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Novel Beta-lactamase Inhibitors: Unlocking Their Potential in Therapy

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Abstract

Carbapenem-resistant *Enterobacteriaceae* are amongst the most feared pathogens due to severely limited treatment options. In response to this threat three novel β-lactamase inhibitors have been developed in an attempt to reinvigorate and sustain our current antimicrobial therapies. Avibactam, vaborbactam, and relebactam are inhibitor agents with high affinity to Ambler class A and C β-lactamases and favorable outcomes in current clinical trials. However, although they do possess key similarities, these agents have unique differences which may have important clinical implications. The microbiologic spectrum, pharmacokinetics, and key clinical trials for each of these novel agents are reviewed. A proposed role in therapy and potential novel combinations are examined.

1. Introduction

The evolution of bacterial resistance to antimicrobials has been a problem since the earliest days of penicillin. This escalation has only intensified with the widespread consumption of antimicrobials as part of agricultural, veterinary, and healthcare practice.

β-lactam antibiotics constitute 60% of worldwide antibiotic usage by weight and are among the most effective agents for treatment. [1] Therefore, β-lactam-hydrolyzing enzymes, (β-lactamases) are considered the most important and clinically relevant mechanism of bacterial resistance. Genes encoding β-lactamases may be present on the bacterial chromosome, and are also often found on mobile genetic elements such as plasmids and transposons. This results in the potential for rapid spread through horizontal as well as vertical genetic transmission.

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There are two major classification schemes of β-lactamases. The Ambler classification is based on amino-acid sequence similarities and the Bush classification is based on functionality. The Ambler Classification divides β-lactamases into four molecular classes, A–D, with classes A, C, and D utilizing a serine moiety, and class B consisting of a metalloenzymatic zinc ion at its active site. The Bush schema is based on enzymatic functionality and results in three major groups: Group 1 cephalosphorinases, Group 2 serine β-lactamases, and Group 3 metallo-β-lactamases (MBL), with each group encompassing further subdivisions. [2] Notably, by the end of 2009, over 890 unique protein sequences of β-lactamases were reported by Jacoby and Bush. [1, 2] In a more recent estimate, >2,000 unique β-lactamases have been described to date. [3]

The first clinically used β-lactamase inhibitors, such as clavulanic acid, sulbactam, and tazobactam were discovered in the mid-to-late 1980s. A conserved similarity with these inhibitors is the shared β-lactam backbone. In essence, these inhibitors form stable intermediates with β-lactamases, thereby allowing their companion β-lactam to effectively bind to a target penicillin binding protein. [4] These agents were a revolutionary advance allowing for the reinvigoration, and expansion of both the spectrum and longevity of then available antimicrobials. However, the ever increasing number of clinically important β-lactamases has spurred a demand for novel inhibitor agents.

Resistance to carbapenems in Gram-negative bacteria is of particular concern, as carbapenems are still regarded the first line therapeutic option for many Gram-negative, multi-drug resistant (MDR) bacterial infections. Globally, enzymatic carbapenem resistance in Enterobacteriaceae is most often conveyed by carbapenemases in the family of serine-based *Klebsiella pneumoniae* carbapenemases (KPC). Other important carbapenemases include New Delhi metallo-β-lactamases (NDM), Verona integron-encoded metallo-β-lactamases (VIM) and oxacillinase-48-like (OXA-48) carbapenemases. Carbapenemases have a global distribution with substantial regional variability. [5] KPC-producing *Enterobacteriaceae* predominate in the United States, Italy, Greece, Italy and South America, while MBL are most commonly found within the Indian Subcontinent and in particular specific countries in Europe including Romania, Denmark, Spain, and Hungary. [5] The distribution of OXA-48 is centered in Turkey and its surrounding counties. [5] This global epidemiology underscores the widespread occurrence, and the risk of regional spread due to increasing worldwide interconnectivity, utilization of intensive care units, and the rising availability of medical tourism.

Carbapenemase-producing organisms (CPO) are often resistant to other drug classes as well and few therapeutic options remain for patients infected with CPO. Salvage agents such as polymyxins and tigecycline may display high toxicity and low efficacy. Mortality rated in invasive carbapenem-resistant Enterobacteriaceae (CRE) infections are estimated between 32 to 44%. [6]

In this review, we will discuss 3 novel inhibitors. These 3 novel compounds – avibactam (formerly AVE1330A and NXL104), relebactam (formerly MK7655), and vaborbactam, (formerly RPX7009) – each have unique pharmacokinetic and pharmacodynamic properties (see chemical structures in Figure 1). Whereas avibactam is currently available in co-

formulation with ceftazidime in the US, and has been approved by the European Medicines Agency (June 2016), none of the other agents are currently available outside of studies. The most obvious benefit of these newer agents over older-generation β-lactamase inhibitors, such as tazobactam, clavulanate, and sulbactam, is their ability to inhibit certain extended-spectrum β-lactamases and carbapenemases.

