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CLINICAL THERAPEUTICS

Comparison of Treatment Outcomes between Analysis Populations in the RESTORE-IMI 1 Phase 3 Trial of Imipenem-Cilastatin-Relebactam versus Colistin plus Imipenem-Cilastatin in Patients with Imipenem-Nonsusceptible Bacterial Infections

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ABSTRACT The RESTORE-IMI 1 phase 3 trial demonstrated the efficacy and safety of imipenem-cilastatin (IMI) combined with relebactam (REL) for treating imipenem-nonsusceptible infections. The objective of this analysis was to compare the outcomes among patients meeting eligibility requirements based on central laboratory susceptibility versus local laboratory susceptibility. Patients with serious infections caused by imipenem-nonsusceptible, colistin-susceptible, and imipenem-REL-susceptible pathogens were randomized 2:1 to IMI-REL plus placebo or colistin plus IMI for 5 to 21 days. The primary endpoint was a favorable overall response. Key endpoints included the clinical response and all-cause mortality. We compared outcomes between the primary microbiological modified intent-to-treat (mMITT) population, where eligibility was based on central laboratory susceptibility testing, and the supplemental mMITT (SmMITT) population, where eligibility was based on local, site-level testing. The SmMITT ($n = 41$) and MITT ($n = 31$) populations had similar baseline characteristics, including sex, age, illness severity, and renal function. In both analysis populations, favorable overall response rates in the IMI-REL treatment group were >70%. Favorable clinical response rates at day 28 were 71.4% for IMI-REL and 40.0% for colistin plus IMI in the mMITT population, whereas they were 75.0% for IMI-REL and 53.8% for colistin plus IMI in the SmMITT population. Day 28 all-cause mortality rates were 9.5% for IMI-REL and 30.0% for colistin plus IMI in the mMITT population, whereas they were 10.7% for IMI-REL and 23.1% for colistin plus IMI in the SmMITT population. The outcomes in the SmMITT population were generally consistent with those in the mMITT population, suggesting that outcomes may be applicable to the real-world use of IMI-REL for treating infections caused by imipenem-nonsusceptible Gram-negative pathogens. (This study has been registered at ClinicalTrials.gov under identifier NCT02452047.)

KEYWORDS carbapenem resistant, supplemental analysis population, local microbiology data, β-lactamase inhibitor

Carbapenems are a mainstay of treatment in patients with serious Gram-negative bacterial infections (1). Infections caused by multidrug-resistant *Pseudomonas* spp. and carbapenem-resistant *Enterobacteriaceae* (new taxonomy, *Enterobacterales*), including carbapenemase-producing *Klebsiella pneumoniae* strains, are associated with high morbidity and mortality (2–4), and these bacterial pathogens are considered serious and urgent threats to public health, respectively (1). Conventional treatment options for carbapenem-nonsusceptible infections include polymyxins (polymyxin B and colistin),

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fosfomycin, tigecycline, and aminoglycosides; however, the causative pathogens are frequently resistant to one or more of these antibacterial agents (5–7). In addition, safety issues associated with these therapies can present a challenge, particularly in patients with complex conditions at high risk of adverse clinical outcomes. Tigecycline therapy carries an elevated risk of all-cause mortality, and the nephrotoxicity of polymyxins is associated with a high risk of acute kidney injury (7–10). Similarly, aminoglycosides may cause acute kidney injury or ototoxicity (11, 12). Despite advantages over the conventional therapy used to treat carbapenem-resistant infections, β-lactam–β-lactamase inhibitor combinations, including ceftazidime-avibactam, may not be effective against pathogens that develop certain resistance mechanisms (13). New antibacterial agents or combinations effective against carbapenem-resistant bacteria with favorable safety profiles are urgently needed.

Unlike other carbapenem antibacterial agents, imipenem induces the overproduction of *Pseudomonas*-derived cephalosporinase (PDC), a chromosomal AmpC β-lactamase, in *Pseudomonas aeruginosa*. Imipenem resistance development in this pathogen is due to the overproduction of PDC with the concomitant loss of the imipenem entry porin OprD (14, 15). Relebactam (REL) restores imipenem susceptibility in imipenem-nonsusceptible *P. aeruginosa* isolates and potentiates the activity of imipenem in imipenem-susceptible *P. aeruginosa* strains via inhibition of PDC, and unlike other β-lactamase–β-lactamase inhibitor combinations, neither imipenem nor REL is a substrate for the major efflux mechanisms of *P. aeruginosa* (15, 16). REL can also restore the activity of imipenem against many imipenem-nonsusceptible isolates of *Enterobacteriaceae* through its inhibition of class A carbapenemases (such as *K. pneumoniae* carbapenemases) (17, 18). Therefore, the combination of REL with imipenem-cilastatin (IMI), a well-established carbapenem for the treatment of serious infections, is a potential treatment option for infections caused by carbapenem-resistant pathogens (19, 20). In global surveillance studies, REL restored imipenem susceptibility to 53.5% to 84.9%, 71.4%, and 23.9% to 100.0% of imipenem-nonsusceptible isolates of *P. aeruginosa*, *K. pneumoniae*, and other *Enterobacteriaceae*, respectively (15, 21–23).

