Sulopenem Etzadroxil/Probenecid (Oral Sulopenem) for Treatment of Uncomplicated Urinary Tract Infections

September 9, 2024

Iterum Therapeutics

Antimicrobial Drugs Advisory Committee

Introduction

Michael Dunne, MD, FIDSA

Board Member, Consultant

Iterum Therapeutics

Agenda

Introduction	**Michael Dunne, MD, FIDSA** Board Member, Consultant Iterum Therapeutics
Unmet Need	**Marjorie Golden, MD, FIDSA** Site Chief, Infectious Disease St. Raphael Campus Yale New Haven Hospital
Efficacy, Microbiology and Pharmacology	**Michael Dunne, MD, FIDSA**
Safety	**Steven Aronin, MD, FIDSA** Senior VP and Head of Clinical Development Iterum Therapeutics
Benefit-Risk	**Michael Dunne, MD, FIDSA**

History of Key Oral Antibiotics for uUTI

Antibiotic	FDA Approval Date	Resistance Rate Iterum uUTI Studies, % (n)
Nitrofurantoin	February 1953	**16.7%** (344)
Cephalexin	January 1971	**15.9%*** (328)
TMP-SMX	July 1973	**31.0%** (638)
Amoxicillin/clavulanate	August 1984	**13.2%** (272)
Ciprofloxacin	October 1987	**26.9%** (554)
Fosfomycin	December 1996	**3.0%** (61)

*Based on resistance rates for Enterobacterales versus cefazolin from Iterum's 301 and 310 studies combined using urinary breakpoints; per the FDA, CLSI-published urinary cefazolin breakpoints should be used to predict the susceptibility of oral cephalosporins including cephalexin

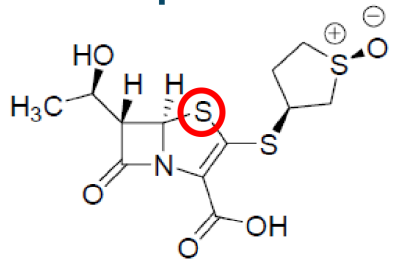
uUTI Claims Analysis - Total uUTI Market Estimate and Distribution of Utilization

	2023 TRx in adult women (oral solids) (EVERSANA Claims)	Share of uUTI infections receiving product (EVERSANA Claims)	Implied 2023 adult women TRx in uUTI*
Nitrofurantoin	12,094,341	30%	12,094,341
Cephalexin	-	18%	7,321,051
Trimethoprim-sulfamethoxazole	-	14%	5,791,496
Ciprofloxacin	-	14%	5,812,856
Amoxicillin/Other*	-	7%	2,797,655
Amoxicillin/Clavulanate	-	8%	3,330,438
Cefdinir	-	5%	2,187,931
Levofloxacin	-	4%	1,578,098
Total	-	100%	40,913,867

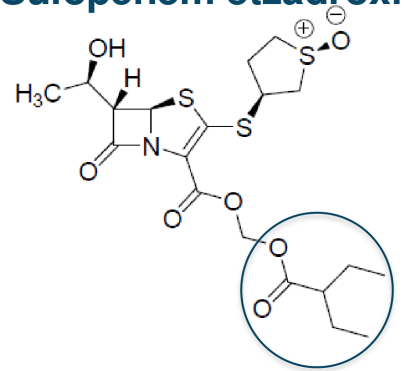
*2023 TRx in adult women multiplied by uUTI infection shares relative to nitrofurantoin
Source: Extrapolated from EVERSANA's longitudinal pharmacy and medical claims data within ACTICS Platform (December 2022-November 2023)

Sulopenem Etzadroxil / Probenecid (Oral Sulopenem)

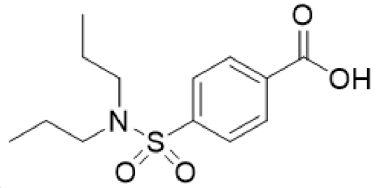
Sulopenem



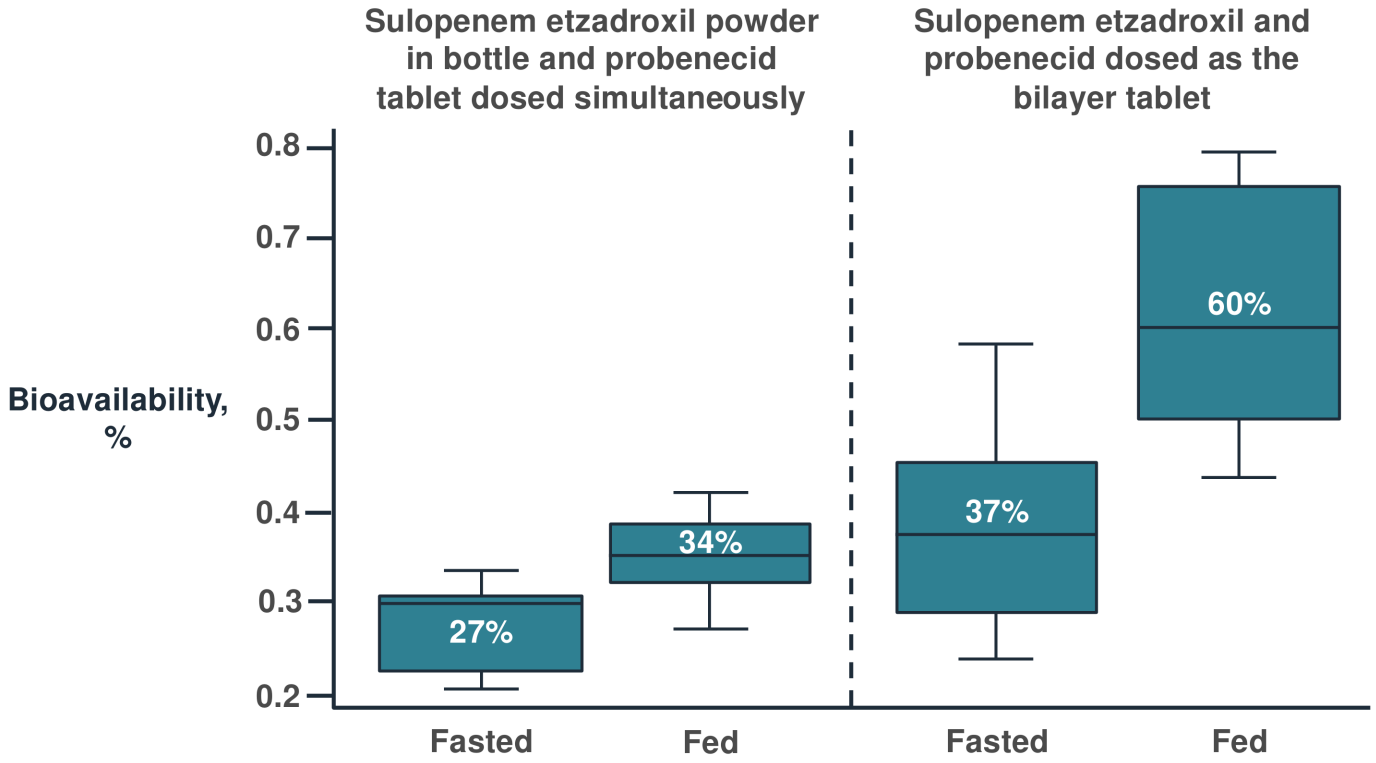
Sulopenem etzadroxil

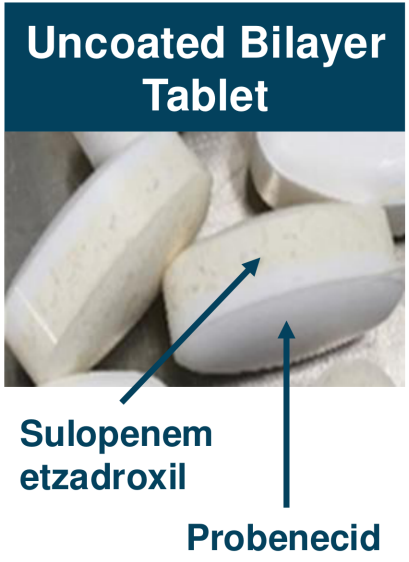


Probenecid



Sulopenem Etzadroxil / Probenecid (Oral Sulopenem)





Sulopenem Mechanism of Action

- High affinity for penicillin binding proteins
- Broad activity against most common UTI Enterobacterales
  - *E. coli, K. pneumoniae*, and *P. mirabilis*

Phase 3 Development Program Includes > 5,900 Patients

Study 301	Study 310	Study 302	Study 303
Uncomplicated UTI N = 1671	**Uncomplicated UTI** N = 2222	**Complicated UTI** N = 1395	**Complicated IAI** N = 674
Oral Sulopenem vs **Ciprofloxacin**	**Oral Sulopenem** vs **Amoxicillin / Clavulanate**	**IV Sulopenem / Oral Sulopenem** vs **IV Ertapenem / Ciprofloxacin** or **Amoxicillin / Clavulanate**	**IV Sulopenem / Oral Sulopenem** vs **IV Ertapenem / Ciprofloxacin + Metronidazole or Amoxicillin / Clavulanate**
Primary Endpoint Clinical and microbiologic success at Day 12	Primary Endpoint Clinical and microbiologic success at Day 12	Primary Endpoint Clinical and microbiologic success at Day 21	Primary Endpoint Clinical success at Day 28

Sulopenem will Address an Unmet Medical Need for Effective Treatment of uUTI

- Existing antibiotics do not provide confidence in coverage because of increasing resistance rates
  - Approaching and exceed 20% for standard of care options which challenges use of empiric therapy
- Consistent results from Study 301 and 310 demonstrate benefit of treatment with oral sulopenem
- Oral sulopenem was found to be safe and well tolerated

Proposed Indication

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

Important Topics for Today's Discussion

1. Review of Efficacy Data to Support the Proposed Indication
   - Study 301
   - Study 310
   - Study 302 (lessons learned from cUTI study)
2. Review discussion topics posed by the FDA as they relate to oral sulopenem
   - Antibiotic stewardship
   - Target patient population

Unmet Need for uUTI Therapy

Marjorie Golden, MD, FIDSA

Associate Professor of Medicine;

Site Chief, Infectious Disease,

St. Raphael Campus Yale New Haven Hospital

UTIs Are Most Common Outpatient Infection in Women

- 40 million outpatient prescriptions for uUTI in the US annually
  - 60% of women will have an uUTI in their lifetime[1]
  - *E. coli, K. pneumoniae* and *P. mirabilis* are the most common pathogens responsible for infection
- Up to 40% of women with history of uUTI will have a recurrence of their infection[2]
- Rising rates of antibiotic resistance, aging population with growing comorbidities, and antibiotic allergies are making antibiotic selection more challenging

1. Suskind, 2016; 2. Gupta, 2013

IDSA Guidelines for Treatment of uUTIs

Nitrofurantoin

Trimethoprim-sulfamethoxazole

Fosfomycin
Inferior efficacy than other agents

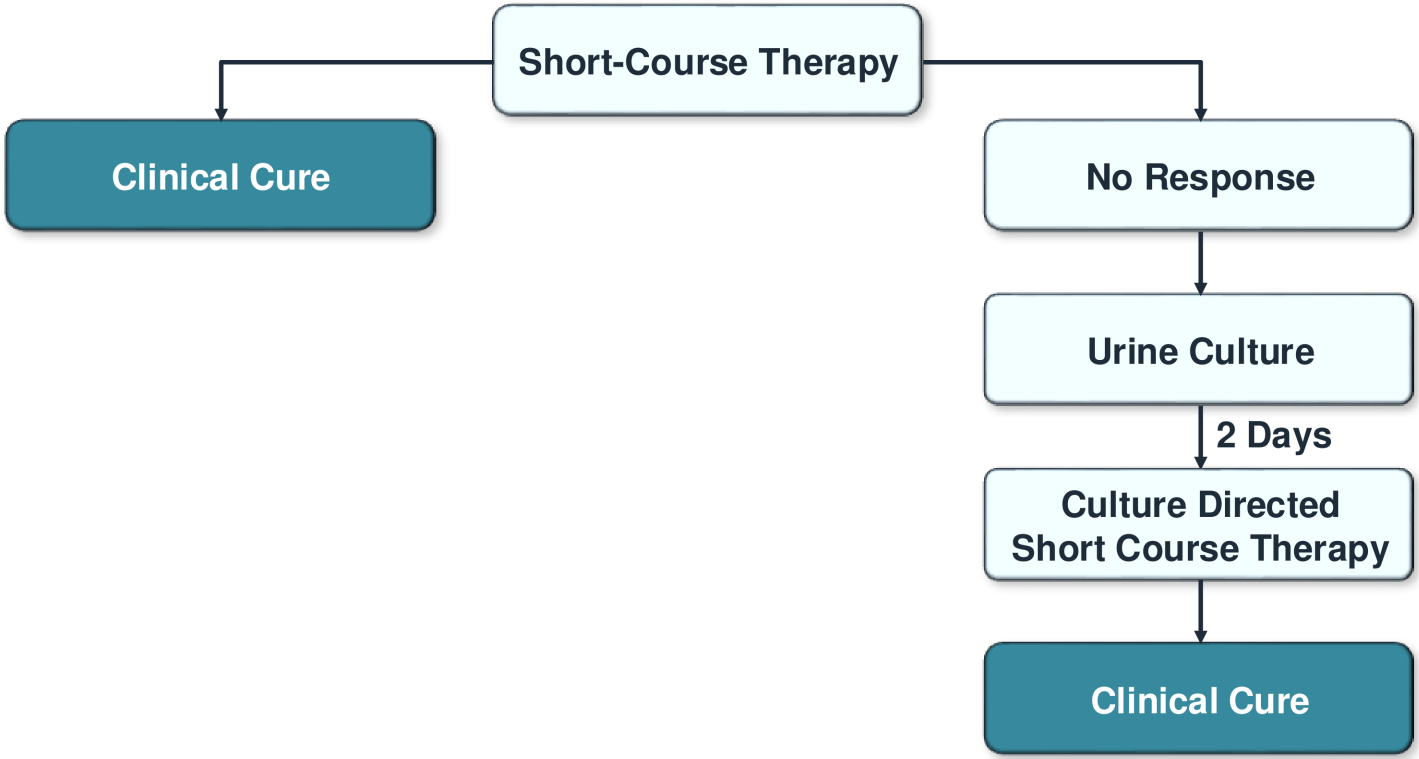
Pivmecillinam
Possible inferior efficacy

Fluoroquinolones

β-lactams

Gupta, Clin Infect Dis 2011

Short-Course Antibiotic Without Prior Culture is Standard of Care for Uncomplicated UTIs



Adapted from Mandell, 2019

Selection of Appropriate Antibiotic Therapy

- For practicing clinicians, decision about treatment is made based on IDSA guidelines, but also requires a thoughtful assessment of the patient's overall condition
- Underlying medical conditions
  - Medication list
  - Allergy history
  - Understanding risk/benefit profile
- History of resistant pathogens

Representative Clinical Scenario

- 70-year-old woman with Diabetes mellitus, interstitial lung disease (ILD) and Parkinson's disease developed lower abdominal pain, low grade fever, dysuria
- Urinalysis with 560 WBC
- Sulfa allergy (rash and acute kidney injury)
- Prefer to avoid nitrofurantoin in setting of known ILD
- Intolerable diarrhea with prior courses of Fosfomycin
- No current viable oral options

Representative Clinical Scenario

	Escherichia coli	
	MIC Susceptibility	Kirby Bauer Susceptibility
Amikacin	Susceptible	
Ampicillin	Resistant	
Ampicillin + Sulbactam	Susceptible	
Cefazolin	Resistant[1]	
Ceftriaxone	Resistant	
Cefuroxime	Resistant	
Ciprofloxacin	Resistant	
Ertapenem	Susceptible	
Fosfomycin		Susceptible
Gentamicin	Resistant	
Nitrofurantoin	Susceptible	
Piperacillin + Tazobactam	Susceptible	
Tobramycin	Resistant	
Trimethoprim + Sulfamethoxazole	Susceptible	

Rising Rates of Resistance Increase Risk of Failure With Empiric Therapy

Antibiotic Prescribed	Non-Susceptible Pathogen N = 5395	Second Prescription at Day 28	
		Non-Susceptible	Susceptible
Fluoroquinolone	22.8%	35.9%	16.0%
Trimethoprim-sulfamethoxazole	27.6%	36.8%	17.8%
Nitrofurantoin	15.9%	37.0%	20.3%

Dunne, Microbiol Spectrum 2022

IDSA Guidelines Imply that Prescribers Should Avoid an Antibiotic if Resistance Prevalence > 20%

Antibacterial Agent / Class	Percent Resistance Among Urine Isolates Collected		
	2011-2020[1*] N = 2,228,515	IT001-301 2018-2020 N = 1,071	IT001-310 2022-2023 N = 990
β-lactam[2]	57.5%	63.0%	29.7%
ESBL+	6.9%	13.5%	9.9%
Fluoroquinolone	20.6%	27.4%	26.4%
Trimethoprim-sulfamethoxazole	23.1%	31.6%	30.3%
Nitrofurantoin	20.2%	17.9%	15.4%