For this non-systematic, narrative review, we have reviewed the following databases up to 2/23/2017: pubmed, clinicaltrials.gov, Google Scholar. In addition, we have used reference list from published articles and we have searched abstract banks of national meetings and press releases where applicable.

2. Avibactam

2.1. Avibactam: Introduction

Avibactam (previously NXL104, AVE1330A) is a synthetic diazabicyclooctane non-β-lactam inhibitor which inhibits Ambler class A and C and some class D β-lactamases. It was the first novel inhibitor to receive FDA approval as the combination of ceftazidime-avibactam. Ceftazidime-avibactam received approval in February, 2015 for the treatment of complicated urinary tract infections (cUTI) and for the treatment of complicated intra-abdominal infection (cIAI) when used in combination with metronidazole.

Ceftazidime, as the active companion agent, is a β-lactam which inhibits peptidoglycan synthesis via the inhibition of penicillin-binding proteins (PBPs). The inhibition of PBPs leads to cell wall instability and subsequent lysis of bacterial cells.

2.2. Mechanism of Avibactam

Avibactam has been shown to exert its inhibition properties via a two-stage process. There is an initial non-covalent association with a susceptible β-lactamase binding site followed by a covalent acylation at the β-lactamase serine residue. [7, 8] A unique feature of avibactam in comparison to earlier generation inhibitor agents is that avibactam binds reversibly to β-lactamases allowing for re-cyclization and inhibition of additional β-lactamase molecules. Additionally, *in vitro* studies have found that avibactam did not appreciably induce *Enterobacter cloacae* chromosomal AmpC production. [8]

2.3. Microbiologic Spectrum of Avibactam

The crucial advantage of avibactam over older β-lactamase inhibitors is its ability to inhibit a wide range of β-lactamases, including the extended spectrum (ESBL), AmpC, and Class A and D carbapenemases, in particular KPC and OXA-48 (Table 1). [9, 10]

In a large *in vitro* study of clinical US Enterobacteriaceae, only 11 isolates of >20,000 isolates had a ceftazidime-avibactam MIC > 8 μg/mL. Two of the 11 resistant isolates expressed an MBL, which are intrinsically resistant to avibactam inhibition. [9] This highlights a key limitation of avibactam, in that it is not active against class B metallo-β-lactamases. Furthermore, Livermore et al. also showed that avibactam also was able to restore the activity of ceftazidime against bacterial strains with the OXA-48 enzyme. [11]

These studies highlighted the finding that non-MBL mechanisms of resistance exist for avibactam. Variants of SHV-1 and KPC-2 possessing a single point mutation were able to confer avibactam resistance. [12] Experimentally, three AmpC derepressed *Enterobacter cloacae* isolates had a significantly elevated MIC to the combination of ceftaroline and avibactam. One isolate had an OmpC and OmpF deficiency and in the remaining two, there were point mutations in the AmpC gene. [8] These findings also highlighted that resistance to ceftazidime-avibactam was identified in selected *Enterobacter* strains and postulated to have occurred due to a combination of impermeability and an overproduction of AmpC overwhelming inhibitor capacity. [11] Importantly, avibactam resistance in clinical isolates after treatment of patients with ceftazidime-avibactam has been reported. [13] Various $bla_{\text{KPC-3}}$ mutations that rendered avibactam inactive against the resulting KPC-3 enzyme were identified. Of concern, these mutated genes were found to be plasmid-borne. Some of these mutations decreased the carbapenemase activity of KPC-3 and led to carbapenem-susceptible isolates. [14]

In addition to its role in MDR Enterobacteriaceae, ceftazidime-avibactam is also active against certain MDR *Pseudomonas aeruginosa* strains.. [9] In a 4 year US study, 81% of ceftazidime-resistant *P. aeruginosa* strains were susceptible to ceftazidime-avibactam.. [15] In contrast, the addition of avibactam to ceftazidime does not improve its activity against *Acinetobacter baumannii*.

While the combination of ceftazidime-avibactam did exhibit improved activity for *Bacteroides fragilis*, *Clostridium perfringens*, and both *Prevotella* and *Porphyromonas* species, ceftazidime-avibactam does not exhibit reliable anaerobic activity. [8, 16] Furthermore, anti-staphylococcal and anti-streptococcal activity is limited as well.

