You follow the clues. Now discover RECARBRIO

A carbapenem/novel BLI combination

When you suspect certain CRE, including KPC-producing Enterobacterales, or CR *P. aeruginosa* but you do not have time to wait for confirmation, consider RECARBRIO.[1]

1 Prior treatment with a carbapenem

2 Admitted from LTC facility

3 Recent antibiogram shows Enterobacteriaceae with KPCs and CR *P. aeruginosa*

4 Patient declining on current antibiotic treatment

Not an actual patient.

BLI, beta-lactamase inhibitor; **CR**, carbapenem-resistant; **CRE**, carbapenem-resistant Enterobacterales; **KPC**, *Klebsiella pneumoniae* carbapenemase; **LTC**, long-term care; *P. aeruginosa, Pseudomonas aeruginosa.*

Reference: 1. Young K, Painter RE, Raghoobar SL, et al. In vitro studies evaluating the activity of imipenem in combination with relebactam against *Pseudomonas aeruginosa.* BMC Microbiol. 2019;19(1):150. doi:10.1186/s12866-019-1522-7

MSD

RECARBRIO™ (imipenem, cilastatin, and relebactam) for injection 1.25 g

Mortality Nearly Doubles in Patients With Infections Caused by CR and MDR Pathogens[1,2]

Infections caused by CR and MDR pathogens exacerbate an already elevated risk of mortality[1-3]

Klebsiella pneumoniae

Pooled mortality

~21% carbapenem-susceptible (n=2239)

vs

~42% carbapenem-resistant (n=2462)

Pseudomonas aeruginosa

30-day mortality

~25% non-MDR (n=2388)

vs

~45% MDR (n=813)

K. pneumoniae: A systematic review and meta-analysis of 62 qualifying studies published from 1999 to 2015, 22 of which included CSKP infections, estimated the mortality of patients infected with CRKP (including KPC and VIM producers). The analysis involved 4701 patients, of whom 2462 had a CRKP infection.

P. aeruginosa: A meta-analysis of qualifying studies between 2006 and 2016 evaluated the association of MDR, the presence of the *bla*SPM-1 gene, and the risk of mortality in patients with *P. aeruginosa* infection. MDR was defined as resistance to at least 3 different classes of antimicrobials, including carbapenems, antipseudomonal cephalosporins, fluoroquinolones, aminoglycosides, and beta-lactams with inhibitors.

***bla*SPM**, beta-lactamase SPM; **CR**, carbapenem-resistant; **CRKP**, carbapenem-resistant *Klebsiella pneumoniae*; **CSKP**, carbapenem-susceptible *Klebsiella pneumoniae*; **KPC**, *Klebsiella pneumoniae* carbapenemase; **MDR**, multidrug-resistant; **VIM**, Verona integron-encoded metallo-beta-lactamase.

References: 1. Xu L, Sun X, Ma X. Systematic review and meta-analysis of mortality of patients infected with carbapenem-resistant *Klebsiella pneumoniae*. *Ann Clin Microbiol Antimicrob*. 2017;16(1):18. doi: 10.1186/s12941-017-0191-3 **2.** de Matos ECO, Andriolo RB, Rodrigues YC, et al. Mortality in patients with multidrug-resistant *Pseudomonas aeruginosa* infections: a meta-analysis. *Rev Soc Bras Med Trop*. 2018;51(4):415-420. doi: 10.1590/0037-8682-0506-2017 **3.** Shi Q, Huang C, Xiao T, Wu Z, Xiao Y. A retrospective analysis of *Pseudomonas aeruginosa* bloodstream infections: prevalence, risk factors, and outcome in carbapenem-susceptible and -nonsusceptible infections. *Antimicrob Resist Infect Control*. 2019;8:68. https://doi.org/10.1186/s13756-019-0520-8

RECARBRIO: Imipenem/Cilastatin/Relebactam

A broad-coverage carbapenem/novel BLI combination[1]

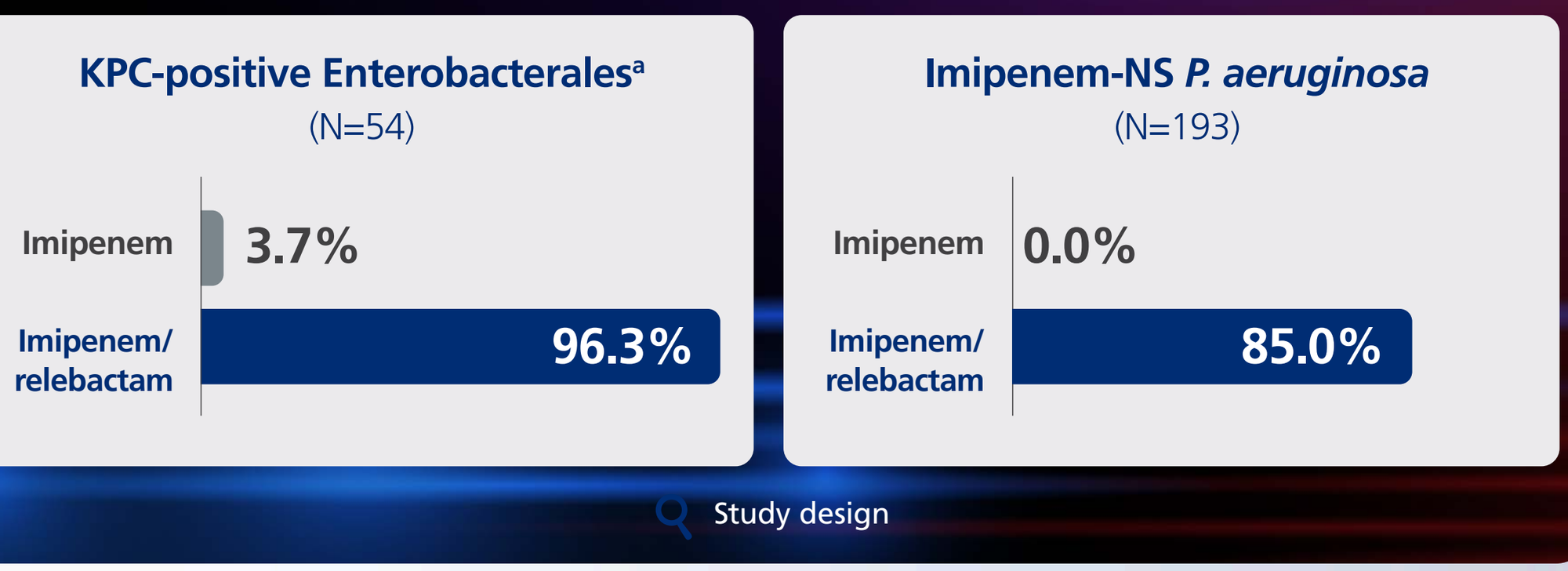
Imipenem / Cilastatin

+

Relebactam

A novel BLI that restores the activity of imipenem

Percent of isolates susceptible *in vitro*[1]



Study design

[a]Non-Proteeae Enterobacteriaceae species.

The clinical significance of *in vitro* data is unknown.

RECARBRIO is not active against metallo-beta-lactamases, oxacillinases with carbapenemase activity, or certain alleles of GES.

BLI, beta-lactamase inhibitor; **KPC**, *Klebsiella pneumoniae* carbapenemase; **NS**, nonsusceptible; **GES**, Guiana-extended-spectrum beta-lactamase.

References: 1. Karlowsky JA, Lob SH, Kazmierczak KM, Young K, Motyl MR, Sahm DF. In vitro activity of imipenem-relebactam against Enterobacteriaceae and *Pseudomonas aeruginosa* isolated from intraabdominal and urinary tract infection samples – SMART Surveillance United States 2015-2017. *J Glob Antimicrob Resist*. 2020;21:223-228. https://doi.org/10.1016/j.jgar.2019.10.028 **2.** SMART Data on File, 2018.

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RECARBRIO: Imipenem/Cilastatin/Relebactam

A broad-coverage carbapenem/novel BLI combination[1]

Imipenem / Cilastatin

+

Relebactam

A novel BLI that restores the activity of imipenem

Percent of isolates susceptible *in vitro*[1]

Study design

Study design:

The SMART program was initiated by Merck in 2002 to monitor the *in vitro* susceptibility of clinical aerobic and facultative Gram-negative bacterial isolates, enabling longitudinal analyses to determine if susceptibility patterns change over time.[2]

The activity of imipenem/relebactam, as assessed against Gram-negative bacilli from intra-abdominal infections and urinary tract infections submitted to the SMART global surveillance program in 26 participating hospital laboratories in 18 states in the United States from 2015 to 2017.[1]

The limitations of this study included a lack of identifiable patient-specific information regarding clinical presentation or antimicrobial therapy, which would have allowed differentiation between complicated and uncomplicated intra-abdominal infections and urinary tract infections and more detailed stratified analyses. Generalizability is limited since the described resistance patterns are based on data from 26 hospitals in 18 states in the United States. Since the majority of hospitals participating in the SMART surveillance program are tertiary care centers, resistance rates seen here are likely higher than would be found in smaller hospitals and in the community.[1]

BLI, beta-lactamase inhibitor; **KPC**, *Klebsiella pneumoniae* carbapenemase; **NS**, nonsusceptible; **GES**, Guiana-extended-spectrum beta-lactamase.

References: 1. Karlowsky JA, Lob SH, Kazmierczak KM, Young K, Motyl MR, Sahm DF. In vitro activity of imipenem-relebactam against Enterobacteriaceae and *Pseudomonas aeruginosa* isolated from intraabdominal and urinary tract infection samples – SMART Surveillance United States 2015-2017. *J Glob Antimicrob Resist*. 2020;21:223-228. https://doi.org/10.1016/j.jgar.2019.10.028 **2.** SMART Data on File, 2018.

