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

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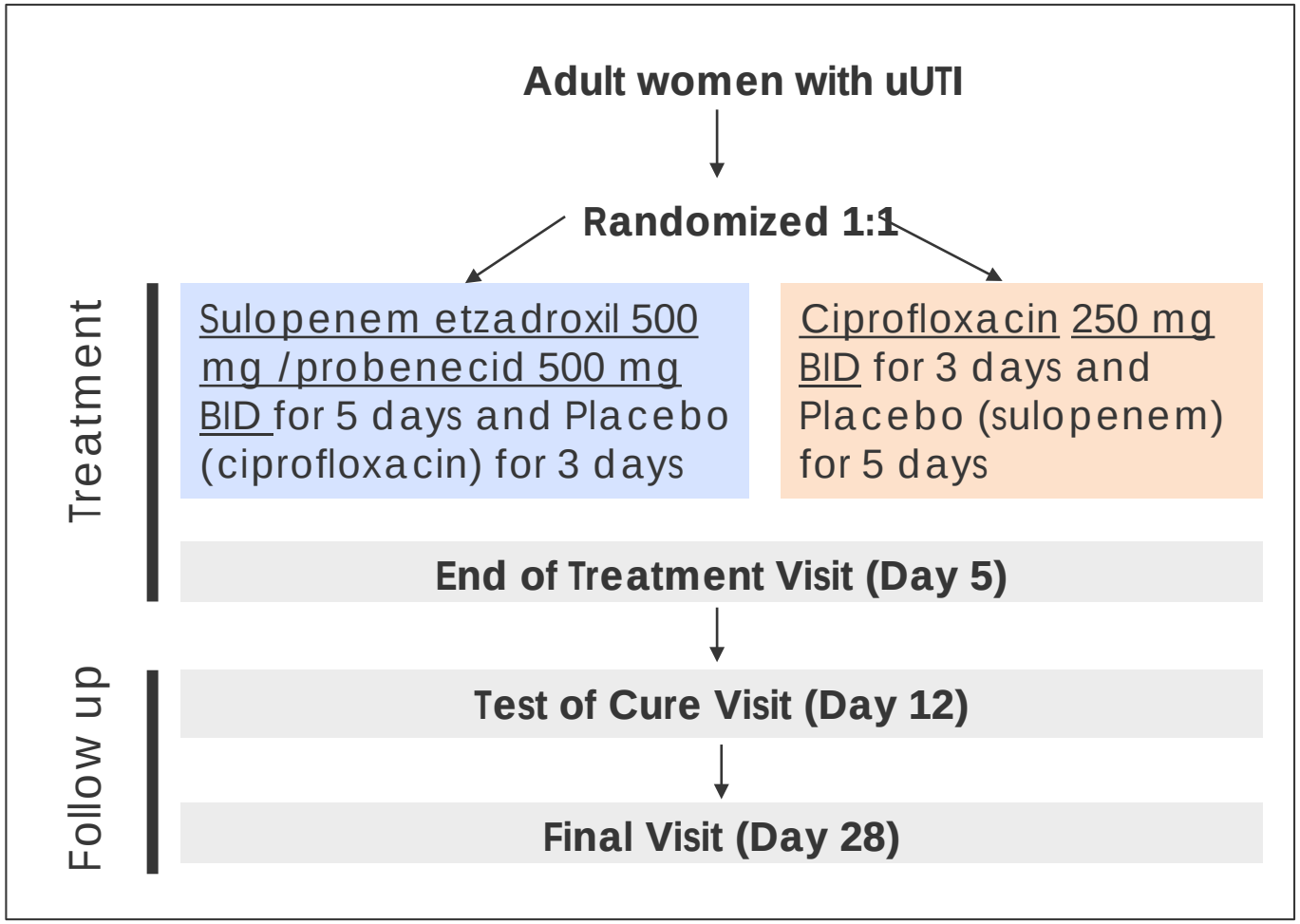
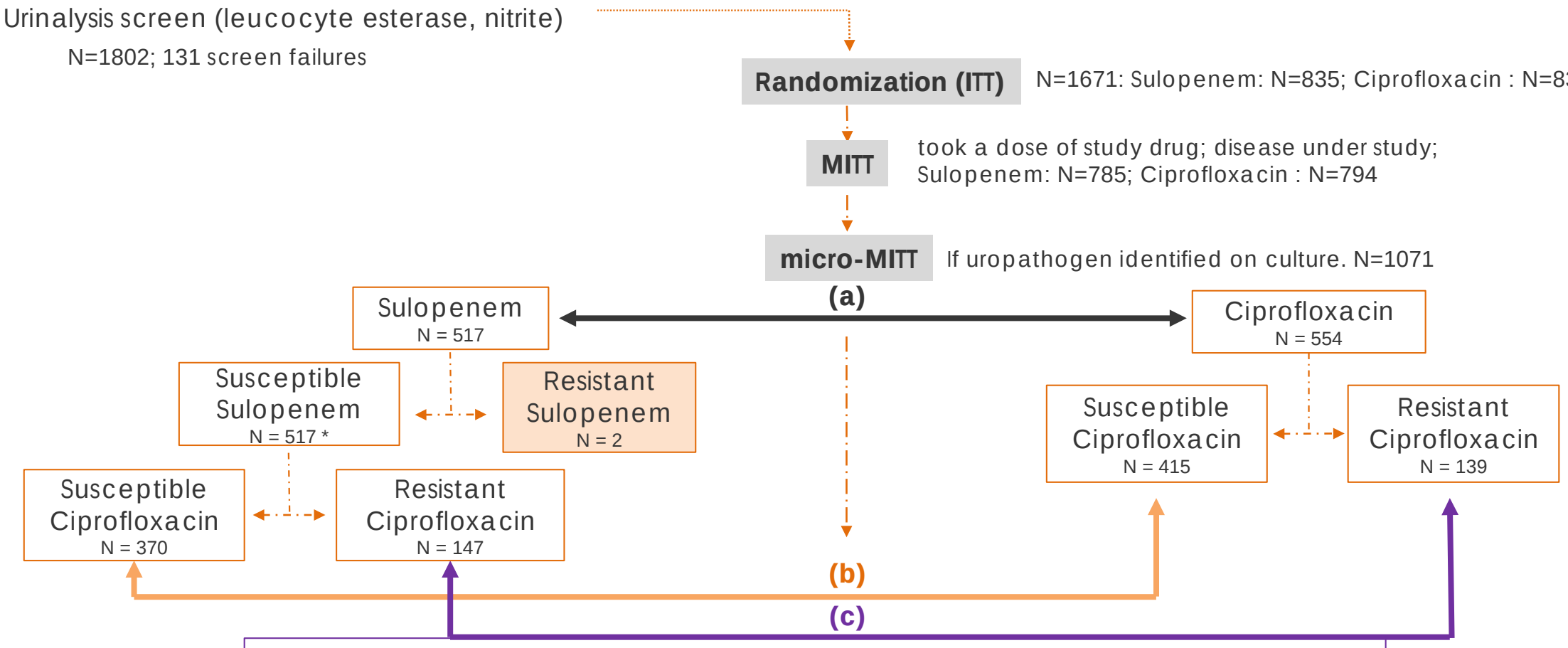
SURE 1: Sulopenem for Uncomplicated Urinary Tract Infection Inclusion Criteria and Study Schedule

