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REVIEW ARTICLE

Imipenem–Relebactam and Meropenem–Vaborbactam: Two Novel Carbapenem-β-Lactamase Inhibitor Combinations

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Abstract Relebactam (formerly known as MK-7655) is a non-β-lactam, bicyclic diazabicyclooctane, β-lactamase inhibitor that is structurally related to avibactam, differing by the addition of a piperidine ring to the 2-position carbonyl group. Vaborbactam (formerly known as RPX7009) is a non-β-lactam, cyclic, boronic acid-based, β-lactamase inhibitor. The structure of vaborbactam is unlike any other currently marketed β-lactamase inhibitor. Both inhibitors display activity against Ambler class A [including extended-spectrum β-lactamases (ESBLs), *Klebsiella pneumoniae* carbapenemases (KPCs)] and class C β-lactamases (AmpC). Little is known about the potential for relebactam or vaborbactam to select for resistance; however, inactivation of the porin protein OmpK36 in *K. pneumoniae* has been reported to confer resistance to both imipenem–relebactam and meropenem–vaborbactam. The addition of relebactam significantly improves the activity of imipenem against most species of Enterobacteriaceae [by lowering the minimum inhibitory concentration (MIC) by 2- to 128-fold] depending on the presence or absence of β-lactamase enzymes. Against *Pseudomonas aeruginosa*, the addition of relebactam also improves the activity of imipenem (MIC reduced eightfold). Based on the data available, the addition of relebactam does not improve the activity of imipenem against *Acinetobacter baumannii*, *Stenotrophomonas maltophilia* and most anaerobes. Similar to imipenem–relebactam, the addition of vaborbactam significantly (2- to > 1024-fold MIC reduction) improves the activity of meropenem against most species of Enterobacteriaceae depending on the presence or absence of β-lactamase enzymes. Limited data suggest that the addition of vaborbactam does not improve the activity of meropenem against *A. baumannii*, *P. aeruginosa*, or *S. maltophilia*. The pharmacokinetics of both relebactam and vaborbactam are described by a two-compartment, linear model and do not appear to be altered by the co-administration of imipenem and meropenem, respectively. Relebactam's approximate volume of distribution (V_d) and elimination half-life ($t_{½}$) of ∼ 18 L and 1.2–2.1 h, respectively, are similar to imipenem. Likewise, vaborbactam's V_d and $t_{½}$ of ∼ 18 L and 1.3–2.0 h, respectively, are comparable to meropenem. Like imipenem and meropenem, relebactam and vaborbactam are both primarily renally excreted, and clearance correlates with creatinine clearance. In vitro and in vivo pharmacodynamic studies have reported bactericidal activity for imipenem–relebactam and meropenem–vaborbactam against various Gram-negative β-lactamase-producing bacilli that are not inhibited by their respective carbapenems alone. These data also suggest that pharmacokinetic–pharmacodynamic

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parameters correlating with efficacy include time above the MIC for the carbapenems and overall exposure for their companion β-lactamase inhibitors. Phase II clinical trials to date have reported that imipenem–relebactam is as effective as imipenem alone for treatment of complicated intra-abdominal infections and complicated urinary tract infections, including acute pyelonephritis. Imipenem–relebactam is currently in two phase III clinical trials for the treatment of imipenem-resistant bacterial infections, as well as hospital-associated bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP). A phase III clinical trial has reported superiority of meropenem–vaborbactam over piperacillin–tazobactam for the treatment of complicated urinary tract infections, including acute pyelonephritis. Meropenem–vaborbactam has recently demonstrated higher clinical cure rates versus best available therapy for the treatment of carbapenem-resistant Enterobacteriaceae (CRE), as well as for HABP and VABP. The safety and tolerability of imipenem–relebactam and meropenem–vaborbactam has been reported in various phase I pharmacokinetic studies and phase II and III clinical trials. Both combinations appear to be well tolerated in healthy subjects and hospitalized patients, with few serious drug-related treatment-emergent adverse events reported to date. In conclusion, relebactam and vaborbactam serve to broaden the spectrum of imipenem and meropenem, respectively, against β-lactamase-producing Gram-negative bacilli. The exact roles for imipenem–relebactam and meropenem–vaborbactam will be defined by efficacy and safety data from further clinical trials. Potential roles in therapy for these agents include the treatment of suspected or documented infections caused by resistant Gram-negative bacilli-producing ESBL, KPC, and/or AmpC β-lactamases. The usage of these agents in patients with CRE infections will likely become the standard of care. Finally, increased activity of imipenem–relebactam against *P. aeruginosa* may be of clinical benefit to patients with suspected or documented *P. aeruginosa* infections.

1 Introduction

Carbapenems, which are increasing in usage worldwide, have the broadest spectrum of activity of all β-lactam antimicrobials and therefore are often reserved for severe, complicated, and multidrug-resistant (MDR) infections [1, 2]. Resistance to carbapenems has emerged in Enterobacteriaceae, *P. aeruginosa*, and *A. baumannii* [3]. The World Health Organization ranks MDR and carbapenem-resistant Enterobacteriaceae (CRE), particularly *K. pneumoniae* and *Escherichia coli*, as well as carbapenem-resistant *P. aeruginosa* and *A. baumannii* as the three most critical antimicrobial-resistant bacteria on their global priority list to guide research, discovery, and development of new antimicrobials [4]. For infections where effective antimicrobial agents are limited, older agents with well-defined toxicities such as polymyxins, aminoglycosides, and tigecycline may be necessary to treat MDR infections [5, 6]. There is a critical need for new antimicrobials that have increased efficacy and/or decreased toxicity to treat patients with carbapenem-resistant and MDR infections.

Resistance to carbapenems arises from increased antimicrobial efflux, decreased permeability, and most importantly the production of β-lactamases, including carbapenemases [6]. In Enterobacteriaceae, carbapenem resistance is frequently attributable to the production of carbapenemases such as *K. pneumoniae* carbapenemases (KPCs) as well as to the production of class B metallo-β-lactamases (e.g., NDM, IMP, VIM), and class D β-lactamases (OXA-type) [6, 7]. In *P. aeruginosa*, the carbapenem resistance is often a combination of decreased expression of OprD (a porin protein), increased efflux, and increased production of AmpC [7].

Older β-lactamase inhibitors such as tazobactam, clavulanic acid, and sulbactam are effective in potentiating the activities of β-lactam antimicrobials against some class A β-lactamase-producing Enterobacteriaceae [8]. However, these older β-lactamase inhibitors have no activity against carbapenemases and limited to no effect versus some class C enzymes, including AmpC [8]. The novel β-lactamase inhibitors relebactam (formerly known as MK-7655) and vaborbactam (formerly known as RPX7009) are being developed to address the need for agents with activity against carbapenem-resistant Gram-negative bacilli.

Relebactam and vaborbactam are the first β-lactamase inhibitors developed for use in combination with carbapenems, specifically with imipenem (relebactam) and meropenem (vaborbactam). Both relebactam and vaborbactam have displayed in vitro activity against class A β-lactamases (e.g. KPC) and class C β-lactamases (e.g. AmpC) [5]. In vitro, both novel β-lactamase inhibitors have restored the activity of carbapenems against various phenotypes and genotypes of CRE, especially in KPC-producing isolates [7, 9]. Relebactam has also been shown to be effective in potentiating imipenem activity against *P. aeruginosa* [6, 7].

Vaborbactam in combination with meropenem (proprietary name, Vabomere) was the first of these two combination agents to complete a randomized, comparative Phase III clinical trial (TANGO I). In the TANGO I trial, meropenem–vaborbactam was assessed for the treatment of complicated urinary tract infections (cUTI), including acute pyelonephritis (AP) (http://clinicaltrials.gov, identifier NCT02166476) and was shown to provide superior

efficacy compared to piperacillin-tazobactam and to be safe [10]. In a phase III randomized, comparative trial (TANGO II), meropenem–vaborbactam has recently demonstrated higher clinical cure rates versus best available therapy for the treatment of patients with CRE infections, including patients with hospital-associated bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) (NCT02168946 and NCT03006679). Relebactam is currently in phase III clinical trials in combination with imipenem and the renal dehydropeptidase-1 inhibitor cilastatin, for the treatment of imipenem-resistant bacterial infections, HABP, and VABP (NCT02452047 and NCT02493764). Whenever imipenem is referred to in the review, unless otherwise stipulated, it refers to imipenem/cilastatin. Two completed Phase II clinical trials have reported efficacy and safety of imipenem–relebactam in the treatment of complicated intra-abdominal infections (cIAI) and cUTI/AP compared to imipenem treatment alone (NCT01506271 and NCT01505634).

This review considered all published data for imipenem–relebactam and meropenem–vaborbactam, including chemistry, mechanisms of action, mechanisms of resistance, microbiology, pharmacokinetics, pharmacodynamics, and efficacy and safety results from animal studies and clinical trials. Literature was obtained via a standard comprehensive search (up to October 2017) of PubMed for all materials including the terms "imipenem" and "relebactam" or "MK-7655", "meropenem" and "vaborbactam" or "RPX7009", and "Carbavance". All results were reviewed by at least two authors and supplemented with abstracts and posters from scientific meetings as well as citations from relevant review articles.

Vaborbactam has been previously studied with biapenem, a carbapenem marketed in Japan. Compared to meropenem, biapenem demonstrates stability against certain Ambler class B and D β-lactamases (e.g. NDM-1 and OXA-48) and is more resistant to efflux by *P. aeruginosa* [8, 11, 12]. However, meropenem's safety record and ultimately its registration status lead to further clinical development in combination with vaborbactam [11]. As biapenem is only currently approved for use in Japan and is no longer being studied in combination with vaborbactam, these studies will not be discussed in this review [13, 14].

2 Chemistry

Carbapenems originated from the compound thienamycin, which is an antimicrobial produced by the soil bacterium *Streptomyces cattleya* [2]. However, due to thienamycin's chemical instability, carbapenems with increased stability such as imipenem and meropenem were developed and approved for use in the USA in 1987 and 1996, respectively [1]. Carbapenems (imipenem and meropenem) differ from penicillins by having a carbon in place of the sulfur atom at position 1 and an unsaturated double bond between carbons 2 and 3 in their thiazolidine ring structure (Fig. 1) [2]. Carbapenems are well known for their intrinsic resistance to β-lactamases, including class A extended-spectrum β-lactamases (ESBLs) and class C β-lactamases (AmpCs) [2, 6]. The stability of carbapenems to β-lactamases arises from the *trans*-1α-hydroxyethyl substituent at carbon 6 [2]. The *trans* configuration at carbon 6 is characteristic of carbapenems compared to the *cis* side chains of penicillins and cephalosporins [1].

Even though imipenem demonstrated increased chemical stability compared to thienamycin, it is still susceptible to degradation by dehydropeptidase-1 (DHP-1) in the proximal renal tubules of mammals [1]. Therefore, imipenem must be administered with cilastatin, an inhibitor of DHP-1. Unlike imipenem, meropenem is intrinsically resistant to DHP-1 degradation due to the addition of a 1-β-methyl group on carbon 1 located in the carbapenem core [2]. Structurally, meropenem also differs from imipenem with a pyrrolidinyl substituent at position 2, which presumably increases its activity against Gram-negative bacteria, including *P. aeruginosa* [1]. With regard to the MexAB-OprM efflux system in *P. aeruginosa*, meropenem acts as a substrate due to the presence of a hydrophobic side chain at position 2 versus imipenem, which possesses a hydrophilic side chain making it a poor substrate for the MexAB-OprM efflux system [15, 16].

2.1 Imipenem–Relebactam

Relebactam is a potent non-β-lactam, bicyclic diazabicyclooctane, β-lactamase inhibitor (Fig. 1) [17]. It is structurally related to avibactam (a β-lactamase inhibitor currently approved for use in combination witsh ceftazidime) with the main distinguishing feature being the addition of a piperidine ring to the 2-position carbonyl group (Fig. 1) [17, 18]. Relebactam is highly reactive due to its highly strained bicyclic urea core and electron withdrawing aminoxy sulfate moiety [19]. The high reactivity results in limited stability in the presence of base or nucleophiles; however, this is also the same property that makes this compound a potent β-lactamase inhibitor [19]. Stability is only achieved at pH 4–8 in aqueous solution [19]. The positive charge on the piperidine side chain at physiological pH was shown to be essential in preventing efflux of relebactam from bacterial cells [18].

2.2 Meropenem–Vaborbactam

Vaborbactam is a non-β-lactam, cyclic boronic acid with high affinity to serine β-lactamases (Fig. 1) [11, 17].

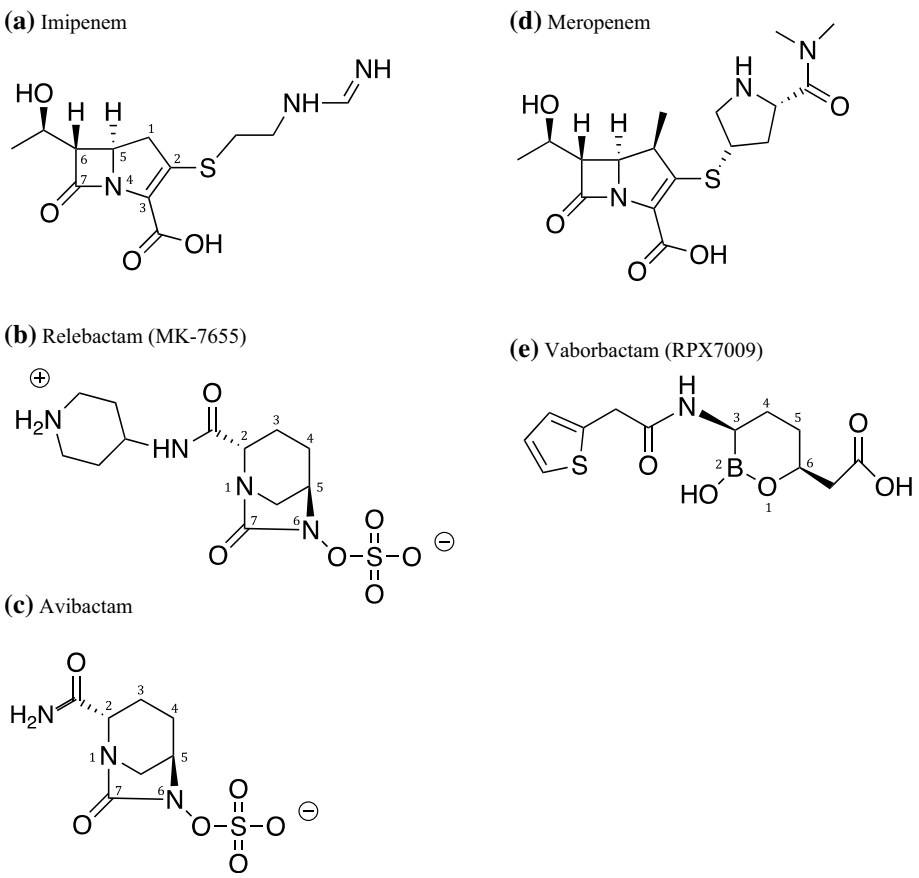

Fig. 1 Chemical structures of imipenem (**a**), relebactam (**b**), avibactam (**c**), meropenem (**d**), and vaborbactam (**e**)

Vaborbactam's boronic ester ring was designed with the intention of constraining the inhibitor into a preferred conformation to increase potency [11]. The boron atom in vaborbactam acts as an electrophile and forms a reversible covalent bond with the catalytic serine of specific β-lactamases [11, 17]. As boronic acids are potent serine protease inhibitors, there was concern vaborbactam would potentially inhibit other important mammalian serine proteases in vivo [5, 11]. However, Hecker et al showed that vaborbactam had IC_{50} values ≥ 1000 μM for inhibition of 11 common mammalian serine proteases, confirming selective inhibition exclusively to serine β-lactamases [11]. Vaborbactam also has a 2-thienylacetyl side chain similar to the side chains of cephalothin and cefoxitin [11, 20].

3 Mechanisms of Action

Carbapenems, like other β-lactam antimicrobials, inhibit cross-linking of peptidoglycan, the structural component in bacterial cell walls by binding to penicillin binding proteins (PBPs) [1]. The inability of bacterial cells to form an intact cell wall ultimately leads to cell death, which classifies β-lactams as bactericidal antimicrobials [1]. Carbapenems enter the periplasmic space of Gram-negative bacteria by passing through outer membrane proteins (OMPs) [2]. Important OMPs include OprD in *P. aeruginosa* and OmpK in *K. pneumoniae*, as decreased expression can limit uptake and consequently decrease the activity of antimicrobials [2].

Increased potency of meropenem compared to imipenem against Gram-negative bacilli is partially explained by differing affinities to various PBPs [1]. Imipenem has weak affinity for PBP3 but preferentially binds to PBP2, followed by PBPs 1a and 1b [1]. Alternatively, meropenem preferentially binds to PBP2, followed by PBPs 3, 1a, and 1b [1]. The preferable affinity to PBPs is unlike aminopenicillins and cephalosporins, which primarily bind PBP3 [1, 2]. The low affinity of carbapenems to PBP3 is predicted to be responsible for their ability to achieve cell lysis without filamentation, which allows for a less significant increase in cell mass before lysis and less lipopolysaccharide (endotoxin) release [1, 2, 21].