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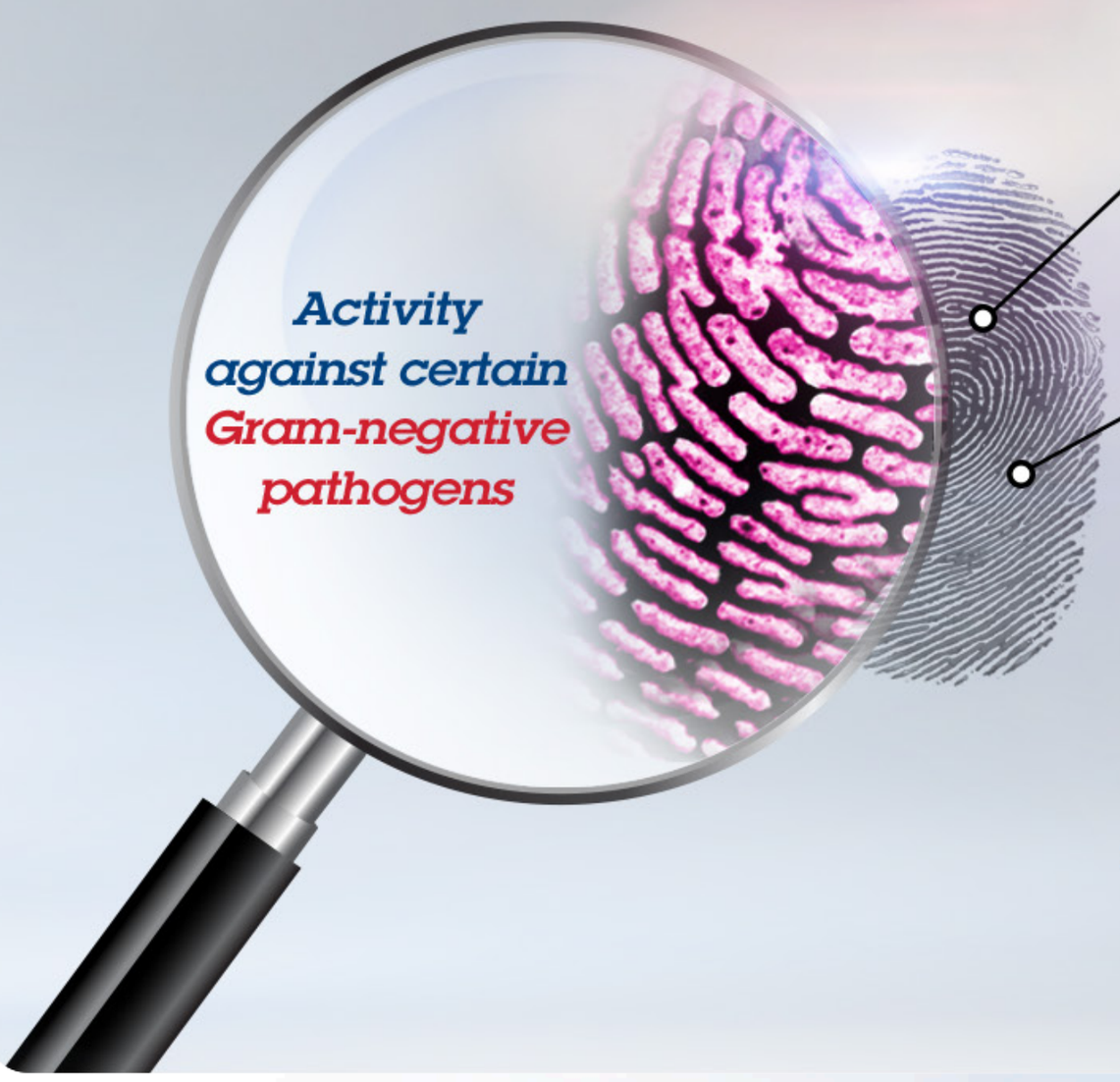
RECARBRIO: Antimicrobial Coverage[1]



Enterobacteriaceae with some
• KPCs • ESBLs

+

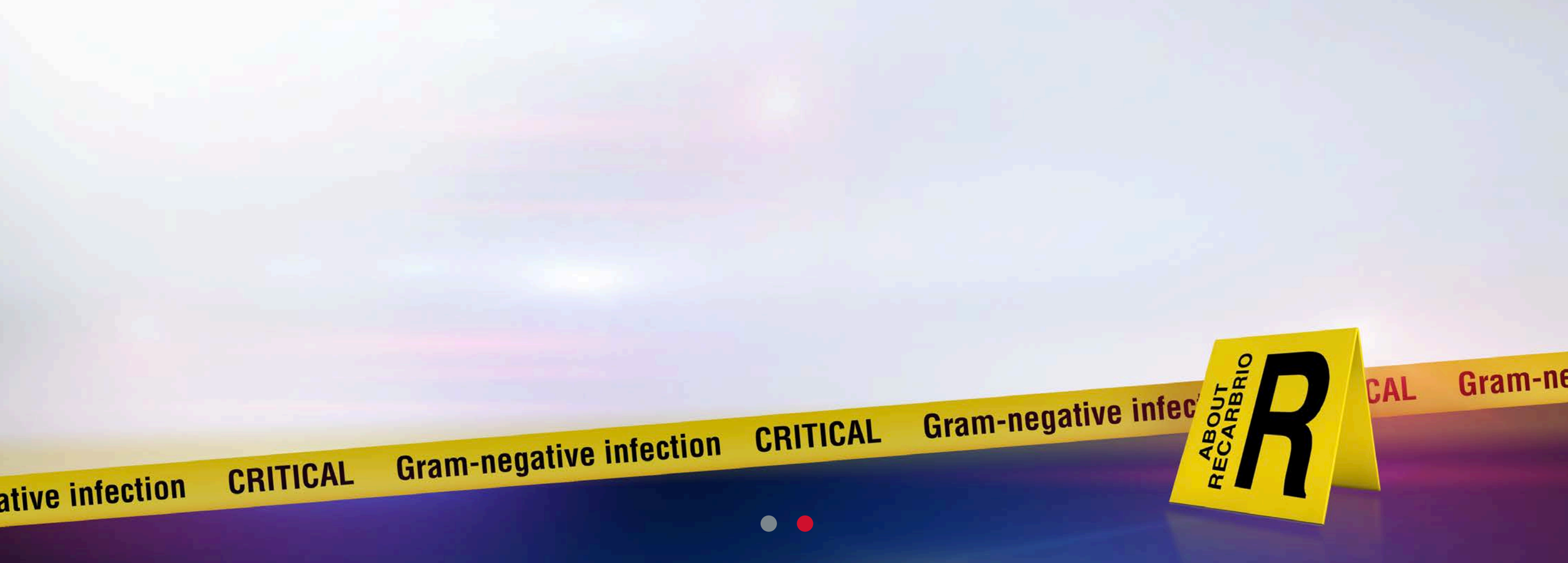
P. aeruginosa isolates with the most prevalent mechanisms of resistance
- Upregulation of AmpC or PDC
- Loss of outer membrane porin
- Upregulation of efflux pumps

+

Some Gram-positive aerobic bacteria have also been shown to be susceptible *in vitro*

RECARBRIO is not active against metallo-beta-lactamases, oxacillinases with carbapenemase activity, or certain alleles of GES.

The clinical significance of *in vitro* data is unknown.



AmpC, Ambler class beta-lactamase; **ESBLs**, extended-spectrum beta-lactamases; **GES**, Guiana-extended-spectrum; **KPCs**, *Klebsiella pneumoniae* carbapenemases; ***P. aeruginosa***, *Pseudomonas aeruginosa;* **PDC**, *Pseudomonas*-derived cephalosporinase.

Reference: 1. RECARBRIO. Summary of product characteristics. MERCK SHARP & DOHME LLC February 2021

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Supporting the Case for RECARBRIO

RESTORE-IMI 2: a multinational, noninferiority, randomized, double-blind, active-controlled, phase 3 trial in adult patients with HABP or VABP[1]

Screening
537 patients with HABP/VABP

RANDOMIZED 1:1
Stratified by pneumonia type (HABP, VABP/vHABP) and APACHE II score (<15, ≥15)

RECARBRIO (n=264)
(500 mg imipenem/500 mg cilastatin/
250 mg relebactam) IV every 6 hours for 30 min
Treatment duration:
7-14 days (no oral switch)

PIP/TAZ (n=267)
4 g/500 mg IV every 6 hours for 30 min
Treatment duration:
7-14 days (no oral switch)

PRIMARY EFFICACY END POINT: Day 28 all-cause mortality in MITT population[a]

[a]MITT population is defined as all randomized participants who received at least 1 dose of trial treatment and whose baseline Gram stain did not show only Gram-positive cocci.

APACHE II, Acute Physiology and Chronic Health Evaluation II; **HABP**, hospital-acquired bacterial pneumonia; **IV**, intravenous; **MITT**, modified intent-to-treat; **PIP/TAZ**, piperacillin/tazobactam; **VABP**, ventilator-associated bacterial pneumonia; **vHABP**, ventilated hospital-acquired bacterial pneumonia.

