Efficacy and Safety of Intravenous Sulopenem Followed by Oral Sulopenem etzadroxil/ Probenecid Versus Intravenous Ertapenem Followed by Oral Ciprofloxacin or Amoxicillin-clavulanate in the Treatment of Complicated Urinary Tract Infections (cUTI): Results from the SURE-2 Trial

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ABSTRACT

Background

Sulopenem is a broad-spectrum IV and oral penem antibiotic being developed for the treatment of infections caused by multidrug-resistant bacteria to allow for earlier discharge of hospitalized patients.

Methods

1,395 hospitalized adults with pyuria, bacteriuria, and clinical signs and symptoms of cUTI were randomized to sulopenem IV once daily for 5 days followed by a bilayer tablet of sulopenem-etzadroxil and probenecid bid or ertapenem IV once daily for 5 days followed by either oral ciprofloxacin or amoxicillin-clavulanate bid, depending on susceptibility of the baseline uropathogen. The primary endpoint was overall (clinical and microbiologic) response at Day 21 [Test of Cure (TOC)] in the micro-MITT population.

Results

The sulopenem and ertapenem treatment arms were well-balanced at baseline.

Outcome	Sulopenem n (%) N=444	Ertapenem n (%) N=440	Difference (%), (95% CI)
All patients			
Overall response	301 (67.8)	325 (73.9)	-6.1 (-12.0, -0.1)
Clinical success	397 (89.4)	389 (88.4)	1.0 (-3.1, 5.1)
Microbiologic success	316 (71.2)	343 (78.0)	-6.8 (-12.5, -1.1)
Patients with ciprofloxacin susceptible isolates			
	Sulopenem IV/ oral Sulopenem n (%) N=248	Ertapenem IV/ oral Ciprofloxacin n (%) N=215	
Overall response	168 (67.7)	186 (86.5)	-18.8 (-26.1, -11.0)
Patients with all other isolates			
	Sulopenem IV only or Sulopenem IV/ oral Sulopenem n (%) N=196	Ertapenem IV only or Ertapenem IV/ Amoxicillin-clavulanate n (%) N=225	
Overall response	133 (67.9)	139 (61.8)	6.1 (-3.1, 15.1)

The difference in overall response was driven by a difference in asymptomatic bacteriuria occurring between the end of treatment (EOT) and TOC in the subgroup of patients with a ciprofloxacin susceptible uropathogen at baseline who received ertapenem IV followed by oral ciprofloxacin. No difference in overall response was identified at EOT [86.7% vs 88.9%, sulopenem and ertapenem, respectively; difference, 95% CI: -2.2% (-6.5, 2.2)].

19% of patients remained on ertapenem IV as the baseline pathogen was both resistant to quinolones and ESBL positive; overall response for patients with these resistant pathogens on IV sulopenem who stepped down to oral sulopenem was higher [64/80 vs 55/84 on sulopenem IV/oral and ertapenem IV, respectively; difference, 95% CI: 14.5% (08, 27.8)]. Treatment emergent adverse events (all, 14.8% vs 16.1%; related, 6.0% vs 9.2%) and serious adverse events (2.0% vs 0.9%) were similar for patients on sulopenem and ertapenem, respectively.

Conclusion

Sulopenem followed by oral sulopenem-etzadroxil probenecid was not non-inferior to ertapenem followed by oral step-down therapy for the treatment of cUTI driven by a lower rate of asymptomatic bacteriuria in patients receiving oral ciprofloxacin. Sulopenem, both IV and oral, was well-tolerated; its oral formulation allowed patients with baseline pathogens resistant to both quinolones and β-lactams an opportunity to successfully step down from IV therapy.

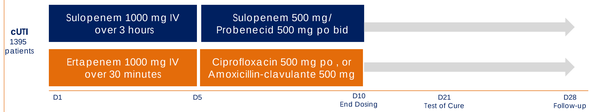
INTRODUCTION

Sulopenem is a broad-spectrum IV and oral penem antibiotic being developed for the treatment of infections caused by multidrug-resistant bacteria to allow for earlier discharge of hospitalized patients.

METHODS

- 1,395 hospitalized adults with pyuria, bacteriuria, and clinical signs and symptoms of cUTI were randomized to sulopenem IV once daily for 5 days followed by a bilayer tablet of sulopenem-etzadroxil and probenecid bid or ertapenem IV once daily for 5 days followed by either oral ciprofloxacin or amoxicillin-clavulanate bid, depending on susceptibility of the baseline uropathogen.

Figure 1: Trial Design



- If Baseline isolate not susceptible to Ciprofloxacin:
  - For ertapenem patients: oral follow on in amoxicillin-clavulanate
  - For sulopenem patients: step down to oral sulopenem-etzadroxil
- If Baseline isolate resistant to both Ciprofloxacin and Amoxicillin/clavulante
  - For ertapenem patients, remain on IV ertapenem
  - For sulopenem patients, step down to oral sulopenem etzadroxil
- The pharmacist was unblinded so as to be able prepare the blinded regimens
- The primary endpoint was overall (clinical and microbiologic) response at Day 21 [Test of Cure (TOC)] in the micro-MITT population.
- Key secondary endpoints include microbiologic response, and clinical response