Mechanistically both relebactam and vaborbactam exhibit their effects by inhibiting β-lactamase enzymes produced by Gram-negative bacilli. Available published

Table 1 IC_{50} values for relebactam and comparator β-lactamase inhibitors against various β-lactamase enzymes

	β-lactamase inhibitor IC_{50} (μM)			References
	Relebactam	Avibactam	Tazobactam	
Class A				
TEM-1	0.03	0.01	0.01	[33]
SHV-1	0.03	NA	0.07	[33]
SHV-5	0.36	NA	0.01	[33]
KPC-2	0.21	0.17	43.00	[33]
KPC-2[a]	0.21	NA	NA	[18]
Class C				
AmpC[b]	0.47	0.13	1.49	[18, 33]
AmpC[c]	4.10	NA	NA	[18]
P99	0.13	0.10	12.00	[33]
Class D				
OXA[c]	>50	NA	58.00	[33]
OXA-40[c]	>50	NA	NA	[18]

IC_{50} half maximal inhibitory concentration, *NA* data not available

[a] *Klebsiella pneumoniae*

[b] *Pseudomonas aeruginosa*

[c] *Acinetobacter baumannii*

data displaying the activities of relebactam and vaborbactam against different β-lactamases can be found in Tables 1 and 2, respectively. The current prevalence of the various β-lactamases per individual country is beyond the scope of this review; however, β-lactamases, including ESBL, and carbapenemases, such as KPC and NDM continue to spread worldwide The studies summarized in Tables 1 and 2 used assays that measured the ability of each β-lactamase inhibitor to prevent degradation of nitrocefin [11, 18, 22–24]. K_i and IC_{50} values from various studies are not directly comparable due to small variations in assays; however, Tables 1 and 2 are useful for a general comparison of relebactam and vaborbactam to other β-lactamase inhibitors currently used in clinical practice. Table 3 provides a comparative summary of activities for various β-lactamase inhibitors including relebactam, vaborbactam, avibactam, clavulanic acid, sulbactam, and tazobactam, compiled from available studies and publications [5, 24–27].

β-lactamase enzymes are either classified based on genetic similarly (amino acid sequence), as described by Ambler et al which groups enzymes into classes A, B, C, and D, or based on functional similarity as described by Bush et al [28–30]. For simplicity, only the Ambler classification system will be referred to in this review. Vaborbactam and relebactam demonstrate potent activity against class A β-lactamases, especially KPCs, and class C β-lactamases (Tables 1 and 2). Of interest, it was recently shown that vaborbactam demonstrates activity against the newly discovered class A carbapenemases BKC-1 and FRI-1 found in clinical isolates of *K. pneumoniae* and *E. cloacae*, respectively (Table 2) [22].

As demonstrated in Table 1, relebactam has no activity against OXA class D β-lactamases produced by *A. baumannii* [18]. However, relebactam has been shown to demonstrate variable potentiation of imipenem in vitro against OXA-48 producing Enterobacteriaceae [6, 7]. Neither relebactam nor vaborbactam has consistently demonstrated activity against class B metallo-β-lactamases (e.g. NDM, IMP, VIM), which utilize a zinc atom in their active site or class D β-lactamases (e.g. OXA) [5, 31].

Table 2 K_i values for vaborbactam and comparator β-lactamase inhibitors against various β-lactamase enzymes

	β-lactamase inhibitor K_i (μM)				References
	Vaborbactam	Avibactam	Clavulanic acid	Tazobactam	
Class A					
TEM-10	0.11	NA	0.02	0.01	[11]
SHV-12	0.03	NA	≤0.04	0.0004	[11]
CTX-M-15	0.04	NA	0.03	0.001	[11, 24]
KPC-2	0.07	NA	41.20	1.60	[11, 24]
KPC-2	0.03	0.01	NA	NA	[23]
KPC	0.08	NA	>10	3.30	[22]
BKC-1	0.02	NA	0.01	0.31	[22]
FRI-1	0.18	NA	0.71	0.34	[22]
Class C					
P99	0.05	NA	1106	1.10	[11, 24]
CMY-2	0.10	NA	845	0.71	[11]

K_i inhibitory dissociation constant, *NA* data not available

Table 3 Activities of β-lactamase inhibitors against various β-lactamase enzymes

	β-lactamase inhibitor					
	Relebactam	Vaborbactam	Avibactam	Clavulanic acid	Sulbactam	Tazobactam
Class A						
TEM	+	+	+	+	+	+
SHV	+	+	+	+	+	+
CTX-M	+	+	+	+	+	+
KPC	+	+	+	−	−	−
Class B						
MBL	−	−	−	−	−	−
Class C						
AmpC	+	+	+	−	±[a]	−
Class D						
OXA	±	−[b]	±	−	−	−
Reference	[5]	[5]	[5, 24]	[25, 26]	[27]	[27]

− no inhibitory activity, + inhibitory activity, *MBL* metallo-β-lactamase

[a]Enterobacteriaceae resist inhibition by sulbactam, although *Klebsiella* spp., *Salmonella* spp., and *Proteus* spp. normally do not harbor chromosomal bla_{AmpC} genes

[b]Limited data available

Winkler et al identified reduced activity of relebactam against the class A carbapenemase, GES-2 ($K_{i\ app}$, 19 ± 2 μM), potentially revealing a limitation to class A carbapenemase inhibition by relebactam [32].

3.1 Imipenem–Relebactam

The mechanism of action of relebactam is not well described in the literature; however, relebactam is predicted to have a mechanism of action similar to avibactam because of their similar chemical structures [12, 17, 31]. Avibactam rapidly acylates β-lactamases and slowly reversibly de-acylates from these enzymes, producing a regenerated enzyme and an active inhibitor capable of rebinding [33]. Acylation occurs between the active site serine residue of the β-lactamase and the carbonyl at position 7 in the cyclic urea core of avibactam [24]. The recyclization of the 5-membered ring is unlike other β-lactamase inhibitors such as clavulanic acid, which have 4-membered rings and require much more energy to reform their ring structures [31].

Barnes et al determined that relebactam has more potent activity against PER-2, a β-lactamase produced by *P. aeruginosa*, compared to avibactam ($K_{i\ app}$ 5.8 ± 0.6 and 29 ± 3 μM, respectively) [34]. However, when comparing imipenem–relebactam to ceftazidime–avibactam, ceftazidime is hydrolyzed by PER unlike imipenem [34]. In a similar study, both relebactam and avibactam were determined to have activity against PDC-3, an ESBL produced by *P. aeruginosa* ($K_{i\ app}$ 3.4 ± 0.4 and 2.5 ± 0.3 μM, respectively) [35].

3.2 Meropenem–Vaborbactam

Crystallography studies have shown that the catalytic serine residue of both CTM-M-15 and AmpC covalently bound to the boron atom of vaborbactam [11]. These studies also demonstrated insight into the coordination of vaborbactam in the active site of these β-lactamase enzymes [11]. The boron atom in vaborbactam mimics the carbonyl carbon of the β-lactam ring, which forms an association with the serine residue in β-lactamases ultimately mimicking the tetrahedral transition state of β-lactam hydrolysis [11, 17]. Even though vaborbactam forms a covalent bond with theses enzymes, this association is reversible, and therefore vaborbactam serves as a competitive inhibitor and is not hydrolyzed [5, 31].

4 Mechanisms of Resistance

Carbapenem resistance can arise due to various mechanisms such as decreased permeability via reduced expression of OMPs, expression of efflux systems, alteration of PBPs thus decreasing affinity of β-lactams, and most importantly the production of carbapenemases [2]. In 2011, the Clinical and Laboratory Standards Institute (CLSI) reduced the carbapenem MIC (minimum inhibitory concentration) breakpoints four-fold against Enterobacteriaceae, including imipenem and meropenem [2]. This change was made because of resistance mechanisms that were undetected at higher MIC breakpoints [2].

The addition of the β-lactamase inhibitors relebactam and vaborbactam prevent degradation of imipenem and meropenem, respectively, by certain β-lactamases. These novel β-lactamase inhibitors have displayed synergy in potentiating carbapenems against Ambler class A and C β-lactamases, especially KPCs and AmpCs; however, they have not been proven to significantly inhibit class B (e.g. IMP, VIM, NDM) or D enzymes (e.g. OXA) [6, 7, 9, 36]. Therefore, organisms that produce specific carbapenemases outside the spectrum of inhibition of relebactam and vaborbactam will continue to be resistant to imipenem and meropenem, respectively.

Generally, pathogens that remain resistant to imipenem–relebactam and meropenem–vaborbactam include *S. maltophilia*, *Elizabethkingia meningoseptica*, and *Aeromonas* spp., which produce class B metallo-β-lactamases that are chromosomally encoded and utilize a zinc atom at their active site [1, 2, 37]. Other resistant organisms include *A. baumannii* and some isolates of *K. pneumoniae,* which produce OXA class D β-lactamases [2, 37, 38].

Some pathogens have intrinsic resistance to carbapenems due to mechanisms other than β-lactamase production and therefore the addition of β-lactamase inhibitors provides no benefit. One example is pathogens that produce altered PBPs with low affinities to β-lactam antimicrobials. These organisms include MRSA (methicillin-resistant *Staphylococcus aureus*) due to production of PBP2a as well as *Enterococcus faecium,* which produces PBP5 [1, 2]. Another example of a resistance mechanism other than β-lactamase production is overexpression of multi-drug efflux pumps such as the MexA-MexB-OprM efflux system in *P. aeruginosa* [1, 2]. In particular, meropenem is susceptible to *P. aeruginosa* efflux compared to imipenem, which is unaffected by this mechanism of resistance [39]. Likewise, relebactam is unaffected by *P. aeruginosa* efflux, which makes this compound an optimal inhibitor to be used in combination with imipenem [6, 7].

P. aeruginosa resistance to carbapenems is a significant and growing problem [1, 2]. The most common mechanism of imipenem resistance in *P. aeruginosa* is a combination of overproduction of AmpC β-lactamase and decreased expression of OprD, an OMP specific to the uptake of imipenem [6, 39]. However, relebactam in combination with imipenem helps to prevent resistance via this mechanism by inhibiting AmpC; this effect has not been described with meropenem–vaborbactam [7, 9, 36]. Similarly, the decreased expression of various OmpK porin proteins in *K. pneumoniae* and OmpC and OmpF in *Enterobacter* spp. is another mechanism of resistance [2, 37]. Down-regulation of OmpK36 or major mutations in this porin have been shown to increase imipenem–relebactam MICs [36, 40].

Haidar et al. described that variant KPC-3 enzymes, which confer resistance to ceftazidime-avibactam, do not affect the activity of imipenem–relebactam as this mutation causes the enzyme to no longer function as a carbapenemase, but rather as an ESBL [40]. Similarly, Lomovskaya and Tsivkovski determined that Asp179Tyr amino acid substitutions in KPC-2 and KPC-3 do not affect activity of meropenem–vaborbactam in contrast to causing resistance to ceftazidime-avibactam [41].

Two recent studies explored enzyme-inhibitor interactions of vaborbactam and KPC-2, which provide insight on different interactions that allow resistance to form against β-lactamase inhibitors such as avibactam and clavulanic acid but not against vaborbactam [23, 42]. Tsivkovski and Lomovskaya determined that substitutions in Trp105 (an amino acid residue in KPC-2, which is important for recognition of substrates) that confer resistance to ampicillin-clavulanic acid, had no effect on vaborbactam's whole cell potency in combination with antimicrobials [42]. The authors determined this effect may be due to very slow K_{off} rates of vaborbactam, which reserves its potency [42]. Tsivkovski et al determined that inhibition of KPC-2 by vaborbactam does not involve S130, which is important for inhibition by avibactam [23]. This was a significant finding as a point mutation, KPC-2-S130G, caused approximately a 6000-fold decrease in K_i for avibactam but had no significant effect on the K_i of vaborbactam [23].

Sun et al. identified exposure levels of meropenem and vaborbactam in order to prevent resistance development using sub-optimal exposures of both drugs in seven meropenem-resistant strains of *K. pneumoniae* [43]. The authors concluded that concentrations of 8 mg/L meropenem along with 8 mg/L vaborbactam were associated with a resistance frequency $< 10^{-9}$ [43]. The mutants that were selected for in isolates incubated at sub-inhibitory concentrations had a resistant phenotype involving inactivation of OmpK36 due to various insertions, deletions, stop mutations, or substitutions [43]. This study provided target exposures for clinical use in order to prevent the development of resistance due to changes in OmpK35 and OmpK36 [43].

Interestingly, in another study by Sun et al, loss of resistance was observed in an in vitro hollow fiber infection model (HFIM) with 6 KPC-producing isolates of *K. pneumoniae* when treated with meropenem–vaborbactam [44]. Approximately 5–10% of cells that survived exposure to meropenem–vaborbactam became susceptible to carbapenems as well as other β-lactam antimicrobials due to the loss of bla_{KPC} [44]. It is predicted that the loss of the bla_{KPC} gene was due to loss of a plasmid rather than genetic recombination to remove the gene in the isolates studied [44]. In summary, resistance developing upon administration of imipenem–relebactam and meropenem–

vaborbactam is currently limited. As the usage of these agents increases, novel resistance mechanisms may arise and will require investigation.

5 Microbiology

The in vitro activities of imipenem–relebactam compared with imipenem alone against various Gram-negative aerobes and anaerobes, including drug-resistant and specific β-lactamase-producing isolates are presented in Tables 4, 5, and 6 [6, 7, 32, 36, 40, 45–57]. The MIC values presented in these tables are modal MIC values derived from a review of available in vitro studies conducted with similar methods. Comparative data for imipenem alone was also pooled from these studies and included when data were available. Susceptible and resistant phenotypes are described using the current CLSI breakpoints for imipenem against Enterobacteriaceae (susceptible ≤ 1 mg/L, resistant ≥ 4 mg/L), *P. aeruginosa* and *Acinetobacter* spp. (susceptible ≤ 2 mg/L, resistant ≥ 8 mg/L), and anaerobes and other non-Enterobacteriaceae (susceptible ≤ 4 mg/L, resistant ≥ 16 mg/L) [58].

5.1 Imipenem–Relebactam

Table 4 shows the activities of imipenem–relebactam and imipenem alone against common Gram-negative aerobes [6, 7, 36, 40, 45, 47–54, 57]. Also included in this table are various resistant phenotypes such as imipenem non-susceptible isolates, ESBL, KPC, and serine carbapenemase producers and MDR isolates. The activity of imipenem against Gram-negative bacteria is either retained or enhanced with the addition of relebactam. Significant increases in activity of imipenem with the addition of relebactam are observed against imipenem non-susceptible and β-lactamase (ESBL, KPC, and serine carbapenemase) producing Enterobacteriaceae (2- to 128-fold MIC reductions) and against *P. aeruginosa* (eightfold MIC reduction). The addition of relebactam has little impact on the activity of imipenem against *A. baumannii*, *Chryseobacteria* and *S. maltophilia*.

Table 5 shows in vitro activity of imipenem–relebactam compared to imipenem alone against Enterobacteriaceae and *P. aeruginosa* expressing specific β-lactamase enzymes [7, 32, 36, 45, 46]. Overall, relebactam significantly improved the activity of imipenem against Enterobacteriaceae isolates producing Ambler class A ESBLs (2- to 16-fold MIC reduction) and KPC carbapenemases (32- to 128-fold MIC reduction) (Tables 4 and 5). The addition of relebactam showed significant benefit in potentiating the activity of imipenem against imipenem non-susceptible *P. aeruginosa* with AmpC production and OprD porin loss [7, 36, 46]. The addition of relebactam did not potentiate imipenem against *A. baumannii* isolates producing OXA-23 and had minimal impact on the activity of imipenem against Gram-negative isolates producing OXA-48. As expected based on relebactam's spectrum of activity, the addition of relebactam did not potentiate the activity of imipenem against organisms producing Ambler class B metallo-β-lactamases, including IMP, VIM, and NDM. Overall, the majority of isolates with elevated imipenem–relebactam will likely contain multiple resistance mechanisms including production of β-lactamases not inhibited by relebactam (most Ambler class B and D β-lactamases), porin alterations, and overexpression of efflux pumps.

Table 6 shows the activities of imipenem–relebactam and relebactam against anaerobic bacteria [55, 56]. Overall, imipenem–relebactam demonstrated little or no improvement compared to imipenem alone; however, imipenem alone demonstrated excellent activity against most anaerobes presented in Table 6. Two exceptions were *Bilophila wadsworthia* and *Fusobacterium varium* with MIC_{90} values that dropped from a CLSI resistant MIC of 16 mg/L to a susceptible MIC of 4 mg/L (fourfold reduction). There was also a fourfold reduction in imipenem MIC_{90} values for *Fusobacterium necrophorum* with the addition of relebactam, which dropped from 2 to 0.5 mg/L (both CLSI susceptible values). *Bacteriodes* spp. with decreased imipenem susceptibility showed no benefit with the addition of relebactam, the majority of isolates continued to remain above the CLSI breakpoint for imipenem (MIC_{50}, 8 mg/L; MIC_{90}, >32 mg/L). Limited data have been published on the activity of imipenem–relebactam versus Gram-positive bacteria.