The efficacy and safety of IMI-REL have been investigated in several randomized, controlled clinical trials. Results from 2 phase 2, dose-ranging studies demonstrated that IMI-REL is well tolerated and noninferior to IMI alone for the treatment of adults with complicated urinary tract infection (cUTI) and complicated intra-abdominal infection (cIAI) (24, 25). A recent phase 3 trial, RESTORE-IMI 1, investigated IMI-REL for the treatment of serious, imipenem-nonsusceptible bacterial infections and demonstrated that IMI-REL was effective and generally well tolerated (20). RESTORE-IMI 1 was a small, descriptive study conducted in patients with infections confirmed to be caused by imipenem-nonsusceptible pathogens, without formal hypothesis testing for efficacy endpoints.

Identification of appropriate study populations using microbiological criteria presents a challenge to conducting clinical trials for antibacterial agents. To initiate effective treatment as rapidly as possible, which has demonstrated clinical benefit, including improved survival rates, patients potentially eligible for such trials need to be identified at the investigational site level, using results from local susceptibility testing (4). However, to standardize trial data appropriately for regulatory review, confirmation of local test results by a central laboratory is a requirement (26, 27). Repeat susceptibility testing of isolates at different facilities can contribute to complexity, as the results between tests for any isolate may vary by $\geq$4 dilutions, even under standardized conditions within the same facility, which may impact the designation of the susceptibility or the nonsusceptibility of isolates to the tested agents (28). Determination of patient eligibility for inclusion in the primary analysis population of our trial was based on centrally assessed susceptibility results. In this study, we evaluated the outcomes for a study population in which IMI-REL was used in a manner that more closely represents the real-world use of IMI-REL, where treatment decisions are made based on local laboratory results. We addressed this objective by comparing the results from the RESTORE-IMI 1 microbiological modified intent-to-treat (mMITT) population with those

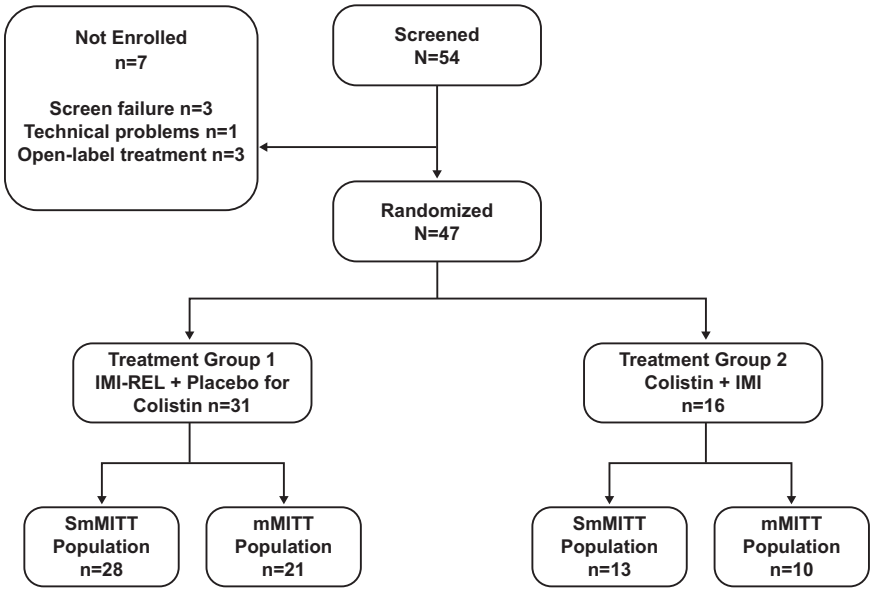

FIG 1 Trial enrollment and summary of patients in analysis populations. IMI, imipenem-cilastatin; mMITT, microbiological modified intent-to-treat; REL, relebactam; SmMITT, supplemental microbiological modified intent-to-treat.

from an expanded supplemental microbiological modified intent-to-treat (SmMITT) population that included those patients who were eligible based on local laboratory results but not central laboratory results. Expanding the eligibility criteria for the study population also allowed the evaluation of RESTORE-IMI 1 results in a more traditional intent-to-treat population.