Reference: 1. Titov I, Wunderink RG, Roquilly A, et al. A randomized, double-blind, multicenter trial comparing efficacy and safety of imipenem/cilastatin/relebactam versus piperacillin/tazobactam in adults with hospital-acquired or ventilator-associated bacterial pneumonia (RESTORE-IMI 2 Study). *Clin Infect Dis.* 2020;ciaa803. doi.org/10.1093/cid/ciaa803

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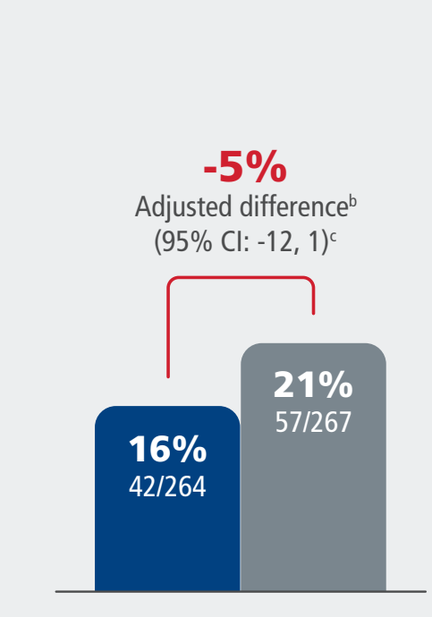
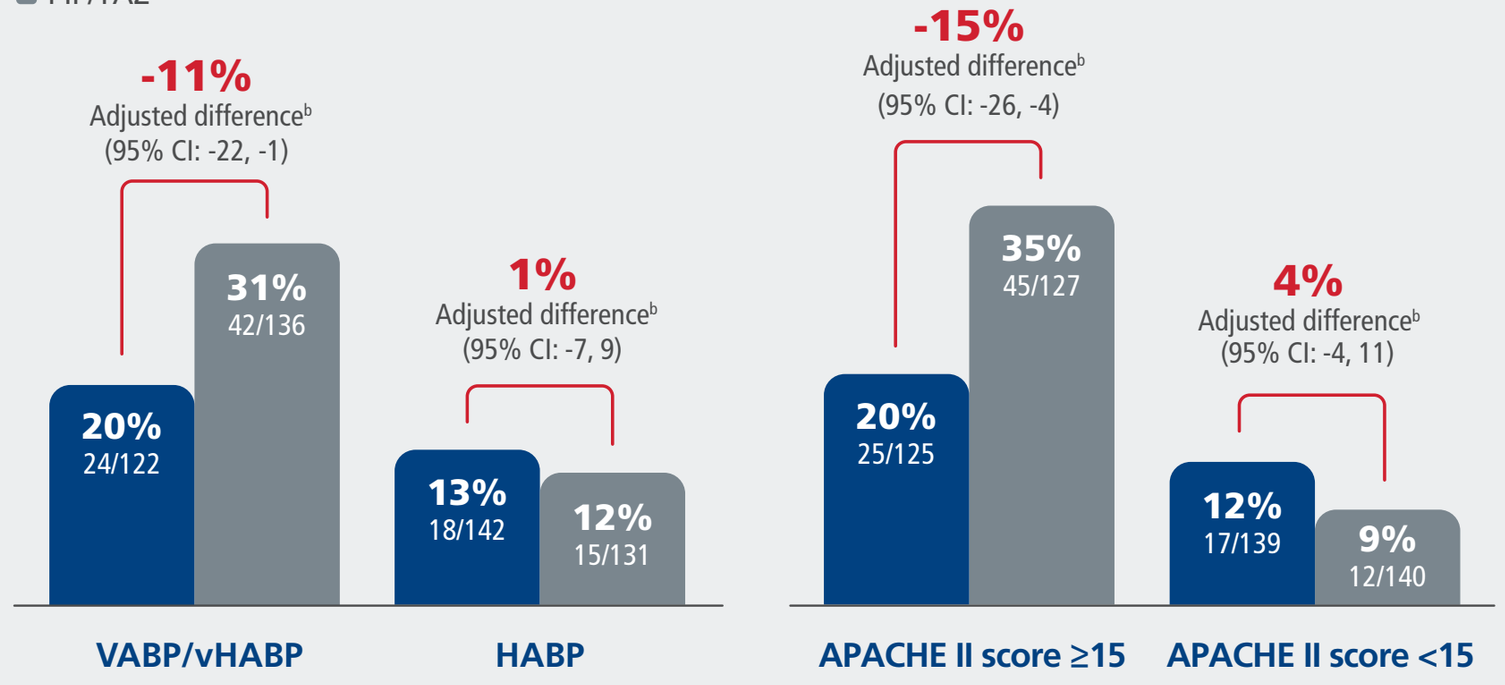
RECARBRIO Achieved the Primary End Point of Noninferiority vs PIP/TAZ in Day 28 All-Cause Mortality in Adult Patients With HABP or VABP in the MITT Population[1,2,α]

Primary end point



Subgroup analyses



RECARBRIO demonstrated a favorable response in certain high-risk subgroups:

- Ventilated HABP and VABP patients
- Patients with APACHE II scores ≥15

[a]MITT population is defined as all randomized participants who received at least 1 dose of trial treatment and whose baseline Gram stain did not show only Gram-positive cocci.

[b]Adjusted differences and confidence intervals stratified by pneumonia type (nonventilated HABP vs ventilated HABP/VABP) and by baseline APACHE II score (<15 vs ≥15) using the Miettinen & Nurminen method.

[c]The upper bound of the CI is less than the predefined noninferiority margin of 10 percentage points, indicating success for the noninferiority hypothesis.

APACHE II, Acute Physiology and Chronic Health Evaluation II; **HABP**, hospital-acquired bacterial pneumonia; **MITT**, modified intent-to-treat; **PIP/TAZ**, piperacillin/tazobactam; **VABP**, ventilator-associated bacterial pneumonia; **vHABP**, ventilated hospital-acquired bacterial pneumonia.

References: 1. Titov I, Wunderink RG, Roquilly A, et al. A randomized, double-blind, multicenter trial comparing efficacy and safety of imipenem/cilastatin/relebactam versus piperacillin/tazobactam in adults with hospital-acquired or ventilator-associated bacterial pneumonia (RESTORE-IMI 2 Study). *Clin Infect Dis.* 2020;ciaa803. doi:10.1093/cid/ciaa803 **2.** Titov I, Wunderink RG, Roquilly A, et al. A randomized, double-blind, multicenter trial comparing efficacy and safety of imipenem/cilastatin/relebactam versus piperacillin/tazobactam in adults with hospital-acquired or ventilator-associated bacterial pneumonia (RESTORE-IMI 2 Study) [supplementary appendix]. *Clin Infect Dis.* 2020;ciaa803. Accessed July 28, 2021. https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa803/5891450#supplementary-data

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RESTORE-IMI 2: Adverse Events[1]

Summary of adverse events in patients with HABP or VABP receiving RECARBRIO or PIP/TAZ and the 14-day follow-up period in the safety population[1,a]

Patients With AEs	RECARBRIO (n=266[b]) n (%)	PIP/TAZ (n=269[b]) n (%)
At least 1 AE	226 (85)	233 (86.6)
Drug-related[c] AEs	31 (11.7)	26 (9.7)
Serious AEs	71 (26.7)	86 (32.0)
Serious drug-related[c] AEs	3 (1.1)	2 (0.7)
Deaths	40 (15.0)	57 (21.2)
Drug-related[c] deaths	0 (0.0)	0 (0.0)
Discontinued drug due to AE	15 (5.6)	22 (8.2)
Discontinued drug due to drug-related[c] AE	6 (2.3)[d]	4 (1.5)[e]

- The incidence of drug-related AEs was generally similar between treatment arms[1]
- The most commonly reported drug-related AEs with RECARBRIO were diarrhea, increased aspartate aminotransferase, and increased alanine aminotransferase, each with an incidence of 2.3%[1]

[a]The safety population included all patients who received ≥1 dose of study treatment.

[b]Overall values indicate the total number of patients in the safety population of the particular treatment arm.

[c]AE causality in relation to the study therapy was determined by the investigator.

[d]Drug-related AEs that led to study therapy discontinuation were as follows: liver function abnormalities (n=2), rash (n=2), and thrombocytopenia/decreased platelet count (n=2).

[e]Drug-related AEs that led to study therapy discontinuation were as follows: liver function abnormalities (n=1),hallucinations (n=1), generalized tonic-clonic seizure (n=1), and pyrexia (n=1).

AE, adverse event; **HABP**, hospital-acquired bacterial pneumonia; **PIP/TAZ**, piperacillin/tazobactam; **VABP**, ventilator-associated bacterial pneumonia.

Reference: 1. Titov I, Wunderink RG, Roquilly A, et al. A randomized, double-blind, multicenter trial comparing efficacy and safety of imipenem/cilastatin/relebactam versus piperacillin/tazobactam in adults with hospital-acquired or ventilator-associated bacterial pneumonia (RESTORE-IMI 2 Study). *Clin Infect Dis*. 2020;ciaa803. doi:10.1093/cid/ciaa803

Supporting the Case for RECARBRIO

RESTORE-IMI 1: a randomized, noninferential, double-blind, active-controlled phase 3 trial[1]

AT BASELINE

Hospitalized adult patients with cUTI, cIAI, or HABP/VABP caused by imipenem-nonsusceptible but colistin- and imipenem/relebactam-susceptible Gram-negative bacterial infection

Randomized 2:1 (N=47)

RECARBRIO
(500 mg imipenem/500 mg cilastatin/ 250 mg relebactam) IV Q6H
(N=31)

Colistin
(150 mg CBA[a]) IV Q12H
+
Imipenem/cilastatin
(500 mg/500 mg) IV Q6H
(N=16)

Primary end point

Composite favorable overall response (mMITT population) measured by:

- All-cause mortality through day 28 post-randomization in patients with HABP/VABP (N=11)
- Clinical response at day 28 post-randomization in patients with cIAI (N=4)
- Composite clinical and microbiologic response in patients with cIAI with cUTI (N=16)

Secondary end points

- Clinical response at day 28 post-randomization (mMITT population)
- 28-day all-cause mortality (mMITT population)
- Treatment-emergent nephrotoxicity (safety population)

APACHE II score >15 in 29% of mMITT patient population.

Study Limitations

This was a noninferential, descriptive, estimation trial without formal statistical testing for efficacy end points. The trial had several limitations, including the small sample size. Sample size was based on logistical feasibility and not statistical considerations.

The trial was intended to generate limited clinical data in the target population as part of a streamlined drug development program.

Minimum treatment duration was 5 days (cIAI, cUTI) or 7 days (HABP/VABP), with a 21-day maximum.

[a]Corresponding to ~360 mg colistimethate sodium or ~4.5 million IU, after a loading dose of 300 mg colistin base activity.

CBA, colistin base activity; **cIAI**, complicated intra-abdominal infection; **cUTI**, complicated urinary tract infection; **HABP**, hospital-acquired bacterial pneumonia; **mMITT**, microbiologic modified intent-to-treat; **VABP**, ventilator-associated bacterial pneumonia.