5.2 Meropenem–Relebactam

The in vitro activities of meropenem–vaborbactam compared with meropenem alone against various Gram-negative aerobes, including antimicrobial-resistant and specific β-lactamase-producing isolates are presented in Tables 7 and 8 [9, 59–73]. The MIC values presented in these tables are modal MIC values derived from a review of available in vitro studies conducted with similar methods. Comparative data on meropenem alone was also pooled from these studies and included when data were available. Susceptible and resistant phenotypes are described using the current CLSI breakpoints for meropenem, which are the same as those for imipenem, as stated above.

Table 7 shows the activities of meropenem–vaborbactam and meropenem alone against common Gram-negative aerobes [9, 59–68]. Also included in this table are various resistant phenotypes such as meropenem non-susceptible isolates, β-lactamase-producers, MDR and XDR

Table 4 In vitro activity (MIC, mg/L) of imipenem and imipenem–relebactam against Gram-negative aerobes

Gram-negative aerobes	Imipenem			Imipenem–relebactam[a]			MIC fold reduction[c]
	MIC_{50}	MIC_{90}[b]	Range	MIC_{50}	MIC_{90}[b]	Range	
Acinetobacter baumannii	4	> 32	≤ 0.03 to > 32	2	> 32	≤ 0.03 to > 32	–
Imipenem non-susceptible[d]	32	> 32	4 to > 32	32	> 32	4 to > 32	–
Chryseobacteria	64[e]	NA	32 to > 64	32[e]	NA	32–64	2
Enterobacter cloacae	NA	NA	4 to 8	≤ 0.25	NA	≤ 0.25 to ≤ 0.25	NA
Enterobacter spp.	≤ 0.5	1	≤ 0.03 to 32	0.25	0.5	≤ 0.03 to 2	2
Imipenem non-susceptible[f]	NA	NA	2–32	NA	NA	0.12–1	NA
Escherichia coli	0.25	0.25	≤ 0.03 to > 30	0.25	0.25	≤ 0.03 to 1	–
Klebsiella pneumoniae	≤ 0.5	≤ 0.5	≤ 0.5 to > 32	0.25	0.25	≤ 0.03 to 4	–
Imipenem non-susceptible[f]	8	32	4 to > 32	0.25	2	0.06–4	16
KPC producers	16	> 16	0.5 to > 16	0.25	1	0.12–2	> 16
ESBL producers	0.25	0.5	0.25–1	0.12	0.25	0.12–0.5	2
Pseudomonas aeruginosa	1	16	≤ 0.03 to > 32	0.5	2	≤ 0.03 to > 32	8
Imipenem non-susceptible[d]	16	32	4 to > 32	2	4	0.25 to > 32	8
KPC producers	≥ 8	≥ 8	≥ 8 to ≥ 8	≥ 8	≥ 8	1 to ≥ 8	–
ESBL producers	≥ 8	≥ 8	≥ 8 to ≥ 8	4	≥ 8	1 to ≥ 8	–
Imipenem susceptible[g]	1[e]	NA	0.25–2	0.5[e]	NA	0.12–0.5	2
MDR[h], non-CF	32[e]	NA	8–64	4[e]	NA	2–8	8
MDR[h], CF	64[e]	NA	64	16[e]	NA	8–16	4
Serratia marcescens	NA	NA	4 to > 16	NA	NA	≤ 0.25 to 4	NA
Stenotrophomonas maltophilia	> 64	> 64	2 to > 64	> 64	> 64	2 to > 64	–
Serine carbapenemase producers	8	> 16	2 to > 16	≤ 0.25	1	≤ 0.25 to 4	> 16
Enterobacteriaceae, non-Proteeae[i]	≤ 0.5	1	≤ 0.5 to > 32	0.12	0.5	≤ 0.03 to > 32	2
Imipenem non-susceptible[f]	2	> 32	2 to > 32	1	2	≤ 0.5 to > 32	> 16
ESBL producers	2[e]	NA	2 to ≥ 8	0.5[e]	NA	≤ 0.25 to 4	4
KPC producers	8	64	0.5 to > 128	0.25	0.5	0.06–2	128

Adapted from references [6, 7, 36, 40, 45, 47–54, 57]

ESBL extended-spectrum β-lactamase, *CF* cystic fibrosis, *KPC Klebsiella pneumoniae* carbapenemase, *MDR* multidrug-resistant, MIC_{50}, minimum concentration (mg/L) to inhibit growth of 50% of isolates, *MIC_{90}* minimum concentration (mg/L) to inhibit growth of 90% of isolates, *NA* data not available

[a]Fixed relebactam concentration of 4 mg/L

[b]MIC_{90} not calculated when there were less than ten isolates

[c]Fold reductions calculated using MIC_{90} values or MIC_{50} values if MIC_{90} data not available, represents reduction in MIC values with the addition of relebactam, – no reduction

[d]Imipenem MIC ≥ 4 mg/L

[e]Median MIC, less than ten isolates

[f]Imipenem MIC ≥ 2 mg/L

[g]Imipenem MIC ≤ 2 mg/L

[h]Resistant to multiple antimicrobial agents

[i]Species not identified, all isolates were non-Proteeae due to intrinsic non-susceptibility to imipenem

(extensively drug resistant) isolates and CRE. The activity of meropenem against Gram-negative bacteria is either retained or enhanced with the addition of vaborbactam. Significant increases in activity of meropenem with the addition of vaborbactam are observed against meropenem non-susceptible, β-lactamase- (ESBL, KPC and other carbapenemase) producing, and MDR Enterobacteriaceae including CRE (32 to ≥ 256-fold MIC reductions). The addition of vaborbactam had little impact on the activity of meropenem against *A. baumannii* and *P. aeruginosa*. Meropenem–vaborbactam MIC_{90} values for *Acinetobacter* spp., *S. maltophilia*, non-KPC-producing CRE, and metallo-β-lactamase-producing and XDR Enterobacteriaceae

Table 5 In vitro activity (MIC, mg/L) of imipenem and imipenem–relebactam against Enterobacteriaceae and *Pseudomonas aeruginosa* expressing specific β-lactamase enzymes

Organism	β-lactamase enzyme	*n*	Imipenem			Imipenem–relebactam[a]			MIC fold reduction[b]
			MIC_{50}[c]	MIC_{90}[d]	Range	MIC_{50}[c]	MIC_{90}[d]	Range	
Acinetobacter baumannii									
	OXA-23	58	> 16	> 16	≤ 0.03 to > 16	> 16	> 16	≤ 0.03 to > 16	–
Enterobacter spp.									
	AmpC	10	0.5	1	0.12–1	0.12	0.25	0.12–1	4
Klebsiella pneumoniae									
	KPC-2 (OmpK35-/OmpK36red)	1	16	NA	16	0.125	NA	0.125	128
	KPC-3 (OmpK35red/OmpK36red)	1	4	NA	4	0.125	NA	0.125	32
	OXA-48	5	4	NA	4 to > 64	2	NA	0.5 to > 64	2
Pseudomonas aeruginosa									
	AmpC	8	2	NA	2–32	1	NA	0.5–4	2
Pseudomonas aeruginosa, Imipenem non-susceptible[e]									
	AmpC	1	≥ 8	NA	≥ 8	≥ 8	NA	≥ 8	–
	AmpC constitutive (OprD-)	2	32	NA	8–32	2	NA	0.5–2	16
	AmpC inducible (OprD-)	2	8	NA	4–8	0.5	NA	0.25–0.5	16
	ESBL ± GES	9	≥ 8	NA	≥ 8 to ≥ 8	≥ 8	NA	≥ 8 to ≥ 8	–
	GES-2, OXA-5, PDC-8	1	32	NA	32	8	NA	8	4
	GES-1, GES-5, GES-11, GES-14, OXA-2, PDC-19	1	64	NA	64	32	NA	32	2
	IMP	6	≥ 8	NA	4 to ≥ 8	≥ 8	NA	4 to ≥ 8	–
	IMP, VIM	3	≥ 8	NA	≥ 8 to ≥ 8	≥8	NA	≥ 8 to ≥ 8	–
	MBL (9 IMP, 10 VIM)	19	> 64	> 64	8 to > 64	> 64	> 64	8 to > 64	–
	VIM	26	≥ 8	≥ 8	≥ 8 to ≥ 8	≥ 8	≥ 8	≥ 8 to ≥ 8	–
E. coli, *K. pneumoniae*, *Enterobacter* spp.									
	IMP	2/12/7	16	64	4 to > 64	16	64	4 to > 64	–
	NDM	5/10/5	64	> 64	16 to > 64	64	> 64	16 to > 64	–
	VIM	1/12/7	32	> 64	16 to > 64	32	> 64	16 to > 64	–
K. pneumoniae, *Enterobacter* spp.									
	AmpC or ESBL with impermeability	5/5	4	8	2–16	0.5	1	0.25–1	8
	KPC	5/5	16	64	4 to > 64	0.25	0.5	0.12–1	128
NPE[f], Imipenem non-susceptible[g]									
	AmpC	1	2	NA	2	0.5	NA	0.5	4
	AmpC ± ESBL ± KPC	187	≥ 8	≥ 8	2 to ≥ 8	≤ 0.25	1	≤ 0.25 to 2	≥ 8
	ESBL, KPC, OXA-48	2	≥ 8	NA	≥ 8 to ≥ 8	1	NA	≤ 0.25 to 1	≥ 8
	ESBL ± NDM	33	≥ 8	≥ 8	4 to ≥ 8	≥ 8	≥8	4 to ≥ 8	–
	ESBL, VIM	2	4	NA	2–4	4	NA	2–4	–
	OXA-48	1	2	NA	2	1	NA	1	2

Adapted from references [7, 32, 36, 45, 46]

ESBL extended-spectrum β-lactamase, *KPC Klebsiella pneumoniae* carbapenemase, *MBL* metallo-β-lactamase, *MIC_{50}* minimum concentration (mg/L) to inhibit growth of 50% of isolates, *MIC_{90}* minimum concentration (mg/L) to inhibit growth of 90% of isolates, *n* number of isolates, *NA* data not available, *NPE* non-Proteeae Enterobacteriaceae, *OmpK35red/OmpK36red Klebsiella* outer membrane porin 35/36 reduced, *OmpK35- Klebsiella* outer membrane porin 35 negative, *OprD* outer membrane porin D negative

[a]Fixed relebactam concentration of 4 mg/L

[b]Fold reductions calculated using MIC_{50} values or MIC_{90} values when available, represents reduction in MIC values with the addition of relebactam, – no reduction

[c]Actual MIC recorded for n of 1; median MIC recorded for less than ten isolates

[d]MIC_{90} not calculated when there were less than ten isolates

[e]Imipenem MIC ≥ 4 mg/L

[f]Species not identified, all isolates were non-Proteeae due to intrinsic non-susceptibility to imipenem, original spectrum β-lactamases (e.g. TEM-1) and intrinsic chromosomally-encoded AmpC β-lactamase common to *Enterobacter* and *Serratia* spp. are not included

[g]Imipenem MIC ≥ 2 mg/L

Table 6 In vitro activity (MIC, mg/L) of imipenem and imipenem–relebactam against anaerobes

Organism	Imipenem			Imipenem–relebactam[a]		
	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}	Range
Gram-negative anaerobes						
Bacteroides caccae	0.25	0.25	≤ 0.03 to > 32	0.25	0.25	≤ 0.03 to > 32
Bacteroides fragilis	0.25	0.5	≤ 0.06 to 16	0.25	0.5	≤ 0.03 to 16
Bacteroides non-fragilis group	0.5	1	≤ 0.06 to 16	0.25	1	≤ 0.06 to 16
Bacteroides ovatus	0.25	1	≤ 0.06 to 8	0.25	0.5	0.12 to 4
Bacteroides thetaiotaomicron	0.25	1	≤ 0.06 to 16	0.25	0.5	≤ 0.06 to 16
Bacteroides uniformis	0.25	0.5	≤ 0.06 to 1	0.25	0.5	0.12 to 1
Bacteroides vulgatus	0.5	1	0.06 to 4	0.5	1	0.06 to 2
Bacteroides spp.	0.5	2	0.125 to 2	0.25	2	0.125 to 2
Decreased imipenem susceptibility	8	> 32	4 to > 32	8	> 32	0.5 to > 32
Bilophila wadsworthia	16	16	0.5 to > 32	0.25	4	0.125 to > 32
Desulfovibrio spp.	0.5	0.5	0.25 to 0.5	0.25	0.5	0.125 to 0.5
Parabacteroides distasonis	0.5	1	0.12 to 8	0.5	1	0.12 to 4
Parabacteroides goldsteinii	1	2	0.5 to 4	1	2	0.25 to 4
Parabacteroides merdae	1	8	0.5 to 16	1	4	0.5 to 16
Prevotella bivia	0.06	0.125	≤ 0.03 to 0.125	0.06	0.125	≤ 0.03 to 0.125
Prevotella buccae	0.125	0.125	0.06 to 0.25	0.125	0.125	0.06 to 0.25
Prevotella melaninogenica	≤ 0.03	0.06	≤ 0.03 to 0.06	≤ 0.03	≤ 0.03	≤ 0.03 to ≤ 0.03
Prevotella spp.	0.06	0.125	≤ 0.03 to 0.125	0.06	0.125	≤ 0.03 to 0.125
Porphyromonas spp.	≤ 0.03	0.06	≤ 0.03 to 0.06	≤ 0.03	≤ 0.03	≤ 0.03 to ≤ 0.03
Fusobacterium nucleatum	0.06	0.06	0.06 to 0.125	≤ 0.03	0.03	≤ 0.03 to 0.06
Fusobacterium necrophorum	0.5	2	0.06 to 2	0.125	0.5	≤ 0.03 to 0.5
Fusobacterium mortiferum	2	2	1 to 4	2	2	1 to 2
Fusobacterium varium	16	16	2 to 16	4	4	2 to 4
Veillonella spp.	0.5	1	0.06 to 1	0.5	0.5	0.06 to 0.5
Gram-positive anaerobes						
Clostridium clostridioforme group	2	4	1 to 4	2	4	1 to 4
Clostridium innocuum	1	2	0.25 to 4	2	2	0.5 to 4
Clostridium perfringens	0.125	0.125	0.06 to 0.25	0.125	0.125	0.06 to 0.25
Clostridium spp.	0.25	0.5	0.06 to 0.5	0.25	0.5	0.06 to 0.5
Clostridium difficile	4	8	4 to 8	4	4	4 to 8
Eggerthella lenta	0.5	0.5	≤ 0.03 to 0.5	0.5	0.5	≤ 0.03 to 0.5
Finegoldia magna	0.06	0.06	≤ 0.03 to 0.06	0.06	0.06	≤ 0.03 to 0.06
Parvimonas micra	≤ 0.03	0.06	≤ 0.03 to 0.06	≤ 0.03	0.06	≤ 0.03 to 0.06
Peptoniphilus harei	≤ 0.03	≤ 0.03	≤ 0.03 to ≤ 0.03	≤ 0.03	≤ 0.03	≤ 0.03 to ≤ 0.03
Peptostreptococcus anaerobius	0.06	0.06	≤ 0.03 to 0.25	0.06	0.06	≤ 0.03 to 0.5
Non-spore-forming bacilli	0.06	0.5	≤ 0.03 to 2	0.06	0.5	≤ 0.03 to 0.5

Adapted from references [55, 56]

MIC_{50} minimum concentration (mg/L) to inhibit growth of 50% of isolates, *MIC_{90}* minimum concentration (mg/L) to inhibit growth of 90% of isolates

[a]Fixed relebactam concentration of 4 mg/L

continued to remain above the CLSI breakpoint for meropenem.

