Imipenem/Cilastatin/Relebactam in Hospital-Acquired/Ventilator-Associated Bacterial Pneumonia: Subgroup Analyses of Critically Ill Participants in the RESTORE-IMI 2 Trial

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Background

- Hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia (HABP/VABP) are among the most common health care–associated infections and are associated with a mortality rate as high as 50%; critically ill patients with HABP/VABP are at particularly high risk of adverse clinical outcomes[1-4]
- The results of the recently completed RESTORE-IMI 2 trial showed that imipenem/cilastatin/relebactam (IMI/REL) was non-inferior to piperacillin/tazobactam (PIP/TAZ) for the treatment of adults with HABP/VABP in both primary and key secondary end points[5]
- IMI/REL was recently approved for HABP/VABP by the United States Food & Drug Administration[6]
- Elevated Acute Physiology and Chronic Health Evaluation (APACHE) II score, renal impairment, and receipt of vasopressors have been shown to be reliable predictors of poor outcome and can be considered markers of critical illness[7,8]
- We conducted retrospective subgroup analyses of RESTORE-IMI 2, comparing the efficacy and safety of IMI/REL and PIP/TAZ using various definitions of critically ill participants

Methods

- RESTORE-IMI 2 (ClinicalTrials.gov: NCT02493764) was a multicenter, randomized, controlled, double-blind, phase 3 trial in adults with HABP/VABP[5]
  - Lower respiratory tract (LRT) specimens were obtained ≤48 hours prior to screening
- Participants were randomly assigned 1:1 to receive either imipenem/cilastatin/relebactam 500 mg/500 mg/250 mg or PIP/TAZ 4 g/500 mg, administered by a 30-minute intravenous infusion every 6 hours for 7–14 days
- The primary end point was Day 28 all-cause mortality (ACM) and the key secondary end point was clinical response at early follow-up (7–14 days after completing therapy) in the modified intent-to-treat (MITT) population (randomized participants who received ≥1 dose of study treatment and whose baseline Gram stain did not show only gram-positive cocci)
- Baseline pathogens per participant were assessed in the microbiological MITT (mMITT) population (participants in the MITT population with ≥1 baseline LRT pathogen species against which imipenem plus REL is expected to have antibacterial activity based on prior in vitro studies [eg, not methicillin-resistant *Staphylococcus aureus, Legionella* spp., or *Stenotrophomonas* spp.])
- Adverse events (AEs) were evaluated in all participants who received ≥1 dose of study therapy
- The current analysis assessed efficacy and safety outcomes in:
  - Participants with an APACHE II score ≥15 at baseline, a prespecified subgroup and stratification factor
  - Participants in the intensive care unit (ICU) at baseline
  - Participants with baseline moderate/severe renal impairment (creatinine clearance <60 mL/min)
  - Participants who received vasopressors within 72 hours of the first dose of study drug or during the study

Results

Participants

- At baseline among participants in the overall MITT population (N=531), 66.1% were in the ICU, 47.5% had APACHE II scores ≥15, 24.7% had moderate/severe renal impairment, and 20.9% were treated with vasopressors within 72 hours of the first study dose or during the study
- Participants with APACHE II scores ≥15 also had other characteristics associated with critical illness, including being in the ICU at baseline (76.6%) and renal impairment (50.4%)
- Demographics and baseline characteristics (MITT population) were generally similar between the treatment arms across the 4 critically ill participant subgroups (**Table 1**)

Table 1. Demographics and Baseline Characteristics (MITT Population)