- Inclusion Criteria
  - Female patients ≥18 years and ≤96 hours of symptoms
  - At least two of the following symptoms/signs:
    - urinary frequency, urinary urgency, pain or burning on micturition, suprapubic pain
  - A mid-stream urine specimen with:
    - a machine-read dipstick positive for nitrite
    - evidence of pyuria
  - Able to provide informed consent



SURE 1: Sulopenem for Uncomplicated Urinary Tract Infection Disposition of Patients and Analysis Subgroups



* The 2 patients with CRE were included in the sulopenem susceptible group.

Baseline Demographics in Susceptible and Nonsusceptible Populations are Different

Parameter	**microMITT S** Quinolone Susceptible	**microMITT R** Quinolone Non-susceptible	**p-value**
N	785	286	
Age (years), Median	51.0	57.0	<0.001
Age group ≥65 years	28.2%	40.6%	<0.001
Female	100%	100%	NS
Ethnicity: Hispanic/Latinx; not Hispanic/Latinx	23%; 76%	39%; 61%	<0.001
Geographic region: US	52%	57%	0.126
Race: White	90%	90%	NS
Diabetes	12%	18%	0.008
Weight (kg)	73.1	74.0	NS
BMI (kg/m^2): Median	26	27	0.008
Categorized BMI (kg/m^2)			0.001
<25	44%	32 %	
25-30	26%	30%	
>30	29%	37%	
Creatinine clearance (mL/min): Mean	78.4	72.7	0.001
Creatinine clearance < 60 ml/min	212 (27%)	110 (38%)	