Table 8 shows in vitro activity of meropenem–vaborbactam compared to meropenem alone against Enterobacteriaceae expressing specific β-lactamase enzymes [9, 59, 64, 69–73]. Vaborbactam significantly improved the activity of imipenem against Enterobacteriaceae isolates producing β-lactamases from Ambler class A and C (4- to ≥ 1024-fold MIC reduction), including KPC carbapenemases (> 32- to ≥ 128-fold reduction). The addition of

Table 7 In vitro activity (MIC, mg/L) of meropenem and meropenem–vaborbactam against Gram-negative aerobes

Gram-negative aerobes	Meropenem			Meropenem–vaborbactam[a]			MIC fold reduction[c]
	MIC_{50}	MIC_{90}[b]	Range	MIC_{50}	MIC_{90}[b]	Range	
Acinetobacter baumannii	32	64	4 to > 64	32	64	1 to > 64	–
Acinetobacter spp.	NA	NA	NA	32	> 32	0.03 to > 32	NA
Citrobacter freundii species complex	NA	NA	NA	≤ 0.015	0.03	≤ 0.015 to 8	NA
KPC producers	4	8	1–8	≤ 0.06	0.12	≤ 0.06 to 0.25	64
Citrobacter spp.	NA	NA	NA	≤ 0.015	0.03	≤ 0.015 to 0.06	NA
Citrobacter koseri	NA	NA	NA	≤ 0.015	0.03	≤ 0.015 to 0.03	NA
Enterobacter aerogenes	NA	NA	NA	0.03	0.03	≤ 0.015 to 2	NA
Enterobacter cloacae	4	16	≤ 0.03 to > 64	≤ 0.06	0.25	0.03–4	64
Enterobacter cloacae species complex	NA	NA	NA	≤ 0.015	0.03	≤ 0.015 to 8	NA
KPC producers	8	> 32	2 to > 32	≤ 0.03	0.12	≤ 0.03 to 0.12	> 256
Escherichia coli	≤ 0.015	0.03	≤ 0.015 to > 32	≤ 0.015	0.03	≤ 0.015 to > 32	–
Meropenem non-susceptible[d]	4[e]	NA	2 to 8	≤ 0.015[e]	NA	≤ 0.015 to 0.5	≥ 256
KPC producers	4	8	0.5 to 32	≤ 0.03	≤ 0.03	≤ 0.03 to 0.12	≥ 256
ESBL producers	≤ 0.015	0.06	≤ 0.015 to 8	≤ 0.015	0.03	≤ 0.015 to 2	2
Klebsiella oxytoca	NA	NA	NA	0.03	0.03	≤ 0.015 to 16	NA
KPC producers	4	32	2 to > 64	≤ 0.06	0.5	≤ 0.06 to 2	64
Klebsiella pneumoniae	0.03	0.03	≤ 0.015 to > 32	0.03	0.03	≤ 0.015 to > 32	–
Carbapenem non-susceptible[d]	16	> 32	2 to > 32	0.03	0.5	≤ 0.015 to > 32	> 64
KPC producers	16	64	0.25 to > 64	0.03	1	≤ 0.004 to > 64	64
ESBL producers	0.03	NA	≤ 0.015 to 2	0.03	0.5	≤ 0.015 to 2	–
Klebsiella spp., KPC producers	> 32	> 32	2 to > 32	0.12	1	≤ 0.03 to > 32	> 32
Proteus mirabilis	NA	NA	NA	0.06	0.12	≤ 0.015 to 16	NA
Proteus spp., indole-positive	NA	NA	NA	0.06	0.06	≤ 0.015 to > 32	NA
Pseudomonas aeruginosa	0.5	8	≤ 0.015 to > 64	0.5	8	≤ 0.015 to 64	–
Serratia marcescens	NA	NA	NA	0.03	0.06	≤ 0.015 to 32	NA
Serratia spp.	NA	NA	NA	0.06	0.06	≤ 0.015 to 0.2	NA
Stenotrophomonas maltophilia	NA	NA	NA	> 32	> 32	≤ 0.015 to > 32	NA
Enterobacteriaceae[f]	≤ 0.015	0.06	≤ 0.015 to > 32	≤ 0.015	0.06	≤ 0.015 to > 32	–
CRE[g]	16	> 32	2 to > 32	0.03	2	≤ 0.015 to > 32	> 16
Non-KPC-producing CRE[g]	8	> 32	0.25 to > 32	4	> 32	≤ 0.015 to > 32	–
Serine carbapenemase producers	16	> 64	≤ 0.06 to > 64	≤ 0.06	1	≤ 0.06 to > 64	> 64
Carbapenemase producers	16	> 32	0.5 to > 32	0.03	1	≤ 0.015 to 2	> 32
Carbapenemase-negative	4	16	0.25 to > 32	1	4	≤ 0.015 to 32	4
KPC producers	32	> 32	0.5 to > 64	0.25	1	≤ 0.015 to > 64	> 32
Multiple β-lactamase producers	32	> 64	2 to > 64	≤ 0.06	1	≤ 0.06 to 16	> 64
KPC/ESBL producers	> 32	> 32	2 to > 32	0.06	1	≤ 0.03 to 4	> 32
ESBL producers	0.03	16	≤ 0.015 to > 32	≤ 0.015	0.12	≤ 0.015 to 2	128
Non-CRE[g] ESBL producers	0.03	0.06	≤ 0.015 to 2	0.03	0.03	≤ 0.015 to 2	2
MBL producers	32	> 32	1 to > 32	32	> 32	1 to > 32	–
MDR[h]	0.06	32	≤ 0.015 to > 32	0.03	1	≤ 0.015 to > 32	32

Table 7 continued

Gram-negative aerobes	Meropenem			Meropenem–vaborbactam[a]			MIC fold reduction[c]
	MIC_{50}	MIC_{90}[b]	Range	MIC_{50}	MIC_{90}[b]	Range	
XDR[i]	16	> 32	≤ 0.015 to > 32	0.5	32	≤ 0.015 to > 32	> 1

Adapted from references [9, 59–68]

CRE carbapenem-resistant Enterobacteriaceae, *ESBL* extended-spectrum β-lactamase, *KPC Klebsiella pneumoniae* carbapenemase, *MBL* metallo-β-lactamase, *MDR* multi-drug resistant, MIC_{50} minimum concentration (mg/L) to inhibit growth of 50% of isolates, MIC_{90} minimum concentration (mg/L) to inhibit growth of 90% of isolates, *NA* data not available, *XDR* extensively drug resistant

[a]Fixed vaborbactam concentration of 8 mg/L

[b]MIC_{90} not calculated when there were less than ten isolates

[c]Fold reductions calculated using MIC_{90} values or MIC_{50} values if MIC_{90} data not available, represents reduction in MIC values with the addition of vaborbactam, – no reduction

[d]Meropenem MIC ≥ 2 mg/L

[e]Median MIC, less than ten isolates

[f]Species not identified

[g]CRE defined as isolates with doripenem, imipenem, and or meropenem MIC values ≥ 2 mg/L, *P. mirabilis* and indole-positive Proteeae not included due to intrinsic resistance

[h]MDR defined as non-susceptible to at least one agent in ≥ 3 antimicrobial classes

[i]XDR defined as non-susceptible to at least one agent in all but ≤ 2 antimicrobial classes

vaborbactam did not potentiate the activity of meropenem against Enterobacteriaceae producing OXA-48-like β-lactamases. Similar to imipenem–relebactam, the majority of isolates with elevated meropenem–vaborbactam MICs will likely contain multiple resistance mechanisms including production of β-lactamases not inhibited by relebactam (most Ambler class B and D β-lactamases), porin alterations, and overexpression of efflux pumps.

No data have been published on the activity of meropenem–vaborbactam versus anaerobic bacteria or Gram-positive bacteria. Of note, neither relebactam nor vaborbactam have been shown to have antimicrobial activity alone [46, 60].

6 Pharmacokinetics

The pharmacokinetics of intravenous imipenem and meropenem have been well established. Imipenem, when administered with cilastatin, has an approximate volume of distribution (V_d) of 0.23 to 0.31 L/kg with 20% serum protein binding, 60–70% renal clearance, and an elimination half-life ($t_{½}$) of 1 h [1]. Meropenem has a V_d of 0.23–0.35 L/kg with 2% protein binding, 70% renal elimination, and half-life ($t_{½}$) of 1 h [1].

6.1 Imipenem–Relebactam

A population pharmacokinetic model of relebactam in combination with imipenem was constructed using data from three phase I trials in healthy adults and one phase II study in patients with cIAIs [74]. Relebactam pharmacokinetics were described by a two-compartment, linear model with first order elimination. Co-administration of imipenem and relebactam had no effect on the pharmacokinetics of either agent. The population estimates for the central volume, peripheral volume, and total clearance of relebactam were 12.1 L [relative standard error (RSE), 5.4%], 5.9 L (RSE, 5.8%), and 8.0 L/h (RSE, 2.7%), respectively.

Results from four Phase I pharmacokinetic studies of relebactam are summarized in Table 9 [75–78]. The phase I studies in healthy individuals describe a total V_d of 11.9–12.3 L in females, 14.0–17.7 L in males, and 22.8 L in hemodialysis patients [75–78]. Relebactam is approximately 20% bound to plasma proteins [74, 77]. A phase I study by Rhee et al evaluated the intrapulmonary pharmacokinetics of relebactam and imipenem after 5 doses of imipenem/cilastatin-relebactam 500/500/250 mg administered q6 h [77]. Epithelial lining fluid (ELF) penetration was determined from the ratio of area under the concentration-time curve (AUC) in ELF to free AUC (*f*AUC) in plasma. The relative exposures in ELF versus plasma were 53 and 54% for imipenem and relebactam, respectively.

Relebactam is at least 90% renally eliminated as unchanged parent, with a total CL and $t_{½}$ ranging from 5.3 to 9.1 L/h and 1.2 to 2.1 h, respectively [74–77]. The AUC achieved with 125 mg and 250 mg of relebactam ranged from 14.9 to 17.1 mg·h/L and 28.6 to 30.0 mg·h/L, respectively, with higher exposures in renal impairment and elderly subjects [75–77]. A study by Rizk et al. of relebactam pharmacokinetics in subjects with varying

Table 8 In vitro activity (MIC, mg/L) of meropenem and meropenem–vaborbactam against Enterobacteriaceae expressing specific β-lactamase enzymes

Organism	β-lactamase enzyme	*n*	Meropenem			Meropenem–vaborbactam[a]			MIC fold reduction[b]
			MIC_{50}[c]	MIC_{90}[d]	Range	MIC_{50}[c]	MIC_{90}[d]	Range	
Enterobacteriaceae									
	KPC-2	242	> 32	> 32	4 to > 32	0.25	1	≤ 0.03 to 16	> 32
	KPC-3	252	> 32	> 32	2 to > 32	0.25	1	≤ 0.03 to 16	> 32
	KPC-9	2	> 32	NA	> 32	0.5	NA	0.5 to 0.5	> 64
	OXA-48-like	25	16	> 32	0.5 to > 32	16	> 32	0.5 to > 32	–
Enterobacter cloacae									
	AmpC, KPC-3	1	32	NA	32	≤ 0.06	NA	≤ 0.06	≥ 512
	KPC-2, TEM-1	1	8	NA	8	≤ 0.06	NA	≤ 0.06	≥ 128
	KPC-3, SHV-11, TEM-1	1	32	NA	32	≤ 0.06	NA	≤ 0.06	≥ 512
	KPC-3, TEM	2	> 256	NA	8 to > 256	4	NA	≤0.06 to 4	> 64
	NMC-A	1	16	NA	16	≤ 0.06	NA	≤0.06	≥ 256
	SHV ESBL, TEM	2	8	NA	2 to 8	≤ 0.06	NA	≤0.06 to ≤ 0.06	≥ 128
Escherichia coli									
	KPC-2, SHV-12	1	32	NA	32	≤ 0.06	NA	≤ 0.06	≥ 512
	KPC-3	1	8	NA	8	≤ 0.06	NA	≤ 0.06	≥ 128
Klebsiella oxytoca									
	FOX-like, TEM	1	4	NA	4	≤ 0.06	NA	≤ 0.06	≥ 64
	OXA-2-like, OXY	1	4	NA	4	≤ 0.06	NA	≤ 0.06	≥ 64
	OXA-2-like, SHV ESBL	1	16	NA	16	≤ 0.06	NA	≤ 0.06	≥ 256
Klebsiella pneumoniae									
	AmpC, SHV, TEM	1	64	NA	64	≤ 0.06	NA	≤ 0.06	≥ 1024
	CMY-2-like, CTX-M-15-like, SHV, TEM	1	64	NA	64	1	NA	1	64
	CMY-2-like, SHV	1	32	NA	32	≤ 0.06	NA	≤ 0.06	≥ 512
	CMY-2-like, TEM	1	> 64	NA	> 64	1	NA	1	> 64
	CTX-M-15, KPC-2, SHV-11, TEM-1	1	32	NA	32	0.125	NA	0.125	256
	CTX-M-15-like, OXA-1/30, SHV, TEM	1	> 64	NA	> 64	≤ 0.06	NA	≤ 0.06	> 1024
	CTX-M-15-like, SHV ESBL, SHV, TEM	1	16	NA	16	≤ 0.06	NA	≤ 0.06	≥ 256
	CTX-M-15-like, SHV	4	16	NA	4 to > 64	≤ 0.06	NA	≤ 0.06 to 2	≥ 256
	CTX-M-15-like, SHV, TEM	6	64	NA	8 to > 64	0.5	NA	≤ 0.06 to 2	32
	KPC-2	2	128	NA	32 to 128	1	NA	≤ 0.06 to 1	128
	KPC-2, TEM-1, LEN-17	1	512	NA	512	4	NA	4	128
	KPC-2, SHV, TEM	2	> 64	NA	4 to > 64	8	NA	≤ 0.06 to 8	> 8
	KPC-2, SHV-11, TEM-1	2	512	NA	32 to 512	8	NA	≤ 0.06 to 8	64
	KPC-3, SHV, TEM	1	≥ 256	NA	≥ 256	4	NA	4	≥ 64
	KPC-3, SHV-11, TEM	2	128	NA	128 to 128	0.5	NA	0.25 to 0.5	256
	KPC-3, SHV-11, TEM-1	3	16	NA	16 to 64	≤ 0.06	NA	≤ 0.06 to 0.5	≥ 256
	OXA-1/30, SHV ESBL, TEM	1	4	NA	4	≤ 0.06	NA	≤ 0.06	≥ 64
	SHV ESBL, SHV	2	32	NA	16 to 32	≤ 0.06	NA	≤ 0.06 to ≤ 0.06	≥ 512

Table 8 continued

Organism	β-lactamase enzyme	*n*	Meropenem			Meropenem–vaborbactam[a]			MIC fold reduction[b]
			MIC_{50}[c]	MIC_{90}[d]	Range	MIC_{50}[c]	MIC_{90}[d]	Range	
	SHV ESBL, SHV, TEM	39	32	> 64	4 to > 64	≤ 0.06	1	≤ 0.06 to 16	> 64
	SHV ESBL, TEM	13	16	64	2 to > 64	≤ 0.06	≤0.06	≤ 0.06 to 0.5	≥ 1024
	SHV-5, TEM-1	3	2	NA	0.015 to 32	0.015	NA	0.008–0.06	128
	SHV-11	1	0.03	NA	0.03	0.008	NA	0.008	4
	SHV-11, TEM-1	4	4	NA	0.015 to 32	0.015	NA	0.015–0.5	256
	SHV-11, SHV-12	1	0.015	NA	0.015	0.008	NA	0.008	2
	SHV-12	4	0.03	NA	0.015 to 16	0.015	NA	0.008–0.06	2
	SHV-12, TEM-1	10	4	> 64	0.015 to > 64	0.06	1	0.008–2	> 64
	TEM-1	2	0.06	NA	0.06–0.06	0.015	NA	0.008–0.015	4
Raoultella ornithinolytica									
	SHV ESBL, TEM	1	16	NA	16	≤ 0.06[d]	NA	≤ 0.06	≥ 256
Raoultella planticola									
	FOX-like, PSE-like, SHV ESBL	1	16	NA	16	≤ 0.06[d]	NA	≤ 0.06	≥ 256

Adapted from references [9, 59, 64, 69–73]

ESBL extended-spectrum β-lactamase, *KPC Klebsiella pneumoniae* carbapenemase, *MIC_{50}* minimum concentration (mg/L) to inhibit growth of 50% of isolates, *MIC_{90}* minimum concentration (mg/L) to inhibit growth of 90% of isolates, *n* number of isolates, *NA* data not available

[a]Fixed vaborbactam concentration of 8 mg/L

[b]Fold reductions calculated using MIC_{50} values or MIC_{90} values when available, represents reduction in MIC values with the addition of vaborbactam, – no reduction

[c]Actual MIC recorded for n of 1, Median MIC recorded for less than ten isolates

[d]MIC_{90} not calculated when there were less than ten isolates

degree of renal function showed reduced CL with decreasing renal function [78]. The relative increases in AUC compared to healthy matched controls are detailed in Table 9. The study also reported that approximately half of the administered doses of imipenem, cilastatin, and relebactam were removed by hemodialysis. The authors suggested recommending dosing adjustments for imipenem with renal impairment can be maintained with the addition of relebactam.

6.2 Meropenem-Relebactam

The population pharmacokinetics of vaborbactam in combination with meropenem were studied using data from two phase I trials in healthy subjects and two phase II trials in patients with cUTIs or other CRE infections [79]. Vaborbactam pharmacokinetics were described by a two-compartment model with first order elimination. The mean population estimates for the non-renal clearance, maximum renal clearance, V_c, and V_p were 0.169 L/h [standard error of the mean (SEM), 12.5%], 9.34 L/h (SEM, 3.3%), 16.9 L (SEM, 3.9%), and 1.41 L (SEM, 27.2%), respectively.

Results from three phase I pharmacokinetics studies of vaborbactam are summarized in Table 10 [80–82]. Griffith et al determined that co-administration of meropenem and vaborbactam did not alter the pharmacokinetics of either agent [80]. The total V_d for vaborbactam from phase I studies ranged from 17.5 to 21.8 L in healthy adults [80–82]. Vaborbactam is approximately 33% protein bound in plasma [81]. A Phase I study by Wenzler et al. determined ELF penetration following three doses of meropenem–vaborbactam 2000/2000 mg administered q8 h [82]. ELF penetration according to the ratio of AUC in ELF to *f*AUC in plasma, was 65 and 79% for meropenem and vaborbactam, respectively.

