Impact of Asymptomatic Bacteriuria on Primary Efficacy Analyses in the Evaluation of Novel Antimicrobials for the Treatment of Patients with Urinary Tract Infection

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ABSTRACT

Background: Per FDA Guidance, the primary efficacy endpoint for trials evaluating antimicrobials for treatment of uncomplicated urinary tract infection (uUTI) and complicated urinary tract infection (cUTI) is a combined clinical/microbiologic outcome response. Overall success requires both resolution of UTI symptoms and demonstration that the causative uropathogen is reduced to < 10^5 CFU/mL at a fixed time point after randomization, regardless of whether the patient is symptomatic. In clinical practice, it is not standard of care to routinely screen for or treat asymptomatic bacteriuria (ASB), nor to obtain 'proof of cure' cultures. In the clinical trial setting, the impact of post-treatment asymptomatic bladder recolonization on the rates of microbiologic response, re-infection, or emergence of resistance is unknown.

Methods: Study IT001-301 and -302 are double blind, double-dummy, Phase 3 randomized trials comparing sulopenem to comparator for patients with pyuria, bacteriuria, and clinical signs/symptoms of uUTI and cUTI, respectively. In Study 301, 1671 ambulatory female adults with uUTI were randomized to oral sulopenem bid x 5d or oral ciprofloxacin bid x 3d. In Study 302, 1395 hospitalized adults with cUTI were randomized to sulopenem IV once daily x 5d followed by oral sulopenem bid or ertapenem IV once daily x 5d followed by either oral ciprofloxacin or amoxicillin-clavulanate bid, depending on baseline uropathogen susceptibility. The primary endpoint was overall (clinical + microbiologic) response in the micro-MITS and micro-MITR populations at TOC/D12 visit in uUTI study and in the micro-MITT population at TOC/D21 visit in cUTI study.

Results:

IT001-301: Overall Response at TOC and EOT in the micro-MITT Population

Outcome	micro-MITS Population: Sulopenem n (%) N=370	micro-MITS Population: Ciprofloxacin n (%) N=415	micro-MITS Population: Difference (%), (95% CI)	micro-MITTR Population: Sulopenem n (%) N=147	micro-MITTR Population: Ciprofloxacin n (%) N= 139	micro-MITTR Population: Difference (%), (95% CI)
Overall response at TOC	247 (66.8)	326 (78.6)	-11.8 (-18.0, -5.6)	92 (62.6)	50 (36.0)	26.6 (15.1, 37.4) P < 0.001
Overall nonresponse at TOC	105 (28.4)	65 (15.7)		49 (33.3)	84 (60.4)	
Reason for failure: ASB only	**47 (12.7)**	**16 (3.9)**		**27 (18.4)**	**38 (27.3)**	
Indeterminate	18 (4.9)	24 (5.8)		6 (4.1)	5 (3.6)	
Clinical success at TOC	300 (81.1)	349 (84.1)	-3.0 (-8.4, 2.3)	122 (83.0)	87 (62.6)	20.4 (10.2, 30.4) P < 0.001
Microbiologic success at TOC	287 (77.6)	369 (88.9)	-11.3 (-16.7, -6.2)	109 (74.1)	69 (49.6)	24.5 (13.4, 35.1) P < 0.001
Overall response at EOT	240 (64.9)	271 (65.3)	-0.4 (-7.1, 6.2)	95 (64.6)	42 (30.2)	34.4 (23.1, 44.8) P < 0.001

micro-MITTS = microbiologic modified intent-to-treat, ciprofloxacin-microMITTR, micro-MITTR = microbiologic modified intent-to-treat, ciprofloxacin-microMITT, TOC = test of cure, EOT = end of treatment, ASB = asymptomatic bacteriuria

Figure 2. IT001-302: Overall Response at TOC and EOT, and by Stepdown Category (micro-MITT Population)