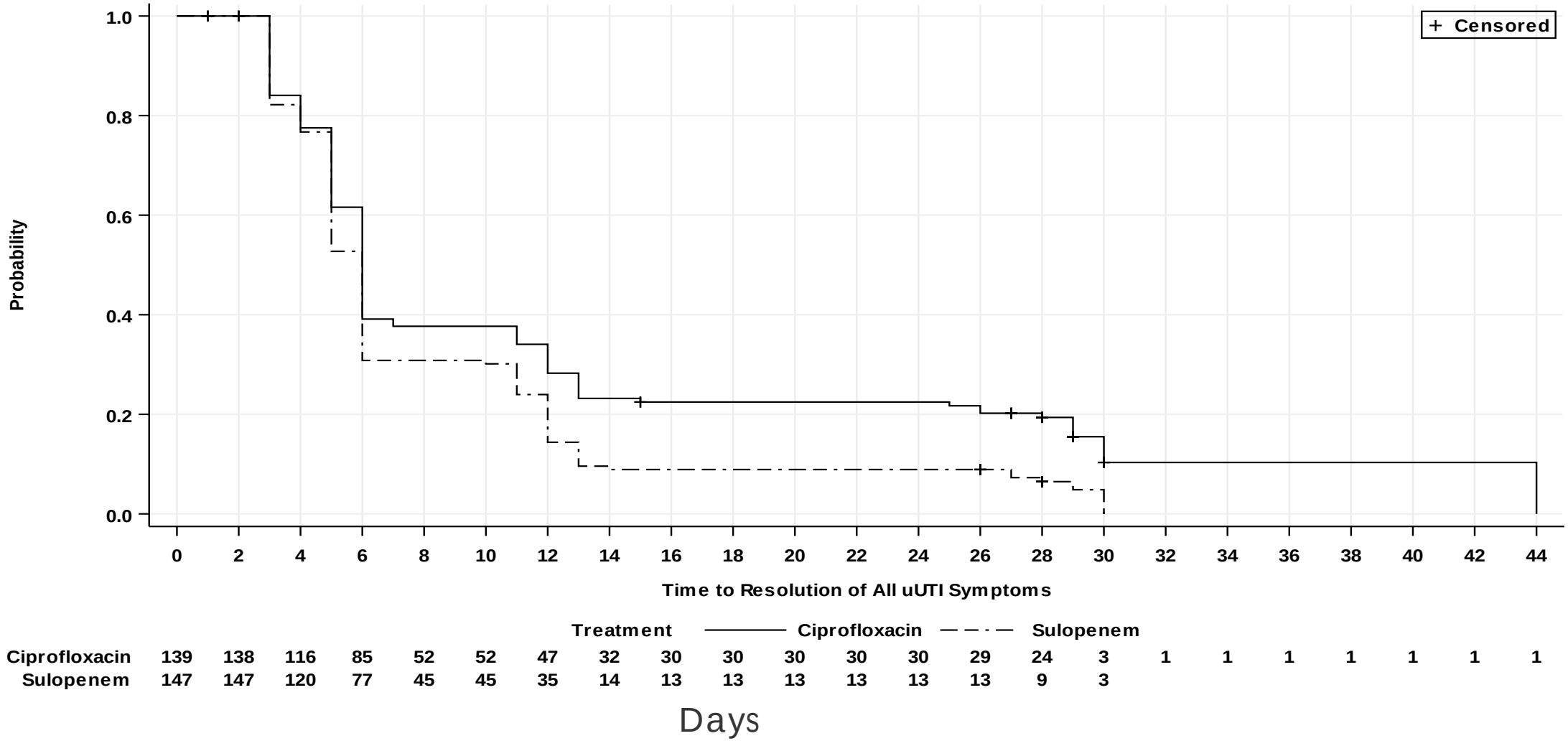
Primary Endpoint: microMITT R
Sulopenem is Superior in Quinolone Non-susceptible Patients

Outcome	Sulopenem n (%) N=147	Ciprofloxacin n (%) N=139	Difference (%) (95% CI)	p-value
Test of Cure (D12)				
Overall response	92 (62.6)	50 (36.0)	26.6 (15.1, 37.4)	<0.001
Overall nonresponse	49 (33.3)	84 (60.4)		
Indeterminate	6 (4.1)	5 (3.6)		
Clinical success	122 (83.0)	87 (62.6)	20.4 (10.2, 30.4)	<0.001
Microbiologic success	109 (74.1)	69 (49.6)	24.5 (13.4, 35.1)	<0.001
End of Treatment (D5)				
Overall Response	95 (64.6)	42 (30.2)	34.4 (23.1, 44.8)	<0.001

Reasons for Overall Nonresponse: microMITT R Differences Seen in Both Clinical and Microbiologic Response

Number of Nonresponders/ Reasons for Overall Nonresponse at TOC	Sulopenem n (%) N=147	Ciprofloxacin n (%) N=139
Total number of nonresponders	49 (33.3)	84 (60.4)
Urine culture at TOC visit demonstrates ≥10^3 CFU/mL of the baseline uropathogen (**microbiologic failure only**)	27 (18.4)	38 (27.3)
No resolution or worsening of symptoms of uUTI present at trial entry and/or new uUTI symptoms (**clinical failure only**)	17 (11.6)	13 (9.4)
Urine culture ≥10^3 and at least one symptom not resolved (**both clinical and microbiologic failure**)	5 (3.4)	25 (18.0)
Receipt of **non-study antibacterial therapy** for uUTI	0 (0.0)	11 (7.9)
Death due to uUTI	0 (0.0)	0 (0.0)

Time to Resolution Symptoms: microMITT R
Kaplan-Meier Analysis Reflects the Primary Endpoint



