Desirability of outcome ranking (DOOR): application to a phase 3 registrational trial evaluating sulopenem for patients with uncomplicated urinary tract infection (uUTI)

Steven I. Aronin, MD[1], Jayanti Gupta, PhD[1], Michael Dunne, MD[1,2], and Sailaja Puttagunta, MD[1]

[1]Iterum Therapeutics, Old Saybrook, CT 06475; [2]Current affiliation: Bill & Melinda Gates Medical Research Institute, Cambridge, MA 02139

ABSTRACT

Background
The DOOR approach has been proposed as an improved way to evaluate novel anti-infective agents by focusing on benefits and harms and providing an assessment of the patient experience. We conducted a Phase 3 uUTI trial comparing oral ciprofloxacin to oral sulopenem. In patients with ciprofloxacin-nonsusceptible baseline pathogens, sulopenem was compared for superiority over ciprofloxacin; in patients with ciprofloxacin-susceptible pathogens, the agents were compared for noninferiority. Using the FDA's current definition of a successful response, one that requires both clinical and microbiologic success, sulopenem's overall success rate in the nonsusceptible population was 62.6% while ciprofloxacin's was 36.0% (treatment difference 26.6%; 95% CI: 15.1, 37.4; P <.001). In the susceptible population, sulopenem's overall success rate was 66.8% while ciprofloxacin's was 78.6% (treatment difference -11.8%; 95% CI: -18.0, -5.6). This difference in overall success rates in the susceptible population was due to the lower incidence of asymptomatic bacteriuria (ASB) among patients who received ciprofloxacin; the presence of ASB posttreatment was not a marker of subsequent clinical failure. To further understand these trial results, an analysis using the DOOR methodology was performed post hoc.

Methods
The DOOR analysis strategy was retrospectively applied to our registrational drug trial for uUTI (SURE-1) to estimate the probability of a more desirable outcome for oral sulopenem.

Results
The DOOR probability of a more desirable outcome is 50.8% [95% CI (48.9%, 52.7%)], indicating no significant difference between the sulopenem and ciprofloxacin treatment arms for patients with uUTI. The probabilities for the analyses prioritizing efficacy and safety were identical to the original outcome ranking, and those for the individual components were very similar.

Table. Desirability of Outcome Rankings by Treatment Arm

	Ranks					
	1 (most desirable)	2	3	4	5 (least desirable)	Total # of subjects
Sulopenem	643 (81.9%)	139 (17.7%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	785
Ciprofloxacin	637 (80.2%)	156 (19.6%)	1 (0.1%)	0 (0%)	0 (0%)	794

Conclusions
Traditional endpoints used in registrational trials for UTI are inadequate. They include microbiologic parameters that do not impact how a patient feels, functions, or survives, and they fail to include a full range of relevant potential clinical outcomes. DOOR incorporates benefits and risks of novel treatment strategies and provides a global assessment of patient experience. Applying DOOR to SURE-1 data showed no significant difference between the sulopenem and ciprofloxacin treatment arms for patients with uUTI.

INTRODUCTION

Traditional endpoints used in registrational trials for UTI require both clinical and microbiologic success for a patient to be considered as having had an overall successful response to the investigational product being evaluated.

This requirement does not align with standard clinical practice where asymptomatic bacteriuria (ASB) is generally clinically irrelevant, and post-treatment cultures are not routinely performed.

The Desirability of Outcome Ranking (DOOR) approach has been proposed by the Antibacterial Resistance Leadership Group (ARLG) as an improved way to evaluate novel anti-infective agents by focusing on benefits and harms and providing an assessment of the patient experience.

SURE-1 was a double-blind, double-dummy, Phase 3 randomized trial that enrolled 1671 ambulatory female adults with uncomplicated UTI (uUTI) and compared sulopenem etzadroxil/probenecid 500 mg/500 mg PO BID x 5 days to ciprofloxacin 250 mg PO BID x 3 days. The primary endpoint was overall (clinical + microbiologic) response in the microbiologic modified intent to treat (micro-MITT) population with baseline uropathogens either susceptible or resistant to the comparator, ciprofloxacin (micro-MITTS and micro-MITTR populations, respectively), at the Test-of-Cure (Day 12) Visit.

An analysis using the DOOR methodology was performed post hoc on the SURE-1 clinical trial data.

METHODS

The DOOR analysis strategy utilized by ARLG for cUTI trials was applied to the SURE-1 data (results displayed in abstract), and further modified in this analysis to include an added benefit-risk outcome, emergence of antibiotic resistance, to supplement the three benefit-risk outcomes utilized by ARLG. Each patient was assigned a rank 1 to 6 in decreasing order of desirability: 1 = alive without any pre-specified outcomes, 2-5 = alive with 1, 2, 3 or 4 outcomes, respectively and 6 = dead. Clinical response implies resolution of uUTI symptoms at TOC without recurrence. Patients with clinical failure or indeterminate/missing outcomes were considered to have an absence of clinical response.

The analysis used the modified ITT population defined as all randomized patients who received at least one dose of study drug. We compared the DOOR distribution between treatment groups and computed the probability of a more desirable outcome with one treatment compared to the other (DOOR probability) along with corresponding 95% CI. A DOOR probability of 50% indicates no difference. We also calculated this probability for each DOOR component. Additionally, we defined and analyzed DOORs prioritizing efficacy or safety, in which absence of clinical failure was ranked above or below SAEs, emergence of resistance, and infectious complications, respectively. Sensitivity analyses were conducted in which patients with indeterminate/missing outcomes were adjudicated as either ranked above those with clinical failure or counted as having clinical cure or were excluded.