RESULTS

A total of 41 and 31 patients were included in the SmMITT and mMITT populations, respectively (Fig. 1). Baseline characteristics and demographics grouped by population and treatment arm are summarized in Table 1. Overall, the SmMITT and mMITT populations were comparable in terms of demographic and clinical characteristics, including age, infection type, Acute Physiologic Assessment and Chronic Health Evaluation II scores, and renal function. Within the SmMITT population, 28 patients were treated with IMI-REL (8 for hospital-acquired bacterial pneumonia [HABP]/ventilator-associated bacterial pneumonia [VABP], 5 for cIAI, 15 for cUTI) and 13 were treated with colistin plus IMI (4 for HABP/VABP, 3 for cIAI, 6 for cUTI). Within the mMITT population, 21 patients were treated with IMI-REL (8 for HABP/VABP, 2 for cIAI, 11 for cUTI) and 10 were treated with colistin plus IMI (3 for HABP/VABP, 2 for cIAI, 5 for cUTI). *P. aeruginosa* was the most common qualifying baseline pathogen (SmMITT population, 27/42 [64.3%]; mMITT population, 24/31 [77.4%]), followed by *K. pneumoniae* (SmMITT population, 8/42 [19.0%]; mMITT population, 4/31 [12.9%]) and other *Enterobacteriaceae* (SmMITT population, 7/42 [16.7%]; mMITT population, 3/31 [9.7%]). Polymicrobial Gram-negative bacterial infections were uncommon (SmMITT population, 3/41 [7.3%]; mMITT population, 1/31 [3.2%]). One patient (2.4%) in the SmMITT population had 2 qualifying baseline pathogens.

Among the qualifying baseline pathogens isolated from the 10 patients in the SmMITT population who were excluded from the mMITT population, the majority of differences in the MIC values obtained by the local laboratory versus those obtained by the central laboratory for imipenem alone, imipenem-REL, or colistin were limited to 1 to 2 dilutions for most qualifying baseline pathogens (Table 2). Of these 10 patients excluded from the mMITT population, central laboratory testing determined that 5 had baseline pathogens that were imipenem susceptible, 4 had baseline pathogens that

TABLE 1 Baseline demographics and clinical characteristics[c]

Characteristic	SmMITT population			mMITT population		
	IMI-REL (n = 28)	Colistin plus IMI (n = 13)	Total (n = 41)	IMI-REL (n = 21)	Colistin plus IMI (n = 10)	Total (n = 31)
No. of patients in population	28	13	41	21	10	31
No. of patients by sex						
Male	18 (64.3)	10 (76.9)	28 (68.3)	13 (61.9)	7 (70.0)	20 (64.5)
Female	10 (35.7)	3 (23.1)	13 (31.7)	8 (38.1)	3 (30.0)	11 (35.5)
No. of patients by age (yr)						
<65	16 (57.1)	6 (46.2)	22 (53.7)	15 (71.4)	5 (50.0)	20 (64.5)
≥65	12 (42.9)	7 (53.8)	19 (46.3)	6 (28.6)	5 (50.0)	11 (35.5)
Median (range) age (yr)	61 (19–77)	65 (49–80)	63 (19–80)	59 (19–75)	61 (49–80)	59 (19–80)
Median (range) wt (kg)	79.3 (53.0–140.0)	75.8 (52.8–117.0)	78.0 (52.8–140.0)	75 (53.0–132.3)	75.6 (52.8–117.0)	75 (52.8–132.3)
No. of patients with the following APACHE II score:						
≤15	20 (71.4)	11 (84.6)	31 (75.6)	14 (66.7)	8 (80.0)	22 (71.0)
>15	8 (28.6)	2 (15.4)	10 (24.4)	7 (33.3)	2 (20.0)	9 (29.0)
No. of patients with the following primary diagnosis:						
HABP	1 (3.6)	1 (7.7)	2 (4.9)	1 (4.8)	1 (10.0)	2 (6.5)
VABP	7 (25.0)	3 (23.1)	10 (24.4)	7 (33.3)	2 (20.0)	9 (29.0)
cIAI	5 (17.9)	3 (23.1)	8 (19.5)	2 (9.5)	2 (20.0)	4 (12.9)
cUTI (urinary tract abnormalities)	8 (28.6)	3 (23.1)	11 (26.8)	5 (23.8)	3 (30.0)	8 (25.8)
cUTI (acute pyelonephritis)	7 (25.0)	3 (23.1)	10 (24.4)	6 (28.6)	2 (20.0)	8 (25.8)
No. of patients with the following creatinine clearance (ml/min):						
≥90	8 (28.6)	5 (38.5)	13 (31.7)	8 (38.1)	3 (30.0)	11 (35.5)
<90 to ≥60	14 (50.0)	4 (30.8)	18 (43.9)	8 (38.1)	4 (40.0)	12 (38.7)
<60 to ≥30	4 (14.3)	3 (23.1)	7 (17.1)	3 (14.3)	2 (20.0)	5 (16.1)
<30 to ≥15	1 (3.6)	1 (7.7)	2 (4.9)	1 (4.8)	1 (10.0)	2 (6.5)
Not available	1 (3.6)	0	1 (2.4)	1 (4.8)	0	1 (3.2)
No. of patients with the following qualifying baseline pathogens:						
Citrobacter freundii	1 (3.4)	0 (0.0)	1 (2.4)	1 (4.8)	0	1 (3.2)
Enterobacter aerogenes	0	1 (7.7)	1 (2.4)	0	0	0
Enterobacter cloacae	2 (6.9)	1 (7.7)	3 (7.1)	1 (4.8)	0	1 (3.2)
Escherichia coli	1 (3.4)	0	1 (2.4)	0	0	0
Klebsiella oxytoca	0	1 (7.7)	1 (2.4)	0	1 (10.0)	1 (3.2)
Klebsiella pneumoniae	6 (20.7)	2 (15.4)	8 (19.0)	3 (14.3)	1 (10.0)	4 (12.9)
Pseudomonas aeruginosa	19 (65.5)	8 (61.5)	27 (64.3)	16 (76.2)	8 (80.0)	24 (77.4)
No. of patients with isolates with the following β-lactamases[a]:						
Class A						
Older-spectrum β-lactamases						
SHV[b]	4 (14.3)	2 (15.4)	6 (14.6)	2 (9.5)	1 (10.0)	3 (9.7)
TEM	12 (42.9)	3 (23.1)	15 (36.6)	7 (33.3)	3 (30.0)	10 (32.3)
ESBLs						
CTX-M	12 (42.9)	6 (46.2)	18 (43.9)	7 (33.3)	4 (40.0)	11 (35.5)
SHV[b]	2 (7.1)	0	2 (4.9)	1 (4.8)	0	1 (3.2)
VEB	0	0	0	0	0	0
KPC serine carbapenemase	5 (17.9)	1 (7.7)	6 (14.6)	4 (19.0)	1 (10.0)	5 (16.1)
Class C						
Chromosomal AmpC (PDC)	19 (67.9)	8 (61.5)	27 (65.9)	16 (76.2)	8 (80.0)	24 (77.4)
Plasmid-mediated AmpC						
ACT	0	0	0	0	0	0
CMY	1 (3.6)	0	1 (2.4)	1 (4.8)	0	1 (3.2)
DHA	1 (3.6)	0	1 (2.4)	1 (4.8)	0	1 (3.2)
Class D, OXA-48	4 (14.3)	2 (15.4)	6 (14.6)	0	1 (10.0)	1 (3.2)