Resolution of symptoms, Survival and Without Non-study Antibiotic Use; p = 0.004

Pathogens at Baseline: microMITT R
E. coli is Predominant Pathogen

Organism	Sulopenem n (%) N=147	Ciprofloxacin n (%) N=139	Total n (%) N=286
Number of Patients	147 (100)	139 (100)	286 (100)
Escherichia coli	127 (86.4)	120 (86.3)	247 (86.4)
Klebsiella pneumoniae	14 (9.5)	16 (11.5)	30 (10.5)
Proteus mirabilis	9 (6.1)	6 (4.3)	15 (5.2)
Morganella morganii	3 (2.0)	1 (0.7)	4 (1.4)
Enterobacter cloacae complex	1 (0.7)	0 (0.0)	1 (0.3)
Providencia stuartii	0 (0.0)	1 (0.7)	1 (0.3)

Consistent Overall Response Among MDR Pathogens: microMITT R 5% with Uropathogen Resistant to All Major Classes of Oral Antibiotics

Resistance Class	Sulopenem n/N (%)	Ciprofloxacin n/N (%)	p-value
Quinolone resistant	90/145 (62.1)	49/137 (35.8)	<0.001
Quinolone Resistant and:			
β-lactam resistant	86/129 (66.7)	43/121 (35.5)	<0.001
ESBL positive	29/50 (58.0)	13/41 (31.7)	0.012
TMP-SMX resistant	61/94 (64.9)	28/78 (35.9)	<0.001
Nitrofurantoin resistant	30/39 (76.9)	16/38 (42.1)	0.002
β-lactam, quinolone, and TMP-SMX resistant	38/63 (60.3)	16/47 (34.0)	0.006
β-lactam, quinolone, TMP-SMX, and nitrofurantoin resistant	19/24 (79.2)	11/27 (40.7)	0.005

Overall Response by Visit: microMITT R

Timepoint	Sulopenem n (%) N=147	Ciprofloxacin n (%) N=139	P value
End of Treatment (Day 5)	95 (64.4)	42 (30.2)	<0.001
Test of Cure (Day 12)	92 (62.6)	50 (36.0)	<0.001
Final Visit (Day 28)	100 (68.0)	62 (44.6)	<0.001

Covariate Analysis: microMITT R

Covariate	Odds Ratio (95% CI)	p-value
Treatment (Sulopenem vs Ciprofloxacin)	3.29 (1.95, 5.55)	<0.001
Age	0.97 (0.95, 0.98)	<0.001
Diabetes	0.37 (0.18, 0.75)	0.006

Primary Endpoint at Test of Cure: microMITT S
Sulopenem is not Noninferior to Ciprofloxacin in Quinolone Susceptible Population

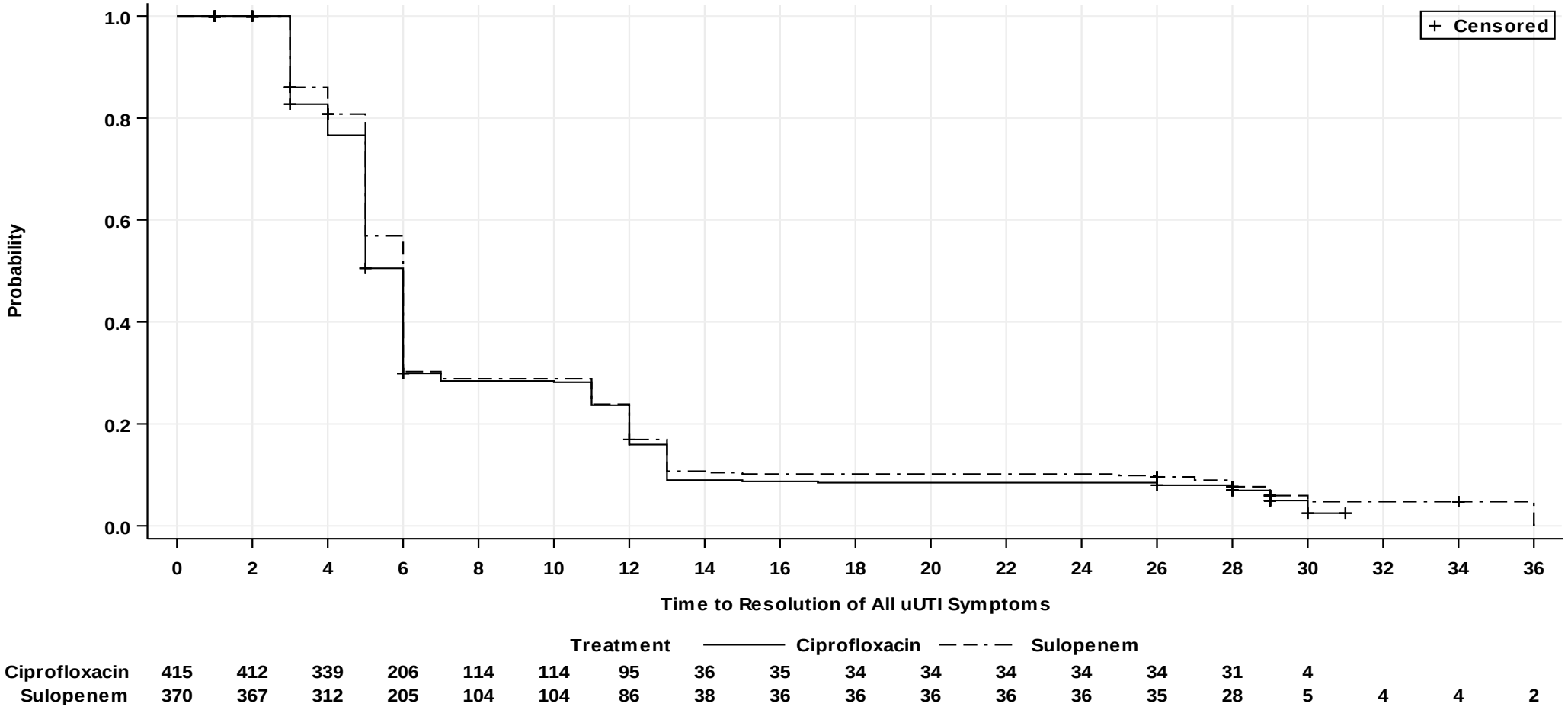
Outcome	Sulopenem n (%) N=370	Ciprofloxacin n (%) N=415	Difference (%) (95% CI)
Test of Cure (D12)			
Overall response	247 (66.8)	326 (78.6)	-11.8 (-18.0, -5.6)
Overall nonresponse	105 (28.4)	65 (15.7)	
Reason for failure: ASB	47 (12.7)	16 (3.9)	
Indeterminate	18 (4.9)	24 (5.8)	
Clinical success	300 (81.1)	349 (84.1)	-3.0 (-8.4, 2.3)
Microbiologic success	287 (77.6)	369 (88.9)	-11.3 (-16.7, -6.2)
End of Treatment (D5)			
Overall response	240 (64.9)	271 (65.3)	-0.4 (-7.1, 6.2)