Outcome	All Patients: Sulopenem IV / Oral Sulopenem n (%) N=444	All Patients: Ertapenem IV +/- Ciprofloxacin or Amox/Clav n (%) N=440	Stepdown Category: Ertapenem IV +/- Amox/Clav Stepdown n (%) N=225	Stepdown Category: Ertapenem IV / Ciprofloxacin Step-down n (%) N=215
Overall response at TOC	301 (67.8)	325 (73.9)	139 (61.8)	186 (86.5)
Difference (%), (95% CI)	-6.1 (-12.0, -0.1)		6.0 (-1.6, 13.8)	-18.8 (-26.1, -11.0)
Overall nonresponse at TOC	126 (28.4)	93 (21.1)		
Reason for failure: ASB	**93 (20.9)**	**59 (13.4)**	**49 (21.8)**	**10 (4.7)**
Indeterminate	17 (3.8)	22 (5.0)		
Clinical success at TOC	397 (89.4)	389 (88.4)		
Difference (%), (95% CI)	1.0 (-3.1, 5.1)			
Microbiologic success at TOC	316 (71.2)	343 (78.0)		
Difference (%), (95% CI)	-6.8 (-12.5, -1.1)			
Overall response at EOT	385 (86.7)	391 (88.9)		
Difference (%), (95% CI)	-2.2 (-6.5, 2.2)			

Conclusion: Different classes of antibiotics appear to have a differential effect on the frequency of post-treatment ASB with quinolones having a lower rate relative to beta-lactams. The presence of ASB a week or more after completing UTI therapy was not associated with a higher rate of clinical relapse for UTI patients; treatment with ciprofloxacin was associated with the selection of resistant pathogens in the post-treatment flora. Inclusion of ASB in the primary endpoint for studies of UTI should be reconsidered as it implies that a post-treatment culture should be obtained to document resolution of infection, a practice inconsistent with available treatment recommendations.

INTRODUCTION

Per FDA *Guidance*, the primary efficacy endpoint for trials evaluating antimicrobials for treatment of uncomplicated urinary tract infection (uUTI) and complicated urinary tract infection (cUTI) is a combined clinical and microbiologic outcome response. Overall success requires both resolution of UTI symptoms and demonstration that the causative uropathogen is reduced to <10^5 CFU/mL at a fixed time point after randomization, regardless of whether the patient is symptomatic. Obtaining "proof of cure" urine cultures after symptomatic resolution is not standard of care in clinical practice. Alternative clinical trial endpoints have been suggested by others which do not rely on microbiologic responses when assessing novel anti-infective agents.

METHODS

Study IT001-301

- Double-blind, double-dummy, Phase 3 randomized trial
- 1671 adult women with uUTI
  - Pyuria, bacteriuria, and clinical signs/symptoms of uUTI
- Compared sulopenem etzadroxil/probenecid (oral sulopenem) 500 mg/500 mg PO BID x 5 days to ciprofloxacin 250 mg PO BID x 3 days
- Primary endpoint: overall (clinical + microbiologic) response in the micro-MITTS and micro-MITTR populations at the Test-of-Cure (Day 12) Visit

Study IT001-302

- Double-blind, double-dummy, Phase 3 randomized trial
- 1395 hospitalized adults with cUTI
  - Pyuria, bacteriuria, and clinical signs/symptoms of cUTI
- Compared sulopenem 1000 mg IV once daily x 5 days followed by oral sulopenem BID to complete 7-10 days of therapy, or ertapenem 1000 mg IV once daily x 5 days followed by oral ciprofloxacin 500 mg BID or amoxicillin/clavulanate 875 mg BID, depending on baseline uropathogen susceptibility, to complete 7-10 days of therapy
- Primary endpoint: overall (clinical + microbiologic) response in the micro-MITT population at the Test-of-Cure (Day 21) Visit

RESULTS IT001-301

Table 1: Outcomes at TOC and EOT and Reasons for Nonresponse at TOC in the micro-MITT Populations