[a]Qualifying baseline pathogens could have had multiple β-lactamases detected.

[b]Older-spectrum β-lactamases were SHV-1 and SHV-11; ESBLs were SHV-26 and SHV-28.

[c]APACHE II, Acute Physiologic Assessment and Chronic Health Evaluation II; cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; ESBL, extended-spectrum β-lactamase; HABP, hospital-acquired bacterial pneumonia; IMI, imipenem-cilastatin; mMITT, microbiological modified intent-to-treat; REL, relebactam; SmMITT, supplemental microbiological modified intent-to-treat; VABP, ventilator-associated bacterial pneumonia.

TABLE 2 Central versus local MICs of qualifying baseline pathogens for patients included in the SmMITT population but excluded from the mMITT population[b]

Patient no.	TG	Infection type	Qualifying pathogen name	Local interpretive criteria used	MIC (μg/ml [susceptibility])[c]					
					Imipenem		IMI-REL		Colistin	
					Local lab	Central lab	Local lab	Central lab	Local lab	Central lab
1	2	HABP/VABP	*E. aerogenes*	CLSI	**2 (I)**	**1 (S)**	0.5 (S)	0.12 (S)	0.25 (S)	<1 (S)
2[a]	1	cIAI	*K. pneumoniae*	EUCAST	8 (I)	4 (I)	2 (S)	2 (S)	**2 (S)**	**4 (R)**
3	2	cIAI	*E. cloacae*	CLSI	**2 (I)**	**<0.5 (S)**	0.5 (S)	0.12 (S)	1 (S)	<1 (S)
4	1	cIAI	*E. cloacae*	CLSI	**2 (I)**	**<0.5 (S)**	1 (S)	0.12 (S)	1 (S)	<1 (S)
5	1	cIAI	*K. pneumoniae*	CLSI	4 (R)	4 (R)	**1 (S)**	**2 (I)**	0.5 (S)	<1 (S)
6	1	cUTI	*E. coli*	CLSI	2 (I)	2 (I)	**1 (S)**	**2 (I)**	0.12 (S)	<1 (S)
7	2	cUTI	*K. pneumoniae*	CLSI	2 (I)	2 (I)	**1 (S)**	**2 (I)**	0.12 (S)	<1 (S)
8	1	cUTI	*K. pneumoniae*	CLSI	16 (R)	32 (R)	**1 (S)**	**2 (I)**	0.25 (S)	<1 (S)
9	1	cUTI	*P. aeruginosa*	CLSI	**8 (R)**	**2 (S)**	2 (S)	0.5 (S)	1 (S)	<1 (S)
10	1	cUTI	*P. aeruginosa*	CLSI	**16 (R)**	**2 (S)**	1 (S)	0.25 (S)	0.12 (S)	<1 (S)

[a]The participant had a polymicrobial infection, including an infection caused by a qualifying *P. aeruginosa* isolate, but was unevaluable for the mMITT population due to the presence of colistin-nonsusceptible *K. pneumoniae*.