ASB=asymptomatic bacteriuria

Reasons for Failure: microMITT S
Most of the Difference in Outcome is a Result of a Lower Rate of Asymptomatic Bacteriuria on Ciprofloxacin

Reasons for overall nonresponse at TOC	Sulopenem n (%) N=370	Ciprofloxacin n (%) N=415
Number of nonresponders	105 (28.4)	65 (15.7)
Urine culture at the TOC visit demonstrates ≥10^3 CFU/mL of the baseline uropathogen (**microbiologic failure only**)	47 (12.7)	16 (3.9)
No resolution or worsening of symptoms of uUTI present at trial entry and/or new uUTI symptoms (**clinical failure only**)	38 (10.3)	42 (10.1)
Urine culture ≥10^3 and at least one symptom not resolved (**both clinical and microbiologic failure**)	18 (4.9)	4 (1.0)
Receipt of **non-study antibacterial therapy** for uUTI	4 (1.1)	5(1.2)
Death due to uUTI	0 (0.0)	0 (0.0)

Time to Resolution Symptoms: microMITT S
Symptom Resolution Occurs at a Similar Rate on Each Regimen



Days

Resolution of symptoms, Survival and Without Non-study Antibiotic Use; p = 0.252

Overall Response and Clinical Response: microMITT S by Selected Baseline Pathogens

Pathogen	Overall Response (Clinical and Microbiologic)		Clinical Response	
	Sulopenem n/N (%)	Ciprofloxacin n/N (%)	Sulopenem n/N (%)	Ciprofloxacin n/N (%)
E. coli	209/313 (67)	269/349 (77)	254/313 (81)	286/349 (82)
K. pneumoniae	24/37 (65)	25/32 (78)	30/37 (81)	30/32 (94)
P. mirabilis	4/8 (50)	11/11 (100)	8/ 8 (100)	11/ 11 (100)

Overall Response by Visit: microMITT S

Timepoint	Sulopenem n (%) N=370	Ciprofloxacin n (%) N=415	Difference (%), (95% CI)
End of Treatment (D5)	240 (64.9)	271 (65.3)	-0.4 (-7.1, 6.2)
Test of Cure (D12)	247 (66.8)	326 (78.6)	-11.8 (-18.0, -5.6)
Final Visit (D28)	256 (69.2)	323 (77.8)	-8.6 (-14.8, -2.5)