2.4. Pharmacokinetics/Pharmacodynamics of Avibactam

In two cohorts of 8 subjects administered doses of ceftazidime-avibactam at a dose of 1000/250mg and 2000/500mg, the pharmacokinetics of both agents combined were not significantly altered when compared to administration alone. [8] Merdjan et al. conducted early Phase 1 studies on the safety and tolerability of ceftazidime-avibactam administered at a 4:1 ratio. These studies confirmed that avibactam plasma concentrations consistently were related to renal function, and that accordingly avibactam exposure increased with increasing severity of renal impairment. [17] Additional Phase 1 data in healthy volunteers found avibactam pharmacokinetics were linear for doses ranging from 50 – 2000mg. Following infusion, avibactam has rapid distribution, a half-life of 1.7–2.1 hours, and is primarily (95%) renally cleared with rate dependent on creatinine clearance.[8] In six anuric patients on renal replacement therapy, 54 % of avibactam was removed during dialysis.[8] As such, the preliminary data suggests that avibactam pharmacokinetics and clearance is similar to that of its companion agent, ceftazidime.

Based on phase 1 data, the recommended dose for patients with normal renal function is 2000mg/500mg ceftazidime-avibactam administered every 8 hours. The recommended dose adjustment for patients are: 1.25gm every 8 hours for creatinine clearance 31–50mL/min, 0.94 gm every 12 hours for CrCL 16–30mL/min, 0.94 gm every 24 hours for CrCL 6–15 mL/min, and 0.94 gm every 48 HR for CrCL ≤5 mL/min (Both ceftazidime and avibactam

are hemodialyzable; thus the package insert recommends to administer after hemodialysis on hemodialysis days). When penetration into the epithelial lining fluid (ELF) of the lung was evaluated in a phase 1 study on healthy adults, both ceftazidime and avibactam were found to penetrate into ELF dose-proportionally, with ELF exposure to both drugs ~30% of plasma exposure. [18]

2.5. Avibactam: Clinical studies

Clinical studies are summarized in Table 2. Two phase 2 trials were performed to evaluate the potential efficacy of ceftazidime-avibactam. The first, by Vazquez et al. enrolled 137 patients, randomized in a 1:1 fashion to receive either ceftazidime-avibactam or imipenem for the treatment of cUTI. The microbiologic response was comparable; the response of 19/27 (70.4%) in the ceftazidime-avibactam and 25/35 (71.4%) in the imipenem groups. [19] Notably, the renal dose adjustment protocol used differed significantly from the current FDA label. The dosing studied in this trial was 500 mg of ceftazidime and 125 mg of avibactam every 8 hours, a dose that was 4-times lower than the current package insert (2gm/500mg ceftazidime-avibactam every 8 hours) for patients with normal renal function. A second phase 2 trial by Lucasti et al. studied the efficacy of ceftazidime/avibactam plus metronidazole compared with meropenem in the treatment of cIAI. A favorable response was observed in 91.2% (62/68) and 93.4% (71/76) of patients, respectively. [20]

Two key Phase 3 clinical trials form the foundation of clinical data. The RECAPTURE study, evaluated the efficacy of ceftazidime-avibactam compared to doripenem for the treatment of cUTI. Patients were randomized in a 1:1 fashion to receive either ceftazidime-avibactam or doripenem. [21] The microbiological modified intent-to-treat population consisted of 393 and 417 patients in the ceftazidime-avibactam and doripenem groups, respectively. Non-inferiority was met for the co-primary endpoints of patient-reported symptomatic resolution at day 5 (276 of 393 [70.2%] vs 276 of 417 [66.2%] patients) and the combined symptomatic resolution/microbiological eradication at test of cure (280 of 393 [71.2%] vs 269 of 417 [64.5%] patients. The microbiologic response at end-of-treatment was similar for both groups at 95.2% and 94.7% in the ceftazidime-avibactam compared to the doripenem group. When examining susceptibility of baseline pathogens, ceftazidime-avibactam and doripenem were active against 311/400 (77.8%) and 297/419 (70.9%) of organisms, respectively. Of interest, in the subset of patients with bacterial isolates that were non-susceptible to ceftazidime, microbiological cure occurred in 47/75 (62.7%) of the ceftazidime-avibactam treated patients and 51/84 (60.7%) of doripenem treated patients, respectively. [21] In this study, renal impairment did not affect clinical outcome, although patients with a creatinine clearance ≤30 mL/minute or on dialysis were excluded.

Mazuski et al. performed a Phase 3 randomized double-blind study to determine the efficacy of ceftazidime-avibactam with metronidazole compared to meropenem in the treatment of cIAI. [22] As previously, patients with a creatinine clearance ≤30 mL/minute were excluded. An additional limitation is that the study enrolled primarily a high proportion of patients with appendicitis as their primary diagnosis, and in general all patients were not critically ill with over 80% of patients having an APACHE II score of ≤10, and a low incidence of bacteremia. (4.2% ceftazidime-avibactam and metronidazole group vs. 2.7% meropenem