Vaborbactam pharmacokinetic studies demonstrated 80 to 90% renal elimination with total CL and $t_{½}$ of 10.1–14.0 L/h and 1.3–2.0 h, respectively [80–82]. The AUC achieved with 2000 mg of vaborbactam ranged from 145.0 to 204 mg·h/L [80–82]. The population pharmacokinetic study by Trang et al. characterized relationships between glomerular filtration rate and drug CL, which were similar for meropenem and vaborbactam. As such, dose adjustments based upon estimated glomerular filtration rate

Table 9 Pharmacokinetics of relebactam administered alone and co-administered with imipenem/cilastatin

Study	Subject demographics	Relebactam dose (imipenem/cilastatin dose)[a]	*n*	C_{EOI} (mg/L)[b,c]	V_d (L)[b]	CL (L/h)[b]	$t_{½}$ (h)[d]	AUC (mg·h/L)[b,c,e]
Butterton et al. [75]	Healthy males (19–45 years, BMI ≤ 30 kg/m^2, $CL_{CR} \geq 80$ mL/min)	125 mg (0/0 mg) × 1	6	7.9 ± 2.0	17.2 ± 3.2	8.9 ± 0.9	1.6 ± 0.1	14.9 ± 1.6
		250 mg (0/0 mg) × 1		15.6 ± 2.9	18.4 ± 2.9	9.1 ± 1.0	1.6 ± 0.1	29.1 ± 3.3
Jumes et al. [76]	Healthy adult males	125 mg (500/500 mg) q6 h (day 1)	6	9.4 ± 1.4	NA	NA	1.4 ± 0.2	15.7 ± 2.0
		125 mg (500/500 mg) q6 h (day 7)		10.0 ± 1.7	14.0 ± 2.4	7.9 ± 1.9	1.4 ± 0.2	15.8 ± 2.0
		250 mg (500/500 mg) q6 h (day 1)	6	17.2 ± 3.3	NA	NA	1.6 ± 0.2	28.6 ± 4.1
		250 mg (500/500 mg) q6 h (day 7)		17.9 ± 4.0	16.4 ± 2.6	8.3 ± 1.6	1.6 ± 0.2	30.0 ± 4.9
	Healthy females (18–45 years)	125 mg (500/500 mg) × 1	6	10.5 (8.9, 12.4)	12.3 (10.8, 14.0)	7.6 (6.7, 8.7)	1.3 ± 0.1	17.1 (15.0, 22.6)
	Healthy females (60–75 years)	125 mg (500/500 mg) × 1	6	10.9 (9.2, 12.8)	11.9 (10.5, 13.5)	5.3 (4.7, 6.1)	1.9 ± 0.3	24.4 (21.4, 27.9)
	Healthy males (60–75 years)	125 mg (500/500 mg) × 1	6	7.2 (6.1, 8.5)	17.7 (15.6, 20.2)	6.6 (5.8, 7.5)	2.1 ± 0.4	19.8 (17.3, 22.6)
Rhee et al. [77]	Healthy adults (18–45 years, BMI ≤ 32 kg/m^2, $CL_{CR} \geq 80$ mL/min)	250 mg (500/500 mg) q6 h × 5	16	16.7 (C_{max})	NA	NA	1.2	28.3
Rizk et al. [78]	Renal function[f,g]:							
	>50 to <80 mL/min/1.73 m^2	125 mg (250/250 mg) × 1	5–6	9.6 (8.1, 11.2)	16.3 (13.8, 19.1)	5.1 (3.5, 7.5)	2.5 ± 0.6	25.2 (19.1, 33.2) [1.6 × control][f]
	30–50 mL/min/1.73 m^2	125 mg (250/250 mg) × 1	6	8.2 (7.0, 9.5)	19.4 (16.3, 23.0)	3.2 (2.1, 4.8)	4.5 ± 1.3	38.3 (29.5, 49.7) [2.2 × control][f]
	<30 mL/min/1.73 m^2	125 mg (250/250 mg) × 1	6	8.1 (7.0, 9.3)	18.3 (15.6, 21.5)	1.6 (1.1, 2.4)	7.6 ± 2.1	79.6 (62.2, 101.7) [4.6 × control][f]
	Requiring hemodialysis	125 mg (250/250 mg) × 1	4–6	6.1 (5.1, 7.3)	22.8 (19.4, 26.9)	0.7 (0.5, 1.0)	12.5 ± 25.5	108.4 (79.9, 146.9) [6.7 × control][f]

AUC area under the concentration-time curve, *BMI* body mass index, *CL* clearance, CL_{CR} creatinine clearance, C_{EOI} concentration at end of infusion, *NA* data not available, *q6 h* every 6 h, $t_{½}$ half-life, V_d volume of distribution

[a]Intravenously infused over 30 min

[b]Mean ± standard deviation or geometric mean (95% confidence interval)

[c]Original data reported as μM and converted to mg/L using a conversion factor of 0.348 based on the molecular weight of relebactam

[d]Harmonic mean ± standard deviation

[e]AUC from 0 to ∞ for single doses and over a dosing interval for multiple doses

[f]Subjects matched to healthy control subjects with estimated glomerular filtration rate ≥ 80 mL/min/1.73 m^2 based on age, gender, race, and BMI

[g]Reported as 24 h creatinine clearance or estimated glomerular filtration rate

Table 10 Pharmacokinetics of vaborbactam administered alone and co-administered with meropenem

Study	Subject demographics	Vaborbactam dose (meropenem dose)[a]	*n*	C_{max} (mg/L)[b]	V_d (L)[b]	CL (L/h)[b]	$t_{1/2}$ (h)[b]	AUC (mg·h/L)[b,c]
Griffith et al. [81]	Healthy adults (18–55 years, BMI < 30 kg/m^2, $CL_{CR} \geq 80$ mL/min)	2000 mg (0 mg) × 1	6	41.6 ± 4.8	21.8 ± 2.3	14.0 ± 1.4	1.5 ± 0.1	144.0 ± 13.9
		2000 mg (0 mg) q8 h × 7 days	6	40.9 ± 4.7	NA	14.0 ± 1.8	1.7 ± 0.1	145.0 ± 15.8
Griffith et al. [80]	Healthy adults (18–55 years)	2000 mg (0 mg) × 1	8	51.4 ± 16.2	21.4 ± 3.3	13.4 ± 3.2	1.4 ± 0.2	159.2 ± 44.6
		2000 mg (2000 mg) × 1	8	51.7 ± 7.3	21.8 ± 3.5	12.1 ± 2.1	2.0 ± 0.8	170.4 ± 32.0
		2000 mg (2000 mg) q8 h × 3	8	55.6 ± 11.0	17.5 ± 2.0	10.4 ± 1.9	1.4 ± 0.2	190.4 ± 32.9
Wenzler et al. [82]	Healthy adults (18–55 years, weight 80 ± 9 kg[b], CL_{CR} 94 ± 23 mL/min[b])	2000 mg (2000 mg) q8 h × 3	25	59.0 ± 8.4	17.6 ± 2.6	10.1 ± 1.9	1.3 ± 0.2	204 ± 34.6

AUC area under the concentration-time curve, *BMI* body mass index, *CL* clearance, CL_{CR} creatinine clearance, C_{max} maximum plasma concentration, *NA* data not available, *q8 h* every 8 h, $t_{½}$ half-life, V_d volume of distribution

[a]Intravenously infused over 3 h

[b]Mean ± standard deviation[c]AUC from 0 to ∞ for single doses and over a dosing interval for multiple doses

(eGFR) thresholds for meropenem are expected to be appropriate for vaborbactam [79].

7 Pharmacodynamics

7.1 Imipenem–Relebactam

The pharmacodynamics of relebactam were studied by Mavridou et al. in a neutropenic murine thigh model of β-lactamase-producing isolates of *K. pneumoniae* ($n = 2$) and *P. aeruginosa* ($n = 4$) [46]. Treatment included imipenem at various doses every 2 h with or without relebactam at various doses and intervals over 24 h. Antimicrobial activity correlated with relebactam exposure (i.e. $fAUC_{24h}$), where bacteriostasis was associated with a mean $fAUC_{24h}$ of 26.0 mg·h/L and range of 6.3–45.2 mg·h/L depending on imipenem dose and MIC.

The in vivo activity of imipenem–relebactam was evaluated by Powles et al in a neutropenic murine model of pulmonary infection with imipenem-resistant *P. aeruginosa* and systemic infection with imipenem-resistant *P. aeruginosa* and *K. pneumoniae* [83]. Treatment was initiated 15 min post-infection in both models, and also delayed 16.5 h in the pulmonary model. Relebactam doses from 10 to 80 mg/kg were studied in combination with imipenem/cilastatin [5/50 mg/kg q6 h, with a 1-h infusion time (*t*')] for 24 h. Bactericidal activity (≥ 3-$\log_{10}$ bacterial kill) was observed with immediate treatment with regimens containing relebactam 20 mg/kg for systemic *P. aeruginosa* infection, whereas 40 mg/kg was required for bactericidal activity in *P. aeruginosa* pulmonary and *K. pneumoniae* systemic infections. Delayed treatment with relebactam at a dose of 20 mg/kg was bacteriostatic in the *P. aeruginosa* pulmonary model. The authors characterized an association between bacteriostatic activity and a relebactam AUC_{24h} of 52.2 mg·h/L equivalent to a $fAUC_{24h}$ of 41.8 mg·h/L (assuming 20% protein binding).

Bhagunde et al. investigated a pharmacodynamics index for imipenem–relebactam described as the percentage of time that imipenem concentrations exceed the instantaneous MIC (%T > MIC_i), representing the reducing imipenem susceptibility with decreasing relebactam concentrations over time [84]. Their mathematical model simulated various relebactam doses in combination with imipenem (500 mg q6 h, *t*' 30 min). Antimicrobial activity was then tested in a (HFIM using a KPC-2-producing *K. pneumoniae* strain with an imipenem MIC of 64 mg/L. Bacteriostasis was observed over 48 h with an imipenem %T > MIC_i of 69% in combination with relebactam doses that achieved AUC_{24h} values of either 51.9 or 86.6 mg·h/L.

In another HFIM study by Wu et al. the activity of relebactam at doses of 125 and 250 mg in combination with imipenem (500 mg q6 h, *t*' 30 min) was tested against imipenem-resistant isolates of *P. aeruginosa* ($n = 5$) and *K. pneumoniae* ($n = 1$) [85]. Sustained bactericidal activity

was observed within 10 h for both relebactam doses against all isolates except one, *P. aeruginosa* (imipenem MIC = 64 mg/L), which required the higher dose of 250 mg for bactericidal activity. Using a pharmacodynamics parameter (%T > $MIC_{Dynamic}$) similar to the %T > MIC_i defined by Bhagunde et al. data for two *P. aeruginosa* isolates suggested maximum antimicrobial activity with an imipenem %T > $MIC_{Dynamic}$ of 40–50% [84, 85].

Finally, using a population pharmacokinetic model derived from a phase II and three phase I studies, Lucasti et al. simulated the probability of target attainment for imipenem/cilastatin-relebactam (500/500/250 mg q6 h, *t*' 30 min) against *P. aeruginosa* and KPC-producing isolates [86]. The distribution of MICs was obtained from the Study for Monitoring Antimicrobial Resistance Trends (SMART) 2011 global surveillance study. Pharmacodynamic targets were defined as an imipenem $fAUC_{24h}$/MIC of ≥ 30% and relebactam AUC_{24h} ≥ 150 μM·h (52.2 mg·h/L). The authors concluded that target attainment was achieved in at least 90% of simulated cases with imipenem–relebactam MICs at or below 2 mg/L.

7.2 Meropenem–Relebactam

The pharmacodynamics of meropenem–vaborbactam (2000/2000 mg q8 h, *t*' 3 h) were studied by Tarazi et al. in an in vitro HFIM against various carbapenem-resistant isolates over 32 h [71, 87]. Concentration profiles in the model were adapted from the pharmacokinetic data from phase I studies [71, 87]. Sustained bactericidal activity was observed within 8 h against seven β-lactamase and KPC-producing *K. pneumoniae*, three *E. cloacae*, one *E. coli*, and two meropenem non-susceptible *P. aeruginosa* [71, 87].

In another study by Tarazi et al. higher exposures of vaborbactam were also tested based on the pharmacokinetics of infected patients in phase III trials (AUC_{24h} 547 vs 343 mg·h/L), which unlike lower exposures, was able to suppress regrowth of one highly-resistant *K. pneumoniae* isolate (meropenem MIC ≥ 64 mg/L, meropenem–vaborbactam MIC = 16 mg/L) [70]. Sustained bactericidal activity was observed within 10 h against the other four isolates of KPC-producing and carbapenem-resistant *K. pneumoniae* and one isolate of *E. cloaceae*.

Griffith et al studied 17 KPC-producing CRE isolates in an HFIM and 5 isolates in a neutropenic murine thigh infection model (meropenem MICs of 8 to > 64 mg/L and meropenem–vaborbactam MICs ≤ 0.06–64 mg/L) [73]. A clinical dose equivalent to 2000 mg q8 h (*t*' 3 h) of meropenem was simulated in combination with vaborbactam exposures (i.e. AUC_{24h}) of 192, 300, and 550 mg·h/L over 32 h in the HFIM and from 0 to 725 mg·h/L over 24 h in the animal model. The ratio of vaborbactam *f*AUC to meropenem–vaborbactam MIC ($fAUC_{24h}$:MIC) was best correlated with antimicrobial activity in both models ($r^2 = 0.81$ and 0.70 in the HFIM and animal model, respectively) [73]. In the HFIM, $fAUC_{24h}$:MIC values of 12 and 36 were associated with bacteriostatic and bactericidal activity, respectively. In the thigh infection model, $fAUC_{24h}$:MIC values of 9 and 220 were associated with bacteriostasis and 2-log_{10} bacterial kill, respectively. For isolates with elevated meropenem–vaborbactam MICs of 8 to 16 mg/L (meropenem MICs > 64 mg/L), a $fAUC_{24h}$:MIC above 24 was required to prevent the emergence of resistance in the HFIM.

Finally, Bhavnani et al investigated the pharmacodynamics target attainment of meropenem–vaborbactam (2000/2000 mg q8 h, *t*' 3 h) using data from two phase III studies of cUTI, which included 175 microbiologically evaluable patients [88]. Clinical and microbiological responses ranged from 93 to 100% and 76.3 to 100%, respectively. The predicted target attainment for a meropenem %*f*T > MIC of ≥ 45% was 96.6%, with over 90% of patients achieving a %*f* T > MIC of 100%.

8 Animal Studies

The in vivo antimicrobial efficacy of imipenem–relebactam and meropenem–vaborbactam for the treatment of resistant Gram-negative infections has been evaluated in various animal models. Imipenem–relebactam has been studied in murine systemic, pulmonary, and thigh infection models, while meropenem–vaborbactam has been studied in murine thigh and urinary tract infection models. These studies are summarized in Table 11 and represent available data to date [46, 69, 83, 89]. MIC values of isolates tested in each model are included in Table 11.