Primary Endpoint: microMITT

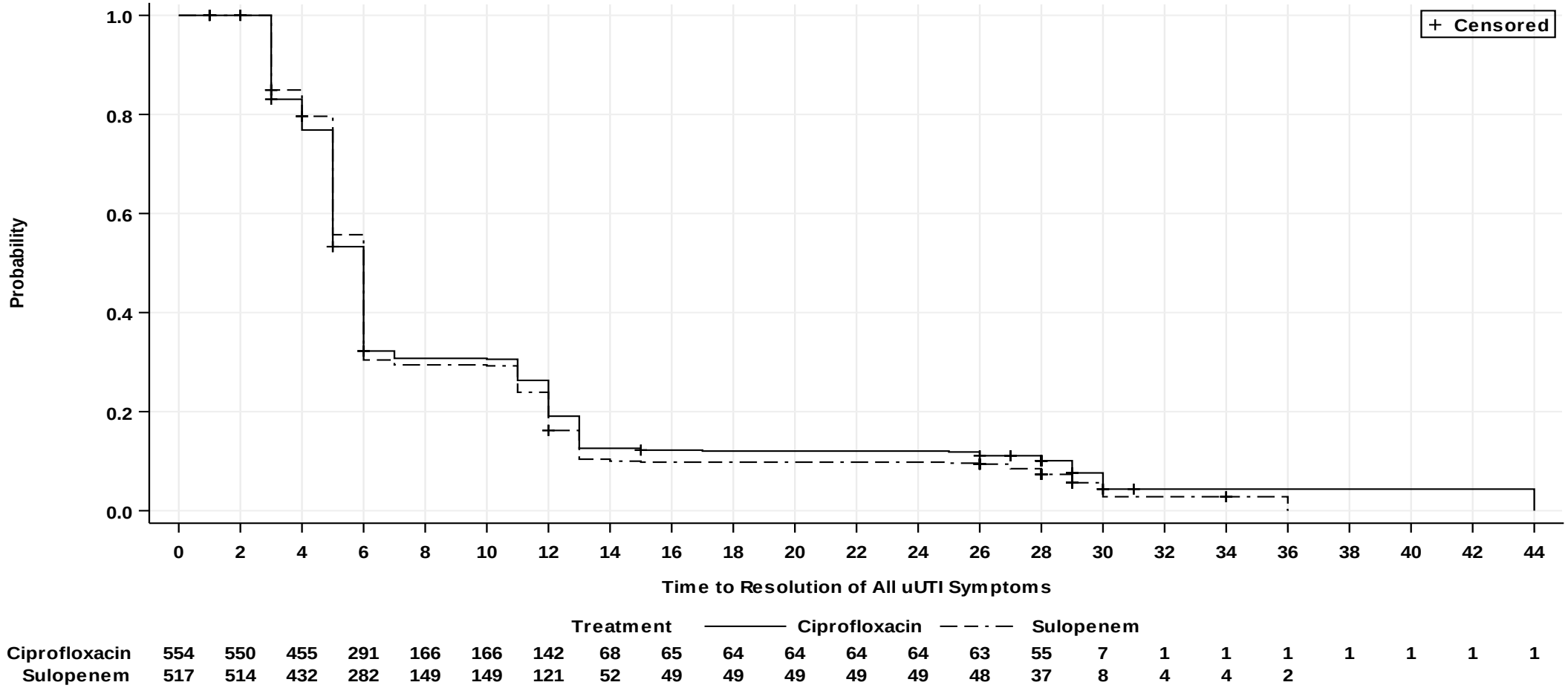
Population/ Outcome	Sulopenem n (%) N= 517	Ciprofloxacin n (%) N=554	Difference (%) (95% CI)	Difference (%) (99% CI)
Test of Cure (D12) microMITT				
Overall responder	339 (65.6)	376 (67.9)	-2.3 (-7.9, 3.3)	-2.3 (-9.7, 5.1)
Reason for failure: ASB	74 (14.3)	54 (9.7)		
Clinical success	422 (81.6)	436 (78.7)	2.9 (-1.1, 6.6)	
Microbiologic success	396 (76.6)	438 (79.1)	-2.5 (-7.5, 2.5)	
End of Treatment (D5) microMITT				
Overall response at EOT	335 (64.8)	313 (56.5)	8.3 (2.4, 14.1)	p = 0.006
Test of Cure (D12) MITT				
Clinical success	647/785 (82.4)	638/794 (80.4)	2.1 (-1.8, 5.9)	

ASB = asymptomatic bacteriuria

Reasons for Overall Nonresponse: microMITT
Generally Balanced Though Slightly Lower ASB Rate on Ciprofloxacin

Number of nonresponders/reasons for overall nonresponse at TOC	**Sulopenem n (%) N=517**	**Ciprofloxacin n (%) N=554**
Number of nonresponders	154 (29.8)	149 (26.9)
Urine culture at the TOC visit demonstrates ≥10^3 CFU/mL of the baseline uropathogen (**microbiologic failure only**)	74 (14.3)	54 (9.7)
No resolution or worsening of symptoms of uUTI present at trial entry and/or new uUTI symptoms (**clinical failure only**)	55 (10.6)	55 (9.9)
Urine culture ≥10^3 and at least one symptom not resolved (**both clinical and microbiologic failure**)	23 (4.4)	29 (5.2)
Receipt of **non-study antibacterial** therapy for uUTI	4 (0.8)	16 (2.9)
Death due to uUTI	0 (0.0)	0 (0.0)

Time to Resolution Symptoms: microMITT
Similar Rate of Resolution of Symptoms



Days

Resolution of symptoms, Survival and Without Non-study Antibiotic Use; p = 0.490

Overall Response by Visit: microMITT

Timepoint	Sulopenem n/N (%)	Ciprofloxacin n/N (%)	Difference (%) (95% CI)
End of Treatment (D5)	335/517 (64.8)	313/554 (56.5)	8.3 (2.4,14.1)
Test of Cure (D12)	339/517 (65.6)	376/554 (67.9)	-2.3 (-7.9, 3.3)
Final Visit (D28)	356/517 (68.9)	385/554 (69.5)	-0.6 (-6.2, 4.9)