group) Of particular interest, in patients with ceftazidime-resistant Gram-negative infections, ceftazidime-avibactam plus metronidazole and meropenem resulted in clinical cure rates of 83.0% (39/47) and 85.9% (55/64), respectively. [22] Mortality rates were also similar at 2.5% (13/520) and 1.5% (8/523) between the ceftazidime-avibactam and meropenem groups. Overall, ceftazidime-avibactam plus metronidazole was non-inferior to meropenem in this trial.[22] In subgroup analysis, patients with moderate renal impairment (estimated creatinine clearance between 30 and 50 mL/min) treated with ceftazidime/avibactam plus metronidazole (45%) had lower cure rates as compared patients with moderate renal impairment treated with meropenem (74%). The reason for this observation may have been an observed delay in dose readjustment to full dosing in those patients who recovered renal function [23]. Of note, in these phase III cIAI trials patients with moderate renal failure were given 1,000/250 mg ceftazidime/avibactam every 12 hours. The current package insert recommendations are to give 1,000/250 mg ceftazidime/avibactam every 8 hours to patients with moderate renal failure.

The REPRISE study compared ceftazidime-avibactam vs best available therapy (BAT) in patients with cUTI or cIAI infections caused by ceftazidime-resistant Enterobacteriaceae or *P. aeruginosa* in a randomized, open-label trial. Of note, the authors stated that “Because of the unfeasibility of recruiting large numbers of patients infected with resistant Gram-negative pathogens, we did not do any formal power calculations for this study, or any formal statistical comparisons between the treatment groups. Rather, we used the corresponding CIs for the efficacy of best available therapy to provide a context for descriptive estimates of ceftazidime-avibactam efficacy.” Using this methodology, 154 ceftazidime-avibactam treated patients (of whom 144 had cUTI) were compared to 148 patients treated with BAT. Numerically, clinical responses were similar and microbiologic responses were somewhat higher in the ceftazidime-avibactam group. [24]

A study comparing ceftazidime-avibactam vs. meropenem in the treatment of hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP) has recently been completed (clinicaltrials.gov identifier NCT01808092), and results should be available in the near future.

Post-marketing clinical experience with ceftazidime-avibactam from observational studies is starting to be reported. These data are important as patients with infections caused by the target organisms (e.g. carbapenemase-producing Enterobacteriaceae) are often not included in registrational trials. At IDweek 2016, a case series of 60 patients with CRE infections treated with ceftazidime-avibactam was presented. [25] In this cohort, 51% had a microbiologic cure, 66% had clinical success as defined by the investigators, and the all-cause hospital mortality was 36%. Shields et al. reported single-center, observational experience using ceftazidime-avibactam for the treatment of CRE infection in 37 patients. [13] Of note, the patients had a variety of infectious syndromes, primarily pneumonia (12/37), but also including soft tissue infection, intra-abdominal infection, primary bacteremia, and even a single case each of subdural empyema and ventriculitis and mediastinitis. No isolates expressed VIM, IMP, NDM, or OXA-48 carbapenemases, and 78% (29/37) expressed *K. pneumoniae* carbapenemase. Thirty-day survival was 76% (28/37) and clinical success was 59% (22/37). Microbiologic failures due to recurrence of infection

occurred in 10 patients of which 3 isolates displayed ceftazidime-avibactam resistance. [13] Collectively, this suggests ceftazidime-avibactam is a potentially viable option with a comparable clinical response to alternative therapies. However, it raises the concern of emergence of resistance following therapy. Randomized controlled trials are needed to more definitively study the relative efficacy of ceftazidime-avibactam in comparison to other available therapies for the treatment of invasive infections caused by carbapenemase-producing Enterobacteriaceae.

2.6. Adverse Effects of Avibactam

Phase 1 data found avibactam well tolerated at multiple dose ranges.[8, 17] Overall, avibactam has had few adverse effects reported. [9] Similarly, ceftazidime-avibactam was reasonably well tolerated even when subjected to supratherapeutic doses of 3000mg ceftazidime with 2000mg avibactam, although 30% of volunteers experienced adverse effects, these consisted of nausea, vomiting, and headache. [9] In Phase 3 trials, adverse event rate was generally low and similar to comparator agents, and consisted most commonly of headache, nausea, or diarrhea which rarely resulted in discontinuation of study drug.[21]

3. Vaborbactam

3.1. Vaborbactam: Introduction

Boronic acids are potent inhibitors of serine proteases and have thus been of considerable interest clinically. Vaborbactam (formerly RPX7009) is the first boronic acid β lactamase inhibitor in current phase III clinical trials. RPX7009 was found to exhibit potent inhibition of KPC enzymes, as well as other Ambler class A and C enzymes (Table 1). However, similar to avibactam, it lacks inhibition of class B MBLs. Based on preliminary phase 3 treatment data, FDA submission of New Drug Application (NDA) was filed in February 2017.

