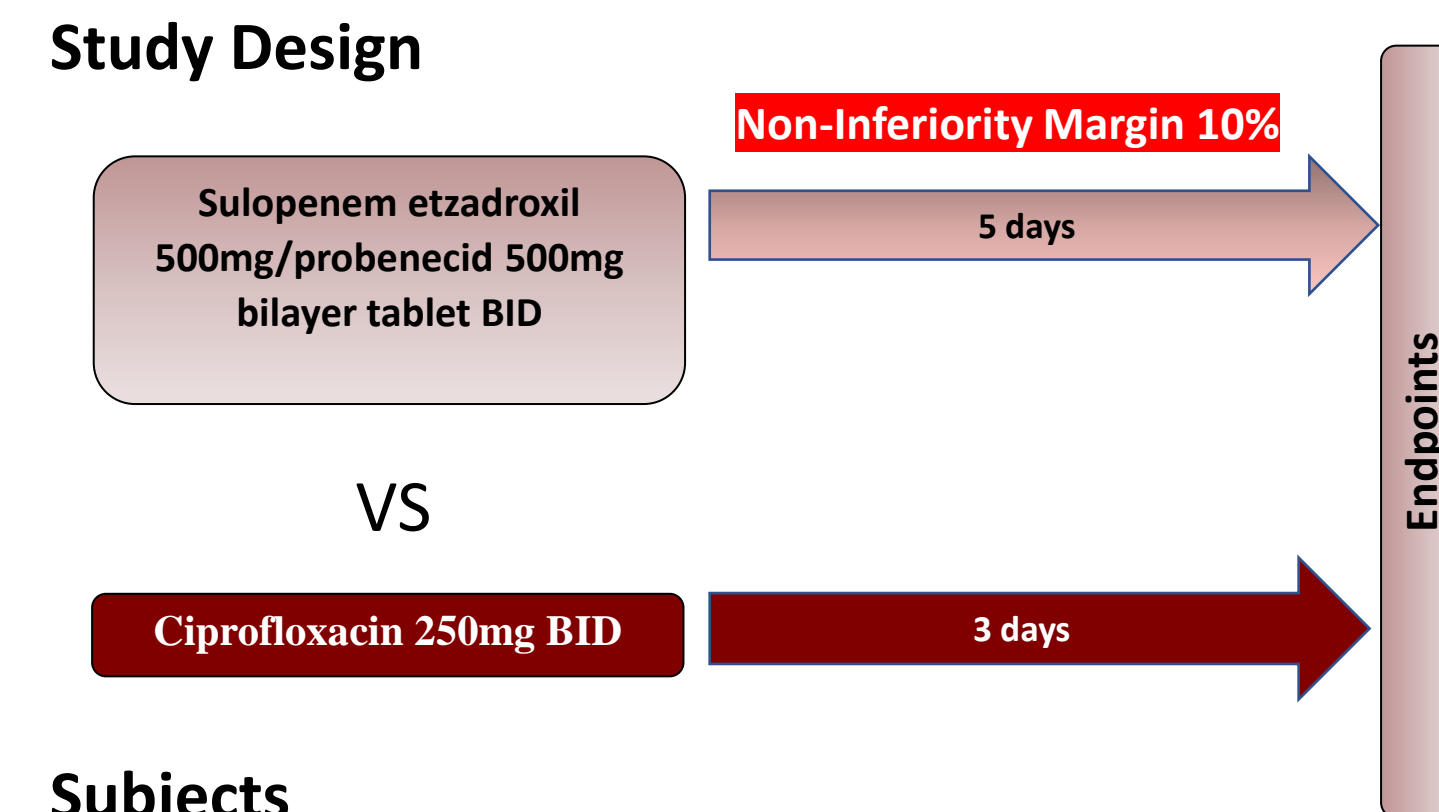
- 77% *E. coli*, 11% *K. pneumoniae*
- 26% ESBL- positive
- 38% FQ-nonsusceptible
- 35% TMP-SMX-nonsusceptible
- 21% ESBL-positive/FQ-nonsusceptible
- 15% ESBL-positive/ FQ-nonsusceptible/ TMP/SMX-nonsusceptible



### Uncomplicated Urinary Tract Infection

- SURE-1 Trial (Dunne et al, 2020).<sup>6</sup>
- NCT03354598 Trial (Dunne et al, 2023).<sup>7</sup>
- Multicenter, randomized, prospective, double-blind, double dummy trial, multicentered, multinational non-inferiority trial

#### Study Design



#### Subjects

- Women aged  $\geq 18$  years with pyuria, bacteriuria, and signs and symptoms of uUTI; average age 55 years, 90% Caucasian, 55% from the U.S.
- 70% with CrCl  $> 90$  mL/min

#### Pathogen Isolates

- 86% *E. coli*, 11% *K. pneumoniae*
- 14% ESBL- positive
- 32% TMP-SMX-nonsusceptible,
- 18% nitrofurantoin-nonsusceptible
- 28% ciprofloxacin-nonsusceptible