[b]cIAI, complicated intra-abdominal infection; CLSI, Clinical and Laboratory Standards Institute; cUTI, complicated urinary tract infection; EUCAST, European Committee on Antimicrobial Susceptibility Testing; HABP, hospital-acquired bacterial pneumonia; I, intermediate; IMI-REL, imipenem-cilastatin plus relebactam; mMITT, microbiological modified intent-to-treat; R, resistant; S, susceptible; SmMITT, supplemental microbiological modified intent-to-treat; TG, treatment group; VABP, ventilator-associated bacterial pneumonia.

[c]Data in boldface indicate differences in susceptibility test interpretation (susceptible versus intermediate versus resistant) between the local laboratory and central laboratory, based on MIC values.

were imipenem-REL nonsusceptible, and 1 had a pathogen that was colistin nonsusceptible.

The results for the SmMITT and mMITT populations were generally consistent, and most patients achieved a favorable overall response (Table 3). Favorable overall response rates in the IMI-REL treatment group were >70% for both the SmMITT and mMITT populations. Favorable clinical response rates at day 28 were 71.4% for IMI-REL and 40.0% for colistin plus IMI in the mMITT population, whereas they were 75.0% for IMI-REL and 53.8% for colistin plus IMI in the SmMITT population. Day 28 all-cause mortality rates were 9.5% for IMI-REL and 30.0% for colistin plus IMI in the mMITT population, whereas they were 10.7% for IMI-REL and 23.1% for colistin plus IMI in the SmMITT population. Among the 10 patients excluded from the mMITT population, a

TABLE 3 Treatment responses in patients in mMITT and SmMITT populations[c]

Response and patient group	n/m (%)		% (90% CI)	
	IMI-REL	Colistin plus IMI	Unadjusted difference	Adjusted difference[a]
Favorable overall response				
mMITT population	15/21 (71.4)	7/10 (70.0)	1.4	−7.3 (−27.5 to 21.4)
HABP/VABP	7/8 (87.5)	2/3 (66.7)	20.8	
cIAI	0/2	0/2	0.0	
cUTI	8/11 (72.7)	5/5 (100.0)	−27.3 (−52.8 to 12.8)[b]	
SmMITT population	21/28 (75.0)	10/13 (76.9)	−1.9	−4.5 (−24.2 to 20.7)
HABP/VABP	7/8 (87.5)	3/4 (75.0)	12.5 (−25.4 to 56.6)[b]	
cIAI	2/5 (40.0)	1/3 (33.3)	6.7	
cUTI	12/15 (80.0)	6/6 (100.0)	−20.0 (−41.4 to 14.2)[b]	
Favorable clinical response (day 28)				
mMITT population	15/21 (71.4)	4/10 (40.0)	31.4	26.3 (1.3 to 51.5)
SmMITT population	21/28 (75.0)	7/13 (53.8)	21.2	17.6 (−5.9 to 42.5)
All-cause mortality (through day 28)				
mMITT population	2/21 (9.5)	3/10 (30.0)	−20.5	−17.3 (−46.4 to 6.7)
SmMITT population	3/28 (10.7)	3/13 (23.1)	−12.4	−10.5 (−35.2 to 9.6)

[a]Adjusted differences and 90% confidence intervals are based on the values obtained by the Miettinen and Nurminen method (36) stratified by infection site.

[b]The 90% confidence intervals were calculated by the Miettinen and Nurminen method (36).

[c]CI, confidence interval; cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; HABP, hospital-acquired bacterial pneumonia; IMI, imipenem-cilastatin; mMITT, microbiological modified intent-to-treat; n/m, number of patients with a favorable response or all-cause mortality/number of patients evaluable; REL, relebactam; SmMITT, supplemental microbiological modified intent-to-treat; VABP, ventilator-associated bacterial pneumonia.

favorable overall response was reported for 6/7 (85.7%) in the IMI-REL-treated group and 3/3 (100.0%) in the colistin plus IMI-treated group; a favorable clinical response at day 28 was reported for 6/7 (85.7%) in the IMI-REL-treated group and 3/3 (100.0%) in the colistin plus IMI-treated group; all-cause mortality was 1/7 (14.3%) in the IMI-REL-treated group, and no patients in the colistin plus IMI-treated group died.