Reference: 1. Motsch J, Murta De Oliveira C, Stus V, et al. RESTORE-IMI 1: a multicenter, randomized, double-blind trial comparing efficacy and safety of imipenem/relebactam vs colistin plus imipenem in patients with imipenem-nonsusceptible bacterial infections. *Clin Infect Dis*. 2020;70(9):1799-1008. doi:10.1093/cid/ciz530

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Results From RESTORE-IMI 1, a Randomized, Noninferential, Double-Blind Trial[1]

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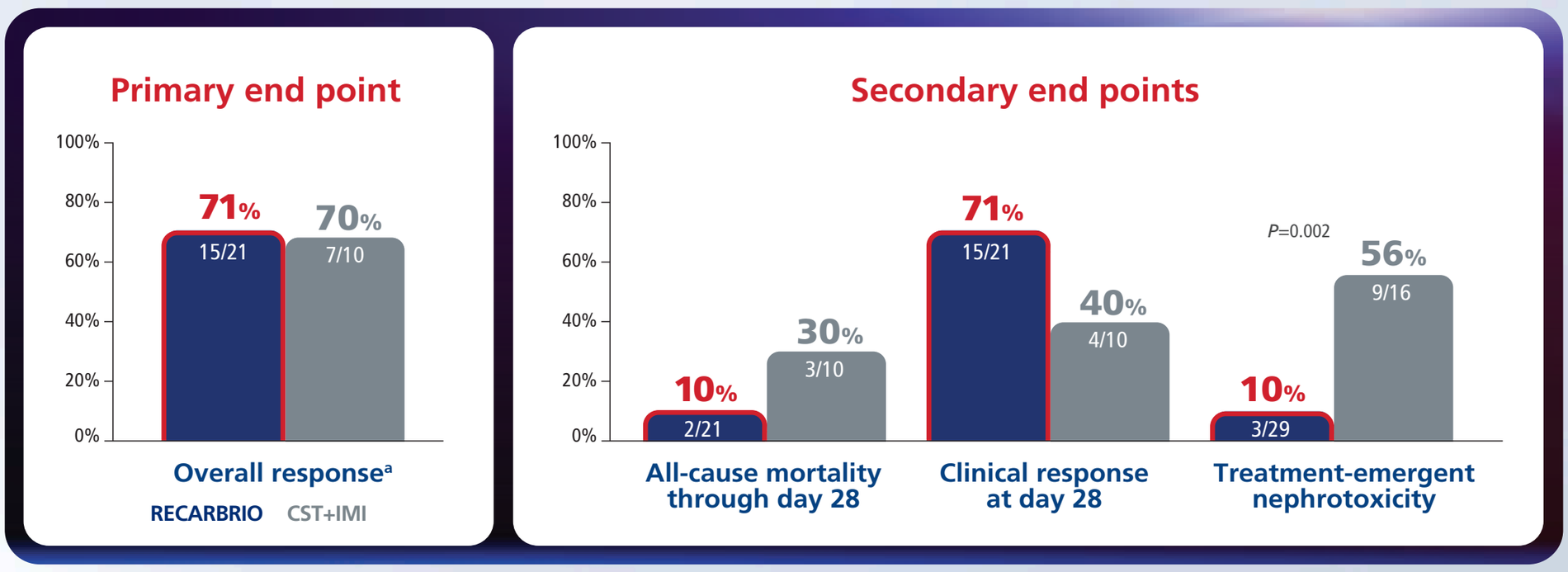
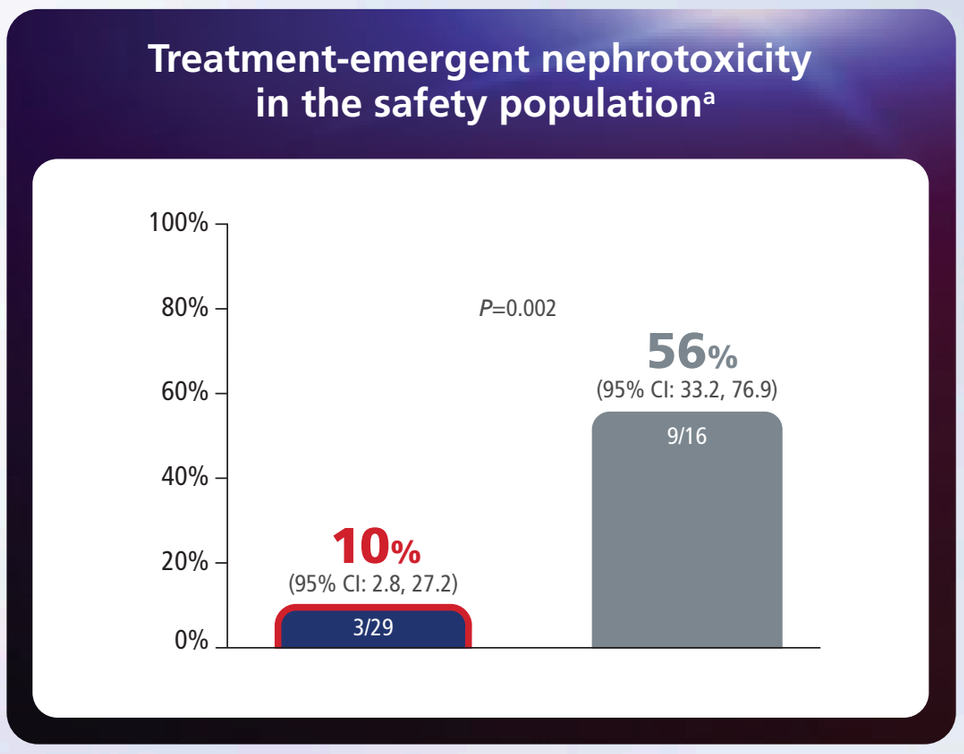


[a]Primary end point: Overall response

- All-cause mortality through day 28 post-randomization in patients with HABP/VABP
- Clinical response at day 28 post-randomization for patients with cIAI
- Composite clinical and microbiologic response at early follow-up for patients with cUTI



[a]Comprised all randomized patients who received ≥1 dose of study treatment.

A lower percentage of patients on RECARBRIO had treatment-emergent nephrotoxicity compared with patients on colistin+imipenem.

CI, confidence interval; **cIAI**, complicated intra-abdominal infection; **CrCl**, creatinine clearance; **cUTI**, complicated urinary tract infection; **HABP**, hospital-acquired bacterial pneumonia; **IMI**, imipenem; **VABP,** ventilator-associated bacterial pneumonia.

Reference: 1. Motsch J, Murta De Oliveira C, Stus V, et al. RESTORE-IMI 1: a multicenter, randomized, double-blind trial comparing efficacy and safety of imipenem/relebactam vs colistin plus imipenem in patients with imipenem-nonsusceptible bacterial infections. *Clin Infect Dis.* 2020;70(9):1799-1808. doi:10.1093/cid/ciz530

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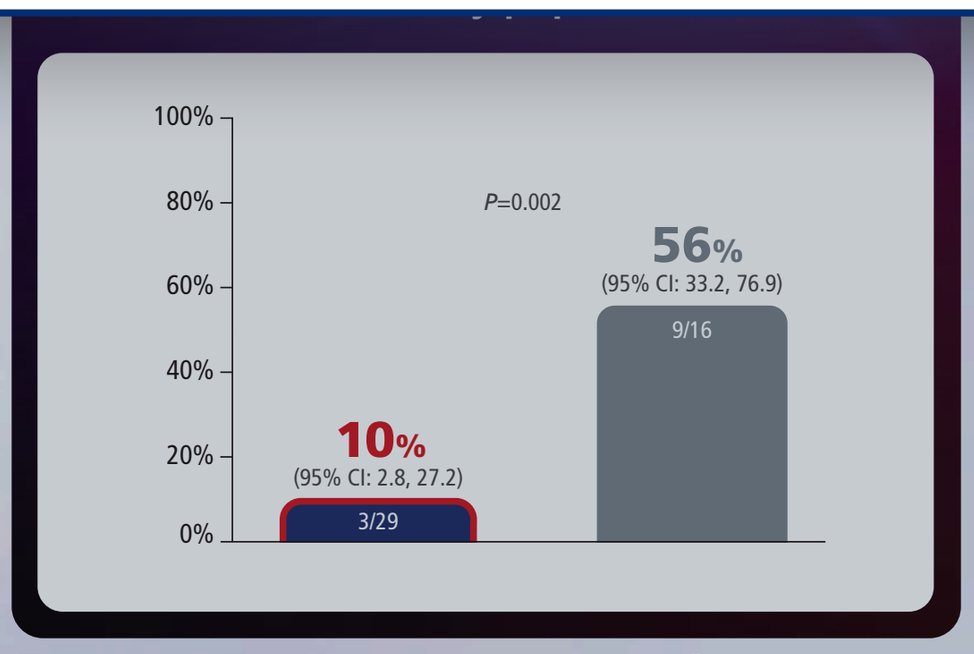
The trial was intended to generate limited clinical data in the target population as part of a streamlined drug development program.