	APACHE II score ≥15 at baseline		ICU at baseline		Moderate/severe renal impairment at baseline		Received vasopressors[a]	
Characteristic, n (%)	IMI/REL N=125	PIP/TAZ N=127	IMI/REL N=175	PIP/TAZ N=176	IMI/REL N=71	PIP/TAZ N=60	IMI/REL N=54	PIP/TAZ N=57
Male sex	80 (64.0)	89 (70.1)	120 (68.6)	124 (70.5)	44 (62.0)	35 (58.3)	36 (66.7)	41 (71.9)
Age ≥65 years	65 (52.0)	66 (52.0)	65 (37.1)	75 (42.6)	57 (80.3)	46 (76.7)	30 (55.6)	29 (50.9)
APACHE II score at baseline								
15 to 19	65 (52.0)	63 (49.6)	38 (21.7)	44 (25.0)	16 (22.5)	15 (25.0)	16 (29.6)	14 (24.6)
20 to 24	45 (36.0)	40 (31.5)	41 (23.4)	35 (19.9)	13 (18.3)	7 (11.7)	13 (24.1)	14 (24.6)
≥25	15 (12.0)	24 (18.9)	13 (7.4)	22 (12.5)	10 (14.1)	11 (18.3)	7 (13.0)	13 (22.8)
Type of pneumonia								
Non-ventilated HABP	45 (36.0)	36 (28.3)	63 (36.0)	56 (31.8)	45 (63.4)	36 (60.0)	13 (24.1)	5 (8.8)
Ventilated HABP/VABP	80 (64.0)	91 (71.7)	112 (64.0)	120 (68.2)	26 (36.6)	24 (40.0)	41 (75.9)	52 (91.2)
Ventilated HABP	22 (17.6)	28 (22.0)	27 (15.4)	28 (15.9)	9 (12.7)	7 (11.7)	11 (20.4)	18 (31.6)
VABP	58 (46.4)	63 (49.6)	85 (48.6)	92 (52.3)	17 (23.9)	17 (28.3)	30 (55.6)	34 (59.6)
ICU admission at randomization	92 (73.6)	101 (79.5)	175 (100)	176 (100)	38 (53.5)	29 (48.3)	47 (87.0)	54 (94.7)
CPIS score								
<6	34 (27.2)	33 (26.0)	63 (36.0)	48 (27.3)	34 (47.9)	35 (58.3)	18 (33.3)	12 (21.1)
≥6	91 (72.8)	94 (74.0)	112 (64.0)	128 (72.7)	37 (52.1)	25 (41.7)	36 (66.7)	45 (78.9)
Stage of renal impairment based on baseline CrCl (mL/min)								
Normal (≥90)	66 (52.8)	59 (46.5)	108 (61.7)	100 (56.8)	0	0	24 (44.4)	24 (42.1)
Mild (<90 to ≥60)	20 (16.0)	35 (27.6)	29 (16.6)	47 (26.7)	0	0	8 (14.8)	18 (31.6)
Moderate (<60 to ≥30)	31 (24.8)	26 (20.5)	35 (20.0)	24 (13.6)	61 (85.9)	48 (80.0)	19 (35.2)	14 (24.6)
Severe (<30 to ≥15)	8 (6.4)	7 (5.5)	3 (1.7)	5 (2.8)	10 (14.1)	12 (20.0)	3 (5.6)	1 (1.8)
Polymicrobial infection	18 (14.4)	25 (19.7)	38 (21.7)	42 (23.9)	14 (19.7)	16 (26.7)	14 (25.9)	9 (15.8)

[a]Treated with vasopressors within 72 hours of the first study dose or during the study.
APACHE, Acute Physiology and Chronic Health Evaluation; CPIS, clinical pulmonary infection score; CrCl, creatinine clearance; HABP, hospital-acquired bacterial pneumonia; ICU, intensive care unit; IMI/REL, imipenem/cilastatin/relebactam; LRT, lower respiratory tract; MITT, modified intent-to-treat; PIP/TAZ, piperacillin/tazobactam; VABP, ventilator-associated bacterial pneumonia.

- Baseline LRT pathogens in the mMITT population were comparable across the 4 critical illness subgroups and between treatment arms within each small pathogen group (**Table 2**)
  - The most common causative pathogens were Enterobacterales (eg, *Klebsiella pneumoniae* [most common overall] and *Escherichia coli*), *Pseudomonas aeruginosa*, and *Acinetobacter calcoaceticus-baumannii* complex

Table 2. Baseline LRT Pathogens (mMITT Population)[a]

	APACHE II score ≥15 at baseline		ICU at baseline		Moderate/severe renal impairment at baseline		Received vasopressors[b]	
Pathogen, n (%)	IMI/REL N=98	PIP/TAZ N=100	IMI/REL N=148	PIP/TAZ N=147	IMI/REL N=57	PIP/TAZ N=44	IMI/REL N=45	PIP/TAZ N=45
K. pneumoniae	22 (22.4)	21 (21.0)	36 (24.3)	30 (20.4)	20 (35.1)	13 (29.5)	16 (35.6)	7 (15.6)
P. aeruginosa	15 (15.3)	23 (23.0)	26 (17.6)	34 (23.1)	14 (24.6)	6 (13.6)	11 (24.4)	8 (17.8)
A. calcoaceticus-baumannii complex	14 (14.3)	15 (15.0)	28 (18.9)	30 (20.4)	5 (8.8)	7 (15.9)	9 (20.0)	7 (15.6)
E. coli	10 (10.2)	19 (19.0)	25 (16.9)	26 (17.7)	5 (8.8)	8 (18.2)	7 (15.6)	10 (22.2)
Serratia marcescens	5 (5.1)	3 (3.0)	9 (6.1)	3 (2.0)	3 (5.3)	2 (4.5)	0	1 (2.2)
Proteus mirabilis	4 (4.1)	2 (2.0)	3 (2.0)	5 (3.4)	2 (3.5)	2 (4.5)	0	2 (4.4)