DISCUSSION

The previously reported efficacy and safety results from the RESTORE-IMI 1 trial support IMI-REL as a suitable treatment option for serious Gram-negative bacterial infections, including those caused by carbapenem-nonsusceptible pathogens in high-risk patients (20). These results were obtained in the primary efficacy population (i.e., the mMITT population), determined by qualifying baseline pathogen susceptibility results from the central microbiology laboratory. Here, we describe the results of a secondary analysis conducted in the protocol-defined SmMITT population, in which eligibility was based on susceptibility results from the local microbiology laboratory. The results of this secondary analysis lend further support to the primary study findings from RESTORE-IMI 1, in that they are consistent, regardless of whether patients were included in the analysis based on local or central laboratory susceptibility testing. In both the secondary SmMITT population and the primary mMITT population, IMI-REL and colistin plus IMI yielded favorable overall response rates of $>$70%. In both analysis populations, there was an apparent trend toward more favorable clinical and mortality outcomes among patients treated with IMI-REL than among those treated with a colistin-based therapy.

In contrast to recent open-label clinical trials comparing the efficacy and safety of new antibacterial agents with the best available therapy (BAT) for the treatment of resistant infections (29–31), the RESTORE-IMI 1 trial was a double-blind study with a single active comparator. Limiting the study to a single comparator rather than BAT reduced treatment variability and ensured that all patients received early appropriate therapy, given that only patients with colistin-susceptible infections were enrolled. Generally, in antibacterial clinical trials, pathogen isolates are commonly cultured in local laboratories for initial pathogen identification and subsequently sent to a central laboratory for confirmatory pathogen identification and susceptibility testing. The use of standardized susceptibility panels in local laboratories for the RESTORE-IMI 1 trial further distinguishes this trial from other similar resistant-pathogen trials in 2 important ways: (i) by ensuring the consistency of the susceptibility results for qualifying baseline pathogens from all sites, thereby allowing the rigorous selection of patients eligible for inclusion into the study, and (ii) by enabling enrollment in the trial (with initiation of appropriate therapy for all patients) at a consistent time point for all patients (i.e., as soon as susceptibility results are known).

The use of microbiological criteria for the identification of study populations for enrollment in clinical trials evaluating antibacterial agents presents a substantial challenge (32). As with similar studies, the primary analysis (mMITT) population in RESTORE-IMI 1 was small due to the difficulty in identifying patients with the desired resistance profile who qualified for a clinical trial, as well as the impact of the global study design with variable clinical practices and clinical trial experience across institutions (29, 30). Also consistent with similar trials, the RESTORE-IMI 1 mMITT population included a limited number of enrolled patients with cIAI, primarily because there were fewer prescreening isolates from intra-abdominal specimens than from urinary and lower respiratory tract specimens (29, 30). This secondary analysis expanded the participant population analyzed and doubled the size of the cIAI cohort from 4 to 8 patients. Compared with the mMITT population, the SmMITT population may better represent patients seen in a real-world setting, where treatment decisions are based on pathogen identification and susceptibility data provided by the local microbiology laboratory.

In this analysis, susceptibility testing results obtained from the local laboratory were similar to those obtained from the central laboratory. Among the 10 patients who were excluded from the mMITT population, most qualifying baseline isolates had minor