Overall Response by Ciprofloxacin MIC at Baseline microMITT

	Sulopenem n/N (%)	Ciprofloxacin n/N (%)
All isolates, N	529	564
Ciprofloxacin MIC (µg/ml)	**Overall Response**	
≤0.06	207/313 (66)	272/335 (81)
0.12	7/10 (70)	6/9 (67)
0.25	18/28 (64)	23/32 (72)
0.5	15/22 (68)	23/33 (70)
1	6/8 (75)	5/11 (46)
≥2	93/148 (63)	55/144 (38)

Overall Response by Ciprofloxacin MIC at Baseline microMITT

	Sulopenem n/N (%)	Ciprofloxacin n/N (%)		
All isolates, N	529	564		
Ciprofloxacin MIC (µg/ml)	**Overall Response**		**Primary Analyses:** **Ciprofloxacin MIC breakpoint of ≥2 µg/ml**	
≤0.06	207/313 (66)	272/335 (81)		
0.12	7/10 (70)	6/9 (67)		
0.25	18/28 (64)	23/32 (72)	-11.8% (-18.0, -5.6)	
0.5	15/22 (68)	23/33 (70)		
1	6/8 (75)	5/11 (46)		
≥2	93/148 (63)	55/144 (38)	p<0.001	

Overall Response by Ciprofloxacin MIC at Baseline microMITT

	Sulopenem n/N (%)	Ciprofloxacin n/N (%)	Primary Analyses: Ciprofloxacin MIC breakpoint of ≥2 µg/ml	Primary Analyses: Ciprofloxacin MIC breakpoint of >0.06 µg/ml
All isolates, N	529	564		
Ciprofloxacin MIC (µg/ml)	**Overall Response**			
≤0.06	207/313 (66)	272/335 (81)	-11.8% (-18.0, -5.6)	-15.1% (-21.7%, -8.3%)
0.12	7/10 (70)	6/9 (67)		p=0.001
0.25	18/28 (64)	23/32 (72)		
0.5	15/22 (68)	23/33 (70)		
1	6/8 (75)	5/11 (46)		
≥2	93/148 (63)	55/144 (38)	p<0.001	

Lower Rate of Asymptomatic Bacteriuria is Concentrated Among Organisms Most Susceptible to Ciprofloxacin

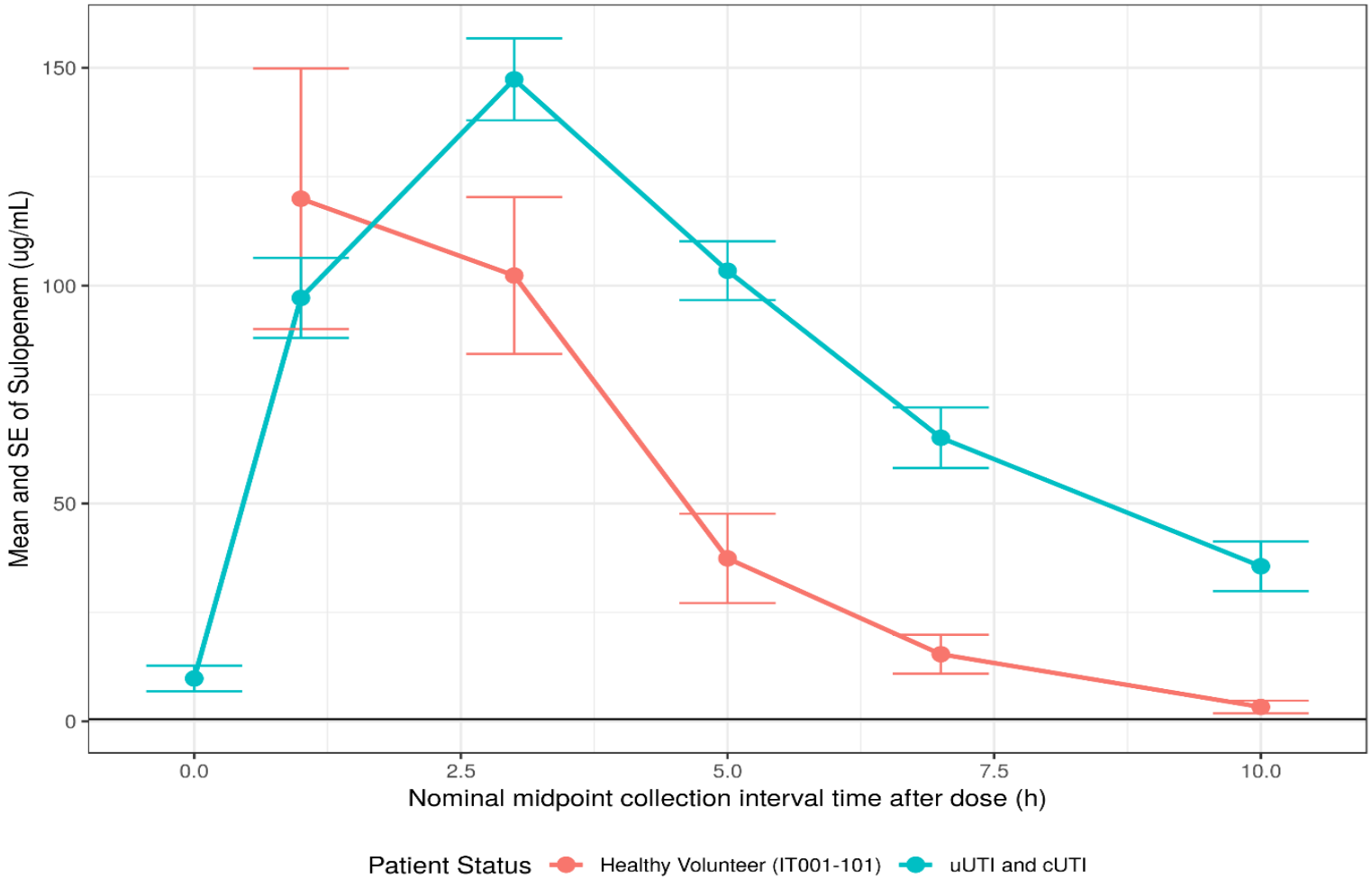
	Overall Response		Asymptomatic Bacteriuria	
	Sulopenem n/N (%)	**Ciprofloxacin n/N (%)**	**Sulopenem n/N (%)**	**Ciprofloxacin n/N (%)**
Ciprofloxacin MIC (µg/ml)	529	564	529	564
≤0.06	207/313 (66)	272/335 (81)	**41/313 (13)**	**9/335 (3)**
0.12	7/10 (70)	6/9 (67)	2/10 (20)	2/9 (22)
0.25	18/28 (64)	23/32 (72)	4/28 (14)	3/32 (9)
0.5	15/22 (68)	23/33 (70)	2/22 (9)	1/33 (3)
1	6/8 (75)	5/11 (46)	1/8 (13)	1/11 (9)
≥2	93/148 (63)	55/144 (38)	27/148 (18)	38/144 (26)