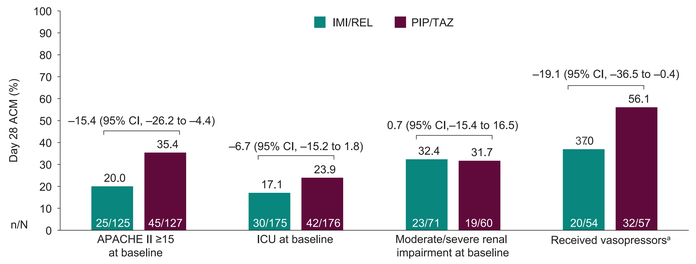
[a]Limited to gram-negative bacillus species with ≥3% frequency in either arm of ≥1 subgroup.
[b]Treated with vasopressors within 72 hours of the first study dose or during the study.
APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; IMI/REL, imipenem/cilastatin/relebactam; LRT, lower respiratory tract; mMITT, microbiological modified intent-to-treat; PIP/TAZ, piperacillin/tazobactam.

Efficacy

Day 28 ACM rates

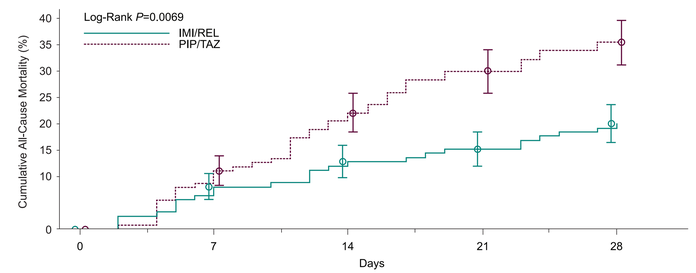
- The Day 28 ACM rate was lower in the IMI/REL treatment arm compared with the PIP/TAZ arm in participants with an APACHE II score ≥15 and in participants who received vasopressors (**Figure 1**)
  - As shown via Kaplan-Meier plot, a survival advantage was observed for participants with APACHE II scores ≥15 who received IMI/REL over PIP/TAZ, with a survival difference being apparent around Day 7 (Log-Rank *P*=0.0069; **Figure 2**)
- In participants with moderate/severe renal impairment and in those in the ICU at baseline, Day 28 ACM rates were similar between treatment arms (**Figure 1**)

Figure 1. Day 28 ACM Among Critically Ill Participants With HABP/VABP (MITT Population)



[a]Treated with vasopressors within 72 hours of the first study dose or during the study.
ACM, all-cause mortality; APACHE, Acute Physiology and Chronic Health Evaluation; HABP, hospital-acquired bacterial pneumonia; ICU, intensive care unit; IMI/REL, imipenem/cilastatin/relebactam; MITT, modified intent-to-treat; PIP/TAZ, piperacillin/tazobactam; VABP, ventilator-associated bacterial pneumonia.

Figure 2. Survival Over Time for Participants With Baseline APACHE II Scores ≥15 (MITT Population)

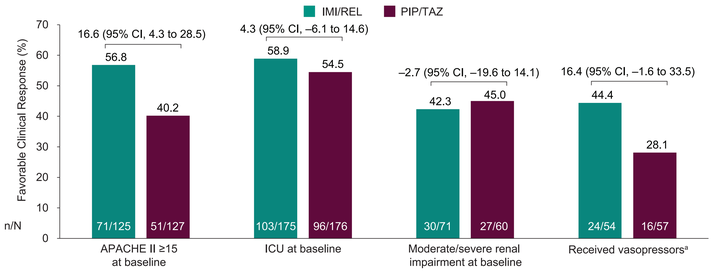


APACHE, Acute Physiology and Chronic Health Evaluation; IMI/REL, imipenem/cilastatin/relebactam; MITT, modified intent-to-treat; PIP/TAZ, piperacillin/tazobactam.