Outcome	micro-MITTS Population: Sulopenem n (%) N=370	micro-MITTS Population: Ciprofloxacin n (%) N=415	micro-MITTS Population: Difference (%), (95% CI)	micro-MITTR Population: Sulopenem n (%) N=147	micro-MITTR Population: Ciprofloxacin n (%) N= 139	micro-MITTR Population: Difference (%), (95% CI)
Overall response at TOC	247 (66.8)	326 (78.6)	-11.8 (-18.0, -5.6)	92 (62.6)	50 (36.0)	26.6 (15.1, 37.4) P < 0.001
Overall nonresponse TOC	105 (28.4)	65 (15.7)		49 (33.3)	84 (60.4)	
Reason for failure: ASB only	**47 (12.7)**	**16 (3.9)**		**27 (18.4)**	**38 (27.3)**	
Clinical failure only	38 (10.3)	42 (10.1)		17 (11.6)	13 (9.4)	
Both clinical and microbiologic failure	18 (4.9)	4 (1.0)		5 (3.4)	25 (18.0)	
Receipt of non-study antibacterial therapy for uUTI	4 (1.1)	5 (1.2)		0 (0.0)	11 (7.9)	
Antibacterial therapy alone	2 (0.5)	3 (0.7)		0 (0.0)	8 (5.8)	
Indeterminate	18 (4.9)	24 (5.8)		6 (4.1)	5 (3.6)	
Clinical success at TOC	300 (81.1)	349 (84.1)	-3.0 (-8.4, 2.3)	122 (83.0)	87 (62.6)	20.4 (10.2, 30.4) P < 0.001
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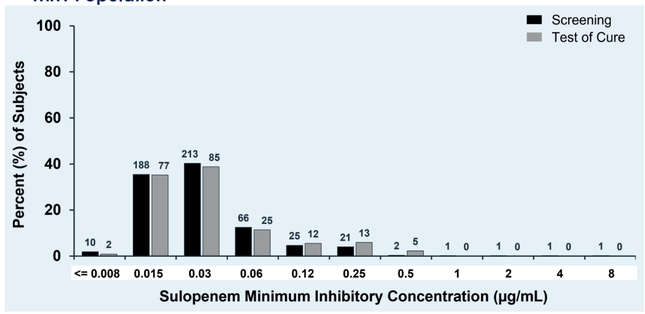
Overall response at EOT	240 (64.9)	271 (65.3)	-0.4 (-7.1, 6.2)	95 (64.6)	42 (30.2)	34.4 (23.1, 44.8) P < 0.001

Table 2: Asymptomatic Bacteriuria did Not Predict Clinical Failure at Later Visits: micro-MITTS Population

	Assessment Day 5 (N)	Clinical Failure Day 12 [n(%)]
Overall Success	240	22 (9.2%)
Asymptomatic Bacteriuria	11	1 (9.1%)
	Assessment Day 12 (N)	**Clinical Failure Day 28 [n(%)]**
Overall Success	247	15 (6.1%)
Asymptomatic Bacteriuria	47	4 (8.5%)

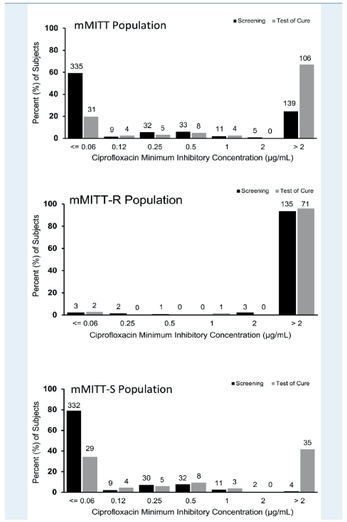
Figure 1: Susceptibility of Uropathogens after Sulopenem Treatment in the micro-MITT Population



Figures 1 and 2: Organisms at screening and baseline include any uropathogen isolated in the urine culture, regardless of colony count; N above columns indicates number of organisms.

RESULTS IT001-301

Figure 2: Susceptibility of Uropathogens after Ciprofloxacin Treatment in the micro-MITT, micro-MITTR and micro-MITTS Populations



RESULTS IT001-302

Table 3: Outcomes at TOC and EOT, and by Stepdown Category, and Reasons for Nonresponse at TOC: micro-MITT Population

Outcome	All Patients: Sulopenem IV / Oral Sulopenem n (%) N=444	All Patients: Ertapenem IV +/- Ciprofloxacin or Amox/Clav n (%) N=440	Stepdown Category: Ertapenem IV +/- Amox/Clav Stepdown n (%) N=225	Stepdown Category: Ertapenem IV / Ciprofloxacin Step-down n (%) N=215
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Clinical failure only	18 (4.1)	21 (4.8)		
Both clinical and microbiologic failure	11 (2.5)	8 (1.8)		
Receipt of non-study antibacterial therapy for cUTI	7 (1.6)	6 (1.4)		
Antibacterial therapy alone	4 (0.9)	5 (1.1)		
Indeterminate	17 (3.8)	22 (5.0)		
Clinical success at TOC	397 (89.4)	389 (88.4)		
Difference (%), (95% CI)	1.0 (-3.1, 5.1)			
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Overall response at EOT	385 (86.7)	391 (88.9)		
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ASYMPTOMATIC BACTERIURIA IN UTI STUDIES

