Desirability of outcome ranking (DOOR): application to a phase 3 registrational trial evaluating sulopenem for patients with complicated intra-abdominal infection (cIAI)

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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 cIAI trial comparing IV ertapenem (stepped down to either oral ciprofloxacin and metronidazole or amoxicillin-clavulanate) to IV sulopenem (stepped down to oral sulopenem etzadroxil/probenecid). Using the FDA's current definition of a successful response (clinical response at Day 28 / Test-Of-Cure (TOC) in the microbiological intent-to-treat (micro-ITT) population using a non-inferiority margin of 10%, sulopenem's overall success rate was 85.5% while ertapenem's was 90.2% (treatment difference -4.7%, 95% CI: -10.3, 1.0). In all other study populations including the intent-to-treat (ITT), modified ITT, clinically evaluable (CE), and microbiologically evaluable (ME) populations the lower limit of confidence interval was above -10.0. To further understand these trial results, an analysis using the DOOR methodology was performed post hoc.
Methods
The DOOR analysis strategy, developed by the Antibacterial Resistance Leadership Group (ARLG), was retrospectively applied to our registrational drug trial for cIAI (SURE-3) to estimate the probability of a more desirable outcome for sulopenem.
Results
The DOOR probability of a more desirable outcome is 47.4% [95% CI (44.1%, 50.8%)], indicating no significant difference between the sulopenem and ertapenem treatment arms for patients with cIAI. 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								
	0 (most desirable)	1	2	3	4	5	6	7 (least desirable)	Total # of subjects
Sulopenem	200 (80.3%)	26 (10.4%)	8 (3.2%)	4 (1.6%)	7 (2.8%)	0 (0%)	0 (0%)	4 (1.6%)	249
Ertapenem	226 (85.0%)	27 (10.1%)	6 (2.3%)	3 (1.1%)	0 (0%)	0 (0%)	1 (0.4)	3 (1.1%)	266

Conclusions
Traditional endpoints used in registrational trials for cIAI may be inadequate. They evaluate safety and efficacy separately, and they fail to evaluate the cumulative impact of multiple clinical events. DOOR combines clinical efficacy and safety into a single endpoint that may be more reflective of an individual patient's overall outcome. Applying DOOR to SURE-3 data showed no significant difference between the sulopenem and ertapenem treatment arms for patients with cIAI.

INTRODUCTION

Traditional endpoints used in registrational trials for complicated intra-abdominal infection (cIAI) evaluate safety and efficacy separately, and they fail to evaluate the cumulative impact of multiple clinical events. 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-3 was a double-blind, double-dummy, Phase 3 randomized trial that enrolled 674 hospitalized adults with cIAI and compared sulopenem 1000 mg IV once daily x 5 days followed by oral sulopenem etzadroxil 500 mg co-formulated with oral probenecid 500 mg twice daily to complete 7-10 days of therapy, or ertapenem 1000 mg IV once daily x 5 days followed by oral ciprofloxacin 500 mg twice daily plus oral metronidazole 500 mg four times daily or amoxicillin-clavulanate 875 mg twice daily, depending on baseline pathogen susceptibility, to complete 7-10 days of therapy. The primary endpoint was clinical response in the micro-MITT population at the Test-of-Cure (Day 28) Visit.

An analysis using the DOOR methodology was performed post hoc on the SURE-3 clinical trial data.

METHODS

The DOOR analysis strategy for cIAI trials[1], proposed by collaborators from the Antibacterial Resistance Leadership Group (ARLG) and the FDA, was utilized for this analysis and included 4 key benefit-risk outcome measures: absence of clinical response, infectious complications, surgical/percutaneous procedures, and serious adverse events (SAEs). Each patient was assigned a rank 1 through 7 in decreasing order of desirability: 1 = alive without any of the pre-specified outcomes, 2-6 = alive with 1, 2, 3, 4, or 5 outcomes, respectively and 7 = dead. Clinical response implies resolution of cIAI symptoms at TOC with no new symptoms, and no new non-study antibiotics or interventions for treatment failure. Patients with clinical failure or indeterminate/missing outcomes were considered to have an absence of clinical response.