Clinical response rates

- Favorable clinical response rates were numerically higher in the IMI/REL treatment arm compared with the PIP/TAZ arm in participants with an APACHE II score ≥15 and in participants who received vasopressors (**Figure 3**)
- Favorable clinical response rates were similar between treatment arms in the other critically ill subgroups (**Figure 3**)

Figure 3. Clinical Response Among Critically Ill Participants With HABP/VABP (MITT Population)



[a]Treated with vasopressors within 72 hours of the first study dose or during the study.
APACHE, Acute Physiology and Chronic Health Evaluation; HABP, hospital-acquired bacterial pneumonia; ICU, intensive care unit; IMI/REL, imipenem/cilastatin/relebactam; MITT, modified intent-to-treat; PIP/TAZ, piperacillin/tazobactam; VABP, ventilator-associated bacterial pneumonia.

Safety

- Rates of drug-related AEs were generally low in both treatment arms across all four critically ill subgroups (**Table 3**)
- Overall, there were few serious drug-related AEs and few discontinuations due to drug-related AEs or due to serious drug-related AEs

Table 3. Safety Among Critically Ill Participants With HABP/VABP (Participants Who Received ≥1 Dose Of Study Drug)

	APACHE II score ≥15 at baseline		ICU at baseline		Moderate/severe renal impairment at baseline		Received vasopressors[a]	
Adverse events, n (%)	IMI/REL N=127	PIP/TAZ N=129	IMI/REL N=177	PIP/TAZ N=176	IMI/REL N=71	PIP/TAZ N=61	IMI/REL N=54	PIP/TAZ N=58
≥1 adverse event	113 (89.0)	118 (91.5)	157 (88.7)	156 (88.6)	65 (91.5)	54 (88.5)	52 (96.3)	55 (94.8)
Drug-related[b] adverse events	16 (12.6)	8 (6.2)	8 (4.5)	11 (6.3)	14 (19.7)	9 (14.8)	2 (3.7)	1 (1.7)
Serious adverse event	41 (32.3)	61 (47.3)	50 (28.2)	61 (34.7)	36 (50.7)	25 (41.0)	30 (55.6)	45 (77.6)
Serious drug-related adverse events	3 (2.4)	1 (0.8)	2 (1.1)	1 (0.6)	2 (2.8)	1 (1.6)	0	0
Discontinued drug due to an adverse event	7 (5.5)	13 (10.1)	8 (4.5)	14 (8.0)	7 (9.9)	7 (11.5)	5 (9.3)	13 (22.4)
Discontinued drug due to a drug-related adverse event	3 (2.4)	0	1 (0.6)	1 (0.6)	2 (2.8)	2 (3.3)	0	0
Discontinued drug due to a serious adverse event	6 (4.7)	13 (10.1)	7 (4.0)	12 (6.8)	5 (7.0)	6 (9.8)	5 (9.3)	12 (20.7)
Discontinued drug due to a serious drug-related adverse event	2 (1.6)	0	1 (0.6)	0	1 (1.4)	1 (1.6)	0	0

[a]Treated with vasopressors within 72 hours of the first study dose or during the study.
[b]Determined by the investigator to be related to the drug.
APACHE, Acute Physiology and Chronic Health Evaluation; HABP, hospital-acquired bacterial pneumonia; ICU, intensive care unit; IMI/REL, imipenem/cilastatin/relebactam; PIP/TAZ, piperacillin/tazobactam; VABP, ventilator-associated bacterial pneumonia.

Conclusions

- In the subgroup with APACHE II scores ≥15, the Day 28 ACM rate was lower and the clinical response rate was higher in the IMI/REL treatment arm compared with the PIP/TAZ arm, with a 95% confidence interval that excluded zero, suggesting a potential advantage for IMI/REL in critically ill patients
- In the subgroup who received vasopressors, a post-hoc defined subgroup, the Day 28 ACM rate was lower in the IMI/REL treatment arm compared with the PIP/TAZ arm, with a 95% confidence interval that excluded zero, also suggesting a potential advantage for IMI/REL in critically ill patients
- Regardless of the criteria used to define critical illness, the efficacy and safety trends between treatment arms were similar
- IMI/REL is an efficacious treatment option for critically ill patients with HABP/VABP, including those with APACHE II scores ≥15, in the ICU, with moderate/severe renal impairment at baseline, or who received vasopressors

Disclosures

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