1: Dunne, *BMC Infect Dis* 2022; *Organisms tested: 73% *E. coli*, 14% *K. pneumoniae*, 6% *P. mirabilis; 7%* Other Enterobacterales
2: β-lactams tested: (Dunne[1]: ampicillin-sulbactam, 1st, 2nd, 3rd, and 4th generation cephalosporins, piperacillin-tazobactam, carbapenems; IT001-301: amoxicillin-clavulanate, ampicillin, cefazolin, ceftazidime-avibactam, ceftriaxone, ertapenem, imipenem, meropenem, piperacillin-tazobactam; IT001-310: amoxicillin-clavulanate, cefazolin, ceftriaxone, ertapenem, meropenem)

Increasing Percent of Co-Resistance Among UTI Isolates of *E. coli*

Co-resistant Agent (Class)	Levofloxacin (quinolone) N = 445	Trimethoprim-sulfamethoxazole N = 588
Cefuroxime (β-lactam)	45.7%	31.3%
Ciprofloxacin (quinolone)	100%	44.2%
Trimethoprim-sulfamethoxazole	56.2%	100%

Critchley, 2019

Asymptomatic Bacteriuria (ASB)

IDSA Recommendations[1]

- Screening for and treatment of ASB not recommended for most patients
- Only screen and treat when
  - Patient is pregnant
  - Patient is undergoing an endourologic procedure

My clinical practice, supported by the literature[2]; do not culture if no symptoms and strongly discourage "proof of cure" cultures

1: Nicolle, 2019; Collins, 2016; Leis, 2014; Kelley 2014; Hartley, 2015; Sloane, 2017; USPSTF, 2017; Cai 2012; Gupta, 2011; Brown, 1990; Stevens, 2011
2: AHRQ, 2019; Hooton, 2017; Gupta, 2012; Hooton 2012

Need for New Therapies Effective Against Antibiotic Resistant Pathogens

- Standard of care antibiotics have become less effective due to increased resistance
- Women with uUTIs need new, safe and effective treatments that can be used empirically with confidence
  - Clearly, point of care diagnostics will play an important role in the future in being able to select appropriate antibiotic therapy

Microbiology & Pharmacology

Michael Dunne, MD, FIDSA

Sulopenem Has Broad Activity Against Most Common Organisms in uUTIs

Organism	Region	Year	N	MIC_{90}
E. coli	US-Europe	2016-2017	753	0.03
	US	2019	983	0.03
	US	2023	635	0.03
K. pneumoniae	US-Europe	2016-2017	303	0.12
	US	2019	273	0.06
	US	2023	163	0.06
K. oxytoca	US-Europe	2016-2017	75	0.06
	US	2019	41	0.06
	US	2023	31	0.06
K. aerogenes	US	2019	33	0.25
	US	2023	22	0.25
P. mirabilis	US-Europe	2016-2017	150	0.25
	US	2019	91	0.25
	US	2023	70	0.5
S. saprophyticus	US-Europe	2016-2017	61	0.25

IHMA Surveillance Data from 2016-2017 (hospital isolates from UTI and IAI infections); JMI Surveillance Data from 2019 and 2023

Activity of Sulopenem Consistent with Currently-Marketed Carbapenems

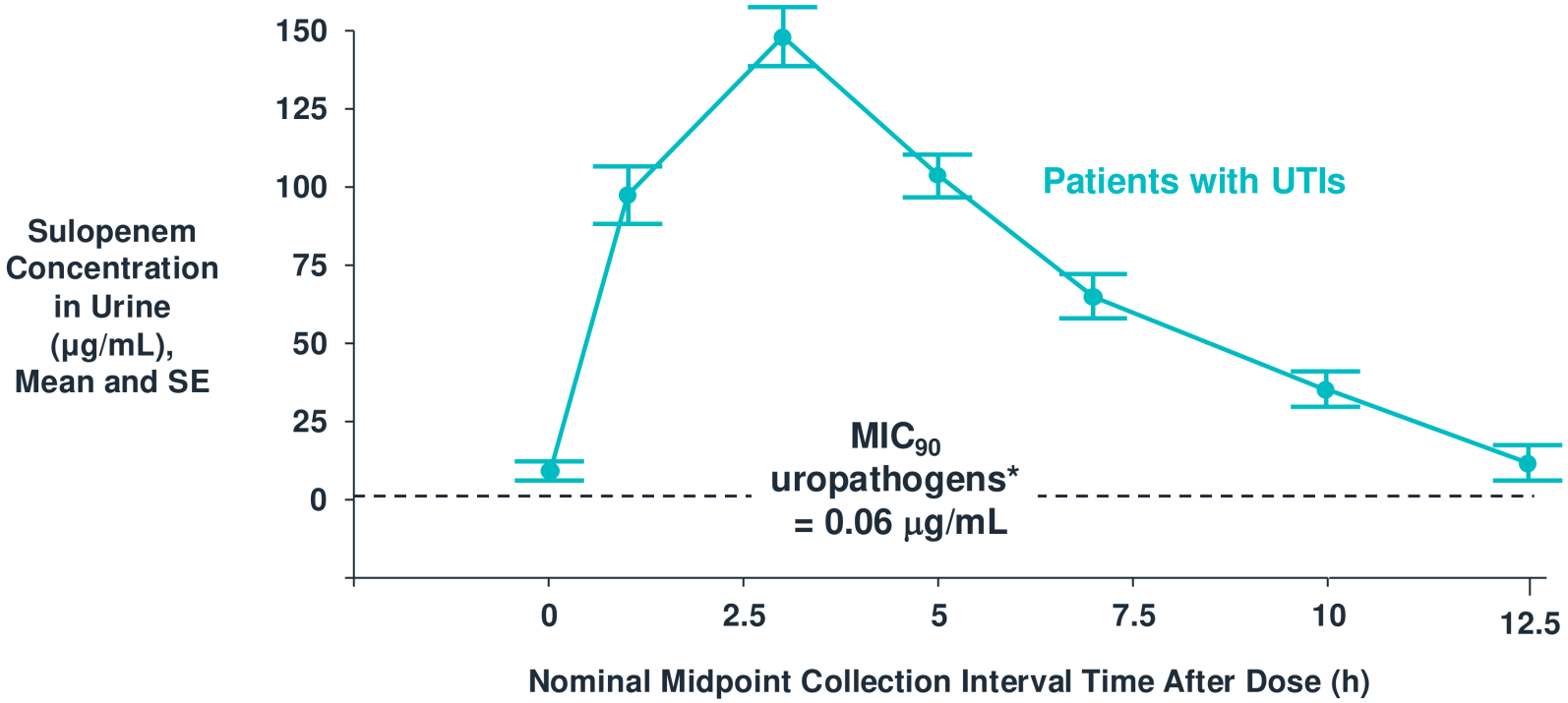
	E. coli N = 635		*K. pneumoniae* N = 163		*P. mirabilis* N = 70	
	MIC_{90}	Resistant	MIC_{90}	Resistant	MIC_{90}	Resistant
Sulopenem[1]	0.03	-	0.06	-	0.5	-
Imipenem[1]	≤0.12	0.2%	0.25	0.6%	4	78.6%
Meropenem[1]	0.03	0.2%	0.03	0.6%	0.12	0%
Ertapenem[2]	0.03	0.3%	0.06	1.8%	0.015	0%

1. JMI Surveillance Data 2023; 2. JMI Surveillance Data 2019 (E. coli N=983, K. pneumoniae N=273, P. mirabilis N=91)

Sulopenem Pharmacokinetics

- Rapidly distributed to tissues; Plasma protein binding is ~ 11%
- Metabolism primarily result of hydrolysis of the β-lactam ring
- Urinary excretion predominant route of elimination
- $T_{1/2}$: 1.1 hour in plasma
- Food increases bioavailability of bilayer tablet from 40% to 60%
- Probenecid increases exposure of sulopenem by ~ 50%
- No inhibition or induction of P450 enzymes
- Sulopenem is an avid substrate of OAT3
  - Explains effect of probenecid on sulopenem
  - Neither a substrate or inhibitor of other efflux transporters
- Sulopenem etzadroxil rapidly converted to sulopenem

Sulopenem Concentrations in Urine Exceed MIC_{90} of Target Uropathogens for 100% of Dosing Interval After Oral Dosing



*weighted distribution of uropathogens

Oral Sulopenem is Not Associated with Clinically Relevant Drug-Drug Interactions

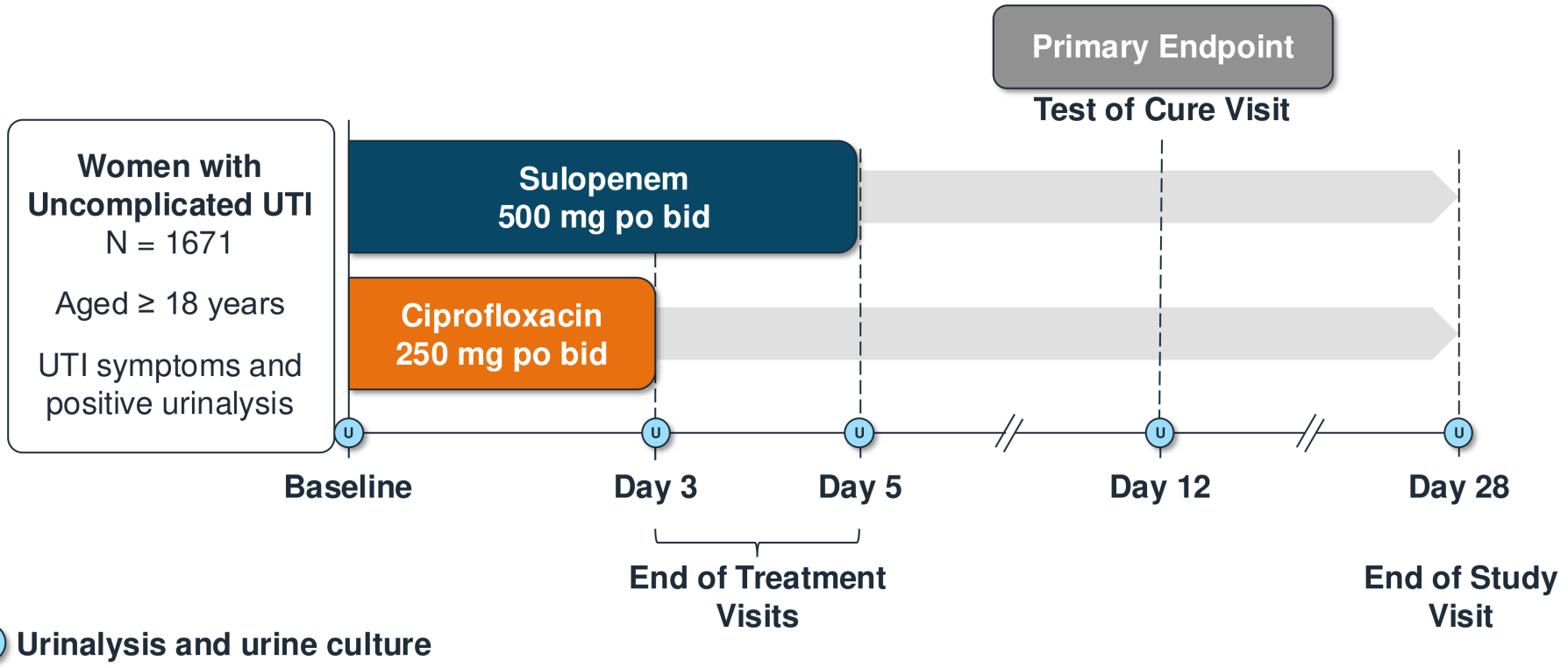
- In vitro studies support a low likelihood of clinically relevant DDIs
  - No interaction between itraconazole and oral sulopenem
- With oral sulopenem bilayer tablet, valproic acid (VPA) levels > 90% relative to baseline when dosed
  - Unexpected, as penems usually lead to decreased VPA levels
  - Beneficial effect with sulopenem etzadroxil possibly due to probenecid
  - Can be safely administered to patients with seizure disorder

Efficacy of Oral Sulopenem in Uncomplicated UTIs

Study 301

Study 310

Study 301: Randomized, Multicenter, Double-Blind, Active-Controlled Study



Study 301: Primary Endpoint

Primary Endpoint:
Proportion of patients achieving an overall response of success at Day 12 test of cure (TOC) visit

Overall Response of Success =

Clinical Success
- Resolution of symptoms, no new symptoms
- Frequency, urgency, pain on micturition or suprapubic pain

+

Microbiologic Eradication
- Urine culture < 10^3 CFU/mL
- Confirmed by susceptibility testing, multilocus sequence typing, resistance gene profiling

Study 301: Key Secondary Endpoints

- Overall Response at Day 5 (End of Treatment)
- Clinical success at Day 12 (TOC)
- Microbiologic eradication at Day 12 (TOC)
- Investigator's Assessment of clinical success at Day 12 (TOC)
- Overall Response at Day 28 (End of Study)
- Safety

Study 301: Pre-Specified Hierarchical Testing Method of Primary Endpoint

Analysis	Populations			
1st Step	1	**micro-MITTR** Superiority of oral sulopenem vs ciprofloxacin in patients with uropathogen non-susceptible to ciprofloxacin	OR 1	**micro-MITTS** Non-inferiority of oral sulopenem vs ciprofloxacin in patients with uropathogen susceptible to ciprofloxacin
2nd Step	2	**micro-MITT** Non-inferiority of oral sulopenem vs ciprofloxacin in uUTI patients with ≥10^5 CFU/mL of Enterobacterales at baseline		

Dunne, et al. Clinical Infectious Diseases 2023 Jan 6; 76(1):66-77

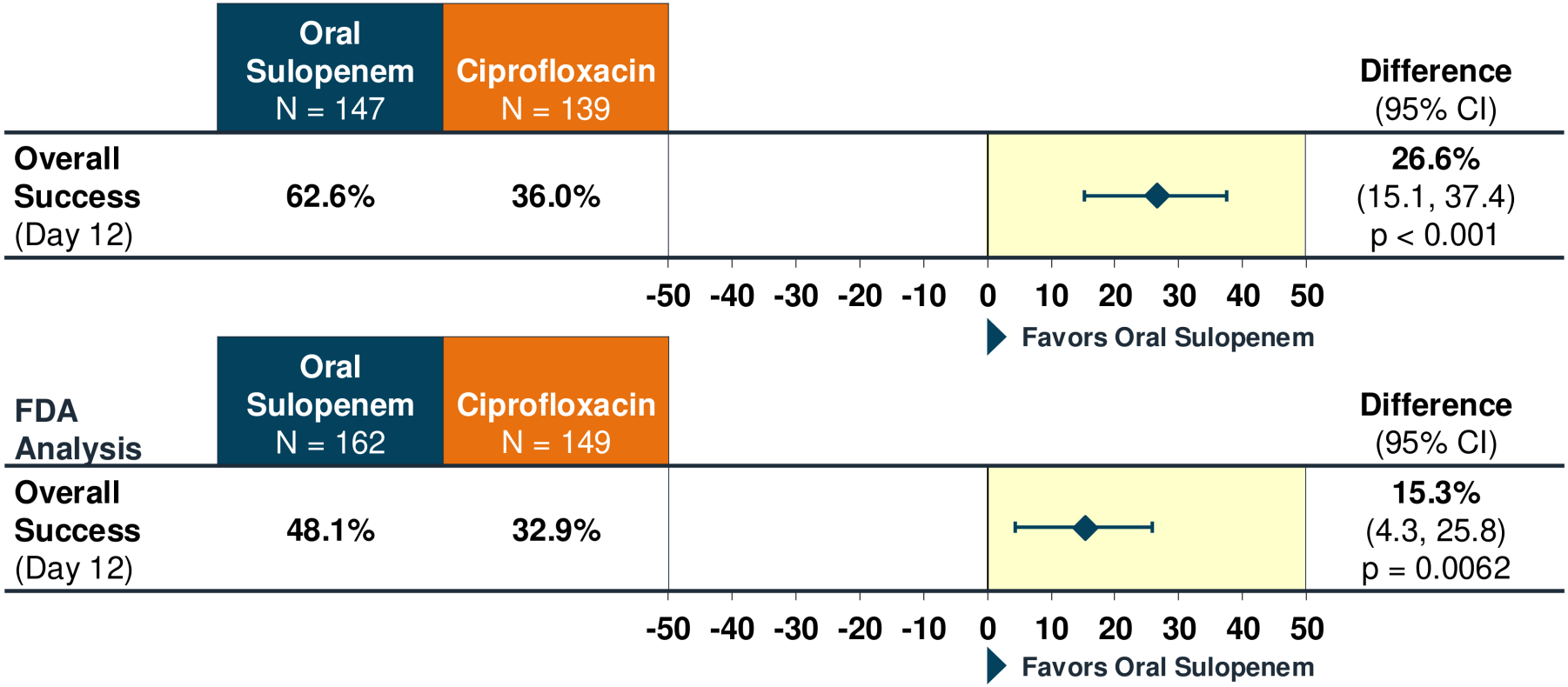
Study 301: Study Disposition

	Oral Sulopenem	Ciprofloxacin
Intent-to-treat (ITT)	**835**	**836**
Safety Received study drug	**833**	**827**
Modified ITT (MITT) Received study drug and uUTI symptoms	**785**	**794**
micro-MITT, (%) n Uropathogen $\geq 10^5$ CFU/mL	**66%** (517)	**70%** (554)
micro-MITTS, (%) n Susceptible to ciprofloxacin	**47%** (370)	**52%** (415)
micro-MITTR, (%) n Non-susceptible to ciprofloxacin	**19%** (147)	**18%** (139)