3.2. Mechanism of Vaborbactam

Boronates have a high affinity for serine proteases resulting in a covalent association between the catalytic serine and the boronate moiety. [26] This is a novel mechanism as compared to current clinically available β-lactamase-inhibitors. By forming a reversible dative bond with the β-lactamase, vaborbactam acts as a competitive inhibitor and is not hydrolyzed by the β-lactamase. Vaborbactam is administered in combination with meropenem, a carbapenem approved in 1996.

3.3. Microbiologic Spectrum of Vaborbactam

In vitro testing of vaborbactam was performed by Castanheira et al. The ability of vaborbactam to augment the activity of meropenem was evaluated *in vitro* against 315 serine carbapenemase-producing Enterobacteriaceae isolates as identified by PCR sequencing and microarray-based assay. As expected, meropenem alone inhibited only 2.2% of the strains at the CLSI susceptibility breakpoint (≤1 μg/ml). However, in the presence of increasing concentrations of vaborbactam, the activity of meropenem was restored. Based on dose escalation studies, activity of meropenem was at least 64-fold greater with a fixed dosed

concentration of vaborbactam at 8 μg/ml, making this concentration the target for additional study.[27] With this fixed concentration vaborbactam, activity of meropenem was restored to MIC ≤1 in 93.7% of isolates and ≤2 in 96.5% of isolates. Seven isolates, all *K. pneumoniae*, had persistent MIC values ≥16 μg/ml despite addition of vaborbactam. Of these isolates, four produced an MBL concurrently with KPC enzyme. The remaining three isolates expressed reduced levels of outer membrane protein OmpK37 and high expression of AcrAB-TolC efflux.[27] Of note, vaborbactam did not restore activity of biapenem against OXA-48-carbapenemase-producing CRE. [28]

Meropenem-vaborbactam also showed favorable activity when tested against 4,500 Gram-negative clinical isolates from 11 New York City hospitals.[29] When examining only multi-drug resistant carbapenemase producing strains of Enterobacteriaceae, inclusive of *Escherichia coli*, *K. pneumoniae*, and *Enterobacter* spp., 131/133 (98.5%) were inhibited by meropenem plus vaborbactam.[29] The combination had reduced activity against two KPC-producing *K. pneumoniae* isolates which had reduced OmpK35 and OmpK36 expression. [29] Notably, vaborbactam did not improve activity of meropenem against *A. baumannii* and *P. aeruginosa* postulated due to alternative mechanisms of drug resistance including the porin alterations and drug efflux. [29] The impact of vaborbactam on the anaerobic spectrum of carbapenems was evaluated in combination with biapenem [30]. As expected, the activity of biapenem alone against anaerobes was excellent, and the addition of vaborbactam did not significantly change the anti-anaerobic activity.

3.4. Pharmacokinetics/Pharmacodynamics of Vaborbactam

In phase I studies, in 36 healthy volunteers vaborbactam was well tolerated and had a half-life of 1.23 hours, and steady state volume of distribution of 21.0 liters.[26] As such, pharmacokinetics mimicked most β-lactams which typically share a short half-life and low volume of distribution. Vaborbactam is given in clinical trials in combination with meropenem in a dosing of 2g-2g intravenous infusion every 8 hours.

Wenzler et al. evaluated the plasma and epithelial lining fluid (ELF) concentrations of meropenem and vaborbactam in healthy subjects following intravenous infusion, as a potential predictor for efficacy in lower respiratory tract infections. In 26 healthy adult subjects, when administered 2gm-2gm meropenem-vaborbactam every 8 hours as a 3-hour extended infusion, a similar time course and magnitude of meropenem and vaborbactam concentrations was observed in serum and ELF, with penetration 65% and 79% for meropenem and vaborbactam, respectively.[31]

3.5. Vaborbactam: Clinical studies

Clinical studies are summarized in Table 3. Phase I clinical studies by Griffith et al. showed vaborbactam was well tolerated in 36 healthy volunteers when administered via 3 h infusions at doses of ranging from 250 to 1500mg. [32]

Two large multi-center phase III trials were initiated in 2014 to evaluate the efficacy of meropenem-vaborbactam clinically. TANGO-1 was the first trial to complete enrollment in early 2016. [33] TANGO-1 was a multi-center, 1:1 randomized, double-blind study comparing meropenem-vaborbactam to piperacillin-tazobactam in the treatment of cUTI in

adults. Clinical success was defined as clinical cure or improvement in symptoms in addition to microbiologic eradication with follow up urine culture reduction to less than 10^4 CFU/mL. In the intent-to-treat population, clinical success occurred in 188/192 patients (98.4%) in the meropenem-vaborbactam and in 171/182 patients (94.0%) in the piperacillin-tazobactam group. This FDA primary endpoint met statistical significance, with a difference of 4.5% (95% CI: 0.7 % to 9.1%). In the microbiologic evaluable group for test-of-cure, microbiological eradication occurred in 118/178 patients (66.3%) in the meropenem-vaborbactam and 102/169 patients (60.4%) in the piperacillin-tazobactam group, a difference of 5.9% which was not statistically significant. (95% CI: −4.2% to 16%). [33, 34]