8.1 Imipenem–Relebactam

As mentioned previously, Powles et al. evaluated the in vivo efficacy of imipenem–relebactam using pulmonary and systemic infection in neutropenic mice caused by imipenem-resistant *P. aeruginosa* and *K. pneumoniae* [83]. In the systemic *P. aeruginosa* and *K. pneumoniae* infection models, mice ($n = 5$ for each regimen) were intraperitoneally (IP) inoculated with 2.2×10^6 colony forming units (CFU) and 5.5×10^5 CFU, respectively. Treatment was initiated intravenously 15 min post-infection with imipenem/cilastatin at 5/50 mg/kg alone or in combination with 10–80 mg/kg relebactam q6 h for 24 h (*t*' 1 h). Spleen bacterial density was determined at the end of treatment and compared to untreated controls sacrificed at the same point in time. In the *P. aeruginosa* systemic

Table 11 Animal studies of imipenem–relebactam and meropenem–vaborbactam

Study	Animal/ infection model	Antimicrobial agent	Dose	Organism [MIC, mg/L] (resistance marker)	*n*	Results
Powles et al. [83]	Mouse/systemic[a]	Imipenem	5 mg/kg IV (*t*' 1 h) q6 h × 4	*K. pneumoniae* CL339 [64][c]	5	0.52 $\log_{10}$ CFU increase[d]
		Imipenem/relebactam	5/20 mg/kg IV (*t*' 1 h) q6 h × 4		5	2.29 $\log_{10}$ CFU reduction[d]
			5/40 mg/kg IV (*t*' 1 h) q6 h × 4		5	3.06 $\log_{10}$ CFU reduction[d]
			5/80 mg/kg IV (*t*' 1 h) q6 h × 4		5	2.36 $\log_{10}$ CFU reduction[d]
	Mouse/systemic[a]	Imipenem	5 mg/kg IV (*t*' 1 h) q6 h × 4	*P. aeruginosa* CLB 24228 [32–64][c]	5	0.45 $\log_{10}$ CFU reduction[d]
		Imipenem/relebactam	5/10 mg/kg IV (*t*' 1 h) q6 h × 4		5	1.72 $\log_{10}$ CFU reduction[d]
			5/20 mg/kg IV (*t*' 1 h) q6 h × 4		5	3.13 $\log_{10}$ CFU reduction[d]
			5/40 mg/kg IV (*t*' 1 h) q6 h × 4		5	3.73 $\log_{10}$ CFU reduction[d]
	Mouse/pulmonary[a]	Imipenem	5 mg/kg IV (*t*' 1 h) q6 h × 4		5	0.11 $\log_{10}$ CFU increase[d]
		Imipenem/relebactam	5/20 mg/kg IV (*t*' 1 h) q6 h × 4		5	2.37 $\log_{10}$ CFU reduction[d]
			5/40 mg/kg IV (*t*' 1 h) q6 h × 4		5	3.59 $\log_{10}$ CFU reduction[d]
			5/80 mg/kg IV (*t*' 1 h) q6 h × 4		5	4.59 $\log_{10}$ CFU reduction[d]
	Mouse/pulmonary[b] (delayed treatment)	Imipenem	5 mg/kg IV (*t*' 1 h) q6 h × 4		5	2.10 $\log_{10}$ CFU increase[e]
						0.78 $\log_{10}$ CFU reduction[d]
		Imipenem/relebactam	5/20 mg/kg IV (*t*' 1 h) q6 h × 4		5	0.06 $\log_{10}$ CFU reduction[e]
						2.94 $\log_{10}$ CFU reduction[d]
			5/40 mg/kg IV (*t*' 1 h) q6 h × 4		3	0.82 $\log_{10}$ CFU increase[e]
						2.06 $\log_{10}$ CFU reduction[d]
			5/80 mg/kg IV (*t*' 1 h) q6 h × 4		5	0.76 $\log_{10}$ CFU increase[e]
						2.12 $\log_{10}$ CFU reduction[d]
Mavridou et al. [46]	Mouse/thigh[f]	Imipenem/relebactam	8/8 mg/kg IP q2 h × 12 + 11.8 mg/kg/d	*K. pneumoniae* 6339 [16/0.125–0.25][g] (KPC-2, OmpK35-, OmpK36red)	≥2	Stasis, REL $fAUC_{24h}$ = 6.3 mg·h/L
			8/8 mg/kg IP q2 h × 12 + 75.9 mg/kg/d	*K. pneumoniae* 6755 [4/0.125][g]		Stasis, REL $fAUC_{24h}$ = 40.3 mg·h/L
			15.9/15.9 mg/kg IP q2 h × 12 + 39.8 mg/kg/d	(KPC-3, OmpK35red, OmpK36red)		Stasis, REL $fAUC_{24h}$ = 21.2 mg·h/L
			2/2 mg/kg IP q2 h × 12 + 61.7 mg/kg/d	*P. aeruginosa* 24226 [8/0.5][g] (OprD-, AmpC)		Stasis, REL $fAUC_{24h}$ = 32.8 mg·h/L
			4/4 mg/kg IP q2 h × 12 + 79.4 mg/kg/d			Stasis, REL $fAUC_{24h}$ = 42.2 mg·h/L
			8/8 mg/kg IP q2 h × 12 + 23.4 mg/kg/d			Stasis, REL $fAUC_{24h}$ = 12.5 mg·h/L
			8/8 mg/kg IP q2 h × 12 + 12.0 mg/kg/d	*P. aeruginosa* 24227 [4/0.25–0.5][g] (OprD-, AmpC)		Stasis, REL $fAUC_{24h}$ = 6.4 mg·h/L
			15.9/15.9 mg/kg IP q2 h × 12 + 51.3 mg/kg/d	*P. aeruginosa* 24228 [8/0.5][g] (OprD-, AmpC)		Stasis, REL $fAUC_{24h}$ = 27.2 mg·h/L
			8/8 mg/kg IP q2 h × 12 + 85.1 mg/kg/d	*P. aeruginosa* 24354 [32/2-4][g] (OprD-, AmpC)		Stasis, REL $fAUC_{24h}$ = 45.2 mg·h/L

Table 11 continued

Study	Animal/ infection model	Antimicrobial agent	Dose	Organism [MIC, mg/L] (resistance marker)	*n*	Results
Sabet et al. [89]	Mouse/thigh[f]	Meropenem	300 mg/kg IP q2 h × 12	*E. cloacae* ECL1004 [16/≤ 0.06][h]	NA	0.31 $\log_{10}$ CFU reduction[e]
		Meropenem/vaborbactam	300/50 mg/kg IP q2 h × 12	(NMC-A)		1.82 $\log_{10}$ CFU reduction[e]
				E. cloacae ECL1026 [8/≤ 0.06][h]		0.26 $\log_{10}$ CFU increase[e]
				(KPC-2, TEM-1)		2.06 $\log_{10}$ CFU reduction[e]
				E. cloacae ECL1055 [8/≤ 0.06][h]		0.11 $\log_{10}$ CFU reduction[e]
				(KPC-3, TEM)		0.95 $\log_{10}$ CFU reduction[e]
				E. coli EC1007 [16/≤ 0.06][h]		0.04 $\log_{10}$ CFU reduction[e]
				(KPC-3)		1.24 $\log_{10}$ CFU reduction[e]
				K. pneumoniae KP1004 [32/≤ 0.06][h]		0.10 $\log_{10}$ CFU reduction[e]
				(KPC-2, TEM-1, SHV-11)		1.73 $\log_{10}$ CFU reduction[e]
				K. pneumoniae KP1074 [64/< 0.5][h]		1.01 $\log_{10}$ CFU increase[e]
				(KPC-3, SHV-11, TEM)		1.21 $\log_{10}$ CFU reduction[e]
				K. pneumoniae KP1099 [128/2][h]		1.75 $\log_{10}$ CFU increase[e]
				(KPC-2)		1.25 $\log_{10}$ CFU reduction[e]
				K. pneumoniae KP1100 [≥ 256/4][h]		2.44 $\log_{10}$ CFU increase[e]
				(KPC-3)		0.82 $\log_{10}$ CFU reduction[e]
				K. pneumoniae KP1093 [128/1][h]		0.58 $\log_{10}$ CFU increase[e]
				(KPC-3, SHV-11, TEM)		1.86 $\log_{10}$ CFU reduction[e]
				K. pneumoniae KP1094 [512/8][h]		0.10 $\log_{10}$ CFU increase[e]
				(KPC-2, TEM-1, LEN-17)		2.37 $\log_{10}$ CFU reduction[e]

Table 11 continued

Study	Animal/ infection model	Antimicrobial agent	Dose	Organism [MIC, mg/L] (resistance marker)	*n*	Results
Weiss et al. [69]	Mouse/urinary tract[i]	Meropenem	100 mg/kg IP q2 h × 12	*E. coli* UNT167-1 [32/≤ 0.06][h] (KPC-2, SHV-12)	7	0.84 $\log_{10}$ CFU reduction[e] 1.31 $\log_{10}$ CFU reduction[d]
			300 mg/kg IP q2 h × 12		6	0.82 $\log_{10}$ CFU reduction[e] 1.29 $\log_{10}$ CFU reduction[d]
		Meropenem/vaborbactam	100/25 mg/kg IP q2 h × 12		7	2.20 $\log_{10}$ CFU reduction[e] 2.68 $\log_{10}$ CFU reduction[d]
			100/50 mg/kg IP q2 h × 12		6	2.51 $\log_{10}$ CFU reduction[e] 2.98 $\log_{10}$ CFU reduction[d]
			300/50 mg/kg IP q2 h × 12		5	2.79 $\log_{10}$ CFU reduction[e] 3.27 $\log_{10}$ CFU reduction[d]
		Meropenem	50 mg/kg IP q2 h × 12	*K. pneumoniae* UNT170-1 [32/≤ 0.06][h] (MR, KPC-2)	9	0.18 $\log_{10}$ CFU reduction[e] 0.44 $\log_{10}$ CFU reduction[d]
			100 mg/kg IP q2 h × 12		9	0.52 $\log_{10}$ CFU reduction[e] 0.78 $\log_{10}$ CFU reduction[d]
			300 mg/kg IP q2 h × 12		10	1.95 $\log_{10}$ CFU reduction[e] 2.21 $\log_{10}$ CFU reduction[d]
		Meropenem/vaborbactam	50/50 mg/kg IP q2 h × 12		10	2.43 $\log_{10}$ CFU reduction[e] 2.69 $\log_{10}$ CFU reduction[d]
			100/50 mg/kg IP q2 h × 12		10	2.34 $\log_{10}$ CFU reduction[e] 2.60 $\log_{10}$ CFU reduction[d]
			300/50 mg/kg IP q2 h × 12		10	2.62 $\log_{10}$ CFU reduction[e] 2.88 $\log_{10}$ CFU reduction[d]

Imipenem implies imipenem/cilastatin dosed at a ratio of 5 mg/50 mg/kg; *INS* imipenem non-susceptible, *IP* intraperitoneal, *IR* imipenem-resistant, *IV* intravenous, *MIC* minimum inhibitory concentration, *MR* meropenem-resistant, *n* number of animals, *NA* data not available, *OmpK35red/OmpK36red Klebsiella* outer membrane porin 35/36 reduced, *OmpK35- Klebsiella* outer membrane porin 35 negative, *OprD-* outer membrane porin D negative, *Stasis* bacteriostasis over 24-h treatment period

[a]Treatment initiated 15 min post-infection

[b]Treatment initiated 16.5 h post-infection

[c]Imipenem MIC, imipenem–relebactam MIC not available

[d]Compared to untreated controls sacrificed at the end of the treatment period

[e]Compared to untreated controls sacrificed at the start of the treatment period

[f]Treatment initiated 2 h post-infection

[g]Imipenem MIC/Imipenem MIC with 4 mg/L relebactam

[h]Meropenem MIC/Meropenem MIC with 8 mg/L vaborbactam

[i]Treatment initiated 4 days post-infection

model, a $\log_{10}$ reduction in CFU of 0.45 was observed for imipenem treatment alone, compared to 1.72, 3.13, and 3.73 $\log_{10}$ reductions in CFU with the addition of 10, 20, and 40 mg/kg relebactam, respectively. In the *K. pneumoniae* systemic model, a $\log_{10}$ increase in CFU of 0.52 was observed for imipenem treatment alone, compared to 2.29, 3.06, and 2.36 $\log_{10}$ reductions in CFU with the addition of 20, 40, and 80 mg/kg relebactam, respectively.

In the *P. aeruginosa* pulmonary infection models by Powles et al, mice ($n = 3$–5 for each regimen) were intranasally inoculated with 1.4×10^5 CFU and 1.8×10^4 CFU in the immediate and delayed treatment models, respectively [83]. Treatment was initiated intravenously 15 min post-infection and 16.5 h post-infection in the immediate and delayed treatment models, respectively. Imipenem/cilastatin at 5/50 mg/kg was administered alone or in combination with relebactam 20, 40, and 80 mg/kg q6 h for 24 h (t' 1 h). Lung bacterial density was determined at the end of treatment and compared to untreated controls sacrificed at the same point in time. For immediate treatment in the *P. aeruginosa* pulmonary model, a $\log_{10}$ increase in CFU of 0.11 was observed for imipenem treatment alone, compared to 2.37, 3.59, and 4.59 $\log_{10}$ reductions in CFU with the addition of 20, 40, and 80 mg/kg relebactam, respectively. For delayed treatment in the *P. aeruginosa* pulmonary model, a $\log_{10}$ reduction in CFU of 0.78 was observed for imipenem treatment alone, compared to 2.94, 2.06, and 2.12 $\log_{10}$ reductions in CFU with the addition of 20, 40, and 80 mg/kg relebactam, respectively. Data comparing lung bacterial density of treated mice and controls sacrificed at the beginning of treatment (16.5 h post-infection) for the delayed treatment *P. aeruginosa* pulmonary model are also represented in Table 11.

Also mentioned previously, Mavridou et al. used a neutropenic murine thigh model of imipenem non-susceptible and β-lactamase-producing isolates of *K. pneumoniae* ($n = 2$) and *P. aeruginosa* ($n = 4$) to determine the dose of relebactam in combination with imipenem required to achieve bacteriostasis [46]. Treatment was initiated 2 h after mice ($n \geq 2$ for each regimen) were infected with approximately 5×10^6 CFU in each thigh. Imipenem/cilastatin 2/2 to 15.9/15.9 mg/kg was administered IP q2 h for 24 h with various doses and intervals of relebactam. Thigh bacterial density was compared to untreated controls sacrificed at the start of treatment (2 h post-infection). Table 11 shows the various total daily doses of relebactam needed to achieve bacteriostasis against each of the six isolates tested as well as the $f\text{AUC}_{24\text{h}}$ achieved with each regimen. Total daily doses to achieve bacteriostasis ranged from 11.8 to 85.1 mg/kg/day (mean 48.9 mg/kg/day) with $f\text{AUC}_{24\text{h}}$ from 6.3 to 45.2 mg·h/L (mean 26.0 mg·h/L), which were highly dependent on the imipenem dose and MIC of each isolate.

8.2 Meropenem–Relebactam

Sabet et al. evaluated the in vivo efficacy of meropenem–vaborbactam against meropenem-resistant and β-lactamase producing Enterobacteriaceae (three *E. cloacae*, one *E. coli*, and six *K. pneumoniae*) in a neutropenic murine thigh model [89]. Mice were infected intramuscularly with approximately 1×10^6 CFU in each thigh. Treatment was initiated 2 h post-infection with either meropenem 300 mg/kg alone or in combination with 50 mg/kg vaborbactam, administered IP q2 h for 24 h. Dosing regimens were humanized to provide exposures equivalent to meropenem 2000 mg alone or in combination with vaborbactam 2000 mg q8 h (t' 3 h). Thigh bacterial density was compared to untreated controls sacrificed at the start of treatment (2 h post-infection). Changes in bacterial density compared to controls for meropenem treatment alone and in combination with vaborbactam against various Enterobacteriaceae are summarized in Table 11. Antimicrobial efficacy of meropenem was greatly improved with the addition of vaborbactam.

Finally, Weiss et al. evaluated the in vivo efficacy of meropenem–vaborbactam in a neutropenic murine urinary tract infection model against meropenem-resistant and KPC-producing *E. coli* and *K. pneumoniae* [69]. Mice ($n = 5$–10) were transurethrally infected, 4–5-day post-infection mean kidney bacterial densities were 4.2×10^6–1.2×10^7 $\log_{10}$ CFU and 3.4 to 6.2×10^6 CFU, respectively. Treatment was initiated four days post-infection with meropenem 50–300 mg/kg alone or in combination with vaborbactam 25–50 mg/kg IP q2 h for 24 h. Kidney bacterial density was compared to untreated controls sacrificed at the start of treatment on day 4. Reductions in bacterial density compared to controls are summarized in Table 11. Overall, the addition of vaborbactam increased the antimicrobial efficacy of meropenem in both models, achieving an additional 1.37–1.98 and 0.67–2.25 $\log_{10}$ CFU reduction in kidney bacterial density compared to meropenem alone, in the *E. coli* and *K. pneumoniae* infection models, respectively. Data comparing kidney bacterial density of treated mice and controls sacrificed at the end of treatment on day 5 are also represented in Table 11.

