Oral Sulopenem and Tebipenem for Complicated Urinary Tract Infection and Pyelonephritis in patients with Extended-Spectrum Beta-Lactamase (ESBL)-producing Gram Negative, Susceptible Bacteria

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Development of Oral Carbapenems

Carbapenems Use in Current Standard's of Care

- Carbapenems are the drug of choice for ESBL-producing gram negative Enterobacteria, such as *E. coli* and *Klebsiella spp*[1]
- Infectious Diseases Society of America (IDSA) guidelines recommend carbapenems, ciprofloxacin, levofloxacin, and trimethoprim-sulfamethoxazole (TMP-SMX) as treatment options for pyelonephritis and complicated UTI[2]

Oral Carbapenems

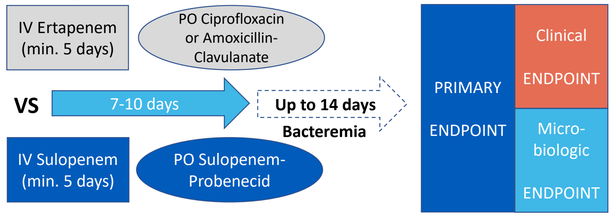
- Increased incidence in ESBL-producing gram-negative Enterobacteria isolates that produce less favorable treatment outcomes in 3rd and 4th generation cephalosporins, including ceftriaxone and cefepime[1]
- Also, increased incidence in fluoroquinolone non-susceptible strains, as well as TMP-SMX-resistant strains[1]
- Carbapenems are a crucial alternative for multi-drug resistant ESBL strains. However, carbapenems are only available in the U.S. as IV formulation[2]
- Development of oral carbapenems could produce favorable clinical and microbiologic outcomes
- The clinical trials for the oral carbapenems such as tebipenem and sulopenem are reviewed here

Table 1. In vitro minimum inhibitory concentration of selected gram-negative organisms[3-5]

	Sulopenem			Tebipenem		
	Range	MIC50	MIC90	Range	MIC50	MIC90
E. Coli	≤0.008-4	0.03	0.06	≤0.015 to 0.12	0.03	0.06
K. pneumoniae	0.03 to >8	0.06	0.12	0.03 to >32	0.03	>32
P. Aeruginosa	≤8 to >128	32	>64	4 to >32	>32	>32
P. Mirabilis	≤0.008-1	0.25	0.5	NR	NR	0.39
E. Cloacae	≤0.016-8	0.12	0.5	NR	NR	NR
S. Marcescens	0.06 to >128	1	16	NR	NR	25
M. Morganii	0.03-4	0.5	1	NR	NR	NR
P. Rettgeri	≤0.008 to >8	0.25	0.5	NR	NR	NR
P. Stuartii	0.03-1	0.12	0.5	NR	NR	NR

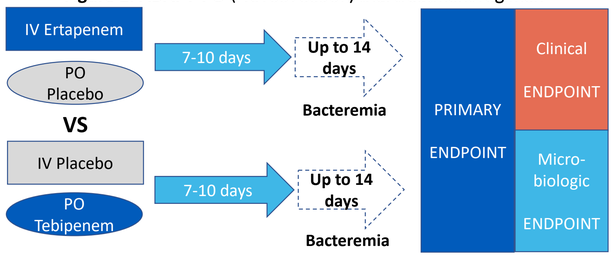
Trial Design

Figure 1. sulopenem (NCT03357614) trial treatment regimen[6]



Ertapenem 1g q24 h; Ciprofloxacin 500 mg Q12H, Amoxicillin-Clavulanate 875-125 mg Q12H
Sulopenem IV 1 g daily, Sulopenem PO and Probenecid 500 mg Q12H

Figure 2. ADAPT-PO (NCT03788967) trial treatment regimen[7]



Ertapenem 1g q24 h; tebipenem 600 mg TID

Subject Baseline Characteristics

Table 2. General baseline characteristics of both sulopenem and tebipenem trial[6,7]

	NCT03357614 (Sulopenem)	ADAPT-PO (Tebipenem)
Central/Eastern Europe	96%	99%
Females	59%	58%
Age (Mean)	58 years	58 years
Caucasian Race	99%	99%
Creatinine clearance >30	95%	NR
Pyelonephritis	59%	49%
Complicated UTI	41%	51%
Common Pathogens	*E. coli, K. pneumoniae* (88%)	*E. coli, K. pneumoniae* (90%)
ESBL-Producing strains	26%	24%
FQ-NON-susceptible	39%	39%
TMP/SMX-NON-susceptible	36%	43%