The TANGO-2 study (ClinicalTrials.gov Identifier: NCT02168946), currently ongoing, is a 60-site randomized at a 2:1 experimental drug, study evaluating meropenem-vaborbactam for the treatment of infections by a suspected carbapenem-resistant Enterobactericiae. Potential infectious syndromes evaluated include cUTI, HABP/VABP, cIAI, and bacteremia when compared to best-available therapy. [33] TANGO-3 (ClinicalTrials.gov Identifier: NCT03006679) is also planned. It will compare meropenem-vaborbactam vs. piperacillin-tazobactam in patients with HABP/VABP. Additionally, a new trial has begun recruitment, as a phase 1 study to evaluate the dose, pharmacokinetics, safety and tolerability of meropenem-vaborbactam in pediatric patients. (ClinicalTrials.gov Identifier: NCT02687906)

3.6. Adverse Effects of Vaborbactam

As vaborbactam remains in clinical trials there is little published data on drug tolerance. However, initial studies suggest it is likely to be well tolerated. TANGO-1 released data treatment emergent adverse event rate was 15.1% and 12.8% in the vaborbactam and piperacillin-tazobactam group respectively. The rate of study drug discontinuation secondary to adverse effect was 2.6% and 5.1% for vaborbactam and piperacillin-tazobactam, a non-significant difference.

Wenzler et al. in testing of pharmacokinetic properties of combination meropenem-vaborbactam in 26 healthy adults had one subject discontinue administration due to chest discomfort, dizziness, and dyspnea which was considered to be potentially related to the investigational drug.[31] The remaining 25 subjects, tolerated the study drug at 2gm-2gm doses without any reportably meaningful laboratory, vital sign, EKG, or physical examination adverse effect. [31]

4. Relebactam

4.1. Relebactam: Introduction

Relebactam (formerly MK-7655) is a bridged bicyclic urea candidate molecule which following discovery has become a clinical candidate due to its broad class A and C β-lactamase inhibition. [35] It is currently in clinical trials in co-formulated combination of the carbapenem imipenem and the renal dehydropeptidase inhibitor cilastatin.

4.2. Mechanism of Relebactam

Similarly to avibactam, relebactam is a small serine based molecule with a diazabicyclooctane core. Relebactam; in contrast, also possesses a piperidine ring. However, the predicted mechanism of action appears to be similar to that of avibactam with potent inhibition of both class A and C β-lactamases.[4]

4.3. Microbiologic Spectrum of Relebactam

Relebactam has a similar activity as avibactam; it inhibits class A and class C β-lactamases including KPC enzymes (Table 1). In this way, the addition of relebactam to imipenem broadens the spectrum of that combination to include certain imipenem-resistant Enterobacteriaceae and *P. aeruginosa* strains. However, the addition of relebactam to imipenem did not provide added benefit against *A. baumannii*. [36] An early *in vitro* study of the potential activity of relebactam was performed by Hirsch et al. utilizing mathematical modeling in a hollow fiber infection model to assess bactericidal activity of relebactam in combination with imipenem.[37] Time-kill studies were performed on a KPC-2-producing *K. pneumoniae* and three *P. aeruginosa* isolates which exhibited OprD porin mutations and AmpC overexpression. For all four isolates, MICs were significantly reduced in the presence of relebactam at 4mg/L. This effect was most pronounced in *K. pneumoniae* with a 64-fold reduction, from 128 mg/liter to 2 mg/liter. In the *P. aeruginosa* strains, although relebactam synergistic activity was seen with imipenem, the effects were far less dramatic. At least a 2-log reduction in bacterial burden was observed in all strains following initial exposure to relebactam; however, regrowth occurred in two *Pseudomonas* strains at 72 hours. [37]

Further analysis by Livermore et al. examined the ability of relebactam to restore imipenem activity in a variety of isolates via *in vitro* agar dilution studies. Relebactam, at a concentration of 4 mg/L, reduced the imipenem MIC for *Enterobacteriaceae* with KPC carbapenemases from 16–64 mg/L to 0.12–1 mg/L. [38] A minimal effect of relebactam was seen in OXA-48 producing isolates. Isolates with an initial carbapenem MIC >64 mg/L had an MIC reduction to 16 mg/L with the addition of high dose 32mg/L relebactam. [38] Given the similarities between avibactam and relebactam, and the fact that the addition of relebactam to a subset of OXA-48-producing *K. pneumoniae* does result in restoration of the activity of imipenem, further studies are needed to determine the effect of relebactam on OXA-48. [38] In *P. aeruginosa*, there was an MIC reduction in OprD-deficient strains from 16–64 mg/L to 1–4 mg/L. [38] This is likely explained by inhibition of the continued AmpC function present in OprD-deficient strains.[39]