Study 301 micro-MITTR: Baseline Demographics Similar Between Groups

	Oral Sulopenem N = 147	Ciprofloxacin N = 139
Age, years (SD)	**55** (19.3)	**56** (20.1)
White	**88%**	**91%**
Black	**10%**	**9%**
Hispanic / Latinx	**40%**	**38%**
US	**55%**	**59%**
Diabetes mellitus	**17%**	**19%**
BMI; median (kg/m^2)	**26.3**	**27.5**
Creatinine clearance; median (mL/min)	**69.0**	**68.0**

Study 301 micro-MITTR: Oral Sulopenem Statistically Superior to Ciprofloxacin for Overall Success



Study 301 micro-MITTR: Superiority of Oral Sulopenem Consistent Over Time

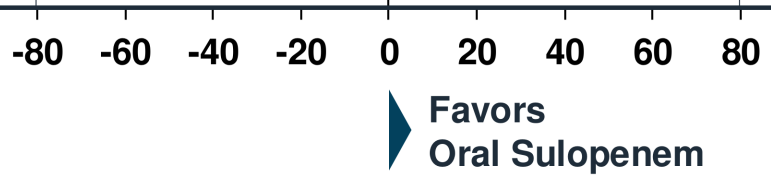
	Oral Sulopenem N = 147	Ciprofloxacin N = 139	Difference (95% CI)
Overall Success (Day 5)	**64.6%**	**30.2%**	**34.4%** (23.1, 44.8)
Overall Success (Day 12)	**62.6%**	**36.0%**	**26.6%** (15.1, 37.4)
Overall Success (Day 28)	**68.0%**	**44.6%**	**23.4%** (12.0, 34.3)

Study 301 micro-MITTR: Consistent Effect in Overall Response Across Baseline Organisms

Pathogen, % (n/N)	Oral Sulopenem	Ciprofloxacin
E. coli	**59.1%** (75/127)	**35.0%** (42/120)
K. pneumoniae	**71.4%** (10/14)	**50.0%** (8/16)
P. mirabilis	**100%** (9/9)	**50.0%** (3/6)

Study 301 micro-MITTR: Overall Response of Sulopenem Superior to Ciprofloxacin Among Multidrug Resistant Uropathogens

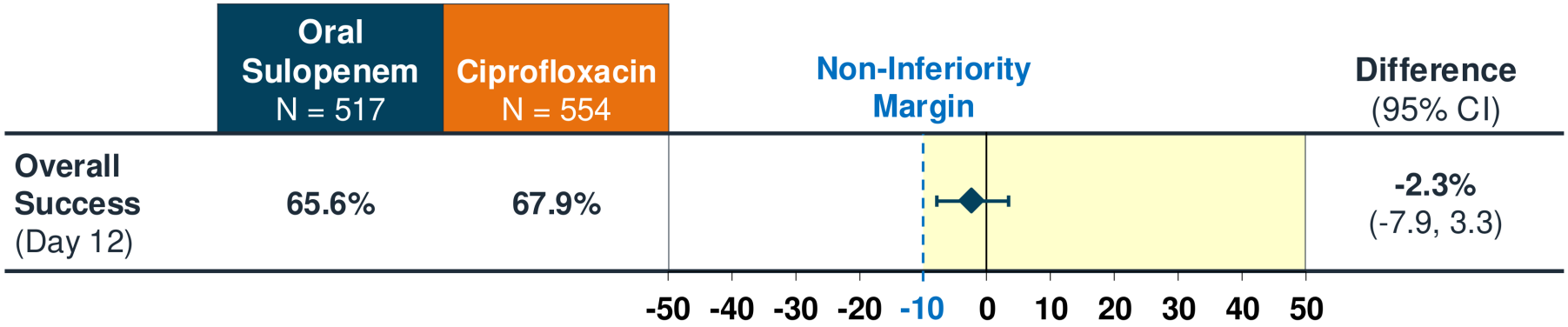
Resistance	Oral Sulopenem	Ciprofloxacin	Difference (95% CI)
Quinolone	**62.6%** (92/147)	**36.0%** (50/139)	**26.6%** (15.1, 37.4)
Quinolone, β-lactam	**66.7%** (86/129)	**35.5%** (43/121)	**31.1%** (18.9, 42.4)
Quinolone, β-lactam, TMP-SMX	**60.3%** (38/63)	**34.0%** (16/47)	**26.3%** (7.40, 43.2)
Quinolone, β-lactam, TMP-SMX, nitrofurantoin	**79.2%** (19/24)	**40.7%** (11/27)	**38.4%** (11.4, 60.1)



Study 301: micro-MITT Population

Analysis	Populations
1st Step	 **micro-MITTR** Superiority of oral sulopenem vs ciprofloxacin in patients with uropathogen non-susceptible to ciprofloxacin OR 1 **micro-MITTS** Non-inferiority of oral sulopenem vs ciprofloxacin in patients with uropathogen susceptible to ciprofloxacin
2nd Step	2 **micro-MITT** Non-inferiority of oral sulopenem vs ciprofloxacin in uUTI patients with ≥10^5 CFU/mL of Enterobacterales at baseline

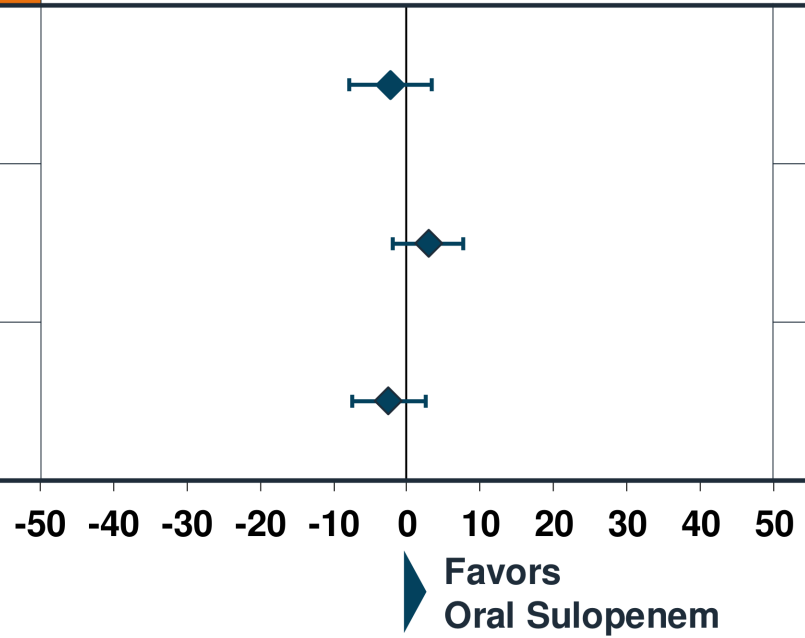
Study 301 micro-MITT: Oral Sulopenem Non-Inferior for Overall Success Compared with Ciprofloxacin



Dunne, et al. Clinical Infectious Diseases 2023 Jan 6;76(1):66-77

Study 301 micro-MITT: Oral Sulopenem Provides Similar Clinical and Microbiologic Response

	Oral Sulopenem N = 517	Ciprofloxacin N = 554	Difference (95% CI)
Overall Success (Day 12)	**65.6%**	**67.9%**	**-2.3%** (-7.9, 3.3)
Clinical Success (Day 12)	**81.6%**	**78.7%**	**2.9%** (-1.9, 7.7)
Microbiologic Success (Day 12)	**76.6%**	**79.1%**	**-2.5%** (-7.5, 2.5)

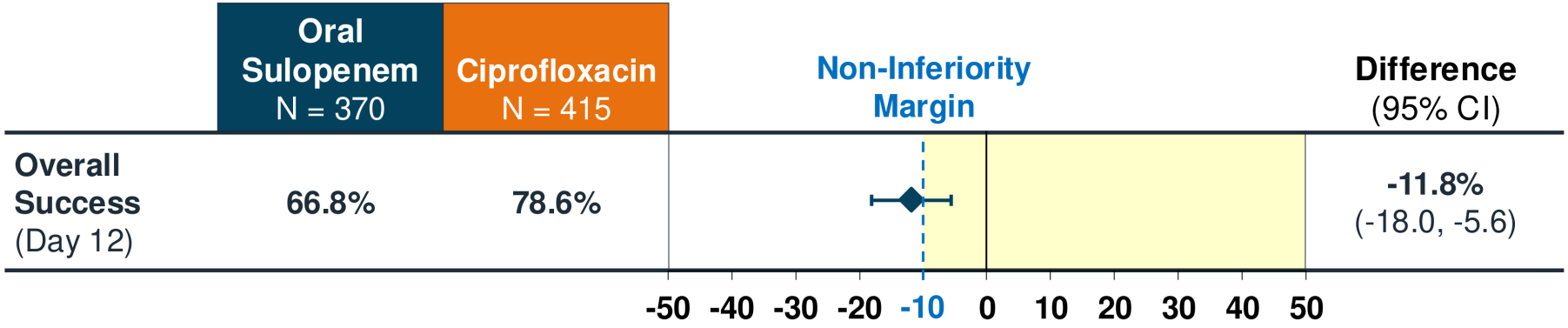


Study 301: micro-MITTS Population

Analysis	Populations
1st Step	**micro-MITTR** Superiority of oral sulopenem vs ciprofloxacin in patients with uropathogen non-susceptible to ciprofloxacin **OR** (1) **micro-MITTS** Non-inferiority of oral sulopenem vs ciprofloxacin in patients with uropathogen susceptible to ciprofloxacin
2nd Step	**micro-MITT** Non-inferiority of oral sulopenem vs ciprofloxacin in uUTI patients with ≥10^5 CFU/mL of Enterobacterales at baseline

Dunne, et al. Clinical Infectious Diseases 2023 Jan 6;76(1):66-77

Study 301 micro-MITTS: Oral Sulopenem Was Not Non-Inferior to Ciprofloxacin for Overall Response



Study 301 micro-MITTS: Difference in Overall Response Driven by Rate of ASB

	Oral Sulopenem N = 370	Ciprofloxacin N = 415
Non-responders for Overall Success (Day 12)	**28.4%**	**15.7%**
Microbiologic failure only, % (n) (asymptomatic bacteriuria, uropathogen ≥ 10^3 CFU/mL)	**12.7%** (47)	**3.9%** (16)
Clinical failure only (no resolution of symptoms)	**10.3%**	**10.1%**
Microbiologic and clinical failure only	**4.9%**	**1.0%**
Other antibiotic treatment for uUTI only	**0.5%**	**0.7%**
Death	**0**	**0**

Study 301 micro-MITTS: Asymptomatic Bacteriuria did Not Lead to Less Clinical Success at Day 28

	Oral Sulopenem N = 370	Ciprofloxacin N = 415	Difference (95% CI)
Clinical Success (Day 5)	**69.2%**	**69.9%**	**-0.7%** (-7.2, 5.7)
Clinical Success (Day 12)	**81.1%**	**84.1%**	**-3.0%** (-8.4, 2.3)
Clinical Success (Day 28)	**79.7%**	**82.2%**	**-2.4%** (-8.0, 3.1)

ASB at Day 12 does Not Affect Clinical Failure Rate at Day 28 in Patients Treated with Oral Sulopenem

	Assessment Day 5	Clinical Failure Day 12	p-value
Overall Success	**335**	31 **(9.3%)**	**1.000**
Asymptomatic Bacteriuria	**12**	1 **(8.3%)**	

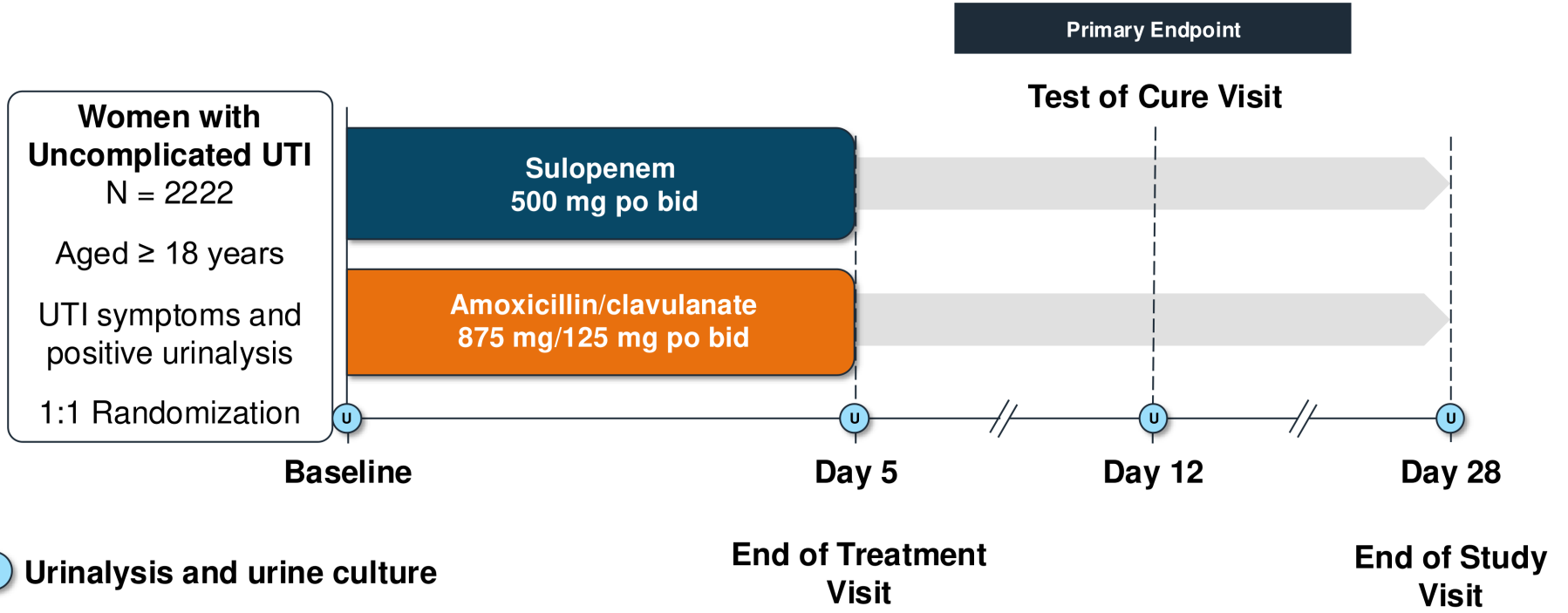
	Assessment Day 12	Clinical Failure Day 28	p-value
Overall Success	**339**	20 **(5.9%)**	**0.128**
Asymptomatic Bacteriuria	**74**	8 **(10.8%)**	

Efficacy of Oral Sulopenem in Uncomplicated UTIs

Study 301

Study 310

Study 310: Randomized, Multicenter, Double-Blind, Active-Controlled Study



Study 310: Primary Endpoint

Primary Endpoint: Proportion of patients achieving an overall response of success at Day 12 test of cure (TOC) visit

Overall Response of Success =

Clinical Success
- Resolution of symptoms, no new symptoms
- Frequency, urgency, pain on micturition or suprapubic pain

+

Microbiologic Eradication
- Urine culture < 10^3 CFU/mL
- Confirmed by genus and species

Study 310: Key Secondary Endpoints

- Overall Response at Day 5 (End of Treatment)
- Clinical success at Day 12 (TOC)
- Microbiologic eradication at Day 12 (TOC)
- Investigator's Assessment of clinical success at Day 12 (TOC)
- Overall Response at Day 28 (End of Study)
- Safety

Study 310: Pre-Specified Hierarchical Testing Method of Primary Endpoint

Analysis	Populations	
1st Step	1 **micro-MITT** Non-inferiority of oral sulopenem vs amox/clav in uUTI patients with ≥10^5 CFU/mL of Enterobacterales at baseline	
2nd Step	2 **micro-MITTS** Non-inferiority of oral sulopenem vs amox/clav in patients with uropathogen susceptible to amox/clav*	2 **micro-MITTR** Superiority of oral sulopenem vs amox/clav in patients with uropathogen non-susceptible to amox/clav