[a]Primary end point: Overall response

Primary analysis population:

Microbiologic modified intent-to-treat, determined by meeting microbiologic entry criteria, receiving ≥1 dose of study drug, and cultures collected within 1 week of enrollment confirming ≥1 qualifying Gram-negative pathogen from the primary infection site.[1]



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Reference: 1. Motsch J, Murta De Oliveira C, Stus V, et al. RESTORE-IMI 1: a multicenter, randomized, double-blind trial comparing efficacy and safety of imipenem/relebactam vs colistin plus imipenem in patients with imipenem-nonsusceptible bacterial infections. *Clin Infect Dis.* 2020;70(9):1799-1808. doi:10.1093/cid/ciz530

Results From RESTORE-IMI 1, a Randomized, Noninferential, Double-Blind Trial[1]

Study Limitations

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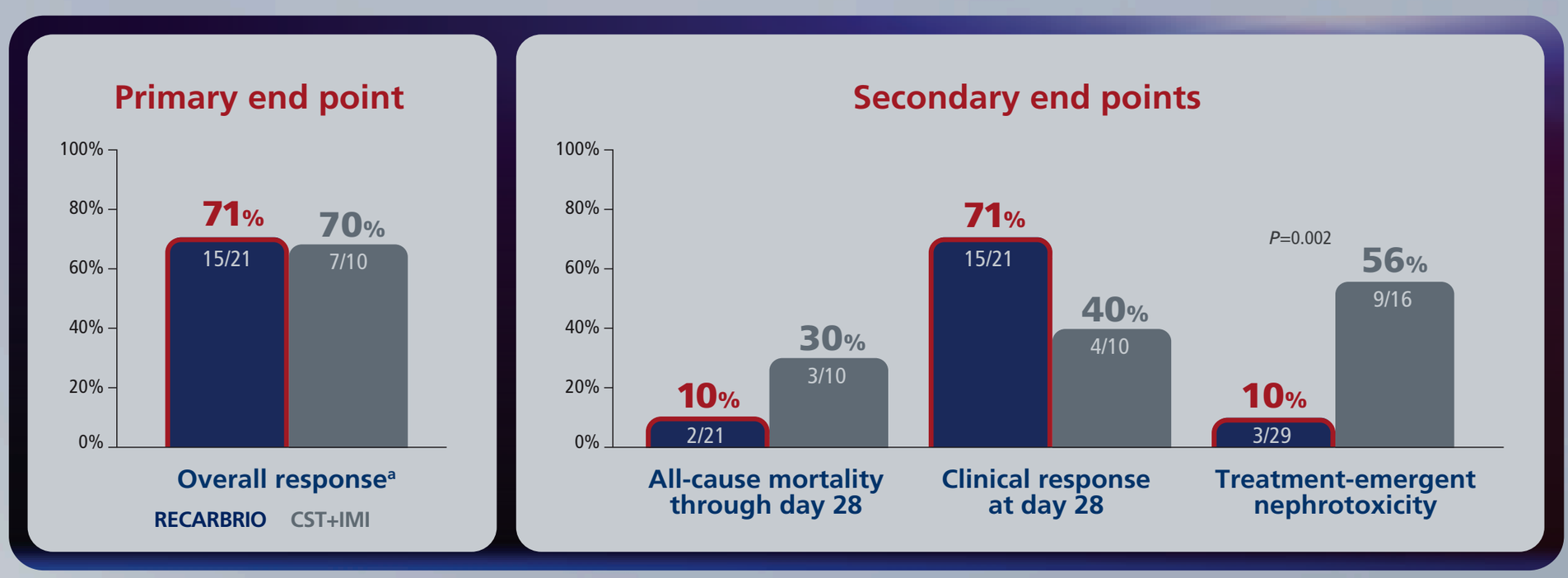
The trial was intended to generate limited clinical data in the target population as part of a streamlined drug development program.

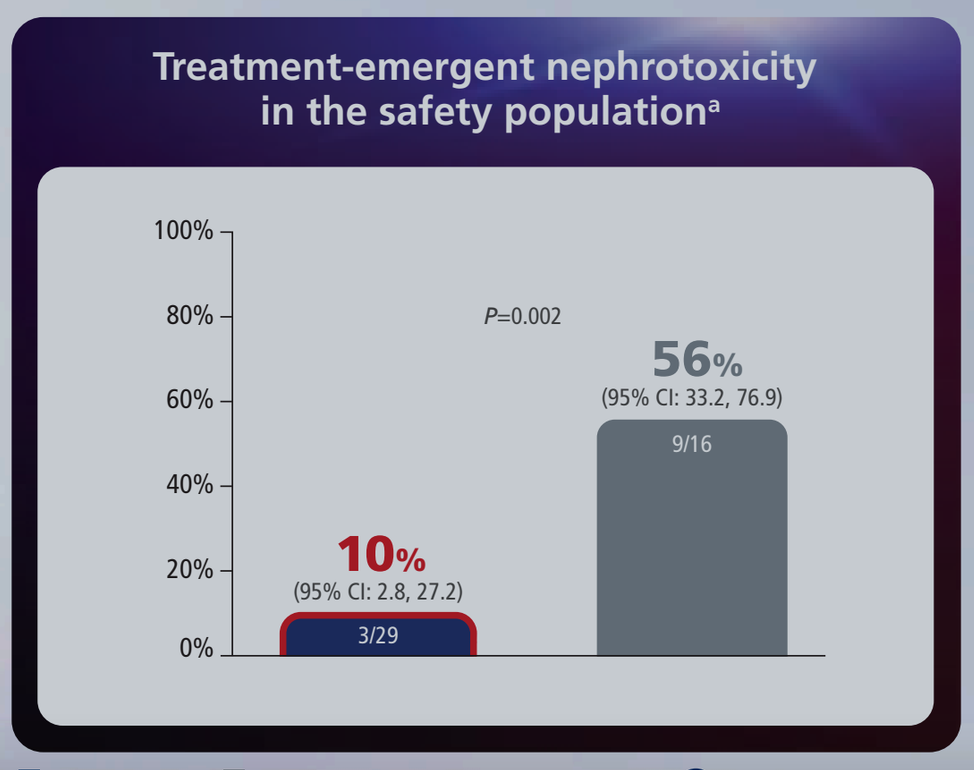


■ RECARBRIO ■ Colistin+imipenem/cilastatin

Study design

[a]Primary end point: Overall response

- All-cause mortality through day 28 post-randomization in patients with HABP/VABP
- Clinical response at day 28 post-randomization for patients with cIAI
- Composite clinical and microbiologic response at early follow-up for patients with cUTI



■ RECARBRIO ■ Colistin+imipenem/cilastatin

Study design

Treatment-emergent nephrotoxicity was assessed by protocol-defined criteria[1]:

- In patients with normal baseline renal function (serum creatinine [Cr] <1.2 mg/dL), treatment-emergent nephrotoxicity was defined as doubling of serum Cr up to >1.2 mg/dL or a ≥50% reduction in creatinine clearance (CrCl)
- In patients with preexisting renal dysfunction (serum Cr ≥1.2 mg/dL), treatment-emergent nephrotoxicity was defined as an increase in serum Cr by ≥1 mg/dL, a ≥20% reduction in CrCl, or a need for renal replacement therapy

CI, confidence interval; **cIAI**, complicated intra-abdominal infection; **CrCl**, creatinine clearance; **cUTI**, complicated urinary tract infection; **HABP**, hospital-acquired bacterial pneumonia; **IMI**, imipenem; **VABP,** ventilator-associated bacterial pneumonia.

Reference: 1. Motsch J, Murta De Oliveira C, Stus V, et al. RESTORE-IMI 1: a multicenter, randomized, double-blind trial comparing efficacy and safety of imipenem/relebactam vs colistin plus imipenem in patients with imipenem-nonsusceptible bacterial infections. *Clin Infect Dis.* 2020;70(9):1799-1808. doi:10.1093/cid/ciz530

Adverse Events

Treatment-emergent adverse events occurring in ≥10% of patients receiving RECARBRIO or colistin+imipenem/cilastatin during therapy and the 14-day follow-up period in the safety population[1,a]

	RECARBRIO (N=31) n (%)	Colistin+imipenem/cilastatin (N=16) n (%)
Pyrexia	4 (13)	2 (13)
Increased aspartate aminotransferase	3 (10)	3 (19)
Increased alanine aminotransferase	2 (7)	3 (19)
Nausea	2 (7)	3 (19)
Decreased creatinine renal clearance	2 (7)	2 (13)
Increased γ-glutamyltransferase	1 (3)	2 (13)
Increased blood alkaline phosphatase	1 (3)	2 (13)
Infusion site phlebitis	1 (3)	2 (13)
Dizziness	0 (0.0)	2 (13)
Increased blood bilirubin	0 (0.0)	2 (13)
Increased blood creatinine	0 (0.0)	4 (25)
Oral hypoesthesia	0 (0.0)	2 (13)

[a]The safety population comprised all randomized patients with ≥1 dose of study treatment according to the actual treatment received.

Drug-related AEs were reported in 16% (5/13) of patients treated with RECARBRIO vs 31% (5/16) of patients treated with colistin+imipenem/cilastatin, and serious AEs were reported in 10% (3/31) vs 31% (5/16), respectively.[1]

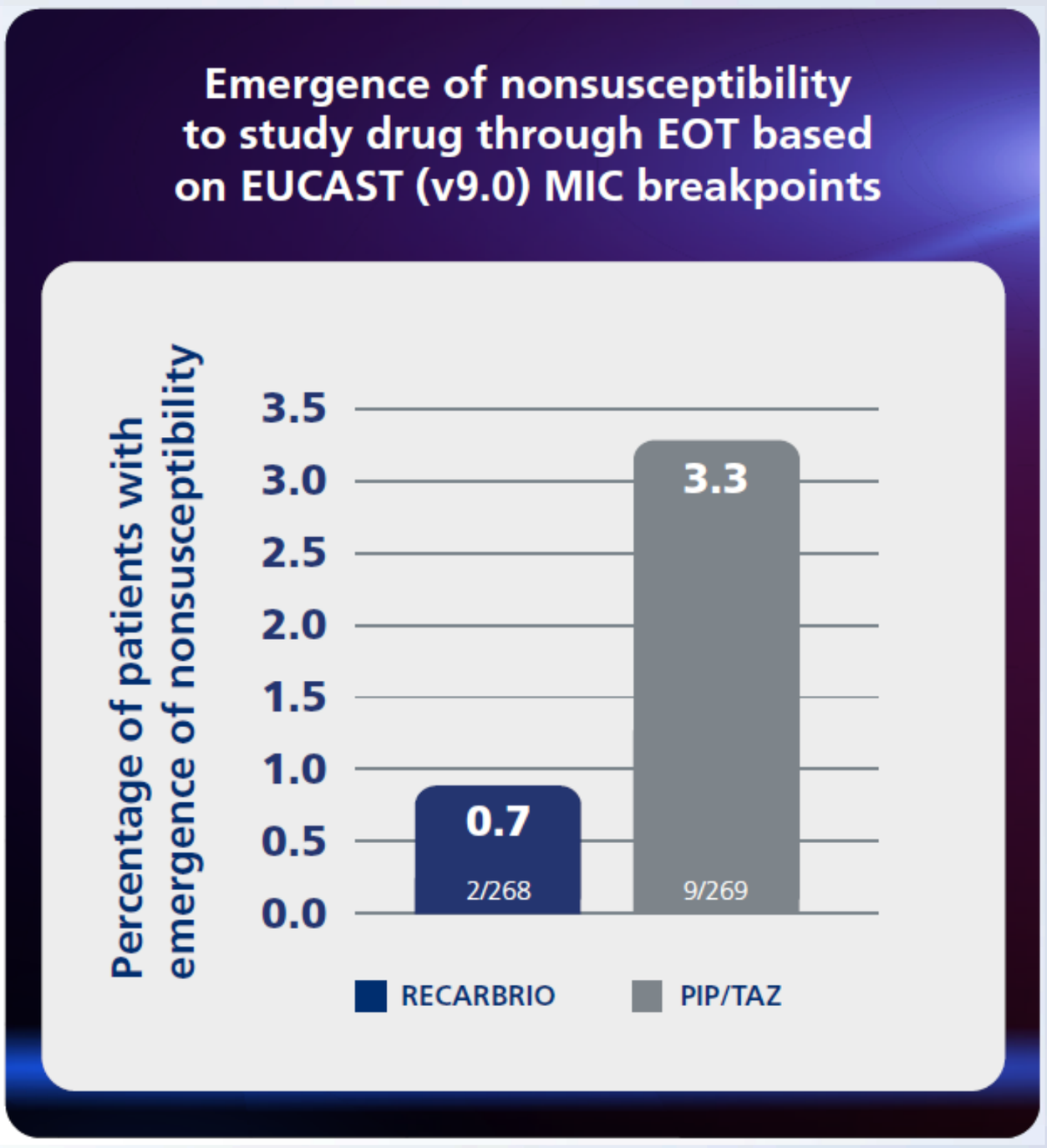
AE, adverse event.