In regard to anaerobic spectrum, the addition of relebactam was found to not add to the potent anaerobic spectrum of imipenem. While imipenem resistance of bacteroides is rare, with an estimated occurence of less than 1%, a study of 451 clinical isolates of the *B. fragilis* showed that the addition of relebactam did not further inhibit imipenem-resistant isolates. [40]

4.4. Pharmacokinetics/Pharmacodynamics of Relebactam

In murine modeling, Mavridou et al. found that the AUC (area under the curve) was the parameter best correlating to efficacy, and confirmed that peak concentration was not a significant determinant of efficacy.[41]

Although the optimal dosing regimen for relebactam has not been determined, phase I studies based on murine and hollow fiber modeling have suggested relebactam doses at or above 125mg every 6 hours was able to achieve an effect PK/PD target.[42] However, certain models did suggest higher concentrations of relebactam may be required for highly resistant strains of *Pseudomonas*.[42]

4.5. Relebactam: Clinical studies

Clinical studies are summarized in Table 4. In the introduction to their phase 2 data, Lucasti et al. refer to phase I unpublished data that relebactam is well tolerated with intravenous administration as either a single dose of up to 1150 mg or when administered at multiple doses of625 mg every 6 hours. [42] Notably, transient liver enzyme elevation did occur in several patients who received multiple administration dosing. [42]

Recently, phase II clinical data from a multicenter randomized controlled double-blind study has been released in the use of imipenem-cilastatin in combination with various doses of relebactam in the treatment of cIAI. Patients were randomized in a 1:1:1 fashion into groups receiving 500 mg imipenem-cilastatin every 6 hours with either relebactam 250 mg, relebactam 125 mg, or placebo. Important to note, patients with APACHE > 30 and those with baseline renal dysfunction were excluded. Approximately 117 subjects were assigned to each treatment group, allowing for study power of 80% to demonstrate non-inferiority of relebactam compared to control predicated upon a non-inferiority margin of -15, and an overall 90% control group clinical response rate. Clinical response rate of all three groups, relebactam 250mg, relebactam 125mg, and placebo group were 99.2%, 98.3%, 99.1% respectively, and treatment between all three groups was considered similar. [42]

Of note, in the 277 patients in the microbiologic intention to treat subset, 36 patients (13%) had an infection with a Gram-negative imipenem non-susceptible organism. This was inclusive of both intermediate and fully resistant organisms. Thirty four of these patients were able to be evaluated at follow up, with all 34 classified as having a favorable clinical response, with 14/14, 9/9, and 11/11 patients responding in the relebactam 250mg, relebactam 125mg, and imipenem alone groups respectively.[42] Notably, this subset of 34 patients were responsible for 40 bacterial isolates. Subsequent testing of these 40 imipenem non-susceptible isolates resulted in 7 which had restored susceptibility to the combination of imipenem-relebactam, but the remaining 33 remained non-susceptible despite relebactam administration. [42] Interestingly, 21 of these isolates were *Proteus* sp., with the majority *Proteus mirabilis*, of which only 2 had restored activity of imipenem in the presence of relebactam. The remainder of isolates were predominantly *Pseudomonas*, *Stenotrophomonas*, and *Acinetobacter* spp.; all species with either intrinsic or a more diverse range of mechanisms for carbapenem resistance.

A second phase II multicenter double-blinded study (Protocol 7655-003) has recently been completed for the evaluation of relebactam 250mg and imipenem in the treatment of cUTI. Initial reported data was that a favorable microbiologic response occurred in three groups of relebactam 250mg with imipenem 500mg, relebactam 125mg with imipenem 500mg, and placebo with imipenem 500mg in 95.5%, 98.6%, and 98.7% respectively. [43] This met criteria for non-inferiority.

Based on phase II data, initiation of two phase III trials is being planned to compare the efficacy of imipenem-relebactam vs. colistin in combination with imipenem, in particular for the treatment of imipenem-resistant bacterial infection. [44] A second Phase III study, is planned to evaluate imipenem-relebactam to piperacillin-tazobactam for treatment of patients with HABP/VABP. [44]

4.6. Adverse Effects of Relebactam

Clinical data from phase I trials have not been published, although in general data presented at American Society for Microbiology conferences have been showed favorable tolerability. In the phase II trial reported by Lucasti et al. the most common adverse events, those with an incidence > 5%, where diarrhea, nausea, and vomiting, which were similar in occurrence rate between relebactam and placebo controlled groups.[42]

5. Proposed Roles in Therapy

All three agents described in this review – in combination with a β-lactam antibiotic – may prove useful in the treatment of patients with infections caused by MDR Gram-negative bacteria such as carbapenem-resistant Enterobacteriacae and MDR *P. aeruginosa*. An important question that remains to be answered is how these novel β-lactamase/β-lactam combinations will perform as compared to current best available therapy in the treatment of carbapenem-resistant bacterial infections. In addition, whether the use of any one of these agents results in superior clinical outcomes as compared to the other novel agents is unclear. Also, the comparative threshold for resistance development after more widespread clinical use is an issue deserving of future studies. Resistance mutations to ceftazidime-avibactam have already been described. This highlights the importance of judicious use and the tenuous balance that exists with resistance selection.