*Primary endpoint for regulatory approval

Study 310: Study Disposition

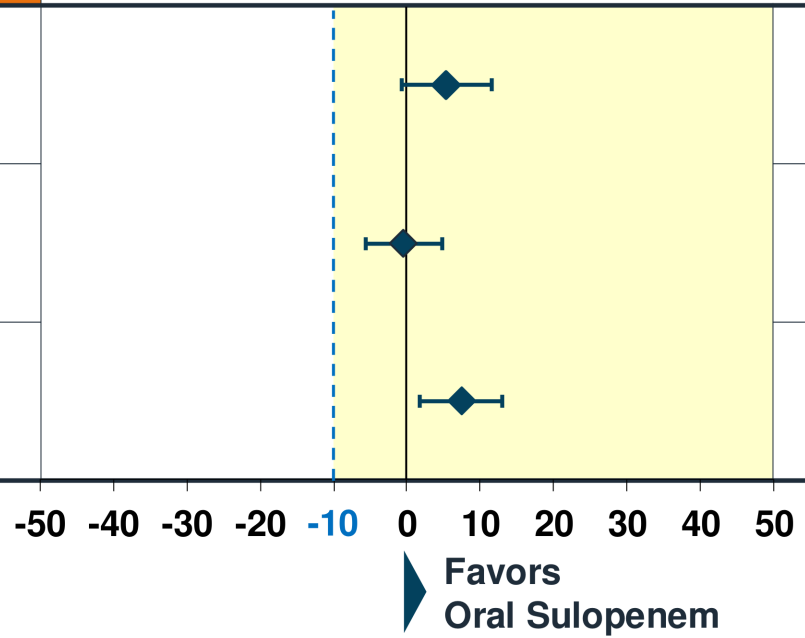
	Oral Sulopenem	Amoxicillin/Clavulanate
Intent-to-treat (ITT)	**1111**	**1111**
Safety / Modified ITT (MITT) Received study drug	**1107**	**1107**
micro-MITT, % (n) Uropathogen $\geq 10^5$ CFU/mL	**47.0%** (522)	**42.1%** (468)
micro-MITTS, % (n) Susceptible to amoxicillin/clavulanate	**43.2%** (480)	**39.8%** (442)
micro-MITTR, % (n) Non-susceptible to amoxicillin/clavulanate	**3.8%** (42)	**2.3%** (25)

Study 310: micro-MITT: Baseline Demographics Similar Between Groups

	Oral Sulopenem N = 522	Amoxicillin/Clavulanate N = 468
Age: mean (SD) (years)	**50.3** (17.3)	**48.6** (17.2)
White	**80.3%**	**79.1%**
Black	**16.1%**	**17.9%**
Hispanic / Latinx	**63.8%**	**63.2%**
US	**100%**	**100%**
Diabetes mellitus	**16.5%**	**14.5%**
BMI, median (kg/m^2)	**28.1**	**27.9**
Creatinine clearance, median (mL/min)	**83.1**	**83.7**

Study 310: micro-MITT: Sulopenem Demonstrated Non-Inferiority to Amoxicillin / Clavulanate at TOC

	Oral Sulopenem N = 522	Amoxicillin/ Clavulanate N = 468	Difference (95% CI)
Overall Success (Day 12)	**60.9%**	**55.6%**	**5.4** (-0.8, 11.5)
Clinical Success (Day 12)	**76.1%**	**76.5%**	**-0.4** (-5.7, 4.9)
Microbiologic Success (Day 12)	**74.7%**	**67.3%**	**7.4** (1.8, 13.1)



Study 310: micro-MITT: Reasons for Failure at TOC for Overall Response

Reasons for Failure at TOC, % (n)	Oral Sulopenem N = 522	Amoxicillin/Clavulanate N = 468
Persistent or new uUTI symptoms only	**13.4%** (70)	**10.7%** (50)
Microbiologic failure only (ASB)	**14.2%** (74)	**19.9%** (93)
Both uUTI symptoms and microbiologic failure	**6.1%** (32)	**8.1%** (38)
Non-study antibacterial therapy for uUTI	**1.9%** (10)	**0.9%** (4)

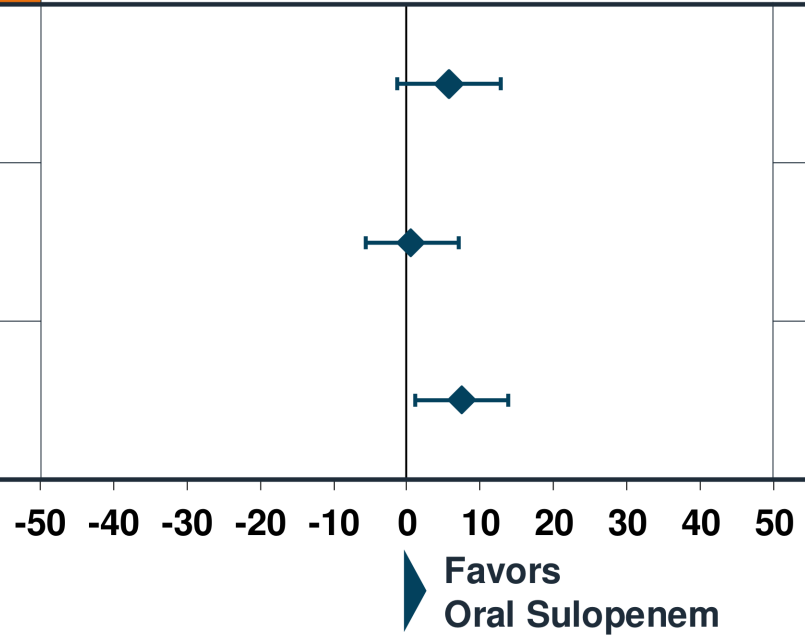
Study 310 micro-MITT: ASB at Day 12 does Not Affect Clinical Failure Rate at Day 28 in Patients Treated with Oral Sulopenem

	Assessment Day 5	Clinical Failure Day 12	p-value
Overall Success	**272**	13 **(4.8%)**	**0.721**
Asymptomatic Bacteriuria	**30**	1 **(3.3%)**	

	Assessment Day 12	Clinical Failure Day 28	p-value
Overall Success	**318**	22 **(6.9%)**	**0.656**
Asymptomatic Bacteriuria	**73**	4 **(5.5%)**	

Study 310: Consistent Effect of Oral Sulopenem in Quinolone Susceptible Population

	Oral Sulopenem N = 392	Amoxicillin/ Clavulanate N = 336	Difference (95% CI)
Overall Success (Day 12)	**63.8%**	**58.0%**	**5.8%** (-1.4, 12.8)
Clinical Success (Day 12)	**74.7%**	**74.1%**	**0.6%** (-5.7, 7.0)
Microbiologic Success (Day 12)	**78.3%**	**70.8%**	**7.4%** (1.2, 13.9)



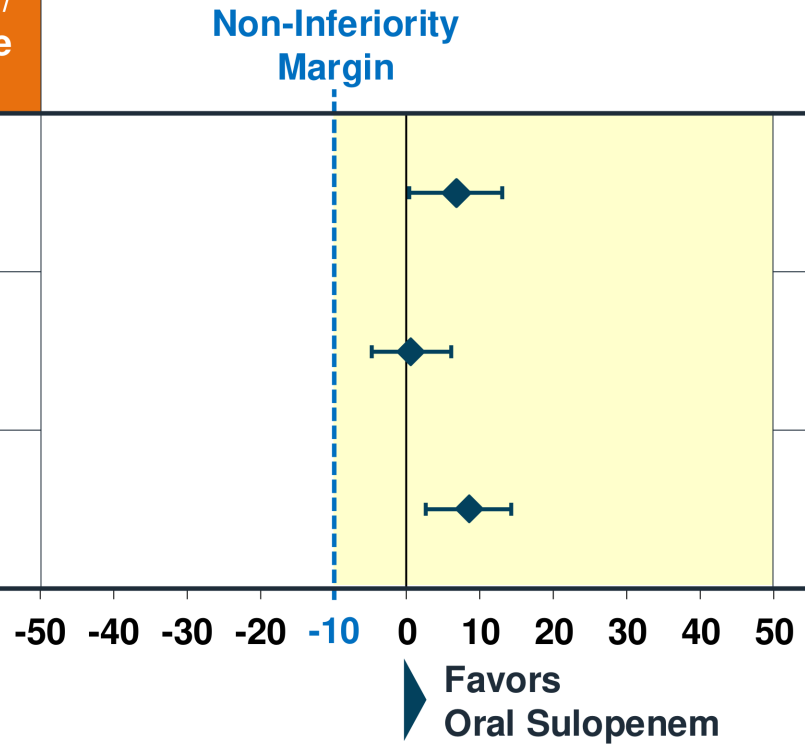
Study 310: Pre-Specified Hierarchical Testing Method of Primary Endpoint

Analysis	Populations	
1st Step	✓ **micro-MITT** Non-inferiority of oral sulopenem vs amox/clav in uUTI patients with ≥10^5 CFU/mL of Enterobacterales at baseline	
2nd Step	2 **micro-MITTS** Non-inferiority of oral sulopenem vs amox/clav in patients with uropathogen susceptible to amox/clav*	2 **micro-MITTR** Superiority of oral sulopenem vs amox/clav in patients with uropathogen non-susceptible to amox/clav

*Primary endpoint for regulatory approval

Study 310: micro-MITTS: Benefits of Oral Sulopenem Supported by Clinical and Microbiologic Response at TOC

	Oral Sulopenem N = 480	Amoxicillin/ Clavulanate N = 442	Difference (95% CI)
Overall Success (Day 12)	**61.7%**	**55.0%**	**6.7%** (0.3, 13.0)
Clinical Success (Day 12)	**77.3%**	**76.7%**	**0.6** (-4.8, 6.1)
Microbiologic Success (Day 12)	**75.2%**	**66.7%**	**8.5** (2.6, 14.3)

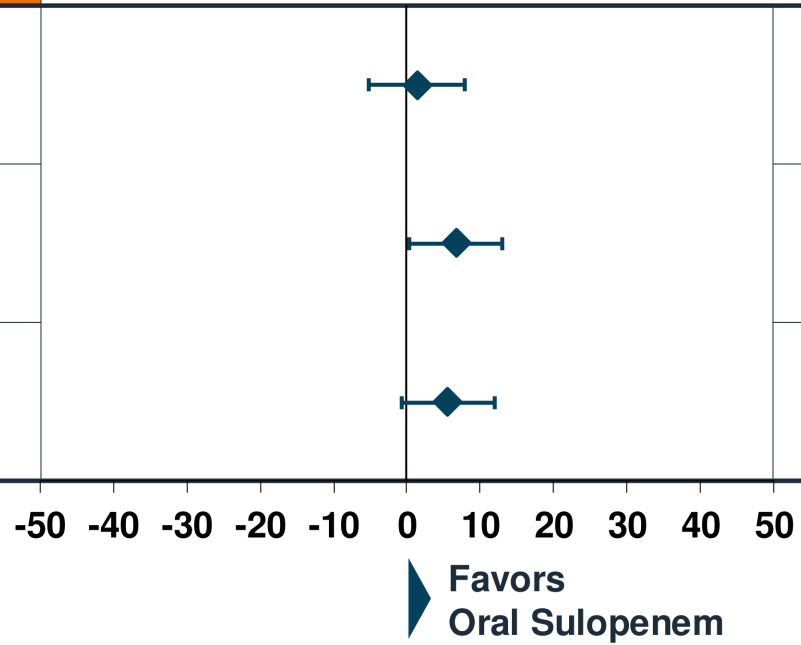


Study 310: micro-MITTS: Reasons for Failure at TOC for Overall Response

Reasons for Failure at TOC, n (%)	Oral Sulopenem N = 480	Amoxicillin/Clavulanate N = 442
Persistent or new uUTI symptoms only	13.1%	10.6%
Microbiologic failure only (ASB)	14.6% (70)	20.6% (91)
Both uUTI symptoms and microbiologic failure	5.4%	7.9%
Non-study antibacterial therapy for uUTI	1.7%	0.9%

Study 310: micro-MITTS: Oral Sulopenem Overall Response Non-Inferior to Amoxicillin/Clavulanate at Every Visit

Overall Success	Oral Sulopenem N = 480	Amoxicillin/ Clavulanate N = 442	Difference (95% CI)
End of Treatment (Day 5)	**52.5%**	**51.1%**	**1.4** (-5.1, 7.8)
Test of Cure (Day 12)	**61.7%**	**55.0%**	**6.7** (0.3, 13.0)
Final Visit (Day 28)	**61.5%**	**55.9%**	**5.6** (-0.8, 11.9)



Study 310 micro-MITTS: Consistent Overall Response for Oral Sulopenem by Major Pathogens at Baseline

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

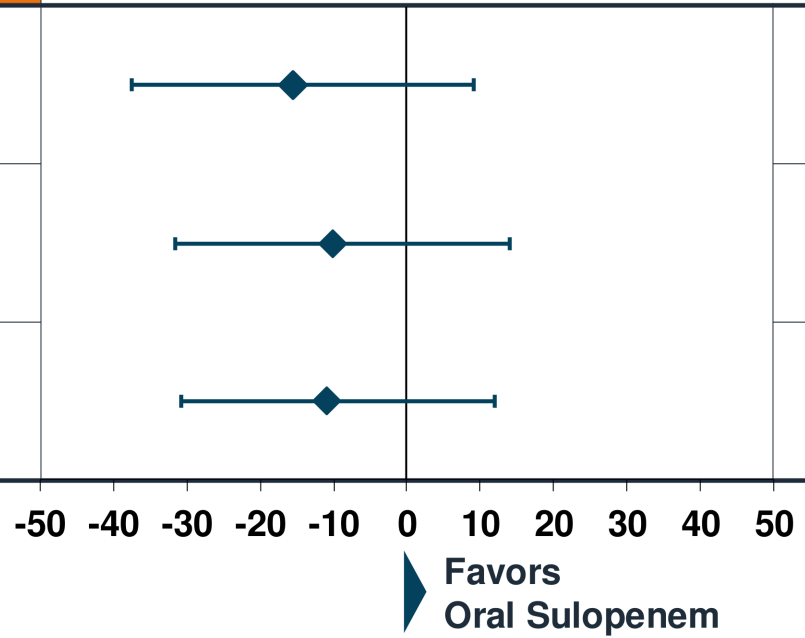
Study 310: Pre-Specified Hierarchical Testing Method of Primary Endpoint

Analysis	Populations	
1st Step	**micro-MITT** Non-inferiority of oral sulopenem vs amox/clav in uUTI patients with ≥10^5 CFU/mL of Enterobacterales at baseline	
2nd Step	**micro-MITTS** Non-inferiority of oral sulopenem vs amox/clav in patients with uropathogen susceptible to amox/clav*	2 **micro-MITTR** Superiority of oral sulopenem vs amox/clav in patients with uropathogen non-susceptible to amox/clav

*Primary endpoint for regulatory approval

Study 310 micro-MITTR: Small Sample Size Limits Ability to Draw Conclusions Based on Treatment Effect

	Oral Sulopenem N = 42	Amoxicillin/ Clavulanate N = 25	Difference (95% CI)
Overall Success (Day 12)	**52.4%**	**68.0%**	**-15.6%** (-37.5, 9.1)
Clinical Success (Day 12)	**61.9%**	**72.0%**	**-10.1%** (-31.5, 14.0)
Microbiologic Success (Day 12)	**69.0%**	**80.0%**	**-11.0%** (-30.7, 12.0)

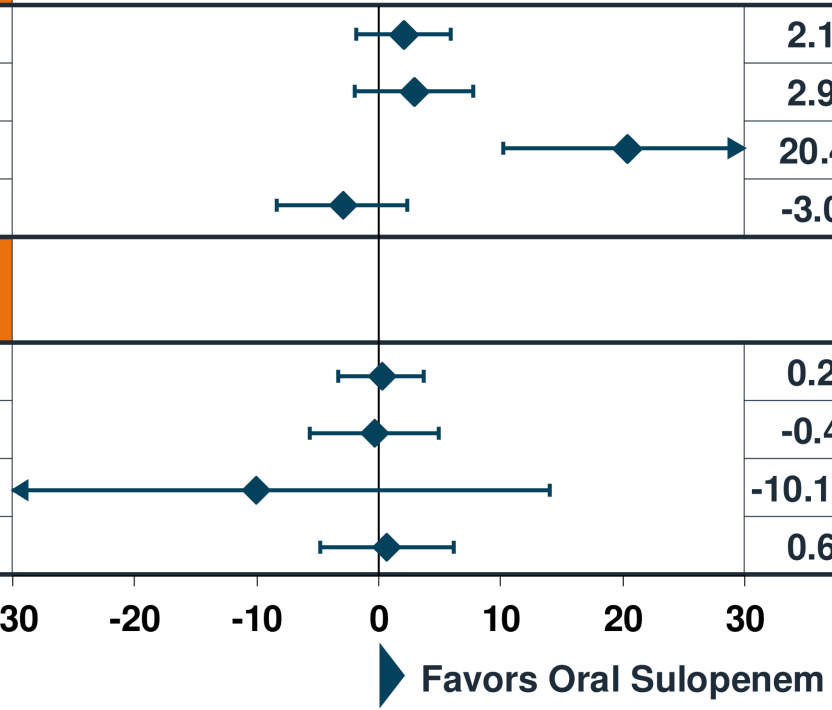


Oral Sulopenem is Effective Oral Antibiotic Treatment Option for Women with uUTI

Overall Success	Study 301 Oral Sulopenem vs Ciprofloxacin	Study 310 Oral Sulopenem vs Amoxicillin/Clavulanate
micro-MITT	**Non-inferior**	**Non-inferior**
micro-MITTR	**Superior**	**N/A** Limited sample size
micro-MITTS	**Not non-inferior** Driven by difference in ASB rate	**Superior**