## Combined clinical and microbiologic response at Test of Cure (TOC)

Treatment Groups	Sulopenem Etzadroxil / Probenecid	Ciprofloxacin	Difference (95% CI)
Quinolone nonsusceptible population (mMITT-R)	92/147 (62.6%)	50/139 (36.0%)	26.6% (15.1% to 37.4%)
Quinolone susceptible population (mMITT-S)	247/370 (66.8%)	326/415 (78.6%)	-11.8% (-18.0% to -5.6%)
Combined (mMITT)	339/517 (65.6%)	376/554 (67.9%)	-2.3% (-7.9% to 3.3%)

## Resistance in Complicated Urinary Tract Infections<sup>5</sup>

	Sulopenem	Ertapenem	Difference. 95% CI
ESBL-positive	79/110 (71.8%)	85/125 (68.0%)	3.8% (-7.9% to 15.5%)
ESBL-positive, Quinolone-resistant	64/92 (69.6%)	64/99 (64.6%)	4.9% (-8.5% to 18.1%)
Quinolone resistant	112/162 (69.1%)	116/179 (64.8%)	4.3% (-5.6% to 14.3%)
TMP-SMX resistant	106/154 (68.8%)	111/161 (68.9%)	-0.1% (-10.3% to 10.1%)
ESBL-positive, quinolone-resistant, TMP-SMX resistant	43/59 (72.9%)	47/75 (62.7%)	10.2% (-5.5% to 26.0%)

## Adverse Events (AEs)

Treatment Groups	Complicated UTI <sup>5</sup>		Uncomplicated UTI <sup>7</sup>	
	Sulopenem	Ertapenem	Sulopenem Etzadroxil / Probenecid	Ciprofloxacin
Any AEs	15.1%	16.4%	25.0%	14.0%
Treatment-Related AEs	6.0%	9.2%	24.8%	13.9%
<b>Most Common Treatment-Related Adverse Event</b>				
Diarrhea	2.7%	3.0%	12.4%	2.5%
Nausea	-	-	3.8%	3.6%
Headache	3.0%	2.3%	2.2%	2.2%
Vomiting	-	-	1.6%	1.3%
Dizziness	-	-	1.1%	0.6%

## Discussion/Conclusion

- The overall responses of sulopenem in the cUTI trial did not demonstrate noninferiority to ertapenem, and the uUTI trial demonstrated sulopenem was noninferiority to ciprofloxacin.
- Sulopenem appeared to be safe and tolerated.
- FDA required additional clinical studies to demonstrate further activity in the quinolone-resistant patient population in cUTI trials, and with additional agents for uUTI trials.
- The FDA approval and commercial availability of sulopenem remains to be determined, similar to oral tebipenem.<sup>8</sup>

#### References

- Zumla A. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. *Lancet Infect Dis.* 2010;10(5):303-304. doi:10.1016/S1473-3099(10)70089-X
- Sabih A, Leslie SW. Complicated Urinary Tract Infections. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; November 28, 2022
- Aboumarzouk OM. Extended spectrum beta-lactamase urinary tract infections. *Urol Ann.* 2014;6(2):114-115.
- Zhanel GG, Pozdirca M, Golden AR, et al. Sulopenem: An Intravenous and Oral Penem for the Treatment of Urinary Tract Infections Due to Multidrug-Resistant Bacteria. *Drugs.* 2022;82(5):533-557. doi:10.1007/s40265-022-01688-1
- Dunne MW, Aronin SI, Das AF, et al. Sulopenem for the Treatment of Complicated Urinary Tract Infections Including Pyelonephritis: A Phase 3, Randomized Trial. *Clin Infect Dis.* 2023;76(1):78-88. doi:10.1093/cid/ciac704
- Dunne MW, Das AF, Zelasky Met al. LB-1. Efficacy and Safety of Oral Sulopenem Etzadroxil/Probenecid Versus Oral Ciprofloxacin in the Treatment of Uncomplicated Urinary Tract Infections (uUTI) in Adult Women: Results from the SURE-1 Trial, *Open Forum Infectious Diseases*, Volume 7, Issue Supplement\_1, October 2020, Page S844, <https://doi.org/10.1093/ofid/ofaa515.1898>
- Dunne MW, Aronin SI, Das AF, et al. Sulopenem or Ciprofloxacin for the Treatment of Uncomplicated Urinary Tract Infections in Women: A Phase 3, Randomized Trial. *Clin Infect Dis.* 2023;76(1):66-77. doi:10.1093/cid/ciac738
- Eckburg PB, Muir L, Critchley IA, et al. Oral tebipenem pivoxil hydrobromide in complicated urinary tract infection. *NEJM.* 2022;386(14):1327-1338. doi:10.1056/nejmoa2105462