Reference: 1. Motsch J, De Oliveira CM, Stus V, et al. RESTORE-IMI 1: a multicenter, randomized, double-blind trial comparing efficacy and safety of imipenem/relebactam vs colistin plus imipenem in patients with imipenem–nonsusceptible bacterial infections. *Clin Infect Dis*. 2020;70(9):1799-1808. doi:10.1093/cid/ciz530

In RESTORE-IMI 1 and RESTORE-IMI 2

Development of Nonsusceptibility to RECARBRIO While on Treatment Was Low[1,2]

Emergence of nonsusceptibility was uncommon in RESTORE-IMI 2, and emergence was numerically lower in the RECARBRIO treatment group[1,a]



- There were no instances of treatment-emergent nonsusceptibility to RECARBRIO in the RESTORE-IMI 1 trial[2]

[a]LRT isolates from patients in RESTORE-IMI 2 (N=537) were analyzed for emergence of resistance. Resistance is defined as participants with a baseline LRT pathogen susceptible to the administered IV study drug from whom a nonsusceptible isolate of the same species was isolated through EOT.

CLSI, Clinical and Laboratory Standards Institute; **EOT**, end of therapy; **EUCAST**, European Committee on Antimicrobial Susceptibility Testing; **LRT**, lower respiratory tract; **MIC**, minimum inhibitory concentration; **PIP/TAZ,** piperacillin/tazobactam.

References: 1. Young K, Hilbert D, Kazmierczak K, et al. Presented at ASM Microbe Online; June 18-22, 2020. **2.** Motsch J, De Oliveira CM, Stus V, et al. RESTORE-IMI 1: a multicenter, randomized, double-blind trial comparing efficacy and safety of imipenem/relebactam vs colistin plus imipenem in patients with imipenem-nonsusceptible bacterial infections. *Clin Infect Dis.* 2020;70(9):1799-1808. doi: 10.1093/cid/ciz530

Dosing and Administration

RECARBRIO 1.25 g is a fixed-dose combination of imipenem, cilastatin, and relebactam (500/500/250 mg) in a single vial, infused over 30 minutes every 6 hours[1]

500 mg imipenem
500 mg cilastatin
250 mg relebactam

30 min intravenous (IV) infusion

Q6H

Dosage in patients 18 years of age and older with creatinine clearance (CrCl) greater than or equal to 90 mL/min

Dosage adjustment is recommended in adult patients with renal impairment

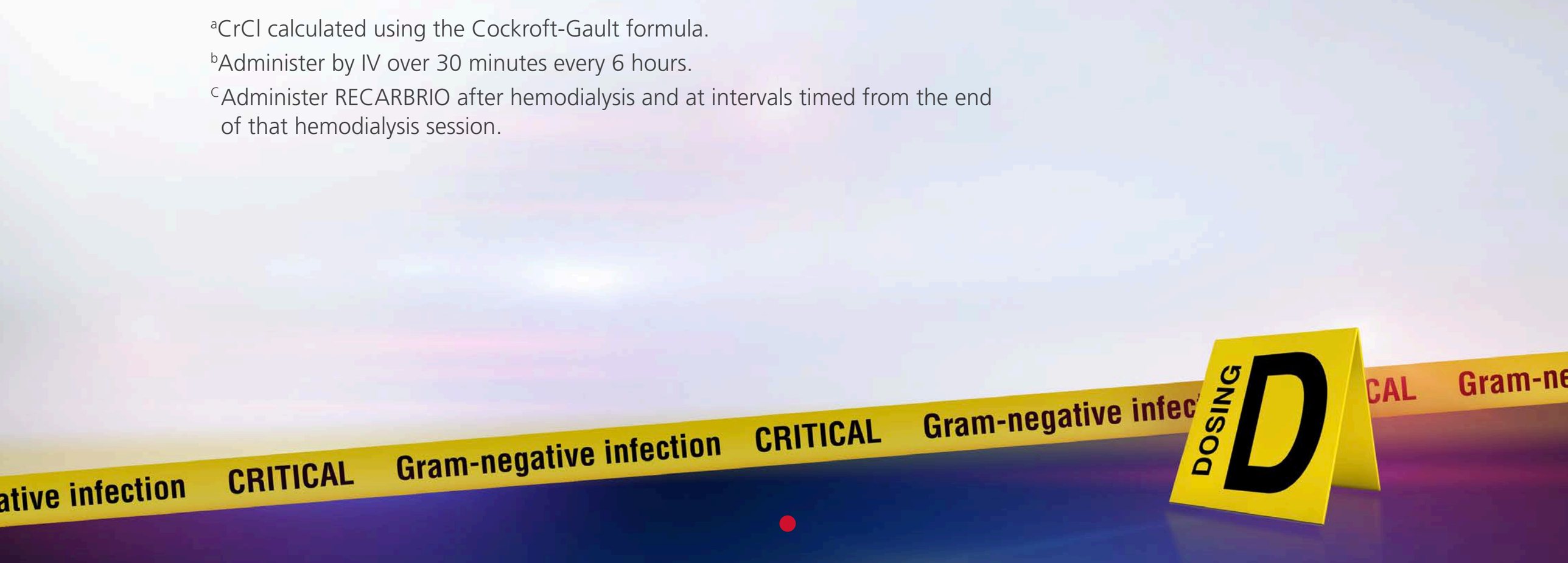
Estimated Creatinine Clearance (mL/min)[a]	<90 to ≥60	<60 to ≥30	<30 to ≥15	End-Stage Renal Disease on Hemodialysis[c]
Recommended Dosage of RECARBRIO (mg)[b]				
imipenem	**400**	**300**	**200**	**200**
cilastatin	**400**	**300**	**200**	**200**
relebactam	**200**	**150**	**100**	**100**

Patients with CrCl less than 15 mL/min should not receive RECARBRIO unless hemodialysis is instituted within 48 hours.

[a]CrCl calculated using the Cockroft-Gault formula.

[b]Administer by IV over 30 minutes every 6 hours.

[C]Administer RECARBRIO after hemodialysis and at intervals timed from the end of that hemodialysis session.



Reference: 1. RECARBRIO. Summary of product characteristics. MERCK SHARP & DOHME LLC February 2021

RECARBRIO™ (imipenem, cilastatin, and relebactam) for injection 1.25 g

RECARBRIO European Surveillance Data[a]

Percent of isolates susceptible to RECARBRIO from SMART Global Surveillance Program[1]

KPC-positive NPE	All *P. aeruginosa*	MDR *P. aeruginosa*[b]
98.6% (n=138)	**93.9%** (n=1959)	**79.8%** (n=595)

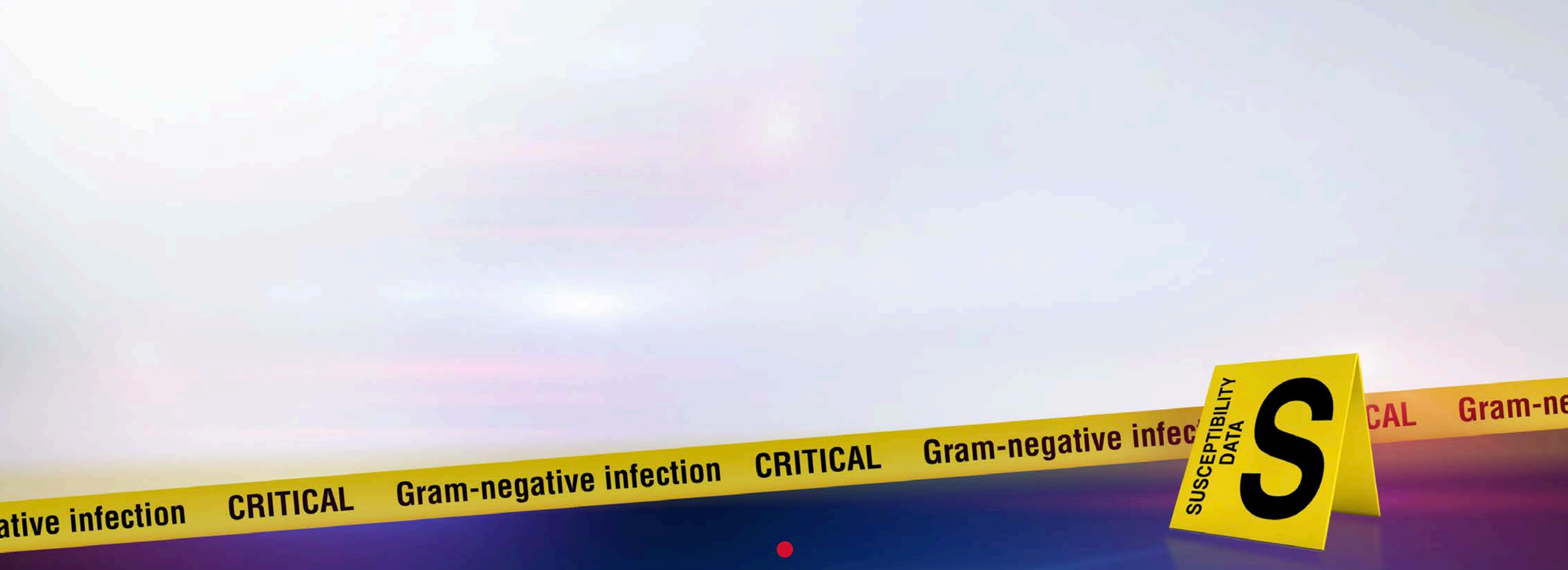
In vitro activity of imipenem/relebactam was evaluated against isolates of pathogens submitted to the SMART global surveillance program from 2015 to 2017 by 67 clinical laboratories in 22 European countries.[1]

