# Efficacy and Safety of Intravenous Sulopenem Followed by Oral Sulopenem Etzadroxil/Probenecid Versus Intravenous Ertapenem Followed by Oral Ciprofloxacin and Metronidazole or Amoxicillin-Clavulanate in the Treatment of Complicated Intraabdominal Infections: The SURE-3 Trial

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## ABSTRACT

**Background**

Sulopenem is a broad-spectrum intravenous (IV) and oral penem antibiotic being developed for treatment of infections caused by multidrug-resistant bacteria, allowing stepdown therapy and earlier discharge of hospitalized patients.

**Methods**

674 hospitalized adults with complicated intra-abdominal infection (cIAI) were randomized to sulopenem IV QD for 5 days followed by a bilayer tablet of oral sulopenem etzadroxil/probenecid twice daily or ertapenem IV QD for 5 days followed by either oral ciprofloxacin and metronidazole or amoxicillin-clavulanate, depending on susceptibilities of baseline pathogens. The primary endpoint was clinical response at Day 28 [Test of Cure (TOC)] in the micro-MITT population.

**Results**

The sulopenem and ertapenem treatment arms were well-balanced at baseline. The median duration of therapy was nine days. *E. coli* and *B. fragilis* were the most frequently isolated aerobic and anaerobic pathogens, respectively. The protocol-specified primary endpoint in the micro-MITT population fell just outside the predefined lower limit required to declare noninferiority. In all other study populations, the lower limit of the confidence interval was above -10.0.

| Population | Sulopenem n/N (%) | Ertapenem n/N (%) | Difference (%), (95% CI) |
|---|---|---|---|
| micro-MITT* **(Primary endpoint)** | 213/249 (85.5) | 240/266 (90.2) | -4.7 (-10.3, 1.0) |
| ITT | 292/338 (86.4) | 300/336 (89.3) | -2.9 (-7.8, 2.0) |
| MITT | 291/334 (87.1) | 299/332 (90.1) | -2.9 (-7.8, 1.9) |
| CE-TOC | 265/283 (93.6) | 265/277 (95.7) | -2.0 (-5.7, 1.7) |
| ME-TOC | 196/212 (92.5) | 212/222 (95.5) | -3.0 (-7.5, 1.4) |

Treatment emergent adverse events (all, 26.0% vs 23.4%; related, 6.0% vs 5.1%) were similar for patients on sulopenem and ertapenem, respectively. Most treatment emergent adverse events were mild to moderate in severity. There were more serious adverse events (SAE) in the sulopenem arm (7.5% vs 3.6%), only two of which (fever, diarrhea) were considered possibly related to sulopenem.

**Conclusion**

Sulopenem followed by oral sulopenem etzadroxil/probenecid was not noninferior to ertapenem followed by oral step-down therapy in treating cIAI. This finding is in the context of regulatory criteria that vary from -10 to -12.5, depending on region, for this indication. 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 step down from IV therapy.

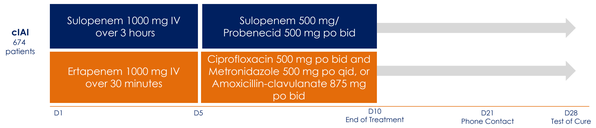
## INTRODUCTION

- Sulopenem is a thiopenem antibiotic being developed for the treatment of infections caused by multi-drug resistant bacteria.
- Sulopenem binds to penicillin-binding proteins and inhibits bacterial cell wall synthesis.
- Sulopenem is available in both intravenous and oral formulations, allowing earlier discharge of hospitalized patients.

## METHODS

- 674 hospitalized adults with cIAI were randomized to sulopenem IV QD for 5 days followed by a bilayer tablet of oral sulopenem etzadroxil/probenecid twice daily or ertapenem IV QD for 5 days followed by either oral ciprofloxacin and metronidazole or amoxicillin-clavulanate, depending on susceptibilities of baseline Enterobacterales. Enrollment could occur intra- or post-operatively following visual confirmation of a cIAI, or pre-operatively when an open laparotomy, percutaneous drainage of an intra-abdominal abscess, or laparoscopic surgery was anticipated within 24 hours of the first dose of study drug.