RESULTS

Table 1: SURE-1 Overall Response at TOC & EOT and Reasons for Nonresponse at TOC, micro-MITT Population using FDA Endpoint Definitions

	micro-MITTS Population			micro-MITTR Population		
Outcome	**Sulopenem n (%) N=370**	**Ciprofloxacin n (%) N=415**	**Difference (%) (95% CI)**	**Sulopenem n (%) N=147**	**Ciprofloxacin n (%) N= 139**	**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)**	
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
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

Table 2: SURE-1: ASB and Subsequent Clinical Response to Treatment Among Sulopenem-Treated Patients, micro-MITTS Population

Overall Response at EOT (Day 5)	Clinical Failure at TOC (Day 12), n/N (%)
Success	22/240 (9.2%)
Asymptomatic Bacteriuria	1/11 (9.1%)
Overall Response at TOC (Day 12)	Clinical Failure at FV (Day 28), n/N (%)
Success	15/247 (6.1%)
Asymptomatic Bacteriuria	4/47 (8.5%)

The table presents patients with ASB at a given visit and the proportion who experienced a clinical failure at the next visit. Clinical failure includes symptoms of uUTI or receipt of an antibiotic or both.
TOC=Test of Cure; FV=Final Visit; EOT=End of Treatment

RESULTS

Table 3: DOOR Analysis Strategy

Rank	Alive?	Number of Events[a]
1 (most desirable)	Yes	0
2	Yes	1
3	Yes	2
4	Yes	3
5	Yes	4
6 (least desirable)	No	Any

[a]Possible events include absence of clinical response, infectious complications, emergence of antibiotic resistance, and serious adverse events

Table 4: Definitions Used in DOOR Analysis

Event Category	Criteria[a]
Absence of clinical response	• Did not meet clinical success as per Study IT001-301 protocol • Recurrent uUTI prior to test of cure
Infectious complications	• Renal or intraabdominal abscess • Septic shock • Bacteremia due to the same bacteria identified in original urine culture • Recurrent UTI or pyelonephritis after test of cure • *Clostridioides difficile infection*

Serious adverse events	• Any untoward medical event that:
	  • Results in death
	  • Is life-threatening
	  • Requires inpatient hospitalization or prolongation of existing hospitalization
	  • Results in persistent or significant disability/incapacity,
	  • Is a congenital anomaly/birth defect
	OR
	• Is assessed as being a medically important event based on medical and scientific judgment

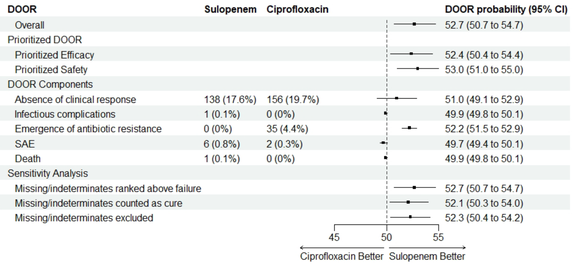
Emergence of antibiotic resistance	• For micro-MITT S patients treated with ciprofloxacin, identification of an organism that is quinolone-resistant at test of cure • For micro-MITT patients treated with sulopenem, identification of an organism that would be considered carbapenem-resistant at test of cure

[a]Modified from criteria used by Antibacterial Resistance Leadership Group for cUTI trials

Table 5: Desirability of Outcome Rankings by Treatment Arm

Treatment Groups	Ranks						
	1 (most desirable) N (%)	2 N (%)	3 N (%)	4 N (%)	5 N (%)	6 (least desirable) N (%)	Total # Subjects
Sulopenem	643 (81.9)	139 (17.7)	1 (0.1)	1 (0.1)	0 (0)	1 (0.1)	785
Ciprofloxacin	608 (76.6)	179 (22.5)	7 (0.9)	0 (0)	0 (0)	0 (0)	794

Figure 1: Forest Plot Demonstrating the Desirability of Outcome Ranking (DOOR) Probabilities for the DOOR, DOOR Prioritized for Efficacy and Safety, and the DOOR Components



CONCLUSIONS

- Traditional primary endpoints used in registrational trials for UTI require both clinical and microbiologic success at the test of cure visit
- In SURE-1, a Phase 3 uUTI trial, using the FDA's current definition of a successful overall response:
  - sulopenem was superior to ciprofloxacin in the population of patients with ciprofloxacin-nonsusceptible baseline pathogens (treatment difference 26.6%, 95% CI: 15.1, 37.4)
  - sulopenem was not non-inferior to ciprofloxacin in the population of patients with ciprofloxacin-susceptible baseline pathogens (treatment difference -11.8%, 95% CI: -18.0, -5.6)
- The DOOR approach proposed by the Antibacterial Resistance Leadership Group (ARLG) for cUTI incorporates benefits and risks of novel treatment strategies and provides a global assessment of patient experience. Applying the ARLG's cUTI DOOR approach, modified to include emergence of antibiotic resistance, to our uUTI trial data indicates that oral sulopenem was comparably more effective than ciprofloxacin in patients with uUTI (DOOR probability of a more desirable outcome for sulopenem is 52.7% [95% CI (50.7%, 54.7%)])
- The inclusion of ASB in the primary endpoint for studies of UTI (both complicated and uncomplicated UTI) should be reconsidered, particularly since lack of microbiologic eradication, in the form of ASB, can drive inappropriate antibiotic use and select for resistant pathogens among post-treatment flora
- This approach would align with guidance from professional societies such as IDSA and key opinion leaders, as expressed during a public hearing convened by the FDA on this topic in June 2022, in addition to being consistent with standard practice for many practicing physicians: not performing follow-up urine cultures on those patients with UTI whose symptoms resolve on antibiotics

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