The Study for Monitoring Antimicrobial Resistance Trends (SMART) is a global study initiated by Merck to monitor the *in vitro* susceptibility of clinical bacterial isolates to antimicrobials in intra-abdominal (since 2002), urinary tract (since 2009), respiratory (since 2015), and bloodstream infections (since 2019). The lack of clinical information does not allow for confirmation of isolates as being "community-acquired" vs "hospital-acquired."

The clinical significance of *in vitro* data is unknown.

[a]The study included 67 clinical laboratories in 22 countries in Europe (Belgium, Croatia, Czech Republic, France, Georgia, Germany, Greece, Hungary, Italy, Latvia, Lithuania, Poland, Portugal, Romania, Russia, Serbia, Slovenia, Spain, Sweden, Turkey, Ukraine, UK).[1]

[b]MDR isolates were defined phenotypically as those isolates nonsusceptible (intermediate or resistant) to any 3 or more of the following 8 sentinel antimicrobial agents: amikacin, aztreonam, cefepime, ceftazidime, ciprofloxacin, colistin, imipenem, and piperacillin-tazobactam.[1]



KPC, *Klebsiella pneumoniae* carbapenemase; **MDR**, multidrug-resistant; **NPE**, non-Proteeae Enterobacteriaceae; ***P. aeruginosa***, *Pseudomonas aeruginosa*; **SMART**, Study for Monitoring Antimicrobial Resistance Trends.

Reference: 1. Lob SH, Karalowsky JA, Young K, et al. *In vitro* activity of imipenem-relebactam against resistant phenotypes of Enterobacteriaceae and *Pseudomonas aeruginosa* isolated from intraabdominal and urinary tract infection samples – SMART Surveillance Europe 2015-2017. *J Med Microb.* 2020:69:207-217. doi:10.1099/jmm.0.001142

IDSA Antimicrobial Treatment Guidance: Gram-negative Bacterial Infections[1]

This guidance document was prepared by a panel of experts from the IDSA and focuses specifically on infections caused by difficult-to-treat Gram-negative pathogens.

Imipenem/cilastatin/relebactam is a recommended treatment option for infections caused by carbapenem-resistant Enterobacterales (CRE) or difficult-to-treat resistance Pseudomonas aeruginosa *(DTR-PsA)*

CRE-associated conditions

- Pyelonephritis/cUTI[a]
- Infections outside of the urinary tract, if resistance to ertapenem, meropenem, AND carbapenemase is unknown or negative
- Infections outside of the urinary tract, if carbapenemase production is present, KPC identified, or carbapenemase positive but identity of carbapenemase is unknown[b]

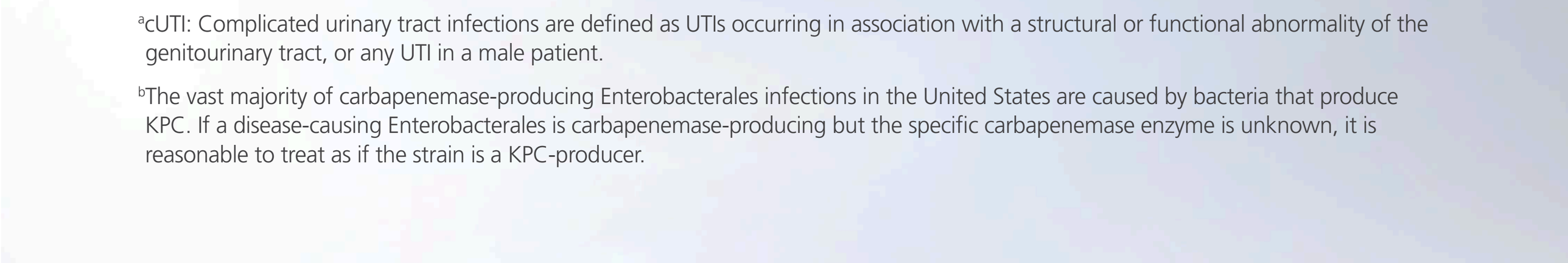
DTR-PsA–associated conditions

- Pyelonephritis/cUTI[a]
- Infections outside of the urinary tract
- Uncomplicated cystitis

Imipenem/cilastatin/relebactam is also recommended as an alternative treatment (when first-line options are not available/tolerated) for cystitis associated with CRE.

[a]cUTI: Complicated urinary tract infections are defined as UTIs occurring in association with a structural or functional abnormality of the genitourinary tract, or any UTI in a male patient.

[b]The vast majority of carbapenemase-producing Enterobacterales infections in the United States are caused by bacteria that produce KPC. If a disease-causing Enterobacterales is carbapenemase-producing but the specific carbapenemase enzyme is unknown, it is reasonable to treat as if the strain is a KPC-producer.



CRE, carbapenem-resistant Enterobacterales; **cUTI**, complicated urinary tract infection; **DTR-PsA**, difficult-to-treat resistance *Pseudomonas aeruginosa*; **IDSA**, Infectious Diseases Society of America; **KPC**, *Klebsiella pneumoniae* carbapenemase.

Reference: 1. Tamma PD, Aitken SL, Bonomo RA, et al. Infectious Diseases Society of America guidance on the treatment of extended-spectrum β-lactamase producing Enterobacterales (ESBL-E), carbapenem-resistant Enterobacterales (CRE), and Pseudomonas aeruginosa with difficult-to-treat resistance (DTR-*P. aeruginosa*). *Clin Infect Dis*. 2020;72(7):e169–e183. doi:10.1093/cid/ciaa1478

Clinical Guidance on the Recommended Use of Antimicrobials

Recommendations from the Sanford Guide, which provides health care professionals with antimicrobial therapy options.

Consider imipenem/cilastatin/relebactam for infections caused by Gram-negative pathogens

For infections caused by *Escherichia coli* or *Klebsiella* spp: Imipenem/cilastatin/relebactam is recommended as a PRIMARY REGIMEN when resistance to aztreonam, ceftriaxone, cefotaxime, ceftazidime, cefepime (ESBL), meropenem, or imipenem and susceptibility to ceftazidime-avibactam and meropenem-vaborbactam are confirmed, in a pattern consistent with the production of KPC.

For infections caused by *Pseudomonas aeruginosa*: Imipenem/cilastatin/relebactam is recommended as a PRIMARY REGIMEN for directed/specific therapy in carbapenem-resistant infections in which *in vitro* susceptibility has been confirmed.

For infections caused by *Enterobacter* spp: Imipenem/cilastatin/relebactam is recommended as a PRIMARY REGIMEN when resistance to meropenem, imipenem, or both, and susceptibility to ceftazidime-avibactam, imipenem-relebactam, and meropenem-vaborbactam (interpreted as production of KPC-type carbapenemases) are confirmed.

ESBL, extended-spectrum beta-lactamase; **KPC**, *Klebsiella pneumoniae* carbapenemase.

Reference: 1. The Sanford Guide to Antimicrobial Therapy. Web edition. Antimicrobial Therapy, Inc. Updated March 20, 2021. Accessed March 24, 2021. https://webedition.sanfordguide.com/en

Not an actual patient.

Discover RECARBRIO

A Broad-Coverage Carbapenem/ Novel BLI Combination

1 Achieved primary end point[1]

- In HABP/VABP, RECARBRIO demonstrated noninferiority to PIP/TAZ in day 28 all-cause mortality: 16% (42/264) vs 21% (57/267), 95% CI: -12, 1

2 Demonstrated favorable response[1]

- RECARBRIO demonstrated a favorable response in certain high-risk subgroups:
  - Ventilated HABP and VABP. There was a favorable response for RECARBRIO vs PIP/TAZ in day 28 all-cause mortality: 20% (24/122) vs 31% (42/136), 95% CI: -22, -1
  - Patients with APACHE II scores ≥15. There was a favorable response for RECARBRIO vs PIP/TAZ in day 28 all-cause mortality: 20% (25/125) vs 35% (45/127), 95% CI: -26, -4

3 Restored imipenem activity[2]

- Relebactam helps to restore the activity of imipenem against KPC-positive Enterobacterales and CR *P. aeruginosa*

The clinical significance of *in vitro* data is unknown.

Before prescribing RECARBRIO, please read the Summary of Product Characteristics .

APACHE II, Acute Physiology and Chronic Health Evaluation II; **BLI**, beta-lactamase inhibitor; **cIAI**, complicated intra-abdominal infection; **CR**, carbapenem-resistant; **cUTI**, complicated urinary tract infection; **HABP**, hospital-acquired bacterial pneumonia; **KPC**, *Klebsiella pneumoniae* carbapenemase; **PIP/TAZ**, piperacillin/tazobactam; ***P. aeruginosa***, *Pseudomonas aeruginosa*; **VABP**, ventilator-associated bacterial pneumonia.