**Figure 1:** Double-blind, double-dummy design




- If baseline isolate was not susceptible to ciprofloxacin:
  - Sulopenem patients: step down to oral sulopenem-etzadroxil/probenecid
  - Ertapenem patients: step down to oral amoxicillin-clavulanate
- If baseline isolate was resistant to both ciprofloxacin and amoxicillin/clavulanate
  - Sulopenem patients: step down to oral sulopenem-etzadroxil/probenecid
  - Ertapenem patients: remain on IV ertapenem
- The site pharmacist was unblinded in order to prepare the IV study medications and to select the appropriate oral follow-on therapy for patients randomized to the ertapenem regimen.
- The primary endpoint was clinical response at Day 28 [Test of Cure (TOC)] in the micro-MITT population.
- Microbiologic response was a key secondary endpoint.

## RESULTS

**Table 1:** Demographics of Patients with cIAI

| Parameter | Sulopenem n/N (%) | Ertapenem n/N (%) | p-value |
|---|---|---|---|
| N | 338 | 336 | |
| Age, y, mean (SD) | 53.9 (18.4) | 54.8 (18.0) | 0.520 |
| Age ≥ 65 | 112 (33.1) | 119 (35.4) | 0.570 |
| Male | 178 (52.7) | 181 (53.9) | 0.758 |
| Non-US | 322 (95.3) | 320 (95.2) | 1.0 |
| White | 337 (99.7) | 332 (98.8) | 1.0 |
| BMI (kg/m$^2$) median | 27.1 | 27.0 | 0.632 |
| Min, max | 16.9, 48.4 | 16.0, 44.4 | |
| CrCl (mL/min) median | 89.0 | 84.0 | 0.225 |
| Min, max | 15.0, 227.0 | 15.0, 198.0 | |
| <30 | 7/325 (2.2) | 12/319 (3.8) | 0.488 |
| APACHE II score at baseline, median | 6.0 | 6.5 | 0.458 |
| Min, max | 0, 19.0 | 0, 21.0 | |

## RESULTS

**Table 2:** Infection Type and Intraoperative Findings

| Parameter | Sulopenem n/N (%) | Ertapenem n/N (%) | p-value |
|---|---|---|---|
| **Type of infection** | | | 0.939 |
| cIAI caused by appendicitis with perforation or periappendiceal abscess | 160/338 (47.3) | 160/335 (47.8) | |
| All other cIAI diagnoses | 178/338 (52.7) | 175/335 (52.2) | |
| **Intra-operative findings for diagnosis of cIAI** | | | |
| Intra-abdominal abscess(es) | 134/334 (40.1) | 135/333 (40.5) | 0.937 |
| Complicated appendicitis | 157/334 (47.0) | 157/333 (47.1) | 1.000 |
| Perforation of the small intestine | 15/334 (4.5) | 21/333 (6.3) | 0.310 |
| Perforation of the large intestine | 17/334 (5.1) | 17/333 (5.1) | 1.000 |
| Secondary peritonitis | 98/334 (29.3) | 93/333 (27.9) | 0.732 |
| Complicated cholecystitis | 75/334 (22.5) | 86/333 (25.8) | 0.321 |
| Diverticular disease with perforation or abscess | 19/334 (5.7) | 12/333 (3.6) | 0.270 |
| Other | 18/334 (5.4) | 18/333 (5.4) | 1.000 |

**Table 3:** Clinical Success at TOC by Analysis Population

| Population | Sulopenem n/N (%) | Ertapenem n/N (%) | Difference (%), (95% CI) |
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| micro-MITT* **(Primary endpoint)** | 213/249 (85.5) | 240/266 (90.2) | -4.7 (-10.3, 1.0) |
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**Table 4:** Clinical Success at TOC by Baseline Infection Type and Presence or Absence of Abscesses – micro-MITT Population

| Infection Type/Abscesses Present or Absent | Sulopenem n/N (%) | Ertapenem n/N (%) | Difference % (CI) |
|---|---|---|---|
| cIAI caused by appendicitis | 127/140 (90.7) | 137/147 (93.2) | -2.5 (-8.8, 3.8) |
| Abscesses present | 79/86 (91.9) | 85/89 (95.5) | |
| Abscesses not present | 48/54 (88.9) | 52/58 (89.7) | |
| All other cIAI diagnoses | 86/109 (78.9) | 103/119 (86.6) | -7.7 (-17.5, 2.2) |
| Abscesses present | 66/83 (79.5) | 69/77 (89.6) | |
| Abscesses not present | 20/26 (76.9) | 34/42 (81.0) | |

