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

Sailaja Puttagunta, MD[1], Jayanti Gupta, PhD[1], Michael Dunne, MD[1,2], and Steven I. Aronin, 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 cUTI trial comparing IV ertapenem (stepped down to either oral ciprofloxacin or amoxicillin-clavulanate) to IV sulopenem (stepped down to oral sulopenem etzadroxil/probenecid). Using the FDA's current definition of a successful response, one that requires both clinical and microbiologic success, sulopenem's overall success rate was 67.8% while ertapenem's was 73.9% (treatment difference -6.1%, 95% CI: -12.0, -0.1). The difference in overall success rates was due to the lower incidence of asymptomatic bacteriuria (ASB) among patients who received ertapenem and stepped down to ciprofloxacin; the presence of ASB post-treatment 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 cUTI (SURE-2) to estimate the probability of a more desirable outcome for sulopenem.

Results
The DOOR probability of a more desirable outcome is 50.7% [95% CI (48.9%, 52.5%)], indicating no significant difference between the sulopenem and ertapenem treatment arms for patients with cUTI. 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	608 (87.5%)	77 (11.1%)	4 (0.6%)	4 (0.6%)	2 (0.3%)	695
Ertapenem	599 (85.9%)	95 (13.6%)	3 (0.4%)	0 (0%)	0 (0%)	697

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-2 data showed no significant difference between the sulopenem and ertapenem treatment arms for patients with cUTI.

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 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-2 was a double-blind, double-dummy, Phase 3 randomized trial that enrolled 1395 hospitalized adults with complicated UTI (cUTI) and 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. The primary endpoint was overall (clinical + microbiologic) response in the micro-MITT population at the Test-of-Cure (Day 21) Visit.

An analysis using the DOOR methodology was performed post hoc on the SURE-2 clinical trial data.

METHODS

The DOOR analysis strategy utilized by the Antibacterial Resistance Leadership Group (ARLG) for cUTI trials was utilized for this analysis and included 3 key benefit-risk outcome measures: absence of clinical response, infectious complications and SAEs. Each patient was assigned a rank 1 through 5 in decreasing order of desirability: 1 = alive without any of the pre-specified outcomes, 2-4 = alive with 1, 2 or 3 outcomes, respectively and 5 = dead. Clinical response implies resolution of cUTI 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 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 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-2 Primary and Secondary Endpoints using FDA Definitions

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 2: SURE-2 Primary Endpoint by Step-down Regimen

Micro-MITT population	Sulopenem n/N (%)	Ertapenem n/N (%)	Difference (%) (95% CI)
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)	
	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)	

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 (least desirable)	No	Any

[a]Possible events include absence of clinical response, infectious complications, 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 IT001-302 protocol • Recurrent cUTI 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 • Epididymo-orchitis • Prostatic abscess

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

[a]Criteria used by Antibacterial Resistance Leadership Group for cUTI trials

Table 5: Desirability of Outcome Rankings by Treatment Arm

	Ranks					
	1 (most desirable)	2	3	4	5 (least desirable)	Total # subjects
Sulopenem	608 (87.5%)	77 (11.1%)	4 (0.6%)	4 (0.6%)	2 (0.3%)	695
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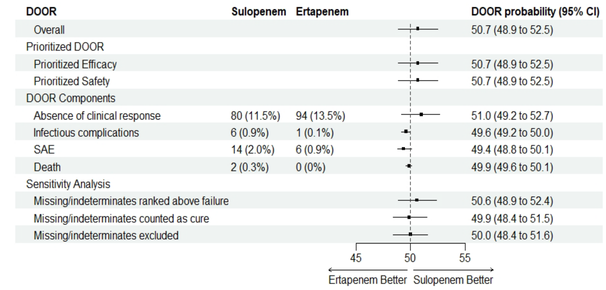
Figure 1: Forest Plot Demonstrating the Desirability of Outcome Ranking (DOOR) Probabilities for the DOOR, DOOR Prioritized for Efficacy and Safety, and the DOOR Components



CONCLUSIONS

- Traditional primary endpoints used in registrational trials for UTI require both clinical and microbiologic success at the test of cure visit
- Using the FDA's current definition of a successful overall response, sulopenem was not non-inferior to ertapenem in SURE-2, a Phase 3 cUTI trial (treatment difference -6.1%, 95% CI: -12.0, -0.1)
- 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 DOOR approach to our cUTI trial data indicates sulopenem provided comparable efficacy to ertapenem in patients with cUTI (DOOR probability of a more desirable outcome for sulopenem 50.7% [95% CI (48.9%, 52.5%)])
- 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

REFERENCES

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