Study 301 and 310: Clinical Success Consistently Seen with Oral Sulopenem Across All Populations

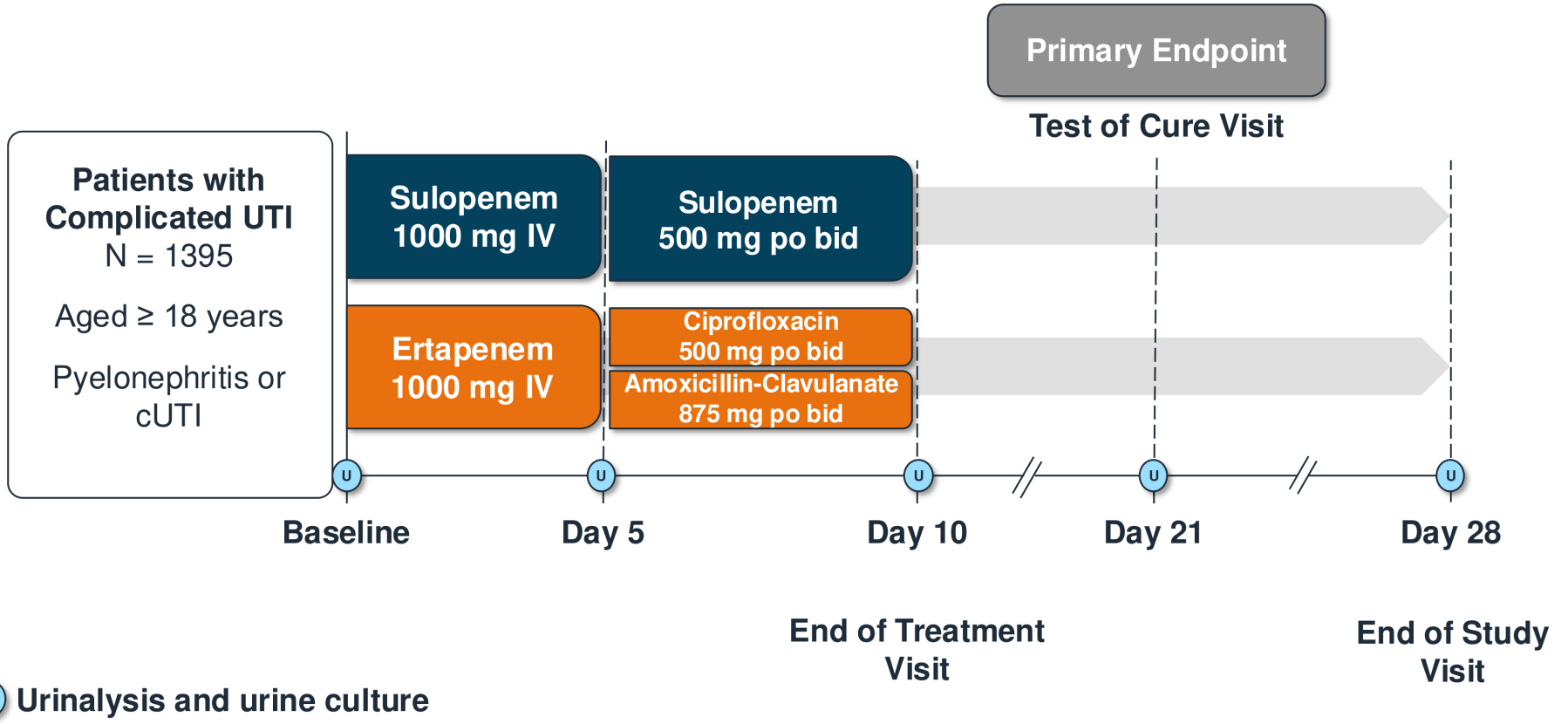
Study 301	Oral Sulopenem	Ciprofloxacin	Difference (95% CI)
MITT	82.4%	80.4%	**2.1%** (-1.8, 5.9)
micro-MITT	81.6%	78.7%	**2.9%** (-1.9, 7.7)
micro-MITTR	83.0%	62.6%	**20.4** (10.2, 30.4)
micro-MITTS	81.1%	84.1%	**-3.0%** (-8.4, 2.3)
Study 310	**Oral Sulopenem**	**Amoxicillin/ Clavulanate**	
MITT	76.9%	76.7%	**0.2%** (-3.3, 3.7)
micro-MITT	76.1%	76.5%	**-0.4%** (-5.7, 4.9)
micro-MITTR	61.9%	72.0%	**-10.1%** (-31.5, 14.0)
micro-MITTS	77.3%	76.7%	**0.6%** (-4.8, 6.1)



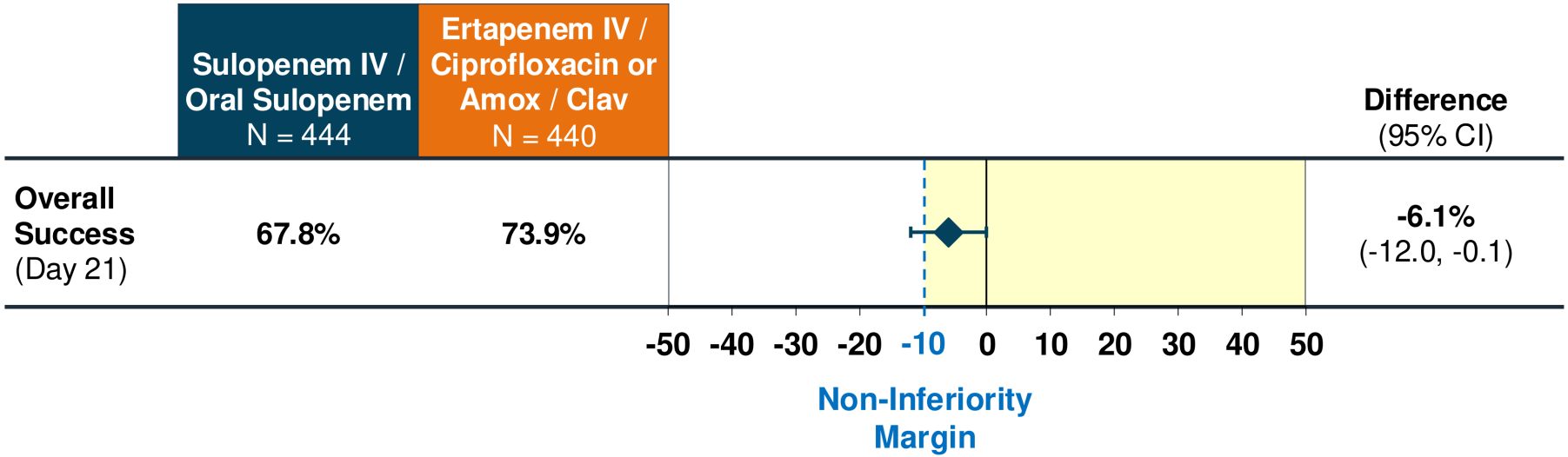
Study 302: Complicated Urinary Tract Infection

Study 301	Study 310	Study 302	Study 303
Uncomplicated UTI N = 1671	**Uncomplicated UTI** N = 2222	**Complicated UTI** N = 1395	**Complicated IAI** N = 674
Oral Sulopenem vs **Ciprofloxacin**	**Oral Sulopenem** vs **Amoxicillin / Clavulanate**	**IV Sulopenem / Oral Sulopenem** vs **IV Ertapenem / Ciprofloxacin** or **Amoxicillin / Clavulanate**	**IV Sulopenem / Oral Sulopenem** vs **IV Ertapenem / Ciprofloxacin + Metronidazole or Amoxicillin / Clavulanate**
Primary Endpoint Clinical and microbiologic success at Day 12	Primary Endpoint Clinical and microbiologic success at Day 12	Primary Endpoint Clinical and microbiologic success at Day 21	Primary Endpoint Clinical success at Day 28

Study 302: Randomized, Multicenter, Double-Blind, Double-Dummy Study



Study 302 micro-MITT: Sulopenem Not Non-Inferior to Ertapenem for Overall Response



Primary Endpoint:
Proportion of patients achieving Overall Response at Day 21 test of cure visit with no rescue antibacterial therapy (micro-MITT)

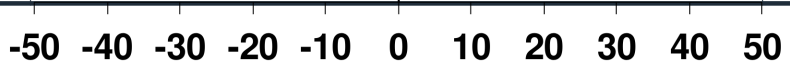
Dunne, et al. Clinical Infectious Diseases 2023 Jan 6; 76(1):78-88

Study 302 micro-MITT: Overall Response Driven by Rate of ASB

	Sulopenem IV / Oral Sulopenem N = 444	Ertapenem IV / Ciprofloxacin or Amox / Clav N = 440
Non-responders for Overall Success	**28.4%**	**21.1%**
Microbiologic failure only, % (n) (asymptomatic bacteriuria, uropathogen ≥ 10^3 CFU/mL)	**20.9%** (93)	**13.4%** (59)
Clinical failure only (no resolution of symptoms)	**4.1%**	**4.8%**
Microbiologic and clinical failure	**2.5%**	**1.8%**
Other antibiotic treatment for uUTI	**1.6%**	**1.4%**
Death	**0**	**0**

Study 302 micro-MITT: Asymptomatic Bacteriuria Not Associated With Less Clinical Success

	Sulopenem IV / Oral Sulopenem N = 444	Ertapenem IV / Ciprofloxacin / Amox / Clav N = 440	Difference (95% CI)
Clinical Success (Day 10)	**89.9%**	**90.7%**	**-0.8%** (-4.7, 3.1)
Clinical Success (Day 21)	**89.4%**	**88.4%**	**1.0%** (-3.1, 5.1)
Clinical Success (Day 28)	**86.9%**	**87.0%**	**-0.1%** (-4.5, 4.3)



Study 302: Overall Response and Rate of ASB by Stepdown Category

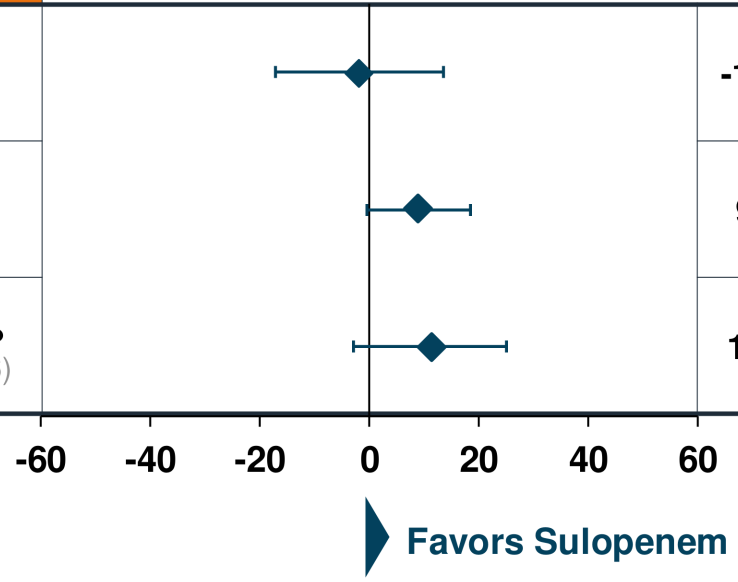
	Sulopenem IV / Oral Sulopenem N = 444	Ertapenem IV +/- Ciprofloxacin or Amox / Clav N = 440
Overall Success (TOC)	**67.8%**	**73.9%**
Difference (95% CI)	**-6.1%** (-12.0, -0.1)	
Non-response: ASB	**20.9%**	**13.4%**

	Sulopenem IV / Oral Sulopenem N = 248	Ertapenem IV / Ciprofloxacin N = 215
Overall Success (TOC)	**67.7%**	**86.5%**
Difference (95% CI)	**-18.8** (-26.1, -11.0)	
Non-response: ASB	**21.8%**	**4.7%**

	Sulopenem IV / Oral Sulopenem N = 196	Ertapenem IV +/- Amox / Clav N = 225
Overall Success (TOC)	**67.9%**	**61.8%**
Difference (95% CI)	**6.1** (-3.1,15.0)	
Non-response: ASB	**19.9%**	**21.8%**

Study 302 (mMITT): Overall Success at TOC using Genus and Species to Determine Response by Stepdown Category

Overall Success (Day 21)	Sulopenem N = 444	Ertapenem N = 440	Difference (95% CI)
Sulopenem IV Only Ertapenem IV Only	50.0% (27/54)	51.8% (73/141)	**-1.8%** (-17.2, 13.7)
Sulopenem IV to PO Ertapenem IV Only	60.8% (233/383)	51.8% (73/141)	**9.1%** (-0.5, 18.6)
Cipro and Amox/Clav Resistant Pathogen	66.3% (53/80)	54.7% (58/106)	**11.5%** (-2.8, 25.2)



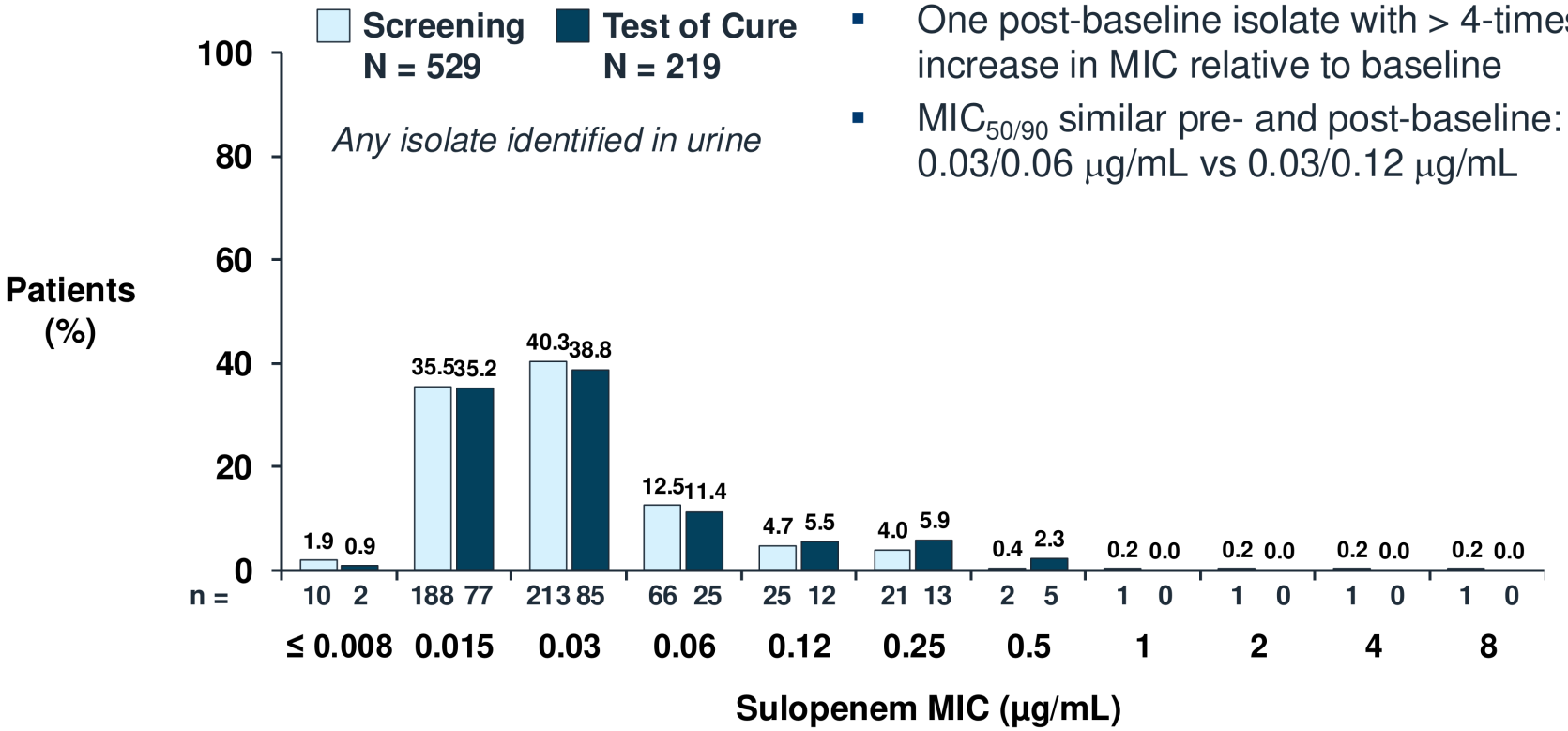
Criteria for step-down:

1. Can tolerate oral medications
2. Clinical signs and symptoms improving
3. Baseline pathogen susceptible to oral regimen