13%

8%

Sulopenem Pharmacokinetics in the Urine

Sulopenem concentrations in urine of patients and healthy volunteers significantly exceed the MIC90 for >80% of the dosing interval



Summary of Adverse Events

Parameter	Sulopenem N=833 n (%)	Ciprofloxacin N=827 n (%)
Number of patients who experienced at least one:		
Adverse Event (AE)	208 (25.0)	116 (14.0)
Treatment Emergent Adverse Events (TEAE)	207 (24.8)	115 (13.9)
TEAE by maximum severity		
Mild	144 (17.3)	87 (10.5)
Moderate	56 (6.7)	27 (3.3)
Severe	7 (0.8)	1 (0.1)
Drug-related TEAE	142 (17.0)	51 (6.2)
TEAE leading to discontinuation of study drug	13 (1.6)	8 (1.0)
TEAE leading to discontinuation from study	0 (0.0)	1 (0.1)
Serious TEAE (SAE)	6 (0.7)	2 (0.2)
Drug-related SAE	1 (0.1)*	0 (0.0)
SAE leading to death	1 (0.1)**	0 (0.0)
SAE leading to premature discontinuation of study drug	1 (0.1)	0 (0.0)

*angioedema; ** lung cancer, unrelated

Treatment-Emergent Adverse Events in ≥1% of Patients

Parameter	Sulopenem (N=833) n (%)	Ciprofloxacin (N=827) n (%)
Diarrhoea	103 (12.4)	21 (2.5)
Clinically significant diarrhea	60 (7.2)	10 (1.2)
Mild	47 (5.6)	9 (1.1)
Number of episodes	781	56
Duration, Median (days)	3.0	2.0
Nausea	31 (3.7)	30 (3.6)
Headache	18 (2.2)	18 (2.2)
Vomiting	13 (1.6)	11 (1.3)
Dizziness	9 (1.1)	5 (0.6)

Conclusions

- Sulopenem was superior to ciprofloxacin in treatment of uUTI in patients with a quinolone non susceptible uropathogen
- Sulopenem was not non-inferior to ciprofloxacin in treatment of uUTI in patients with a quinolone susceptible uropathogen
  - The difference in outcome was a consequence of lower rates of asymptomatic bacteriuria in patients receiving ciprofloxacin
- In a combined analysis without regard to quinolone susceptibility, sulopenem was non-inferior to ciprofloxacin
- Patients with a quinolone non susceptible pathogen are more likely to be older, obese and have Diabetes mellitus with reduced creatinine clearance
- Further study of the influence of asymptomatic bacteriuria on assessments of the outcome of treatment of uUTI is warranted

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