9 Clinical Trials

Clinical trials completed to date are summarized in Table 12 [10, 86, 90–92], including two imipenem–relebactam phase II clinical trials for the treatment of cIAI and

Table 12 Clinical trials of imipenem–relebactam and meropenem–vaborbactam

Trial description	*n*	Treatment regimens	Primary outcomes	Primary outcome results *n*/N (%)	Secondary outcomes	Secondary outcome results n/N (%)
Phase II treatment of cIAI [86] ClinicalTrials.gov ID: NCT01506271	351	Imipenem/relebactam 500/250 mg IV (t' 30 min) q6 h × 4–14 days Imipenem/relebactam 500/125 mg IV (*t*' 30 min) q6 h × 4–14 days Imipenem 500 mg IV (*t*' 30 min) q6 h × 4–14 days	Clinical response[a] in the ME[b] population at DCIV	Relebactam 250 mg: 78/81 (96.3) Relebactam 125 mg: 85/86 (98.8) Imipenem alone: 79/83 (95.2)	Clinical response[a] at EFU (ME[b]) Clinical response[a] at LFU (ME[b]) Microbiologic response[c] at DCIV (ME[b]) Global response[d] at 28 days after randomization (MITT[e])	Relebactam 250 mg: 75/79 (94.9) Relebactam 125 mg: 81/86 (94.2) Imipenem alone: 78/81 (96.3) Relebactam 250 mg: 74/79 (93.7) Relebactam 125 mg: 81/85 (95.3) Imipenem alone: 75/79 (94.9) Relebactam 250 mg: 81/83 (97.6) Relebactam 125 mg: 86/86 (100) Imipenem alone: 82/84 (97.6) Relebactam 250 mg: 77/89 (86.5) Relebactam 125 mg: 86/96 (89.6) Imipenem alone: 78/92 (84.8)
Phase II treatment of cUTI and AP [90] ClinicalTrials.gov ID: NCT01505634	302	Imipenem/relebactam 500/250 mg IV (*t*' 30 min) q6 h × 4–14 days Imipenem/relebactam 500/500/125 mg IV (*t*' 30 min) q6 h × 4–14 days Imipenem 500/500 mg IV (*t*' 30 min) q6 h × 4–14 days Optional oral step-down after 4 days (all regimens): ciprofloxacin 500 mg BID	Microbiological response[c] in the ME[b] population at DCIV	Relebactam 250 mg: 64/67 (95.5) Relebactam 125 mg: 70/71 (98.6) Imipenem alone: 74/75 (98.7)	Microbiological response[c] at EFU/LFU (ME[b]) Clinical response[a] at DCIV/EFU/LFU (ME[b]) Microbiological response[c] at DCIV for INS infections (ME[b])	Relebactam 250 mg: (61.5/68.3) Relebactam 125 mg: (68.1/65.2) Imipenem alone: (70.4/62.5) Relebactam 250 mg: (97.1/89.1/88.7) Relebactam 125 mg: (98.7/91.8/87.3) Imipenem alone: (98.8/93.4/88.2) Relebactam 250 mg: 10/10 (100) Relebactam 125 mg: 7/7 (100) Imipenem alone: 6/6 (100)

Table 12 continued

Trial description	*n*	Treatment regimens	Primary outcomes	Primary outcome results *n*/N (%)	Secondary outcomes	Secondary outcome results n/N (%)
Phase III treatment of cUTI and AP [10, 91, 92] ClinicalTrials.gov ID: NTC02166476	550	Meropenem/vaborbactam 2000/2000 mg IV (t' 3 h) q8 h × 5–10 days Piperacillin/tazobactam 4,000/500 mg IV (t' 30 min) q8 h × 5–10 days Optional oral step-down after 5 days (all regimens): levofloxacin 500 mg OD	Overall success[f] in the m-MITT population at DCIV	Meropenem–vaborbactam: 189/192 (98.4) Piperacillin-tazobactam: 171/182 (94.0)	Microbiological eradication[g] at TOC (m-MITT) Microbiological eradication[g] at TOC (ME)	Meropenem–vaborbactam: 128/192 (66.7) Piperacillin/tazobactam: 105/182 (57.7) Meropenem–vaborbactam: 118/178 (66.3) Piperacillin/tazobactam: 102/169 (60.4)

Imipenem implies imipenem/cilastatin dosed at a ratio of 500 mg/500 mg/kg; *AP* acute pyelonephritis, *cIAI* complicated intra-abdominal infections, *cUTI* complicated urinary tract infections, *DCIV* discontinuation of IV therapy, *EFU* early follow up (5 to 9 days after completion of all study therapy), *INS* imipenem non-susceptible, *IV* intravenous, *LFU* late follow up (28 to 42 days after completion of all study therapy), *ME* microbiologically evaluable, *MITT* microbiological intention-to-treat, *m-MITT* microbiological modified intention-to-treat, *n* number of participants, *q6 h* every 6 h, *q8 h* every 8 h, *TOC* test of cure (at day 15 to 19), *t'*, infusion time

[a]Clinical response, determined from clinical signs/symptoms and physical findings consistent with infection type compared to those at baseline

[b]ME defined as patients with eligible diagnosis, a prestudy/postoperative culture of at least one Gram-negative enteric and/or anaerobic pathogen, no significant protocol deviations, and received ≥ 96 h IV therapy

[c]Microbiological response, imputed from clinical response if follow-up cultures from site of infection were not available for IAI or based on urine cultures relative to pathogen(s) isolated at baseline for UTI

[d]Global response, cure defined as resolution of presenting signs/symptoms of IAI, survival, no unplanned percutaneous or surgical procedures for IAI, no receipt of antimicrobial therapy for initial or emergent IAI, and no other event related to the initial or emergent IAI that resulted in clinical instability or worsening

[e]MITT defined as patients who received at least one dose of IV study therapy and had a prestudy/postoperative culture of at least one Gram-negative enteric and/or anaerobic pathogen

[f]Overall success included clinical cure or improvement and microbiological eradication defined as $< 10^4$ CFU/mL (FDA criteria)

[g]Microbiological eradication defined as $< 10^3$ CFU/mL (EMA criteria)

cUTI/AP (NCT01506271 and NCT01505634) and one meropenem–vaborbactam phase III clinical trial for the treatment of cUTI/AP (NCT02166476).

9.1 Imipenem–Relebactam

The efficacy, tolerability, and safety of imipenem–relebactam has been studied for the treatment of cIAI in a global, double-blind, randomized, phase II, non-inferiority trial (NCT01506271) (Table 12) [86]. Imipenem/cilastatin-relebactam (500/500/250 mg and 500/500/125 mg) were compared to imipenem/cilastatin alone (500/500 mg), administered IV (*t'* 30 min) q6 h (q8 h for renal insufficiency) for 4–14 days. The dose of imipenem was adjusted for renal insufficiency and/or low body weight according to the approved label, and the dose of relebactam was adjusted proportionally. In this study, 351 patients were randomized (1:1:1) with stratification for disease severity (APACHE II score of ≤ 15 or > 15). Inclusion criteria were patients aged ≥ 18 years with an eligible diagnosis of cIAI requiring hospitalization and treatment with IV antimicrobial therapy. Exclusion criteria were: an APACHE II score > 30; patients who received antimicrobial therapy effective against the identified causative pathogen(s) after culture collection and prior to study therapy initiation; patients who received antimicrobial therapy for > 24 h within the preceding 72 h, effective against presumed/documented pathogen(s); renal dysfunction [creatinine clearance (CL_{CR}) < 50 mL/min]; and hepatic dysfunction (ALT or AST > 3 times the upper limit of normal [× ULN]).

The primary outcome was a favorable clinical response in the microbiologically evaluable (ME) population at discontinuation of IV therapy (DCIV). Clinical response was evaluated based on resolution of presenting clinical signs/symptoms including evidence of a systemic inflammatory response (fever, elevated white blood cell count, decreased blood pressure, increased pulse/respiratory rate, hypoxemia, and/or altered mental status) and physical findings associated with IAI (such as abdominal pain and/or tenderness, abdominal wall rigidity, abdominal mass, or ileus). The ME population was defined as subjects with an

eligible diagnosis of cIAI, a prestudy/postoperative culture growing at least one Gram-negative enteric and/or anaerobic pathogen, and no significant protocol deviations, and patients who received at least 4 days of IV study therapy. The ME population included 72.6% of randomized patients, of whom 52.5 and 16.5% had a diagnosis of complicated appendicitis and complicated cholecystitis, respectively. A non-inferiority margin was set at $\geq 15\%$ for the lower bound of the 95% confidence interval (CI) with a one-sided p value ($\alpha = 0.025$) for between-treatment differences, with 80% power to determine non-inferiority of imipenem–relebactam compared to imipenem alone. Clinical response in the ME population at DCIV (primary outcome) for the relebactam 250 mg arm was 96.3 versus 95.2% for imipenem alone, a difference of 1.1% ($p < 0.001$, 95% CI -6.2 to 8.6), while response for the relebactam 125 mg arm was 98.8 versus 95.2% for imipenem alone, a difference of 3.7% ($p < 0.001$, 95% CI -2.0 to 10.8). Therefore, both regimens were non-inferior to imipenem alone for the primary outcome. A sensitivity analysis showed similar results in the microbiological intention-to-treat (MITT) population (defined as patients who received at least one dose of IV study therapy and a prestudy/postoperative culture growing at least one Gram-negative enteric and/or anaerobic pathogen). Clinical response in the MITT population at DCIV for the relebactam 250 mg arm was 89.9 versus 90.2% for imipenem alone, a difference of -0.3% ($p < 0.002$, 95% CI -9.6 to 8.9), while response for the relebactam 125 mg arm was 91.7 versus 90.2% for imipenem alone, a difference of 1.4% ($p < 0.001$, 95% CI -7.2 to 10.3). Neither regimen was superior to imipenem alone for the primary outcome.

The most common pathogens isolated at baseline included *E. coli* ($n = 171$), *K. pneumoniae* ($n = 38$), and *P. aeruginosa* ($n = 37$). Per-pathogen clinical response in the ME population at DCIV was similar among treatment groups for nearly all pathogens. At baseline, 40 imipenem non-susceptible organisms were isolated from 34 patients in the ME population. All 34 patients had a favorable clinical and microbiological response at DCIV. In vitro, 7 of the 40 isolates were non-susceptible to imipenem alone (one isolate of *Alcaligenes xylosoxidans*, one *E. coli*, two *Proteus mirabilis*, and three *P. aeruginosa*), while the remaining 33 isolates were non-susceptible to imipenem alone and imipenem–relebactam (19 isolates of *Proteus* spp., five *M. morganii*, four *Acinetobacter* spp., three *S. maltophilia*, and two *P. aeruginosa*).

Secondary endpoints included clinical response at early follow-up (EFU) 5–9 days after DCIV and late follow-up (LFU) 28–42 days after DCIV, microbiological response, and global response. Microbiologic response was imputed from clinical response if follow-up cultures from the site of infection were not available. Global response (i.e. cure), was defined as resolution of presenting signs/symptoms of IAI, survival, no unplanned percutaneous or surgical procedures for IAI, no antimicrobial therapy needed for initial or emergent IAI, and no other event related to the initial or emergent IAI that resulted in clinical instability or worsening. Global response was measured 28 days after randomization in the MITT population. Results for secondary endpoints were similar across all three treatment groups (Table 12). Clinical response in the ME population at EFU and LFU was similar to the response seen at DCIV, and was similar across all three treatment groups (Table 12). Adverse events observed in this study will be discussed in Sect. 10.

The efficacy, tolerability, and safety of imipenem–relebactam has been studied for the treatment of cUTI and AP in a global, double-blind, randomized, phase II, non-inferiority trial (NCT01505634) (Table 12) [90]. Imipenem/cilastatin-relebactam (500/500/250 mg and 500/500/125 mg) was compared to imipenem/cilastatin alone (500/500 mg), administered IV (*t*' 30 min) q6 h with optional oral step-down to ciprofloxacin after at least 4 days of IV therapy. The total treatment duration was a maximum of 14 days. The dose of imipenem was adjusted for renal insufficiency and/or low body weight according to the approved label, and the dose of relebactam was adjusted proportionally. In this study, 302 patients were block randomized 1:1:1. Inclusion criteria were patients ≥ 18 years of age with an eligible diagnosis of cUTI or AP requiring hospitalization and IV antimicrobial therapy. An eligible diagnosis of cUTI required at least two specific signs and symptoms of UTI (e.g. dysuria, urinary urgency or frequency, fever) and at least one risk factor for cUTI (e.g. indwelling catheter, obstructive uropathy, history of urinary retention, etc.). An eligible diagnosis of AP included patients with a normal urinary tract anatomy and presence of a systemic ascending UTI with at least two specific signs and symptoms (e.g. fever, flank pain, nausea and/or vomiting, costovertebral angle tenderness). Patients also needed to have pyuria and a positive urine culture within 48 h of enrollment. Exclusion criteria were: uncomplicated UTI, patients who received antimicrobial therapy effective against the identified causative pathogen(s) after culture collection and prior to study therapy initiation; patients who received antimicrobial therapy for > 24 h within the preceding 72 h, effective against presumed/documented causative pathogen(s); complete obstruction of any urinary tract portion, ileal loop, intractable vesicoureteral reflux, or temporary indwelling urinary catheter that could not be removed; perinephric or intrarenal abscess, or known/suspected prostatitis; recent pelvic or urinary tract trauma; need for non-study systemic antimicrobial agents; renal dysfunction ($CL_{CR} \leq 5$ mL/min and/or need for dialysis); and hepatic

dysfunction (ALT or AST > 3× ULN, total bilirubin > 2× ULN, or ALT/AST > 2× ULN with total bilirubin > ULN).

The primary outcome was a favorable microbiological response in the ME population at DCIV. Microbiological response was determined based on urine culture results on follow-up relative to the pathogen(s) isolated at baseline. The ME population was defined as subjects with an eligible diagnosis of cUTI or AP, a prestudy culture growing at least one Gram-negative enteric and/or anaerobic pathogen at a sufficient quantity, and no significant protocol deviations, who received at least 4 days of IV study therapy. The ME population at DCIV included 77.2% of randomized patients. A non-inferiority margin was set at ≥ 15% for the lower bound of the 95% CI, with 87% power to determine non-inferiority of imipenem–relebactam compared to imipenem alone. Microbiological response in the ME population at DCIV (primary outcome) for the relebactam arm 250 mg was 95.5 versus 98.7% for imipenem alone, a difference of − 3.1% (95% CI − 11.3 to 3.2), while response for the relebactam 125 mg arm was 98.6 versus 98.7% for imipenem alone (95% CI − 6.4 to 5.9). Therefore, both regimens were non-inferior to imipenem alone for the primary outcome. All patients in the ME population with an unfavorable microbiological response at DCIV had imipenem-susceptible pathogens at baseline. A sensitivity analysis showed similar results in the microbiological intention-to-treat (MITT) population (defined as patients who received at least one dose of IV study therapy and a prestudy culture growing at least one Gram-negative enteric and/or anaerobic pathogen at any quantity). Microbiological response in the MITT population at DCIV for the relebactam 250 mg arm was 87.8 versus 92.6% for imipenem alone, a difference of − 4.8% (95% CI − 15.1 to 4.9), while response for the relebactam 125 mg arm was 87.8 versus 92.6% for imipenem alone, a difference of − 4.8% (95% CI − 14.7 to 4.7). Thus, the two regimens were deemed non-inferior.

The most common pathogens isolated at baseline in the ME population included *E. coli* ($n = 143$), *K. pneumoniae* ($n = 34$), and *P. aeruginosa* ($n = 16$). At baseline, 25 out of 220 patients (11.4%) had a Gram-negative pathogen that was non-susceptible to imipenem, and 15 of these patients had isolates that were also non-susceptible to imipenem–relebactam (five isolates of *P. mirabilis*, four *A. baumannii*, four *M. morganii*, one *Providencia rettgeri*, and one *P. aeruginosa*).

Secondary endpoints were assessed in the ME population and included microbiological response at EFU (5–9 days after completion of all study therapy) and LFU (28–42 days after completion of all study therapy), microbiological response at DCIV in patients with imipenem non-susceptible pathogens, and clinical response at DCIV, EFU, and LFU. A composite of clinical and microbiological response in the ME population at EFU was an additional exploratory endpoint. Clinical response was determined by comparing cUTI signs/symptoms at follow-up with those at baseline. After DCIV, microbiological responses decreased at EFU and LFU with similar reductions across all three treatment groups (Table 12). Clinical responses at DCIV were similar across all three treatment groups, with similar decreases in response at EFU and LFU (Table 12). Of the 25 patients mentioned above with a Gram-negative isolate non-susceptible to imipenem, 23 were ME and had favorable microbiological responses at DCIV (Table 12). The composite for clinical and microbiological response in the ME population at EFU was similar among treatment groups with a response rate of 54.1, 59.8, and 61.7% for the relebactam 250 mg arm, the relebactam 125 mg arm, and imipenem alone, respectively. Adverse events observed in this study will be discussed in Sect. 10.

9.2 Meropenem–Relebactam

The efficacy, tolerability, and safety of meropenem–vaborbactam for the treatment of cUTI and AP have been studied in a multicenter, double-blind, randomized, phase III, non-inferiority trial (TANGO I, NCT02166476) (Table 12) [10, 91, 92]. Meropenem–vaborbactam (2000/2000 mg) IV (*t*' 3 h) q8 h was compared to piperacillin-tazobactam (4000/500 mg) IV (*t*' 30 min) q8 h. Oral step-down to levofloxacin after at least 5 days of IV therapy was permitted in both treatment arms. The total treatment duration was 10 days. In this study, 550 patients were randomized 1:1, stratified by geographic region and type of infection (AP, cUTI with removable source of infection [cUTI-R], and cUTI with a non-removable source [cUTI-NR]). Inclusion criteria were patients ≥ 18 years of age with an eligible diagnosis of cUTI or AP that required at least 5 days of IV antimicrobial therapy, and any indwelling urinary catheter or instrumentation removed or replaced not longer than 12 h after randomization. Key exclusion criteria were renal impairment ($CL_{CR} < 30$ mL/min), and patients who received any potentially therapeutic antimicrobial agent within 48 h before randomization. Exceptions to the exclusion criteria were patients with signs/symptoms of cUTI or AP while on antimicrobials for another indication, clear clinical evidence of treatment failure (worsening signs/symptoms), and those who received a single dose of a short-acting oral or IV antimicrobial (no more than 25% of subjects were to be enrolled who met this criterion).

The primary outcome was overall success in the microbiologic modified intention-to-treat (m-MITT) population at DCIV. Overall success included clinical cure or

improvement and microbiological eradication defined as the baseline pathogen being reduced to $< 10^4$ CFU/mL (FDA criteria). The m-MITT population included 68% of randomized patients who had at least one baseline pathogen at $\geq 10^5$ CFU/mL. In the m-MITT population, 59.1% of patients were diagnosed with AP and 40.9% with cUTI. Overall success in the m-MITT population at DCIV (primary outcome) was 98.4 and 94.0% for meropenem–vaborbactam and piperacillin-tazobactam, respectively, a difference of 4.5% (95% CI 0.7–9.1). Meropenem–vaborbactam was non-inferior to piperacillin-tazobactam for the primary outcome. Overall success in the m-MITT population at DCIV was 97.5, 100, and 100% for patients with AP, cUTI-R, and cUTI-NR treated with meropenem–vaborbactam, while treatment with piperacillin-tazobactam resulted in overall success in 94.1, 92.1, and 95.3%, respectively.