Table 4: Asymptomatic Bacteriuria in Studies of Complicated UTI

	Combined Response at TOC: Regimen A	Combined Response at TOC: Regimen B	Combined Response at TOC: Difference (95%CI)	Clinical Response at TOC: Regimen A	Clinical Response at TOC: Regimen B	Clinical Response at TOC: Difference (95%CI)	Asymptomatic Bacteriuria: Regimen A	Asymptomatic Bacteriuria: Regimen B
Current study	**Sulopenem→ PO sulopenem** 301/444 (67.8)	**Ertapenem→ PO Cipro/AC** 325/440 (73.9)	-6.1 (-12.0, -0.1)	**Sulopenem→ PO sulopenem** 397/444 (89.4)	**Ertapenem→ PO Cipro/AC** 389/440 (88.4)	1.0 (-3.1, 5.1)	**Sulopenem→ PO sulopenem** 22%	**Ertapenem→ PO Cipro/AC** Cipro - S: 5% Amox-clav: 22%
Wagenlehner et al (CID 2016)	**CTZ-AVB→PO Cipro or TMP-SMX** 280/393 (71.2)	**Doripenem→PO Cipro or TMP-SMX** 269/417 (64.5)	6.7 (0.30, 13.12)	**CTZ-AVB→PO Cipro or TMP-SMX** 332/393 (84.5)	**Doripenem→PO Cipro or TMP-SMX** 360/417 (86.3)	-1.9 (-6.78, 3.02)	**CTZ-AVB→PO Cipro or TMP-SMX** 13%	**Doripenem→PO Cipro or TMP-SMX** 22%
Kaye et al (JAMA 2018)	**Meropenem Vaborbactam→ PO Levo[1]** 143/192 (74.5)	**Piperacillin Tazobactam→ PO Levo** 128/182 (70.3)	4.1 (-4.9, 9.1)	**Meropenem Vaborbactam→ PO Levo[1]** 174/192 (90.6)	**Piperacillin Tazobactam→ PO Levo** 157/182 (86.3)	4.4 (-2.2, 11.1)	**Meropenem Vaborbactam→ PO Levo[1]** 16%	**Piperacillin Tazobactam→ PO Levo** 16%
Wagenlehner et al (NEJM 2019)	**Plazomicin→ PO Levo or other** 156/191 (81.7)	**Meropenem→ PO Levo or other** 138/197 (70.1)	11.6 (2.7, 20.3)	**Plazomicin→ PO Levo or other** 170/191 (89.0)	**Meropenem→ PO Levo or other** 178/197 (90.4)	-1.4 (-7.9, 5.2)	**Plazomicin→ PO Levo or other** 7%	**Meropenem→ PO Levo or other** 20%
Wagenlehner et al (Lancet 2015)	**Ceftolozane tazobactam** 306/398 (76.9)	**Levofloxacin*** 275/402 (68.4)	8.5 (2.3, 14.6)	**Ceftolozane tazobactam** 366/398 (92.0)	**Levofloxacin*** 356/402 (88.6)	3.4 (-0.7, 7.6)	**Ceftolozane tazobactam** 15%	**Levofloxacin*** Levo-R: 38%+ Levo-S: 13.4%+
Eckburg et al (NEJM 2022)	**Oral tebipenem pivoxil hydrobromide** 264/449 (58.8)	**Ertapenem** 258/419 (61.6)	−3.3 (−9.7, 3.2)	**Oral tebipenem pivoxil hydrobromide** 418/449 (93.1)	**Ertapenem** 392/419 (93.6)	−0.6 (−4.0 to 2.8)	**Oral tebipenem pivoxil hydrobromide** 34%	**Ertapenem** 32%

CONCLUSIONS

- Post-treatment ASB is not a marker of subsequent failure in uUTI
- Different classes of antibiotics appear to have a differential effect on the frequency of post-treatment ASB with quinolones having a lower rate relative to beta-lactams
- Suppression of post-treatment ASB may be associated with collateral damage
  - Treatment with ciprofloxacin was associated with the selection of resistant pathogens in the post-treatment flora
- ASB in the primary endpoint for studies of UTI should be reconsidered:
  - ASB does not impact how a patient feels, functions, or survives
  - Inclusion of microbiologic results from asymptomatic patients after complete resolution of uUTI symptoms is inconsistent with available treatment recommendations

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