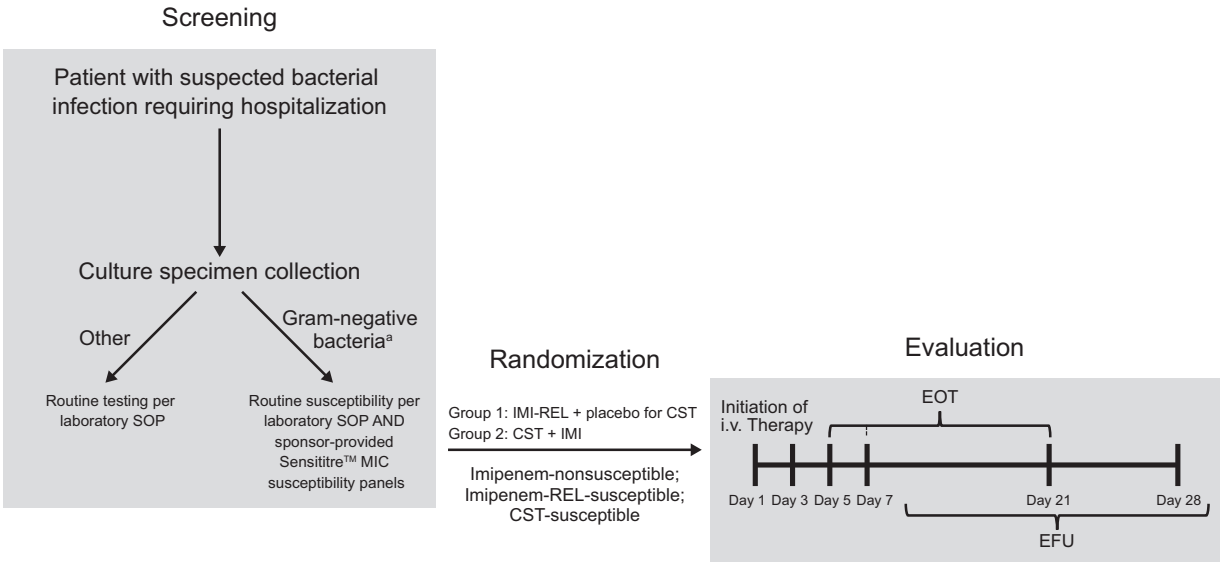

FIG 2 Assessment schedule. [a], from specimen types of interest: blood, urinary, intra-abdominal, or lower respiratory tract sources. CST, colistin; EFU, early follow-up; EOT, end of therapy; IMI, imipenem-cilastatin; i.v., intravenous; REL, relebactam; SOP, standard operating procedure.

differences (1 to 2 dilutions) in MIC results between the 2 laboratory settings, and differences in susceptibility determinations occurred to a similar extent for all 3 tested drugs. The differences in susceptibility results between the 2 laboratory settings, with MICs generally being higher at the local laboratories, may be due to differences inherent to the 2 susceptibility panels used (i.e., Sensititre in local laboratories versus custom frozen panels in the central laboratory). Local laboratory testing identified a patient population consistent with the population in which IMI-REL is expected to be used: those with Gram-negative bacterial infections caused by carbapenem-resistant pathogens. The similarity of the results obtained from both laboratory settings suggests that clinicians can rely on local laboratory data to guide decision-making and the use of IMI-REL. In addition, this analysis offers insight into study design options for antibacterial trials conducted in this challenging patient population.

Overall, IMI-REL was effective for the treatment of adults with imipenem-nonsusceptible, serious Gram-negative bacterial infections, including cIAI, cUTI, and HABP/VABP, with the response rates being comparable to the response rate of a commonly used regimen (20). The results of this secondary analysis, in which treatment response was evaluated among patients with qualifying baseline pathogens identified based only on local microbiology laboratory culture and susceptibility results, provide support for the expected future clinical use of IMI-REL for the treatment of infections caused by multidrug-resistant Gram-negative bacteria, where therapeutic decisions will typically be made based on local laboratory data.

MATERIALS AND METHODS

Study design. RESTORE-IMI 1 (protocol MK-7655A-013) was a phase 3, randomized, double-blind, active comparator-controlled, parallel-group, multicenter clinical trial that evaluated the efficacy and safety of IMI-REL compared with those of colistin plus IMI (ClinicalTrials.gov identifier NCT02452047). The protocol was approved by appropriate institutional review boards and regulatory agencies, and the trial was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. The full methodology was previously published (20).

Patients. Inclusion and exclusion criteria have been previously described (20). Patients were adults (age, ≥18 years) who required hospitalization and treatment with intravenous (i.v.) antibiotics for serious infections (cIAI, cUTI, and HABP/VABP) caused by imipenem-nonsusceptible but imipenem-REL- and colistin-susceptible Gram-negative pathogens. As part of routine standard-of-care testing at each participating investigational site, all Gram-negative pathogens isolated from intra-abdominal, lower respiratory tract, and urinary tract specimens were evaluated for susceptibility to the 3 study drugs by broth microdilution according to Clinical and Laboratory Standards Institute (CLSI) guidelines (Fig. 2) (33). For this purpose, all local microbiology laboratories (i.e., those used by the individual investigational sites)

TABLE 4 Primary endpoint (overall response) definition by infection type[c]

Infection type	Time point	Outcome
HABP/VABP	Day 28	All-cause mortality (survival)
cIAI	Day 28	Favorable clinical response (sustained cure or cure[a])
cUTI	EFU visit	Favorable microbiological response (sustained eradication[b]) and favorable clinical response (sustained cure or cure[a])

[a]All pretherapy signs and symptoms of the index infection(s) had resolved (or returned to preinfection status), no additional intravenous antibiotic therapy was required, and, for patients with cIAI, no unplanned surgical procedures or percutaneous drainage procedures had been performed (cure was sustained if there was no evidence of a resurgence of the index infection).

[b]A culture of urine taken at the EFU visit still showed eradication of the uropathogen found at study entry (i.e., a count of $\geq 10^5$ CFU/ml was reduced to $< 10^4$ CFU/ml).