Development of Resistance

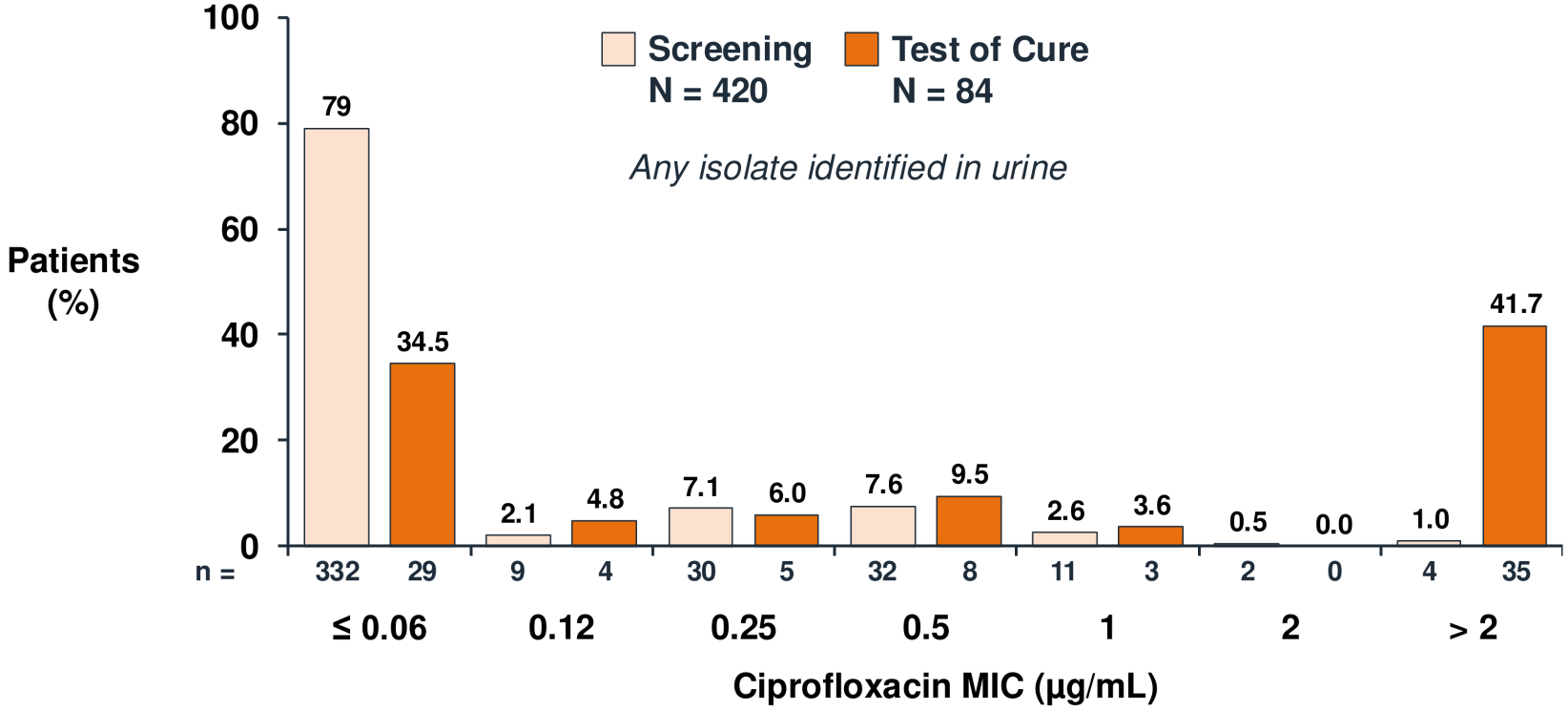
Studies 301 and 310

Study 301 micro-MITT: Sulopenem Treatment Does Not Select for Penem-Resistant Organisms

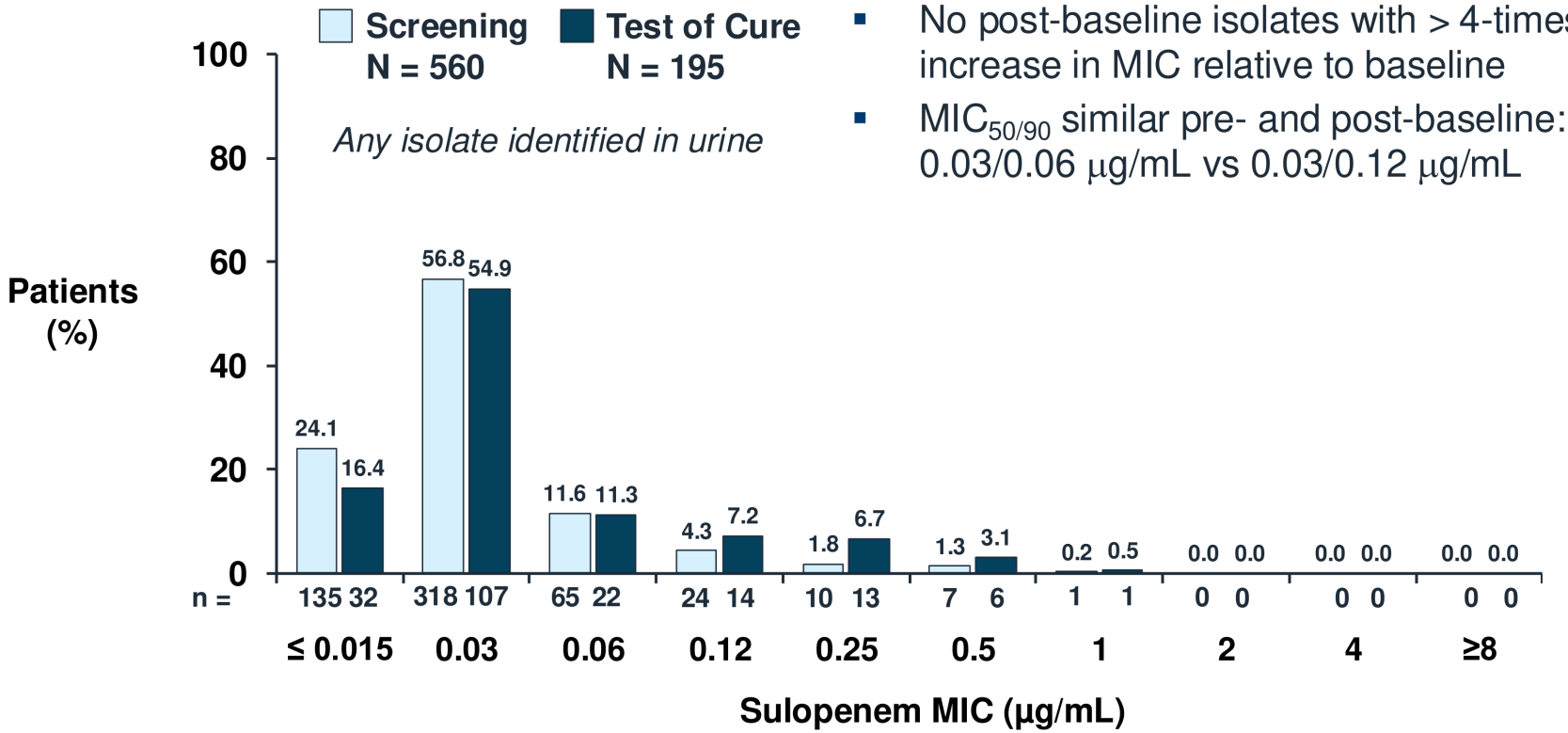


- One post-baseline isolate with > 4-times increase in MIC relative to baseline
- $MIC_{50/90}$ similar pre- and post-baseline: 0.03/0.06 µg/mL vs 0.03/0.12 µg/mL

Study 301: Uropathogens Resistant to Ciprofloxacin Identified in micro-MITTS Population after Treatment

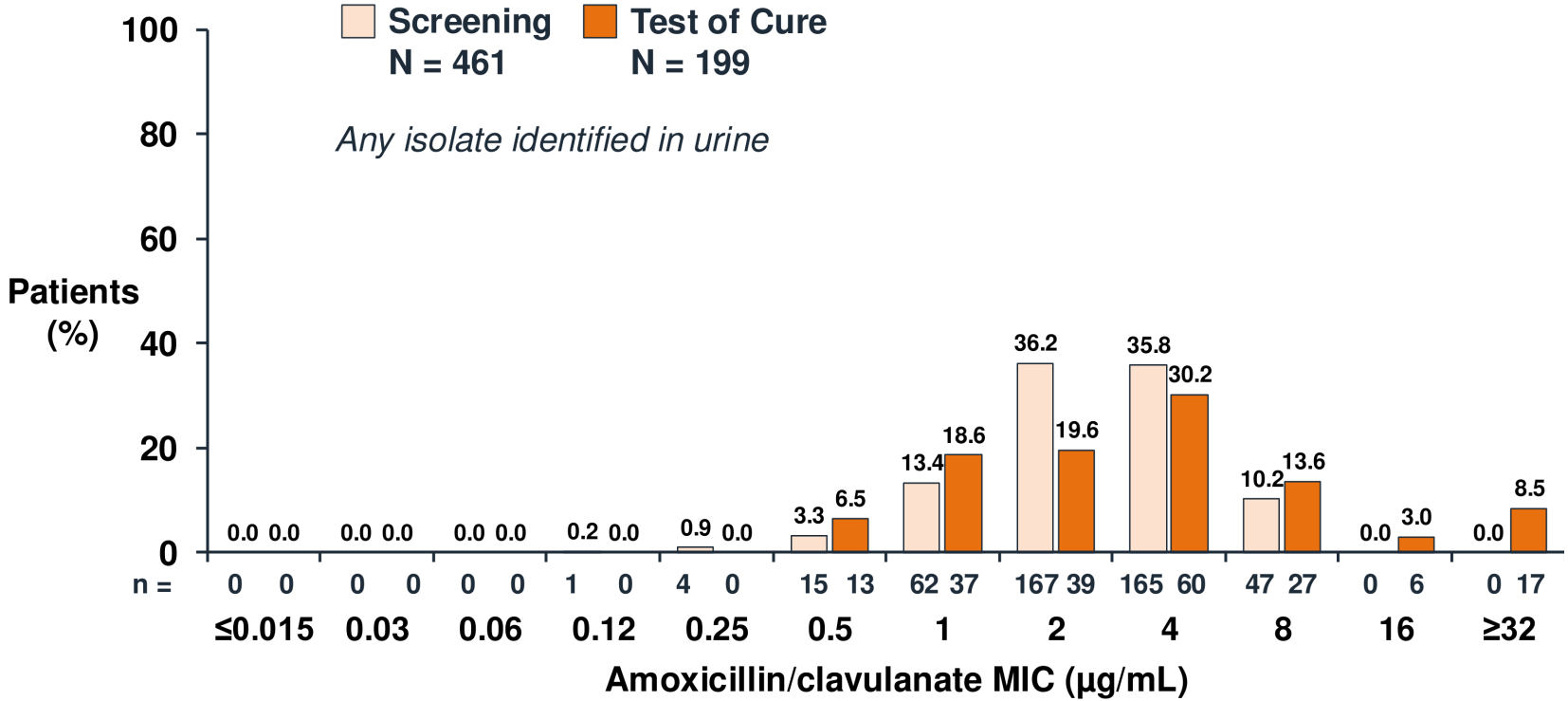


Study 310 micro-MITT: Sulopenem Treatment Does Not Select for Penem-Resistant Organisms



- No post-baseline isolates with > 4-times increase in MIC relative to baseline
- $MIC_{50/90}$ similar pre- and post-baseline: 0.03/0.06 µg/mL vs 0.03/0.12 µg/mL

Study 310: Uropathogens Resistant to Amoxicillin/Clavulanate Identified in micro-MITTS Population after Treatment



Safety

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Senior VP and Head of Clinical Development
Iterum Therapeutics

Phase 3 Safety Data Pooled Across Four Studies

	Phase 3 Integrated[1]		Phase 3 uUTI Studies[2]	
	Oral / IV Sulopenem	Oral / IV Comparators	Oral Sulopenem	Comparators
Safety Population	**2970**	**2964**	**1940**	**1934**

- Safety profile for oral sulopenem consistent across phase 3 studies
- No new safety signals identified beyond those associated with β-lactams

[1] Includes all patients randomized to studies 301, 302, 303 and 310; [2] Includes Studies 301 and 310

Phase 3 uUTI Studies: Oral Sulopenem Has a Similar Safety Profile as Comparators

	Oral Sulopenem N = 1940	Comparator N = 1934
Any AE	**21.6%** (419)	**13.0%** (252)
Treatment emergent AE (TEAE)	**21.4%** (416)	**13.0%** (251)
Drug related TEAE	**15.3%** (297)	**7.0%** (136)
TEAE leading to treatment discontinuation	**1.1%** (21)	**0.6%** (12)
TEAE leading to study discontinuation	**0.4%** (7)	**0.2%** (4)
Serious AE	**0.3%** (6)	**0.4%** (7)
Death	**0.1%** (1*)	**0%** (0)

*Cause of death was poorly differentiated adenocarcinoma of lung >5 months after study period in Study 301 patient

Phase 3 uUTI Studies: Most Common Adverse Events Occurring in > 1% of Patients

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

Phase 3 uUTI Studies: Diarrhea Events Were Mild, Self-limited, and Did Not Lead to Treatment Discontinuation

	Oral Sulopenem N = 1940	Comparator N = 1934
Diarrhea	**8.9%** (172)	**3.1%** (59)
Treatment discontinuation	**0.3%** (5)	**0.2%** (3)
Duration, mean days (SD)	**3.9** (2.8)	**2.8** (1.7)
***Clostridioides difficile* infections**	**0**	**0.05%** (1)

- No *Clostridioides difficile* infections were observed in patients treated with sulopenem

Phase 3 uUTI Studies: Treatment Related Adverse Events Leading to Discontinuation

	Oral Sulopenem N = 1940	Comparator N = 1934
AE leading to treatment discontinuation	**0.9%** (17)	**0.5%** (9)
Nausea	**0.3%** (5)	**0.3%** (5)
Diarrhea	**0.2%** (4)	**0.2%** (3)
Vomiting	**0.2%** (3)	**0.2%** (3)
Dizziness	**0.2%** (3)	**0.1%** (1)
Gastro-esophageal reflux disease	**0.2%** (3)	**0**
Abdominal pain	**0.1%** (2)	**0.1%** (1)
Headache	**0.1%** (1)	**0.1%** (2)

Phase 3 uUTI Studies: Clinically Significant Liver Function Test Elevations Uncommon

% (n)		Oral Sulopenem Normal at BL N = 1654	Comparators Normal at BL N = 1650
ALT	> ULN to 3x ULN	**1.4%** (23)	**1.2%** (19)
	> 3x to 5x ULN	**0.1%** (2)	**0**
	> 5x to 10x ULN	**<0.1%** (1)	**<0.1%** (1)
		Normal at BL N = 1552	**Normal at BL** N = 1559
AST	> ULN to 3x ULN	**1.2%** (19)	**1.1%** (17)
	> 3x to 5x ULN	**<0.1%** (1)	**0**
	> 5x to 10x ULN	**0.1%** (2)	**0**

- No ALT / AST elevations of > 10x ULN
- No cases fulfilled Hy's Law criteria

Study 302 Hy's Law Patient: LFT Abnormalities Attributed to Interaction Between IV Sulopenem and Valproic Acid

Receiving IV Sulopenem with Complicated UTI

- 75-year-old man with a cUTI without pyelonephritis
- Received 5 days of IV sulopenem and 2 days of oral sulopenem
- Concomitant medications included valproic acid (300 mg BID)

TEST	Normal Range	Screening	Day 5 (end IV sulopenem)	Day 10 (EOT) (including 2 days of oral sulopenem)	Day 21 (TOC)
ALT	6-41 U/L	11	269	45	12
AST	9-34 U/L	18	313	19	13
GGT	11-52 U/L	35	229	143	98
AP	37-116 U/L	73	174	130	104
Bilirubin	0.10-1.10 mg/dL	0.70	2.77	1.10	1.13

Hy's Law Patient: LFT Abnormalities Attributed to Interaction Between IV Sulopenem and Valproic Acid

Test	Screening	Day 5	EOT
Valproic acid concentrations* (ng/mL)	**54,800**	**21,000**	**50,600**

- VPA levels decreased as anticipated after IV Sulopenem
- Presumably metabolite of VPA increased and is responsible for increase in LFTs[1]
- Elevated LFTs resolved upon discontinuation of sulopenem

*Either plasma or serum; 1: INVANZ, USPI

Safety Conclusions

- Well tolerated relative to comparators
- No new safety signals beyond those known for β-lactams
- Diarrhea was most common AE
  - Mild, self-limited and generally did not lead to discontinuation
  - No *C. difficile* infections were observed
- No increased risk in elderly patients