References: 1. Titov I, Wunderink RG, Roquilly A, et al. A randomized, double-blind, multicenter trial comparing efficacy and safety of imipenem/cilastatin/relebactam versus piperacillin/tazobactam in adults with hospital-acquired or ventilator-associated bacterial pneumonia (RESTORE-IMI 2 Study). *Clin Infect Dis*. 2020;ciaa803. doi:10.1093/cid/ciaa803 **2.** Karlowsky JA, Lob SH, Kazmierczak KM, Young K, Motyl MR, Sahm DF. In-vitro activity of imipenem/relebactam and key β-lactam agents against Gram-negative bacilli isolated from lower respiratory tract infection samples of intensive care unit patients – SMART Surveillance United States 2015-2017. *Int J Antimicrob Agents*. 2020; 55(1):105841. doi:10.1016/j.ijantimicag.2019.10.022

RECARBRIO™ (imipenem, cilastatin, and relebactam) for injection 1.25 g

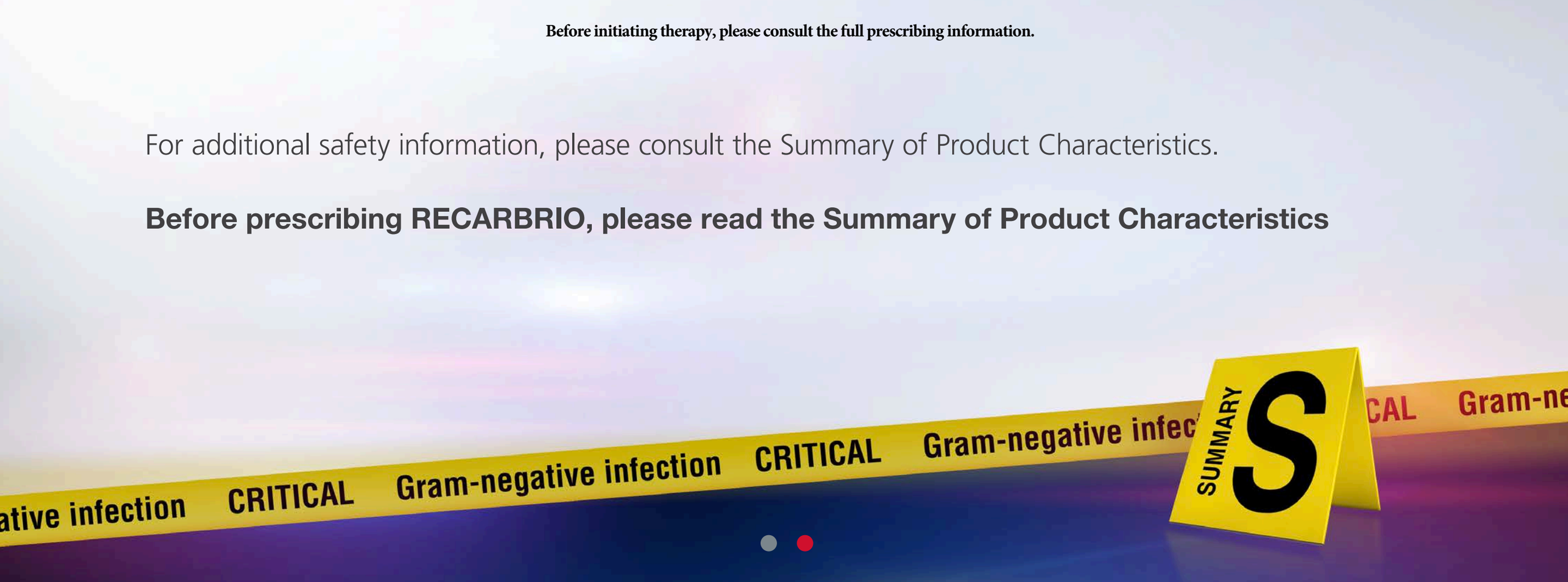
Selected Safety Information

INDICATIONS AND CLINICAL USE RECARBRIO™ 500 mg/500 mg/250 mg is indicated for:
• Treatment of hospital-acquired pneumonia (HAP), including ventilator associated pneumonia (VAP), in adults
• Treatment of bacteraemia that occurs in association with, or is suspected to be associated with HAP or VAP, in adults.
• Treatment of infections due to aerobic Gram-negative organisms in adults with limited treatment options
Consideration should be given to official guidance on the appropriate use of antibacterial agents.
CONTRAINDICATIONS
RECARBRIO™ is contraindicated in:
Hypersensitivity to the active substances or to any of the excipients listed in section
Hypersensitivity to any other carbapenem antibacterial agent.
Severe hypersensitivity (e.g., anaphylactic reaction, severe skin reaction) to any other type of beta-lactam antibacterial agent (e.g., penicillins, cephalosporins or monobactams)
Special warnings and precautions for use
Hypersensitivity reactions
Serious and occasionally fatal hypersensitivity (anaphylactic) reactions have been reported in patients receiving therapy with beta-lactams . These reactions are more likely to occur in individuals with a history of sensitivity to multiple allergens. Before initiating therapy with Recarbrio, careful inquiry should be made concerning previous hypersensitivity reactions to carbapenems, penicillins, cephalosporins, other beta-lactams, and other allergens. If an allergic reaction to Recarbrio occurs, treatment with Recarbrio must be discontinued immediately. Serious anaphylactic reactions require immediate emergency treatment.
Hepatic function
Hepatic function should be closely monitored during treatment with Recarbrio due to the risk of hepatic toxicity (such as increase in transaminases, hepatic failure, and fulminant hepatitis) in patients with liver disease: patients with pre-existing liver disorders should have liver function monitored during treatment with Recarbrio. There is no dose adjustment necessary
Central nervous system (CNS)
CNS adverse reactions, such as seizures, confusional states, and myoclonic activity have been reported during treatment with imipenem/cilastatin, components of Recarbrio, especially when recommended dosages of imipenem were exceeded. These reactions have been reported most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) and/or compromised renal function.
Increased seizure potential due to interaction with valproic acid
The concomitant use of Recarbrio and valproic acid/divalproex sodium is not recommended. Antibacterial other than carbapenems should be considered to treat infections in patients whose seizures are well-controlled on valproic acid or divalproex sodium. If administration of Recarbrio is necessary, supplemental anti-convulsant therapy should be considered
Clostridioides difficile-Associated Diarrhoea (CDAD)
Clostridioides difficile-associated diarrhoea (CDAD) has been reported with Recarbrio. CDAD may range in severity from mild diarrhoea to fatal colitis. CDAD must be considered in all patients who present with diarrhoea during or following the administration of Recarbrio (see section 4.8). Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.
If CDAD is suspected or confirmed, discontinuation of therapy with Recarbrio, and the administration of specific treatment for C. difficile should be considered. Medicinal products that inhibit peristalsis should not be given.
Patients with CrCl ≥ 150 mL/min
Based on pharmacokinetic-pharmacodynamic analyses, the dose of Recarbrio that is recommended for patients with CrCl of ≥ 90 mL/min may not be sufficient to treat patients with HAP or VAP and CrCl > 250 mL/min, or patients with cIAI or cUTI and CrCl > 150 mL/min. Consideration should be given to using alternative therapies for these patients.
Renal impairment
Dose adjustment is recommended in patients with renal impairment (see section 4.2). There is inadequate information to recommend usage of Recarbrio for patients undergoing peritoneal dialysis.
Limitations of the clinical data
Patients who were immunocompromised, including those with neutropenia, were excluded from clinical trials.
Hospital-acquired pneumonia, including ventilator-associated pneumonia
In a single study of hospital-acquired pneumonia, including ventilator-associated pneumonia, 6.2 % (33/535) of patients had bacteraemia at baseline.
Patients with limited treatment options
The use of Recarbrio to treat patients with infections due to aerobic Gram-negative organisms who have limited treatment options is based on experience with imipenem/cilastatin, pharmacokinetic-pharmacodynamic analysis for imipenem/cilastatin/relebactam, and on limited data from a randomised clinical study in which 21 evaluable patients were treated with Recarbrio and 10 evaluable patients were treated with colistin and imipenem/cilastatin for infections caused by imipenem-non-susceptible organisms.
Limitations of the spectrum of antibacterial activity
Imipenem does not have activity against methicillin-resistant Staphylococcus aureus (MRSA) and Staphylococcus epidermidis (MRSE) or against Enterococcus faecium. Alternative or additional antibacterial agents should be used when these pathogens are known or suspected to be contributing to the infectious process.
The inhibitory spectrum of relebactam includes class A beta-lactamases (such as ESBLs and KPC) and Class C beta-lactamases including PDC. Relebactam does not inhibit class D carbapenemases such as OXA-48 or class B metallo-beta-lactamases such as NDM and VIM (see section 5.1).
Non-susceptible organisms
The use of imipenem/cilastatin/relebactam may result in the overgrowth of non-susceptible organisms, which may require interruption of treatment or other appropriate measures.
Antiglobulin test (Coombs test) seroconversion
A positive direct or indirect Coombs test may develop during treatment with imipenem/cilastatin/relebactam (see section 4.8).
Controlled sodium diet
Each vial contains a total of 37.5 mg of sodium (1.6 mmol), equivalent to 1.9 % of the WHO (World Health Organization) recommended maximum daily intake of 2 g sodium for an adult. This should be considered when administering Recarbrio to patients who are on a controlled sodium diet
ADVERSE REACTIONS
Summary of the safety profile
The most frequently occurring adverse reaction (≥ 2 %) in patients receiving imipenem/cilastatin plus relebactam in pooled Phase 2 trials of complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI), including pyelonephritis (N = 431) was diarrhoea. The most frequently occurring adverse reactions (≥ 2 %) in patients receiving Recarbrio in a Phase 3 trial of HAP or VAP (N = 266) were diarrhoea, alanine aminotransferase increased, and aspartate aminotransferase increased. For additional adverse experience information, see the product circular.

Before initiating therapy, please consult the full prescribing information.

For additional safety information, please consult the Summary of Product Characteristics.

Before prescribing RECARBRIO, please read the Summary of Product Characteristics



MSD

RECARBRIO™
(imipenem, cilastatin, and relebactam) for injection 1.25 g