The most common pathogens isolated at baseline in the m-MITT population were Enterobacteriaceae ($n = 333$) and *P. aeruginosa* ($n = 15$). Approximately 29% of Enterobacteriaceae at baseline had an ESBL phenotype (ceftazidime or aztreonam MIC ≥ 2 mg/L). Per-pathogen clinical outcome and microbiological eradication rates at DCIV were similar among treatment groups for nearly all pathogens.

Secondary endpoints were assessed in the m-MITT and ME populations and included microbiological eradication at test of cure [(TOC), day 15–19]. Here microbiological eradication was defined as the baseline pathogen being reduced to $< 10^3$ CFU/mL (EMA criteria). The microbiological eradication rate in the m-MITT population at TOC was 66.7 and 57.7% for meropenem–vaborbactam and piperacillin-tazobactam, respectively, a difference of 9.0% (95% CI -0.9 to 18.7). Results were similar in the ME population (Table 12). Adverse events observed in this study will be discussed in Sect. 10.

9.3 Imipenem–Relebactam

Imipenem–relebactam is currently being studied in two Phase III clinical trials, RESTORE-IMI 1 and RESTORE-IMI 2, with estimated primary completion dates of September 2017 and May 2019, respectively (NCT02452047 and NCT02493764). In the first study, RESTORE-IMI 1, imipenem–relebactam is compared with colistimethate sodium plus imipenem for the treatment of imipenem-non-susceptible bacterial infections (including HABP, VABP, cIAI, and cUTI). In the second study, RESTORE-IMI 2, imipenem–relebactam is compared with piperacillin-tazobactam, with empiric linezolid administered in both treatment arms, for the treatment of HABP/VABP.

9.4 Meropenem–Relebactam

Meropenem–vaborbactam is currently being studied in two phase III clinical trials, TANGO II and TANGO III (NCT02168946 and NCT03006679). Preliminary data with TANGO II were presented at ID week 2017 and will be discussed below. Estimated completion of TANGO III is expected June 2020. In the first study, TANGO II, a randomized, multi-national open-label trial studied patients with complicated urinary tract infection (cUTI), acute pyelonephritis (AP), hospital-acquired or ventilator-associated bacterial pneumonia (HABP/VABP), bacteremia, or complicated intra-abdominal infection (cIAI), due to known or suspected carbapenem-resistant Enterobacteriaceae (CRE) [93, 94]. Patients were randomized in a 2:1 fashion to meropenem–vaborbactam ((2000/2000 mg) IV (*t*' 3 h) q8 h or best available therapy (BAT) for 7–14 days [93]. BAT included alone or in combination: carbapenems, aminoglycosides, polymyxin B, colistin, tigecycline or ceftazidime-avibactam. Clinical cure was defined as a complete resolution of signs or symptoms such that no further antimicrobial therapy as required. Seventy-two patients were enrolled; 50 (69.4%) had a Gram-negative baseline organism (m-MITT), and 43 (59.7%) had a baseline CRE (mCRE- MITT) [93]. Within mCRE-MITT, 20 patients had bacteremia, 15 had cUTI/AP, 5 had HABP/VABP, and 3 had cIAI. The most common baseline CRE pathogens were *K. pneumoniae* (86%) and *E. coli* (7%). There was no consensus BAT regimen; however, combination therapy was used in 66.7% of cases. Treatment duration was similar across arms (mean 8.5 days for meropenem–vaborbactam and 8.1 days for BAT). Although the patient numbers were relatively small ($n = 50$ in m-MITT and $n = 43$ in mCRE-MITT groups, respectively), meropenem–vaborbactam was associated with higher clinical cure rates in the mCRE-MITT group both at EOT (64.3 vs 40.0%, respectively) and TOC (57.1 vs 26.7%, respectively), as well as in the m-MITT group at both EOT (67.7 vs 42.1%, respectively) and TOC (58.0 vs 31.6%, respectively), than BAT across all indications [93]. These superior outcomes in the meropenem–vaborbactam group versus the BAT group occurred even in patients who were immunocompromised [94]. Due to the superiority of meropenem–vaborbactam compared to BAT, this study was terminated prematurely.

In the second study, TANGO III, meropenem–vaborbactam is compared with piperacillin-tazobactam for the treatment of HABP/VABP.

Both imipenem–relebactam and meropenem–vaborbactam are undergoing phase I trials in pediatric populations. The phase I pharmacokinetic study of imipenem–relebactam in serious pediatric Gram-negative infections is set to be completed in August 2020 (NCT03230916). The Phase I

pharmacokinetic study of meropenem–vaborbactam for the treatment of serious bacterial infections in pediatric patients is set to be completed in August 2019 (NCT02687906).

Currently, for adult patients without renal dysfunction, imipenem–relebactam is being dosed at 500/500/250 mg IV (*t*' 30 min) q6 h, while meropenem–vaborbactam is being dosed at 2000/2000 mg IV (*t*' 3 h) q8 h.

10 Adverse Events

The safety and tolerability of relebactam has been reported in one Phase I pharmacokinetic study and imipenem–relebactam in three phase I pharmacokinetic studies and two phase II clinical trials [75–78, 86, 90]. The safety and tolerability of vaborbactam has been reported in one phase I pharmacokinetic study and meropenem–vaborbactam in one phase III clinical trial [10, 81].

10.1 Imipenem–Relebactam

In a phase I pharmacokinetic study by Butterton et al. 16 healthy males received single doses of relebactam ranging from 0 tSo 1150 mg [75]. No subjects discontinued due to an adverse event and no serious adverse events were reported. Adverse events reported by three or more subjects included; headache, coryza, and somnolence.

In a pharmacokinetic study, Jumes et al. reported safety and tolerability of relebactam 50–625 mg with imipenem/cilastatin 500/500 mg IV q6 h for 7–14 days in a cohort of 90 healthy adult males, and a single dose of imipenem/cilastatin-relebactam 500/500/125 mg in a cohort of 24 healthy elderly subjects and adult females [76]. In the cohort of 90 adult men, 6 discontinued the study due to an adverse event including; vasovagal reaction, vomiting, pain at cannula site, skin rash, and elevated transaminases. Both vomiting and vasovagal episodes were considered severe adverse events while all other reported events were mild-to-moderate. Adverse events reported by three or more subjects included; erythema, tenderness, pain or swelling at the infusion or cannula site, diarrhea, yellow discoloration of the tongue, abdominal discomfort, headache, vasovagal episodes, presyncope, light-headedness, dysgeusia, and nausea. For subjects dosed q6 h for seven days with imipenem–relebactam, 8 of 42 subjects (19%) experienced elevations of ALT and/or AST above ULN. For subjects dosed q6 h for 14 days, 4 of 24 subjects (17%) administered imipenem–relebactam experienced ALT elevated above ULN, compared to 2 of 8 subjects (25%) administered imipenem-cilastatin. All increases in transaminases were reversible. For subjects dosed q6 h for 14 days, on day 10 and 11 two patients developed a generalized erythematous maculopapular pruritic rash and were discontinued from study therapy [1 of 24 (4%) administered imipenem–relebactam, 1 of 8 (13%) administered imipenem]. In this same group, 9 of 24 subjects (38%) on imipenem–relebactam and 3 of 8 subjects (38%) on imipenem reported yellow staining of tongue or teeth. In the cohort of 24 healthy elderly subjects and adult females, no severe adverse events were reported, only headache and dizziness were reported, which were considered mild drug-related adverse events.

In a pharmacokinetic study, Rizk et al. reported safety and tolerability of single doses of imipenem–relebactam 250/125 mg in 24 healthy subjects with varying renal function [78]. No severe adverse events were seen, and no subjects discontinued the study due to an adverse event. Drug-related adverse events included headache and left arm muscle irritation.

In an intrapulmonary pharmacokinetic study by Rhee et al, safety and tolerability of five doses of imipenem/cilastatin-relebactam 500/500/250 mg IV q6 h, in 16 healthy adult subjects was reported [77]. No serious adverse events were seen. Drug-related adverse events included fatigue, increased creatinine, nausea, emesis, and diarrhea. The subject who experienced mild diarrhea, and moderate nausea and emesis was discontinued from the study.

In a phase II study comparing the treatment of cIAI, drug-related adverse events occurred in 13.7, 13.8, and 9.6% of patients for treatment with imipenem/cilastatin-relebactam 500/500/250 mg, imipenem/cilastatin-relebactam 500/500/125 mg, and imipenem/cilastatin 500/500 mg, respectively [86]. The most common treatment-emergent adverse events included diarrhea, nausea, and vomiting, which were relatively similar in all three treatment groups (range of 2.6–7.8%). Three deaths occurred in the relebactam 125 mg treatment group due to septic shock, ventricular fibrillation, and intestinal infraction, all determined to be non-drug related. One serious drug-related adverse event, severe thrombocytosis, occurred in the imipenem alone treatment group and this patient consequently discontinued therapy. Drug-related adverse events leading to discontinuation occurred in four patients, 0 (0%), 1 (0.9%), and 3 (2.6%) in the three treatment groups, respectively, due to decreased creatinine clearance, thrombocytosis, nausea, and increased ALT. Four patients experienced AST or ALT $\geq 5\times$ ULN, two receiving relebactam 250 mg and two receiving imipenem alone. One patient experienced AST or ALT $\geq 3\times$ ULN with total bilirubin $\geq 2\times$ ULN and alkaline phosphatase $< 2\times$ ULN in the relebactam 250 mg treatment group; however, this was determined to be non-drug related.

In a Phase II study comparing the treatment of cUTI and AP, drug-related adverse events occurred in 10.1, 9.1, and

9% of patients for treatment with imipenem/cilastatin-relebactam 500/500/250 mg, imipenem/cilastatin-relebactam 500/500/125 mg, and imipenem/cilastatin 500/500 mg, respectively [90]. No deaths occurred; however, serious treatment-emergent adverse events were reported in 3.0, 1.0, and 3.0%, respectively. The most common treatment-emergent adverse events included nausea, headache and diarrhea, which were relatively similar in all three treatment groups (range of 2.0–7.1%). Treatment-related adverse events leading to discontinuation occurred in four patients, 2 (2%), 1 (1%), and 1 (1%) in the three treatment groups, respectively, due to diarrhea, rash, nausea, and diarrhea. One patient in the relebactam 250 mg group experienced AST elevations $\geq 5\times$ ULN, determined to be drug related.

10.2 Meropenem–Relebactam

In a phase I pharmacokinetic study by Griffith et al, 88 healthy males received single or multiple doses of vaborbactam ranging from 0 to 2000 mg, multiple doses were administered q8 h for 7 days [81]. No deaths or severe adverse events occurred in this study. For single doses of vaborbactam, the most common treatment-emergent event was headache; however, there was no correlation with an increasing dose, and rates were similar to placebo [19% (8/42) versus 21% (3/14) for placebo]. Ten adverse events were classified as mild, and four moderate including myalgia (placebo group), musculoskeletal (buttock) pain (vaborbactam 750 mg), pain in extremity (thigh) (vaborbactam 750 mg), and infusion site thrombosis (vaborbactam 2000 mg). For multiple doses, adverse events occurring in at least five subjects included infusion site phlebitis [42% (10/24) vs 50% (4/8) for placebo], headache [29% (7/24) vs 13% (1/8) for placebo], lethargy [21% (5/24) vs 0% (0/8) placebo], and dermatitis contact [13% (3/24) vs 0% (0/8) placebo]. Mild lethargy was most commonly observed in the highest dose (2000 mg) group for vaborbactam (4 of 6 patients in this group, accounting for 4 of 5 events). Drug-related adverse events occurred in 58% of patients, 27 events were mild, and three moderate including infusion-site phlebitis (vaborbactam 250 and 2000 mg) and infusion site erythema (placebo).

In a phase III trial comparing the treatment for cUTI and AP, drug-related adverse events occurred in 15.1% (41/272) and 12.8% (35/273) of patients treated with meropenem–vaborbactam and piperacillin-tazobactam, respectively [10]. Two deaths occurred in each treatment group. Serious adverse events occurred in 4% (11/272) and 4.4% (12/273) of patients treated with meropenem–vaborbactam and piperacillin-tazobactam, respectively. Discontinuation of therapy occurred due to an adverse event in 2.6% (7/272) and 5.1% (14/273) of patients treated with meropenem–vaborbactam and piperacillin-tazobactam, respectively. Specific adverse events reported in this study were not available.

To date, both imipenem–relebactam and meropenem–vaborbactam appear to be well tolerated in healthy subjects as well as patients with infectious diseases, with few serious drug-related treatment-emergent adverse events reported.

11 Drug Interactions

Limited information is currently available regarding specific drug interactions involving co-administration with imipenem–relebactam or meropenem–vaborbactam. However, drug interactions have been well described for imipenem and meropenem without the additions of relebactam and vaborbactam.

Co-administration of probenecid causes a decrease in renal excretion of imipenem or meropenem, therefore increasing plasma concentrations and prolonging $t_{½}$ [1, 95, 96]. Probenecid causes increases in meropenems $t_{½}$ by approximately 33%; alternatively, imipenem plasma concentrations are minimally affected as non-renal clearance mechanisms increase to compensate for a 30% decrease in renal clearance of imipenem [1]. Co-administration is not recommended [95].

Both imipenem and meropenem have been reported to decrease serum concentrations of valproic acid [95, 96]. Meropenem has been reported to decreased valproic acid serum concentrations by 60–100% in approximately two days [96]. Co-administration is not recommended due to the risk of valproic acid serum concentrations falling below a therapeutic range [95, 96].

Generalized seizures have been reported for co-administration of imipenem with ganciclovir [1, 95]. Co-administration is not recommended [95].

The potential of relebactam to be a substrate or inhibitor of human renal uptake and efflux transporters to determine potential drug interactions was investigated (MSD unpublished data). Relebactam was determined to be a substrate of tubular transporters hOAT3, hOAT4, MATE1 and MATE2K, but not a substrate of other common human renal uptake and efflux transporters (hOAT1, hOCT2, MDR1 P-gp, MRP2, MRP4, or BCRP). It was also determined that relebactam was not an inhibitor of common human renal uptake and efflux transporters (MDR1 P-gp, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, MATE2 K, BCRP, or BSEP). Probenecid inhibited hOAT3-mediated relebactam uptake in vitro ($IC_{50} = 1.9 \pm 0.4$ μM in MDCKII-hOAT3 cells). Other common antimicrobials (piperacillin-tazobactam, ciprofloxacin, fluconazole, ampicillin, levofloxacin,

metronidazole, vancomycin, linezolid, daptomycin, and cefazolin) did not inhibit hOAT3-mediated relebactam uptake in vitro ($IC_{50} > 50$ μM in MDCKII-hOAT3 cells). Overall, given that active secretion accounts for only ~ 35% of the total renal clearance of relebactam, the extent of drug interactions due to inhibition of these tubular transporters is expected to be of limited clinical significance.

12 Place of Imipenem–Relebactam and Meropenem–Vaborbactam in Therapy

The addition of relebactam and vaborbactam restore the activity of imipenem and meropenem, respectively, against resistant Gram-negative bacilli that produce Ambler class A and C β-lactamases, including ESBLs and serine carbapenemases. Available safety and pharmacokinetic data currently suggest no additional considerations need to be taken into consideration when administering imipenem and meropenem with the additions of relebactam and vaborbactam, respectively.

Imipenem–relebactam has demonstrated clinical efficacy similar to that of imipenem alone in phase II studies of cIAI and cUTI/AP. Completion of Phase III clinical trials for the treatment of resistant bacterial infections (including HABP/VABP, cIAI, and cUTI) and for the treatment of HABP/VABP will help to define the efficacy and safety of this novel antimicrobial combination in serious and resistant infections. The excellent ELF penetration of imipenem–relebactam combined with potent activity against CRE and *P. aeruginosa* could potentially make this novel antimicrobial combination an important treatment option in HABP and VABP.

In phase III clinical trials, meropenem–vaborbactam has demonstrated clinical efficacy compared to piperacillin-tazobactam in the treatment of cUTI/AP. Recent clinical trial data demonstrated that meropenem–vaborbactam was associated with higher clinical cure rates than "best available therapy" across a variety of infections caused by CRE (including cUTI/AP, HABP/VABP, and bacteremia), including in immunocompromised patients, providing compelling data that meropenem–vaborbactam is a new option for the treatment of CRE infections in seriously ill patients. As with imipenem–relebactam, the excellent ELF penetration of meropenem–vaborbactam combined with potent activity against CRE could also potentially make this novel antimicrobial combination an important treatment option in HABP and VABP.

Potential roles in therapy for imipenem–relebactam and meropenem–vaborbactam include treatment of suspected or documented infections caused by resistant Gram-negative bacilli-producing ESBL, KPC, and/or AmpC β-lactamases. The usage of these agents in patients with CRE infections will likely become the standard of care. The increased activity of imipenem–relebactam against *P. aeruginosa* may also be clinically beneficial in patients with suspected or documented *P. aeruginosa* infections. Although more clinical efficacy and safety data are required, imipenem–relebactam and meropenem–vaborbactam provide clinicians with an alternative option for the empiric treatment of serious infections caused by resistant Gram-negative bacilli, although the lack of activity against isolates producing metallo-β-lactamases remains a limitation.

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Compliance with Ethical Standards

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