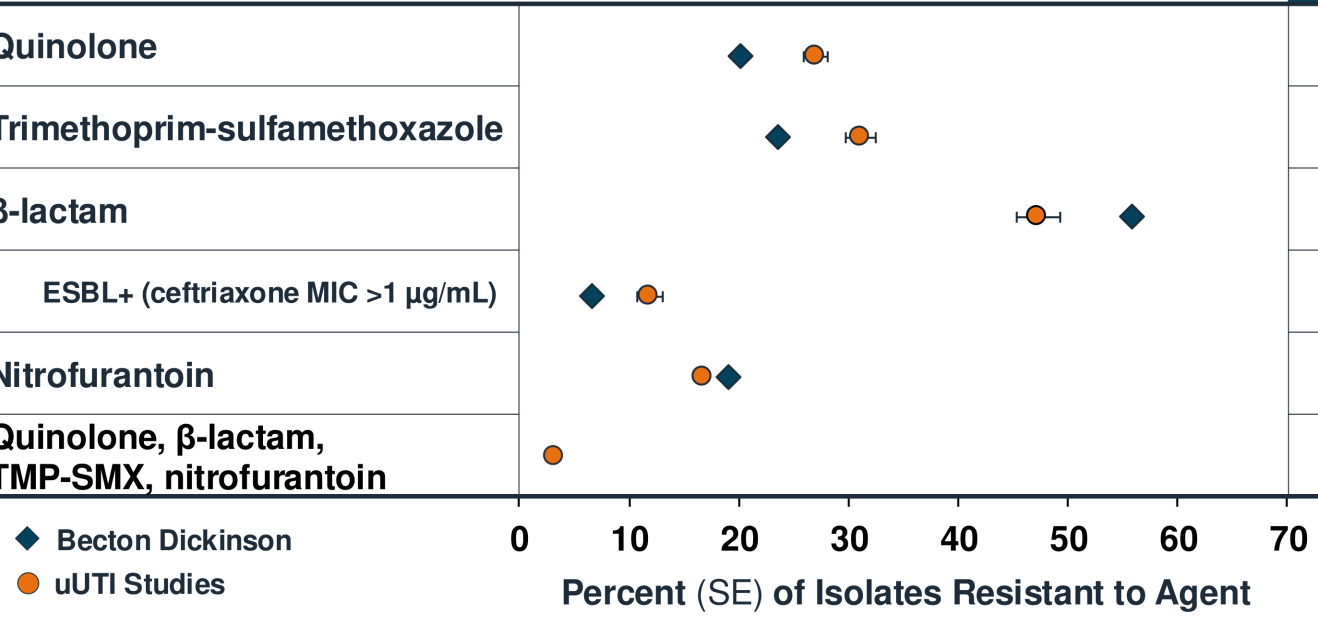
Benefit-Risk

Michael Dunne, MD, FIDSA

Increasing Resistance to Standard of Care Antibiotics for Uncomplicated UTI

Highlights Need for New Treatment Options

Antibacterial Agent/Class	Percent Resistance: Becton Dickinson N = 2,228,515	Percent Resistance: uUTI Studies (micro-MITT) N = 2,061
Quinolone	20.6%	27.0%
Trimethoprim-sulfamethoxazole	23.1%	31.1%
β-lactam	57.5%	47.3%
ESBL+ (ceftriaxone MIC >1 µg/mL)	6.9%	11.9%
Nitrofurantoin	20.2%	16.8%
Quinolone, β-lactam, TMP-SMX, nitrofurantoin	-	3.2%



Oral Sulopenem is Effective Oral Antibiotic Treatment Option for Women with uUTI and Has a Favorable Safety Profile

	Study 301 Oral Sulopenem vs Ciprofloxacin	**Study 310** Oral Sulopenem vs Amoxicillin/Clavulanate
Efficacy / Overall Success		
micro-MITT	**Non-inferior**	**Non-inferior**
micro-MITTR	**Superior**	**N/A** Limited sample size
micro-MITTS	**Not non-inferior** Driven by difference in ASB rate	**Superior**
Safety – Phase 3 uUTI Studies Combined		
Any AE	**21.6%** (419)	**13.0%** (252)
TEAE leading to treatment discontinuation	**1.1%** (21)	**0.6%** (12)

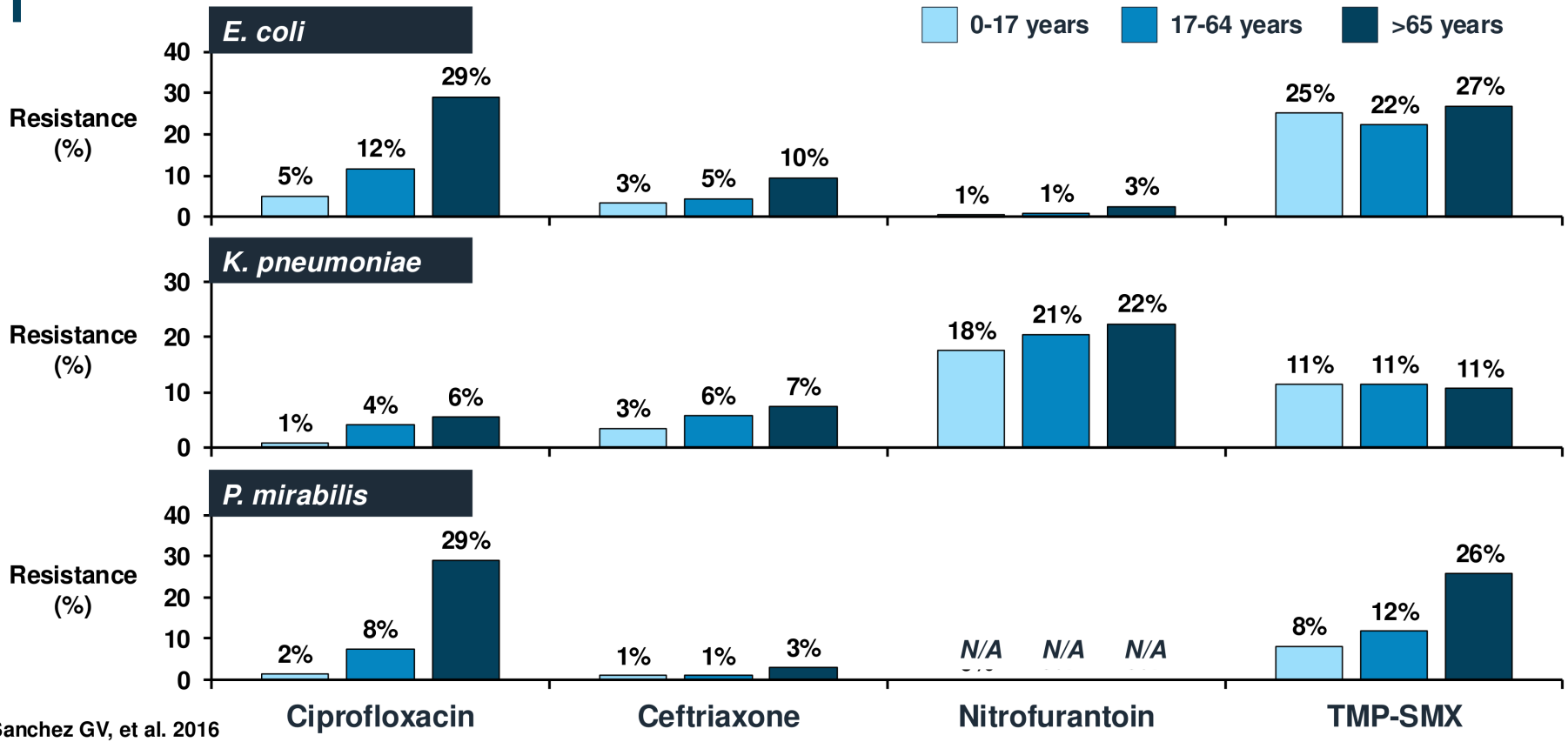
Questions Posed to Advisory Committee

- 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?

Study 301: Characteristics of Patients by Quinolone Susceptibility

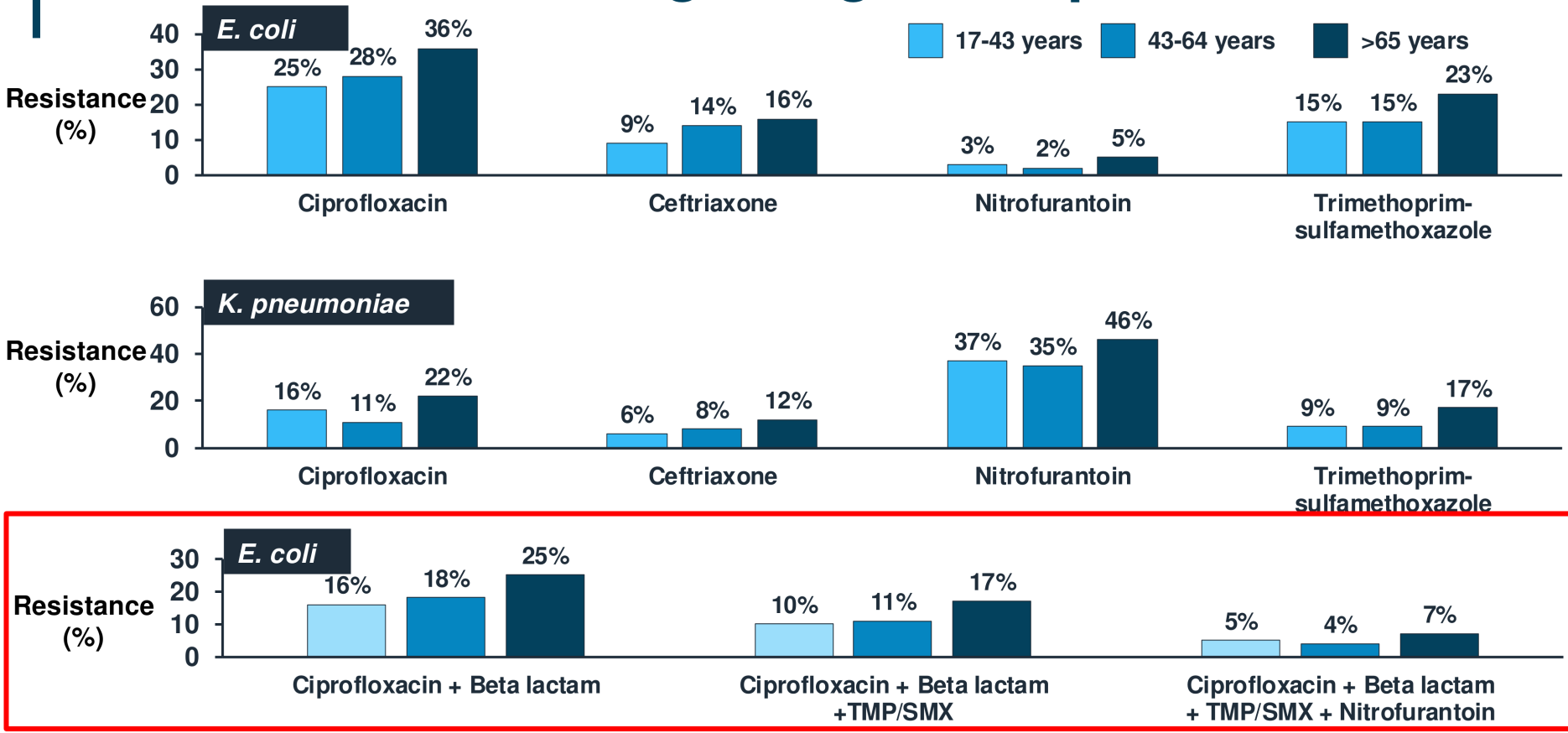
Parameter, % (n)		mMITTS N = 785	mMITTR N = 286	p-value
Age, mean (SD)		**50.4** (18.8)	**55.4** (19.7)	**<0.001**
Ethnicity	**Hispanic or Latinx**	**23%** (184)	**39%** (111)	**<0.001**
	Not Hispanic or Latinx	**76%** (598)	**61%** (174)	
	Not reported	**0.4%** (3)	**0.3%** (1)	
Region	**United States**	**52%** (406)	**57%** (163)	**0.091**
	Not US	**48%** (379)	**43%** (123)	
Race	**Black or African American**	**9%** (67)	**9%** (26)	**0.661**
	Asian	**0.8%** (6)	**0.7%** (2)	
	White	**90%** (706)	**90%** (256)	
	Other	**0.3%** (2)	**0.7%** (2)	
Diabetes mellitus		**12%** (91)	**19%** (53)	**0.004**
Body mass index, mean (SD), **kg/m²**		**27.5** (6.6)	**28.5** (6.8)	**0.008**
Creatinine clearance, mean (SD), **mL/min**		**78.4** (26.2)	**72.7** (28.2)	**0.001**

Antibiotic Resistance Increases with Age Among US Female Outpatients with uUTI



Sanchez GV, et al. 2016

Studies 301 and 310: Prevalence of Antibiotic Resistance According to Age Group



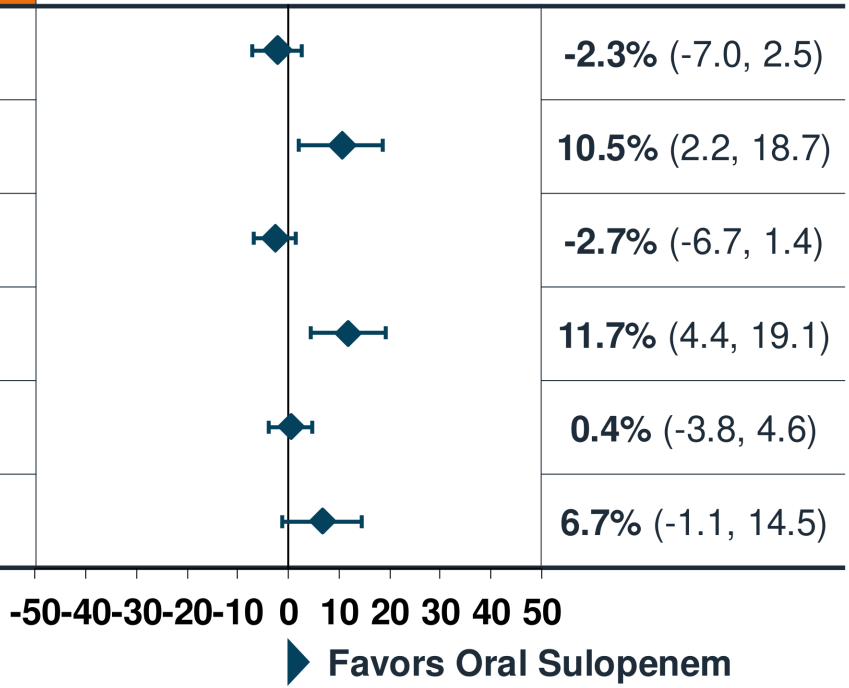
Studies 301 + 310: Treatment Response at TOC in Women ≥ 65 Years of Age Favors Treatment with Sulopenem

≥ 65 Years	Oral Sulopenem N = 286	Comparator N = 269	Difference (95% CI)
Overall Success	57.7%	47.2%	**10.5%** (2.2, 18.7)
Clinical Success	79.0%	67.3%	**11.7%** (4.4, 19.1)
Microbiologic Success	70.3%	63.6%	**6.7%** (-1.1, 14.5)

mMITT population

Studies 301 + 310: Treatment Response in Women ≥ 65 Years vs < 65 Years of Age

	Years	Oral Sulopenem	Comparator	Difference (95% CI)
Overall Success	< 65	65.3% (492/753)	67.6% (509/753)	**-2.3%** (-7.0, 2.5)
	≥ 65	57.7% (165/286)	47.2% (127/269)	**10.5%** (2.2, 18.7)
Clinical Success	< 65	78.8% (593/753)	81.4% (613/753)	**-2.7%** (-6.7, 1.4)
	≥ 65	79.0% (226/286)	67.3% (181/269)	**11.7%** (4.4, 19.1)
Microbiologic Success	< 65	77.7% (585/753)	77.3% (582/753)	**0.4%** (-3.8, 4.6)
	≥ 65	70.3% (201/286)	63.6% (171/269)	**6.7%** (-1.1, 14.5)



mMITT population

Studies 301 + 310: Treatment Response in Women ≥ 65 Years of Age in All Treatment Populations

≥ 65 Years	Success	Oral Sulopenem	Comparator	Difference (95% CI)
MITT	Clinical	**77.1%** (333)	**70.0%** (306)	**7.1%** (1.2, 12.9)
mMITT	Overall	**57.7%** (165/286)	**47.2%** (127/269)	**10.5%** (2.2, 18.7)
	Clinical	**79.0%** (226/286)	**67.3%** (181/269)	**11.7%** (4.4, 19.1)
	Micro	**70.3%** (201/286)	**63.6%** (171/269)	**6.7%** (-1.1, 14.5)
mMITTR	Overall	**46.0%** (29/63)	**15.2%** (10/66)	**30.9%** (15.3, 45.3)
	Clinical	**76.2%** (48/63)	**43.9%** (29/66)	**32.3%** (15.5, 47.2)
	Micro	**58.7%** (37/63)	**36.4%** (24/66)	**22.4%** (5.1, 38.4)
mMITTS	Overall	**61.0%** (136/223)	**57.6%** (117/203)	**3.4%** (-6.0, 12.7)
	Clinical	**79.8%** (178/223)	**74.9%** (152/203)	**4.9%** (-3.0, 13.0)
	Micro	**73.5%** (164/223)	**72.4%** (147/203)	**1.1%** (-7.3, 9.6)

Stewardship of Sulopenem

Opportunities

- In vitro spectrum of activity vs MDR pathogens
- Clinical effectiveness / safety
- Impact on care pathways
  - Nursing Home /
  - Emergency Department
  - Avoidance of PICC lines for uUTI