- Success rates for patients treated with ertapenem were higher in the subsets who had abscesses at baseline (95.5% vs 89.7% and 89.6% vs 81.0% for appendicitis and other cIAI infections, respectively).
- This was an unexpected outcome and, because successful treatment of patients with abscesses requires adequate surgical drainage, raises the question of whether some sulopenem patients could have had incomplete surgical drainage at baseline.
- The pivotal subgroup that might explain the overall difference in outcome in the two treatment arms is the one that had cIAIs other than appendicitis. As seen in Table 4, two findings appear key: 1) a greater proportion of sulopenem patients in this group had abscesses (76% [83/109] compared to ertapenem (65% [77/119) and 2) ertapenem patients had unexpectedly favorable responses.

*Note: the initial review of the primary efficacy tables raised concerns re: imbalances in various outcome measures that did not appear to have a reasonable medical explanation. This prompted a reexamination of programming and, ultimately, a reanalysis of the database to address the identified deficiencies.

**Table 5:** Adverse Events

| Safety Population | Sulopenem (N=335) n (%) | Ertapenem (N=333) n (%) |
|---|---|---|
| Treatment-emergent adverse events (TEAE) | 87 (26.0) | 78 (23.4) |
| Drug-related TEAE | 20 (6.0) | 17 (5.1) |
| IV drug-related TEAE | 12 (3.6) | 14 (4.2) |
| Oral drug-related TEAE | 13 (3.9) | 5 (1.5) |
| TEAE leading to D/C of study drug | 5 (1.5) | 7 (2.1) |
| TEAE leading to D/C from study | 2 (0.6) | 2 (0.6) |
| Serious adverse events | 25 (7.5) | 12 (3.6) |
| Drug-related SAE | 2 (0.6) | 0 |
| SAE leading to death | 4 (1.2) | 4 (1.2) |
| SAE leading to premature D/C of study drug | 3 (0.9) | 3 (0.9) |
| SAE leading to premature D/C from study | 2 (0.6) | 2 (0.6) |
| **Treatment-Emergent Adverse Events Occurring in at Least 2% of Patients** | | |
| Diarrhea | 15 (4.5) | 8 (2.4) |
| Nausea | 12 (3.6) | 8 (2.4) |
| Post-operative wound infection | 4 (1.2) | 8 (2.4) |

## CONCLUSIONS

- In the micro-MITT population, sulopenem → oral sulopenem etzadroxil/probenecid was not non-inferior to ertapenem → oral step-down therapy for the treatment for cIAI.
- The difference in outcomes in all other populations, including the ITT, MITT, and clinically and microbiologically evaluable populations, all had a CI with a lower bound > -10%.
- The oral formulation of sulopenem allowed an additional 15% of patients with baseline pathogens resistant to both quinolones and β-lactams an opportunity to successfully step down from IV therapy.
- Sulopenem was well-tolerated; the incidence of TEAEs and the rate of discontinuations were similar to those of ertapenem.
- There were more SAEs on sulopenem, the difference being related primarily to intraabdominal abscesses that required an additional surgical or percutaneous drainage procedure. In two-thirds of these patients, abscesses had been present at baseline.
- Given increasing rates of antimicrobial resistance in the community, it is important for physicians to be able to discharge their patients from the hospital on a well-tolerated oral therapy, avoiding the potential for nosocomial infections associated with prolonged hospital stays, avoiding the risks associated with percutaneously inserted central catheter (PICC) placement, decreasing the overall cost of treatment, and improving patient satisfaction.



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