Clinical Endpoints

Sulopenem (NCT03357614) Trial

Primary Endpoint
- Clinical cure and microbiologic eradication in the microbiologic modified intent-to-treat (mMITT) population at test-of-cure (TOC)[6]

Clinical Endpoint
- Baseline signs and symptoms resolved and no new symptoms[6]

Microbiologic Endpoint
- Bacterial pathogen reduced to $<10^3$ CFU/mL[6]

Statistical Analysis
- Proposed sample size: 578 patients per treatment regimen for 90% power
- 10% non-inferiority margin with 2-slided 95% confidence interval (CI)[6]

ADAPT-PO (NCT03788967) Trial

Primary Endpoint
- Clinical cure and microbiologic response in the microbiologic intention-to-treat (ITT) population at TOC[7]

Clinical Endpoint
- Baseline signs and symptoms resolved and no new symptoms[7]

Microbiologic Endpoint
- Bacterial pathogen reduced to $<10^3$ CFU/mL[7]

Statistical Analysis
- Proposed sample size: 600 patients per treatment regimen for 90% power
- 12.5% non-interiority margin (FDA consulted to revise from 10% due to COVID-19)[7]

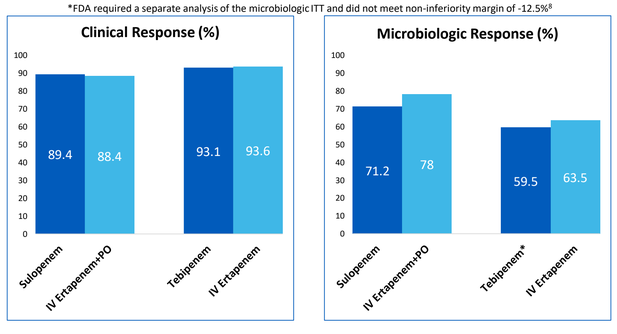
Results

Table 3. Primary endpoint results for both sulopenem and tebipenem trial[6,7]

	NCT03357614 (Sulopenem)		ADAPT-PO (Tebipenem)	
	Ertapenem N=440	Sulopenem N=444	Ertapenem N=419	Tebipenem N=449
PRIMARY Endpoint	73.9%	67.8%	61.1%	58.8%
Difference (95% CI)	-6.1% (-12.5 to -0.1%)		-3.3% (-9.7% to 3.2%)	

Figure 3. Clinical and microbiologic response at test-of-cure point for sulopenem and tebipenem trial[6,7]

*FDA required a separate analysis of the microbiologic ITT and did not meet non-inferiority margin of -12.5%[8]



Adverse Events

Table 4. Summary of adverse drug events for both sulopenem and tebipenem trial[6,7]

	NCT03357614 (Sulopenem)		ADAPT-PO (Tebipenem)	
	Sulopenem	IV Ertapenem + PO	Tebipenem	Ertapenem
Headache	3%	2.3%	3.8%	3.8%
Diarrhea	2.7%	3%	5.7%	4.4%
Any adverse events	15.1%	16.4%	25.7%	25.6%
Drug-related adverse events	6%	9.2%	9.3%	6.1%

Discussion

- Both Study focused on Eastern/Central European population
- Trial design, population, and duration of trial appeared to be appropriate
- Both drugs demonstrated good response rates in clinical outcomes, but inadequate response in microbiologic outcomes
- Both drugs appeared to be safe and tolerated
- In the sulopenem trial, sulopenem demonstrated less overall success in patients with ciprofloxacin-susceptible isolates compared to ertapenem (67.7% vs 86.5%)[6]
  - This may have been due to recipients of ertapenem receiving oral ciprofloxacin for step-down therapy
- In the Tebipenem trial, the study was not powered to assess noninferiority, but still demonstrated inadequate microbiologic outcome[7]
  - Tebipenem's microbiologic response rate was 59.5%, whereas IV Ertapenem was 63.5%[7]
  - Ertapenem treatment was completed as IV only

Conclusion

- While in vitro MIC showed promising results for both sulopenem and tebipenem, phase 3 trials showed contrasting results. Both drugs appeared to be safely tolerated with good clinical response, but insufficient microbiologic response. Additional investigation is warranted.

Clinical Trial Updates

- The FDA requested additional clinical trial information for both sulopenem and tebipenem before granting drug approval for cUTI[8,9]

References
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