Challenges

- Widespread (appropriate) use and pressure on colonizing flora
- Off-label use
  - cUTI

Mitigation Strategies

- Stewardship guidelines
  - Professional societies
  - CDC
  - Local stewards
- Prior authorization
- Outpatient formulary process
- Care pathways
  - History of resistant pathogens
- Further development of point of care diagnostics
- Surveillance
  - National / Local

Proposed Indication

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

Sulopenem Etzadroxil/Probenecid (Oral Sulopenem) for Treatment of Uncomplicated Urinary Tract Infections

September 9, 2024

Iterum Therapeutics

Antimicrobial Drugs Advisory Committee

Back Up Slides Shown

Study 301 + 310 Overall Response by Creatinine Clearance, micro-MITT Population

Outcome	Sulopenem n/N (%)	Comparator n/N (%)
Overall response at TOC		
Creatinine clearance < 60 mL/min	**54.9%** (150/273)	**49.8%** (120/241)
Creatinine clearance ≥ 60 mL/min	**66.2%** (505/763)	**66.4%** (514/774)

Patient Symptom Assessment Questionnaire for Clinical Response

		Severity (check one)				*Impact on Daily Activities (check one)*
		No Symptom/ Resolved or returned to the same as before you had a UTI	Mild	Moderate	Severe	**Question:** What is the impact of your symptom(s) on your daily activities (i.e., how bothersome are the symptoms)?
1	Pain (uncomfortable pressure) in the lower abdomen/pelvic area*	☐	☐	☐	☐	☐ Not at all ☐ Not significantly bothersome ☐ Moderately bothersome ☐ Severely bothersome
* Pain Guidance		• Choose "No symptom" if no significant pain or back to before you had a UTI • Choose "Mild" if occasional pain, but usually overlooked • Choose "Moderate" if considerable pain, but tolerable • Choose "Severe" if severe pain requiring treatment				
2	Burning (dysuria) when passing urine	☐	☐	☐	☐	☐ Not at all ☐ Not significantly bothersome ☐ Moderately bothersome ☐ Severely bothersome
3	Frequency of urination or going to the toilet very often**	☐	☐	☐	☐	☐ Not at all ☐ Not significantly bothersome ☐ Moderately bothersome ☐ Severely bothersome
**For frequency of urination guidance		• Choose "No symptom" if you can hold your urine for more than two hours during the daytime, or you can hold your urine as long as you could before you had a UTI • Choose "Mild" if more frequent than normal, but can hold your urine for 1-2 hours • Choose "Moderate" if considerably more frequent than normal, i.e., cannot hold urine for 1 hour • Choose "Severe" if very frequent, i.e. cannot even hold your urine for 30 minutes				
4	Urgency of urination or a strong and uncontrollable urge to pass urine***	☐	☐	☐	☐	☐ Not at all ☐ Not significantly bothersome ☐ Moderately bothersome ☐ Severely bothersome
***For urgency of urination guidance		• Choose "No symptom" if you can hold your urine for more than two hours during the daytime, or you can hold your urine as long as you could before you had a UTI • Choose "Mild" if you can hold your urine for 1-2 hours • Choose "Moderate" if you cannot hold your urine for 1 hour • Choose "Severe" if you cannot even hold your urine for 30 minutes				

Patient Symptom Assessment Questionnaire for Clinical Response

Symptoms Assessed

1. Pain (uncomfortable pressure) in the lower abdomen/pelvic area
2. Burning (dysuria) when passing urine
3. Frequency of urination or going to the toilet very often
4. Urgency of urination or a strong and uncontrollable urge to pass urine

For each symptom, patients assessed severity and impact on daily activities

Severity Assessment

- No symptom/resolved
- Mild
- Moderate
- Severe

Impact on Daily Activities

- Not at all
- Not significantly bothersome
- Moderately bothersome
- Severely bothersome

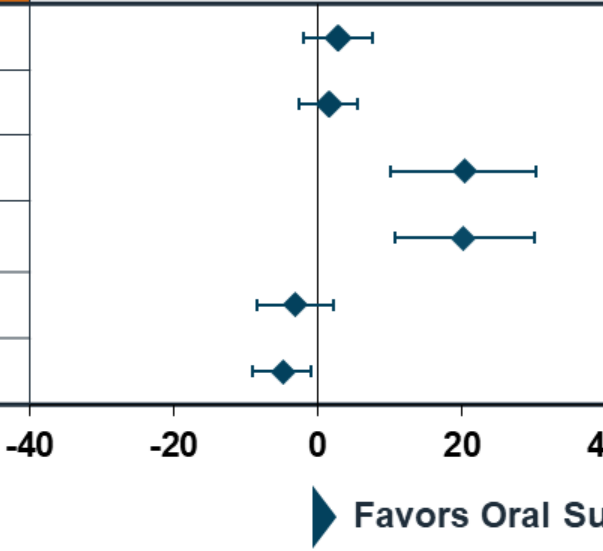
Investigator-Determined Clinical Response Definitions

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

Abbreviations: EOT = end of treatment; FV = final visit; TOC = test of cure; uUTI = uncomplicated urinary tract infection

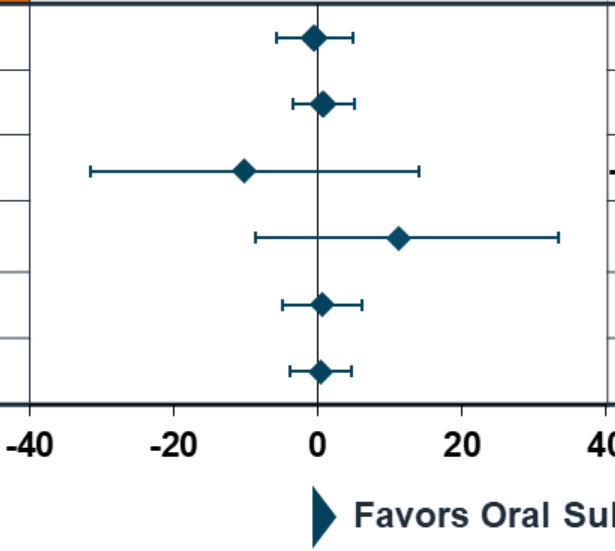
Study 301: Patient- and Investigator-Determined Clinical Success at Test of Cure

Clinical Success (Day 12)		Oral Sulopenem	Ciprofloxacin	Difference (95% CI)
Micro-MITT	Patient	82%	79%	**2.9%** (-1.9, 7.7)
	Investigator	89%	87%	**1.5%** (-2.5, 5.5)
Micro-MITTR	Patient	83%	63%	**20.4%** (10.2, 30.4)
	Investigator	88%	67%	**20.3%** (10.7, 30.0)
Micro-MITTS	Patient	81%	84%	**-3.0%** (-8.4, 2.3)
	Investigator	89%	94%	**-4.8%** (-9.0, -0.9)



Study 310: Patient- and Investigator-Determined Clinical Success at Test of Cure

Clinical Success (Day 12)		Oral Sulopenem	Amox/clav	Difference (95% CI)
Micro-MITT	Patient	76%	75%	**-0.4%** (-5.7, 4.9)
	Investigator	87%	87%	**0.8%** (-3.4, 5.1)
Micro-MITTR	Patient	62%	72%	**-10.1%** (-31.5, 14.0)
	Investigator	83%	72%	**11.3%** (-8.6, 33.4)
Micro-MITTS	Patient	77%	77%	**0.6** (-4.8, 6.1)
	Investigator	88%	87%	**0.4** (-3.9, 4.7)



Study 301: ASB at Day 12 does Not Affect Clinical Failure Rate at Day 28 in Patients Treated with Oral Sulopenem

	Assessment at Day 5	Clinical Failure at Day 12	Day 12 Odds Ratio (95% CI)	p-value
Overall Success	**335**	31 **(9.3%)**	**1.12** (0.14, 8.98)	**1.000**
Asymptomatic Bacteriuria	**12**	1 **(8.3%)**		

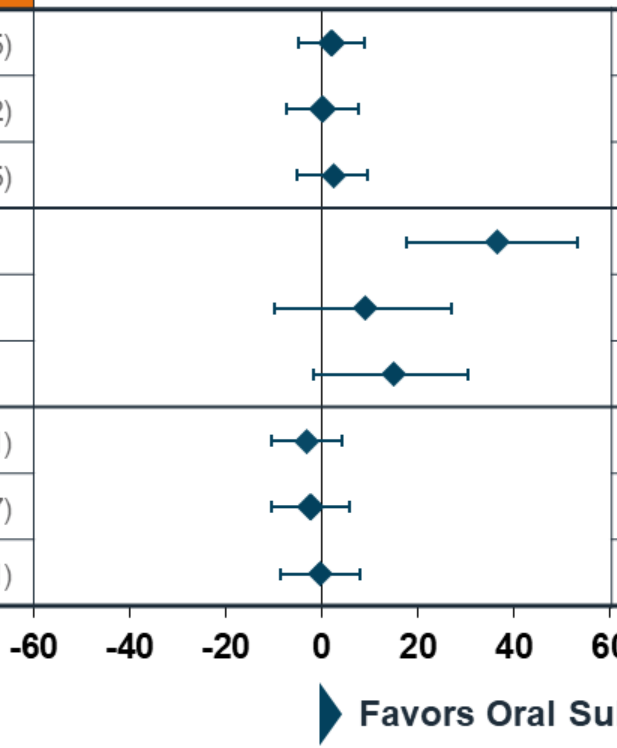
	Assessment at Day 12	Clinical Failure at Day 28	Day 28 Odds Ratio (95% CI)	p-value
Overall Success	**339**	20 **(5.9%)**	**0.52** (0.22, 1.22)	**0.128**
Asymptomatic Bacteriuria	**74**	8 **(10.8%)**		

Study 310: ASB at Day 12 does Not Affect Clinical Failure Rate at Day 28 in Patients Treated with Oral Sulopenem

	Assessment at Day 5	Clinical Failure at Day 12	Day 12 Odds Ratio (95% CI)	p-value
Overall Success	**272**	13 **(4.8%)**	**1.46** (0.18, 11.53)	**0.721**
Asymptomatic Bacteriuria	**30**	1 **(3.3%)**		
	Assessment at Day 12	**Clinical Failure at Day 28**	**Day 28 Odds Ratio (95% CI)**	**p-value**
Overall Success	**318**	22 **(6.9%)**	**1.28** (0.43, 3.84)	**0.656**
Asymptomatic Bacteriuria	**73**	4 **(5.5%)**		

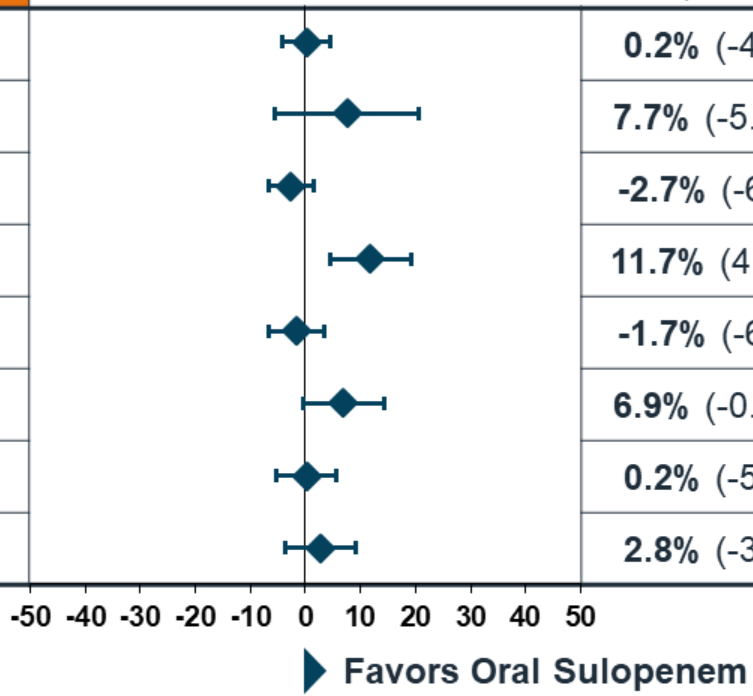
Study 301 + 310: Overall Success by BMI

	BMI (kg/m^2)	Oral Sulopenem	Comparator	Difference (95% CI)
Micro-MITT	< 25	**70.7%** (234/331)	**68.5%** (257/375)	**2.2** (-4.7, 8.9)
	25-30	**64.3%** (223/347)	**64.0%** (187/292)	**0.2** (-7.2, 7.7)
	>30	**55.7%** (200/359)	**53.3%** (184/345)	**2.4** (-5.0, 9.7)
Micro-MITTR	< 25	**77.6%** (45/58)	**40.9%** (18/44)	**36.7** (17.7, 53.4)
	25-30	**57.1%** (32/56)	**48.1%** (26/54)	**9.0** (-9.7, 27.1)
	>30	**49.3%** (37/75)	**34.4%** (22/64)	**15.0** (-1.6, 30.6)
Micro-MITTS	< 25	**69.2%** (189/273)	**72.2%** (239/331)	**-3.0** (-10.3, 4.3)
	25-30	**65.6%** (191/291)	**67.9%** (161/237)	**-2.3** (-10.3, 5.8)
	>30	**57.4%** (163/284)	**57.7%** (162/281)	**-0.3** (-8.4, 7.9)



Studies 301 + 310: Overall Success Treatment Response in Women by Age

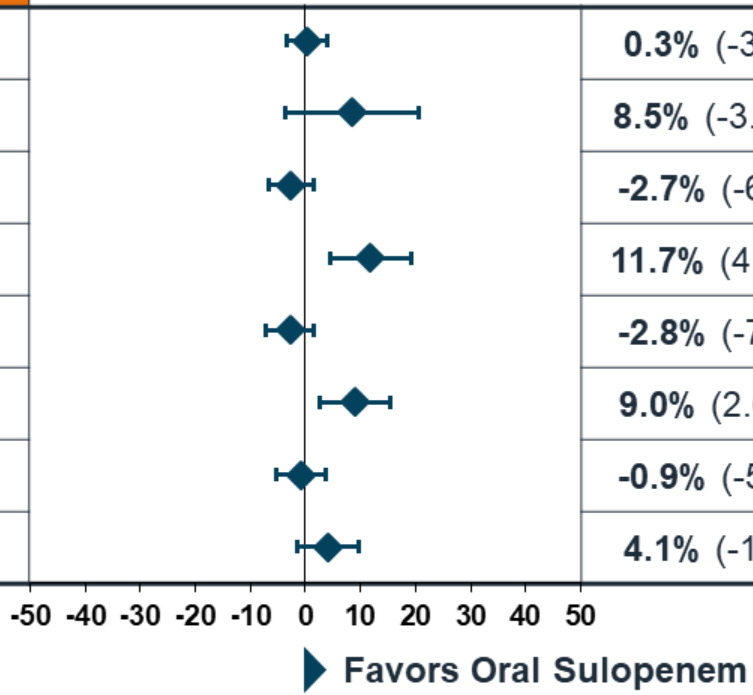
Overall Success	Oral Sulopenem	Comparator	Difference (95% CI)
< 75	**64.5%** (597/925)	**64.3%** (587/913)	**0.2%** (-4.1, 4.6)
≥ 75	**52.6%** (60/114)	**45.0%** (49/109)	**7.7%** (-5.5, 20.5)
< 65	**78.8%** (593/753)	**81.4%** (613/753)	**-2.7%** (-6.7, 1.4)
≥ 65	**79.0%** (226/286)	**67.3%** (181/269)	**11.7%** (4.4, 19.1)
< 60	**66.1%** (442/669)	**67.8%** (461/680)	**-1.7%** (-6.7, 3.3)
≥ 60	**58.1%** (215/370)	**51.2%** (175/342)	**6.9%** (-0.4, 14.2)
< 55	**69.7%** (384/559)	**68.4%** (397/580)	**0.2%** (-5.2, 5.6)
≥ 55	**56.9%** (273/480)	**54.1%** (239/442)	**2.8%** (-3.6, 9.2)



mMITT population

Studies 301 + 310: Clinical Success Treatment Response in Women by Age (micro-MITT)

Clinical Success	Oral Sulopenem	Comparator	Difference (95% CI)
< 75	**79.5%** (735/925)	**79.2%** (723/913)	**0.3%** (-3.4, 4.0)
≥ 75	**73.7%** (84/114)	**65.1%** (71/109)	**8.5%** (-3.6, 20.5)
< 65	**78.8%** (593/753)	**81.4%** (613/753)	**-2.7%** (-6.7, 1.4)
≥ 65	**79.0%** (226/286)	**67.3%** (181/269)	**11.7%** (4.4, 19.1)
< 60	**78.8%** (527/669)	**81.6%** (555/680)	**-2.8%** (-7.1, 1.4)
≥ 60	**78.9%** (292/370)	**69.9%** (239/342)	**9.0%** (2.6, 15.4)
< 55	**81.2%** (454/559)	**82.0%** (476/580)	**-0.9%** (-5.4, 3.7)
≥ 55	**76.0%** (365/480)	**71.9%** (318/442)	**4.1%** (-1.6, 9.8)



mMITT population