RESULTS

Table 1: Demographics

Parameter	Sulopenem n/N (%)	Ertapenem n/N (%)	p-value
N	697	698	
Age (years) Mean (SD)	57.8 (18.2)	59.3 (18.2)	0.095
Age ≥65 years	311 (44.6)	338 (48.4)	0.163
Male	308 (44.2)	318 (45.6)	0.628
Not Hispanic or Latino	672 (96.4)	675 (96.7)	0.848
Non-US	667 (95.7)	667 (95.6)	1.000
White	694 (99.6)	692 (99.1)	0.226
Present	113 (16.2)	112 (16.0)	0.942
BMI (kg/m^2), median	26.7	26.7	0.993
Min, max	16.7, 52.6	14.9, 54.7	
Creatinine clearance (mL/min)[a], median	69.0	68.0	0.534
Min, max	8.0, 220.0	11.0, 231.0	
<30 mL/min	32 (4.6)	42 (6.0)	

RESULTS

Table 2: Primary and Key Secondary Endpoints

Micro-MITT population	Sulopenem n/N (%)	Ertapenem n/N (%)	Difference (%) (95% CI)
Overall Success (TOC)	301/444 (67.8)	325/440 (73.9)	-6.1 (-12.0, -0.1)
Reason for Failure: Asymptomatic bacteriuria	93 (20.9)	59 (13.4)	
Clinical Success (TOC)	397/444 (89.4)	389/440 (88.4)	1.0 (-3.1, 5.1)
Overall Success (EOT)	385/444 (86.7)	391/440 (88.9)	-2.2 (-6.5, 2.2)

Table 3: Primary Endpoint by Quinolone Susceptibility

Micro-MITT population	Sulopenem n/N (%)	Ertapenem n/N (%)	Difference (%) (95% CI)
Primary Endpoint: Overall Success (TOC)	301/444 (67.8)	325/440 (73.9)	-6.1 (-12.0, -0.1)
Reason for Failure: Asymptomatic bacteriuria	93 (20.9)	59 (13.4)	
Patients with ciprofloxacin susceptible isolates by treatment regimen			
	Sulopenem IV: Sulopenem oral	Ertapenem: Ciprofloxacin	
Overall Success (TOC)	168/248 (67.7)	186/215 (86.5)	-18.8(-26.1,-11.0)
Reason for Failure: Asymptomatic bacteriuria	54 (21.8)	10 (4.7)	
Patients with ciprofloxacin non-susceptible isolates by treatment regimen			
	Sulopenem IV	Ertapenem IV (n= 26) Ertapenem: Amox/clav (n=6)	
	19/34 (55.9)	17/32 (53.1)	2.8 (-20.9, 26.2)
Reason for Failure: Asymptomatic bacteriuria	7 (20.6)	7 (21.9)	
Patients with ciprofloxacin non-susceptible isolates by treatment regimen			
	Sulopenem IV or Sulopenem IV: Sulopenem oral	Ertapenem IV or Ertapenem IV: Amox/clav	
	114/162 (70.4)	122/193 (63.2)	7.2 (-2.7, 16.8)
Reason for Failure: Asymptomatic bacteriuria	32 (19.8)	42 (21.8)	

Table 4: Response to IV Treatment (Day 5)

Micro-MITT population		Sulopenem n (%) N=444	Ertapenem n (%) N=440	Difference (%) (95% CI)
Overall Response	Cure	198 (44.6)	193 (43.9)	0.7 (-5.8, 7.3)
	Cured + Improved	360 (81.1)	352 (80.0)	1.1 (-4.2, 6.3)
Clinical Response	Cure	203 (45.7)	196 (44.5)	1.2 (-5.4, 7.7)
	Cured + Improved	369 (83.1)	362 (82.3)	0.8 (-4.2, 5.9)
Microbiologic Response		427 (96.2)	419 (95.2)	0.9 (-1.7, 3.6)

Table 5: Adverse Events

Safety Population	Sulopenem N= 695 n (%)	Ertapenem N=697 n (%)
Treatment emergent adverse events (TEAE)	103 (14.8%)	112 (16.1%)
IV TEAE	72 (10.4%)	94 (13.5%)
Oral* TEAE	42 (6.0%)	27 (3.9%)
Drug related TEAE	42 (6.0%)	64 (9.2%)
IV drug related TEAE	32 (4.6%)	52 (7.5%)
Oral* drug-related TEAE	13 (1.9%)	13 (1.9%)
TEAE leading to d/c of study drug	3 (0.4%)	4 (0.6%)
TEAE leading to d/c from Study	0	0
Serious Adverse Events	14 (2.0%)	6 (0.9%)
Drug-related SAE	0	0
Leading to death	2 (0.3%)	0
Leading to premature d/c of study drug	0	0
Leading to premature d/c from study	0	0
Treatment-Emergent Adverse Events Occurring in at Least 1% of Patients		
Headache	21 (3.0%)	15 (2.2%)
Diarrhea	19 (2.7%)	21 (3.0%)
Nausea	9 (1.3%)	11 (1.6%)

CONCLUSIONS

- Sulopenem: oral sulopenem etzadroxil/probenecid was not non-inferior to ertapenem: oral step-down therapy for the treatment for cUTI
- The difference in outcomes was driven by a lower rate of asymptomatic bacteriuria only in patients receiving oral ciprofloxacin as step down
- Response to treatment after IV therapy was similar on each regimen
- Clinical response, which includes all components of the primary endpoint except asymptomatic bacteriuria, was similar at all timepoints
- Sulopenem, both IV and oral, was well-tolerated
- Oral sulopenem etzadroxil/probenecid allowed patients with baseline pathogens resistant to both quinolones and β-lactams an opportunity to successfully step down from IV therapy.