The analysis used the microbiologic-modified ITT population defined as all randomized patients who received at least 1 dose of study drug, had the disease under study, and had at least 1 Gram-negative study pathogen identified at study entry. 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, infectious complications, and procedures, respectively.

RESULTS

Table 1: SURE-3 Clinical Response at Test of Cure

Population/Clinical Response	Sulopenem n/N (%)	Ertapenem n/N (%)	Difference %(CI)
micro-MITT Population			
Clinical success	213/249 (85.5)	240/266 (90.2)	-4.7 (-10.3, 1.0)
Clinical failure	27/249 (10.8)	17/266 (6.4)	
Indeterminate	9/249 (3.6)	9/266 (3.4)	
ITT Population			
Clinical success	292/338 (86.4)	300/336 (89.3)	-2.9 (-7.8, 2.0)
Clinical failure	32/338 (9.5)	19/336 (5.7)	
Indeterminate	14/338 (4.1)	17/336 (5.1)	
MITT Population			
Clinical success	291/334 (87.1)	299/332 (90.1)	-2.9 (-7.8, 1.9)
Clinical failure	32/334 (9.6)	19/332 (5.7)	
Indeterminate	11/334 (3.3)	14/332 (4.2)	
CE-TOC Population			
Clinical success	265/283 (93.6)	265/277 (95.7)	-2.0 (-5.7, 1.7)
Clinical failure	18/283 (6.4)	12/277 (4.3)	
ME-TOC Population			
Clinical success	196/212 (92.5)	212/222 (95.5)	-3.0 (-7.5, 1.4)
Clinical failure	16/212 (7.5)	10/222 (4.5)	

Abbreviations: CE = clinically evaluable; CI = confidence interval; EOT = end of treatment; ITT = intent-to-treat; ME = microbiologically evaluable; micro-MITT = microbiologic modified intent-to-treat; n = number of patients in study population; N = Number of randomized patients; TOC = test of cure.

Table 2: SURE-3 Reasons for Clinical Nonresponse at Test of Cure – micro-MITT Population

Reasons for clinical nonresponse at TOC	Sulopenem n/N (%)	Ertapenem n/N (%)
Death	1/249 (0.4)	1/266 (0.4)
Signs and symptoms not resolved/new symptoms	10/249 (4.0)	5/266 (1.9)
Fever[a] or hypothermia[b]	--	--
Elevated WBC count[c] or leukopenia[d]	5/249 (2.0)	5/266 (1.9)
SBP <90 mmHg	--	--
Oxygen saturation <90%	--	--
Abdominal pain and/or tenderness, with or without rebound	5/249 (2.0)	--
Localized or diffuse abdominal wall rigidity	1/249 (0.4)	--
Abdominal mass	--	--
Nausea and/or vomiting	1/249 (0.4)	--
Altered mental status	--	--
Unplanned surgical procedures or percutaneous drainage procedures for complication	12/249 (4.8)	8/266 (3.0)
Rescue medication based on documented worsening symptoms or signs of cIAI	13/249 (5.2)	5/266 (1.9)
Wound infection with rescue medication	6/249 (2.4)	2/266 (0.8)

Note: Percentages are calculated as 100 × (n/N). Patients could have more than one reason for failure.
[a]Body temperature >38° C
[b]Body temperature <35° C
[c]WBC count >12,000 cells/mm^3
[d]WBC count <4000 cells/mm^3
Abbreviations: cIAI = complicated intra-abdominal infection; micro-MITT = microbiological modified intent-to-treat; n = number of patients; N = number of patients in a population; SBP = systolic blood pressure; TOC = test of cure; WBC = white blood cell.