[c]cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; EFU, early follow-up; HABP, hospital-acquired bacterial pneumonia; VABP, ventilator-associated bacterial pneumonia.

were provided with Sensititre susceptibility panels (Thermo Fisher Scientific Inc., Waltham, MA, USA), a broth microdilution method, to standardize testing of the susceptibility of the isolates to imipenem, imipenem-REL, and colistin. This prescreening process identified patients with potentially eligible infections caused by imipenem-nonsusceptible, imipenem-REL-susceptible, and colistin-susceptible Gram-negative pathogens. The study investigators then decided whether to enter the identified patients into the formal screening process of this trial (i.e., obtaining informed consent and determining whether all other inclusion and exclusion criteria were met). In order to be eligible, a patient's primary infection-site sample had to be collected within 1 week before study entry. Patients were eligible for enrollment into the study and randomization based on the local susceptibility test results for the Gram-negative isolates. In addition to local laboratory testing, all Gram-negative isolates from infection-site specimens from randomized patients were evaluated at a central microbiology reference laboratory (International Health Management Associates, Inc. [IHMA], Schaumburg, IL, USA). At the central laboratory, species identification was confirmed by matrix-assisted laser desorption ionization–time of flight spectroscopy (Bruker Daltonics, Billerica, MA, USA), and susceptibility testing was performed by broth microdilution according to CLSI guidelines using custom frozen panels prepared at IHMA (33). Repeat testing was performed for isolates for which the susceptibility results obtained at the central and local laboratories were not consistent. MIC values were interpreted using CLSI (34) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) 2017 (35) guidelines. Imipenem susceptibility breakpoints were also applied to imipenem-REL.

Procedures. Patients were randomized 2:1 (stratified by primary infection type) into 2 groups. The first group received i.v. IMI-REL (imipenem at 500 mg and cilastatin at 500 mg plus relebactam at 250 mg every 6 h) plus placebo to colistin; the second group received i.v. colistin (as colistimethate sodium at a loading dose to achieve 300-mg colistin base activity, followed by maintenance doses every 12 h up to 150-mg colistin base activity) plus IMI (imipenem at 500 mg and cilastatin at 500 mg every 6 h). Dosing of both study treatments was adjusted based on renal function. The treatment duration was $\geq$5 days for cIAI and cUTI and $\geq$7 days for HABP/VABP and did not exceed 21 days. Patients were screened for eligibility at $\leq$24 h before randomization (Fig. 2); study visits were performed on day 1 (randomization), on day 3 (on-therapy visit), and at the end of therapy (EOT; day 5/7 to day 21). Patients were also evaluated following completion of the i.v. study therapy at an early follow-up (EFU) visit (5 to 9 days post-EOT) and on day 28 (which could occur on the same day as the EFU visit).

For patients with HABP/VABP or cIAI, the collection of a baseline sample from the infection site was strongly preferred; however, collection at the time of study entry was not required for patients in whom infection-site specimen collection was not medically acceptable (e.g., a patient with cIAI in whom collection of an additional sample would require surgical intervention). Instead, a pure isolate of the suspected causative pathogen from a prior culture of a specimen collected within 1 week of enrollment was submitted to the central laboratory for evaluation. Additional unscheduled cultures of specimens from the infection site with pathogen susceptibility testing were performed at any time that there was clinical or laboratory evidence of infection persistence or progression (e.g., persistent fever, elevated white blood cell count, or significant changes in the patient's clinical condition) and at the time of any surgical or drainage procedure in patients with HABP/VABP or cIAI. For patients with cUTI, infection-site specimens were required for visits on day 1, on day 3, at the EOT, and at the EFU visit.

Treatment response analysis. Treatment response was defined using unique criteria for each infection type (Table 4). Key secondary endpoints included a favorable clinical response (sustained cure or cure) at day 28 after initiation of trial treatment and all-cause mortality (survival) at day 28 after trial treatment.

Treatment responses were evaluated in 2 protocol-prespecified analysis populations: the mMITT population, which was the primary efficacy population from the primary analysis, and the SmMITT population. Both the mMITT and SmMITT populations comprised patients who received $\geq$1 dose of study drug and had $\geq$1 qualifying baseline pathogen, a Gram-negative pathogen isolated from a culture of a specimen obtained from the primary infection site within 1 week of randomization and meeting protocol-specified criteria for susceptibility to imipenem, imipenem-REL, and colistin based on local laboratory susceptibility interpretive criteria (i.e., CLSI or EUCAST criteria). The eligibility of the baseline pathogens for the mMITT population was determined by MIC results obtained from the central laboratory. The SmMITT population included all patients in the mMITT population plus additional patients who had $\geq$1 qualifying baseline pathogen meeting susceptibility criteria according to local laboratory MIC results, regardless of the central laboratory MIC results.

This was an estimation trial; no formal statistical testing was performed for treatment response. Between-group 90% confidence intervals for the primary and key secondary endpoints were calculated using the stratified Miettinen and Nurminen method, an unconditional, asymptotic method (36). The between-group estimates were stratified by infection type, where appropriate.

Data availability. The data sharing policy of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, including restrictions, is available at http://engagezone.msd.com/ds_documentation.php. Requests for access to the clinical study data can be submitted through the EngageZone site or via email to dataaccess@merck.com.

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