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	Yes	5
7 (least desirable)	No	Any

[a]Possible events include absence of clinical response, infectious complications, surgical/percutaneous procedures, and serious adverse events

Table 4: Definitions Used in DOOR Analysis

Event Category[a]	Criteria
Absence of clinical response	• Did not meet clinical success as per Study IT001-303 protocol
Infectious complications	• Newly identified infections that were not initially diagnosed at the start of the trial, including those related and unrelated to the original cIAI
Surgical/Percutaneous Procedures	• Any additional abdominal interventions, to include surgical, percutaneous, or endoscopic procedures, that the participant has after their first operation for cIAI • Any postoperative wound-related surgical or percutaneous interventions that the participant has after their first operation for cIAI

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]Categories used by Antibacterial Resistance Leadership Group for cIAI trials

Table 5: Desirability of Outcome Rankings by Treatment Arm

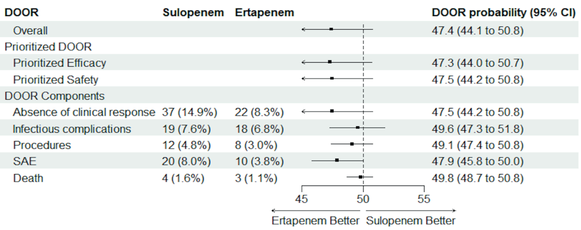
	Ranks								
	0 (most desirable)	1	2	3	4	5	6	7 (least desirable)	Total # of subjects
Sulopenem	200 (80.3%)	26 (10.4%)	8 (3.2%)	4 (1.6%)	7 (2.8%)	0 (0%)	0 (0%)	4 (1.6%)	249
Ertapenem	226 (85.0%)	27 (10.1%)	6 (2.3%)	3 (1.1%)	0 (0%)	0 (0%)	1 (0.4%)	3 (1.1%)	266
DOOR probability: 47.4%, 95% CI (44.1%, 50.8%)									

Table 6: DOOR Analysis Prioritizing Efficacy and Safety

DOOR Analysis (Prioritizing Efficacy)											
Ranks:	0	0.5	1	1.5	2	3	4	5	6	7	Total
Sulopenem	200 (80.3%)	10 (4.0%)	16 (6.4%)	2 (0.8%)	6 (2.4%)	4 (1.6%)	7 (2.8%)	0 (0%)	0 (0%)	4 (1.6%)	249
Ertapenem	226 (85.0%)	15 (5.6%)	12 (4.5%)	3 (1.1%)	3 (1.1%)	3 (1.1%)	0 (0%)	0 (0%)	1 (0.4%)	3 (1.1%)	266
DOOR probability: 47.3%, 95% CI (44.0%, 50.7%)											

DOOR Analysis (Prioritizing Safety)											
Ranks:	0	0.5	1	2	3	4	5	6	7		Total
Sulopenem	200 (80.3%)	16 (6.4%)	10 (4.0%)	8 (3.2%)	4 (1.6%)	7 (2.8%)	0 (0%)	0 (0%)	4 (1.6%)		249
Ertapenem	226 (85.0%)	12 (4.5%)	15 (5.6%)	6 (2.3%)	3 (1.1%)	0 (0%)	0 (0%)	1 (0.4%)	3 (1.1%)		266
DOOR probability: 47.5%, 95% CI (44.2%, 50.8%)											

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 cIAI may be inadequate as they evaluate safety and efficacy separately, and they fail to evaluate the cumulative impact of multiple clinical events.
- Using the FDA's current definition of a successful clinical response, sulopenem was not non-inferior to ertapenem in SURE-3, a Phase 3 cIAI trial (treatment difference -4.7%, 95% CI: -10.3, 1.0).
- The DOOR approach for cIAI[1], proposed by collaborators from the Antibacterial Resistance Leadership Group (ARLG) and the FDA, combines clinical efficacy and safety into a single endpoint that may be more reflective of an individual patient's overall outcome.
- Applying the DOOR approach to our SURE-3 cIAI trial data indicates sulopenem provided comparable treatment outcomes to ertapenem in patients with cIAI (DOOR probability of a more desirable outcome for sulopenem 47.4% [95% CI (44.1%, 50.8%)]).

REFERENCES

1. Kinamon T, Gopinath R, Waack U, Needles M, Rubin D, Collyar D, Doernberg SB, Evans S, Hamasaki T, Holland TL, Howard-Anderson J, Chambers H, Fowler Jr VG, Nambiar S, Kim P, Boucher HW. Exploration of a potential desirability of outcome ranking endpoint for complicated intra-abdominal infections using 9 registrational trials for antibacterial drugs. *Clin Infect Dis* 2023;77(4):649–656.