Unfortunately, approval and marketing of these antibiotics is not accompanied by a timely approval of standardized methods of susceptibility testing. The lack of these methods with availability of only “research-only” methods for susceptibility testing limits the appropriate use of these important novel agents. Furthermore, a lack of CLSI breakpoints further restricts the interpretation of susceptibility testing for these new agents.

The clinical impact of differences in microbiologic spectrum will depend on the specific patient and infection type. For instance, avibactam shows *in vitro* activity against Enterobacteriacae strains with OXA-48 enzymes, whereas both vaborbactam and relebactam did not. [4, 38] However, the companion drug of avibactam, ceftazadime, is susceptible to efflux mechanisms to a greater extent than imipenem.[38, 45] A mutation of outer membrane porins or porin downregulation has a pronounced effect on imipenem

susceptibility.[46] Meanwhile, meropenem exhibits less dramatic MIC increases with OprD mutations due to more rapid porin transit, but the combination of OprD downregulation and in particular expression of MexAB-OprM efflux results in resistance. [45, 47]

This aspect leads into a critical point, specifically, each inhibitor's role and spectrum of activity is closely dependent upon its companion agent. In examining differences for avibactam, vaborbactam, and relebactam, their co-formulations with ceftazadime, meropenem, and imipenem respectively have to be considered. These companion agents have important differences in regard to spectrum and pharmacokinetic considerations. All three combination regimens should primarily be considered as therapeutic options for drug-resistant aerobic Gram-negative rod infections. Ceftazadime has moderate anti-streptococcal, very limited anti-staphylococcal, no anti-enterococcal, and unreliable anaerobic activity. This lack of broader spectrum activity may be a positive attribute to provide less antibiotic pressure on the microbiome. Meropenem, in contrast, has excellent broad spectrum Gram-negative and anaerobic activity, with more modest anti-staphylococcal and enterococcal activity. Imipenem, has more reliable anti-enterococcal activity in conjunction with anaerobic activity, whereas the Gram-negative spectrum may be marginally less broad than meropenem. Of key consideration, *Proteus*, *Providencia*, and *Morganella* based on current CLSI breakpoints have reduced imipenem susceptibility. Therefore, these differences may have a significant impact in the scenario of a polymicrobial infection.

Another important distinction is that although extensive clinical experience exists for each of ceftazidime, meropenem, and imipenem, there is a dearth of clinical treatment experience with all of the novel inhibitors. Thus far, all phase 3 studies for these agents have been for the indication of cUTI and cIAI. Data on pneumonia and bacteremia – the infections that carry the highest mortality risk with CRE – are limited. [48] Alveolar distribution and cerebrospinal fluid penetration have not been adequately studied in critically ill patients. Therefore, the performance of these agents, including appropriate dosing for central nervous system infections has not been clarified. Also, although data exists in healthy adult volunteers in phase I studies, in critically ill patients, altered physiology, renal function, and concurrent tissue injury may drastically affect drug tissue penetrance and ultimately clinical performance. Additionally, phase I and II studies have generally excluded patients with severe renal insufficiency.

Likewise, no sufficiently powered pathogen-specific trials with inferential statistics have been performed. This is particularly important as the majority of studies have included patients with infections caused by mostly carbapenem-susceptible Enterobacteriacae. Larger studies will be needed to study drug efficacy against pathogens with complex multi-faceted resistance mechanisms such as *Pseudomonas*.

None of the three novel inhibitors have activity for class B carbapenemases. In a 10-month study of bloodstream isolates at Texas MD Anderson Cancer Center, 7/11 (64%) CRE were ceftazidime-avibactam resistant, with 6 harboring an MBL phenotype. [49] This underscores the caveat that the use of these agents must be in conjunction with knowledge of patient risk factors and local epidemiology. A reliable commercial method for sensitivity testing must also be available in order to fully utilize these agents, particularly because MDR

Enterobacteriaceae for which they will predominantly be employed often have multifaceted resistance mechanisms. Potentially, new microbiology techniques and the increasing availability of bacterial sequencing, will allow for the identification of organisms based on their production of KPC, VIM, or NDM metallo-β-lactamases. As such, it will be critical to determine how to integrate diagnostic technology into real-time clinical feedback as to which patients may be candidates for novel inhibitor therapy.

Other combinations of inhibitor agents and β-lactams have also been postulated to be of clinical utility and may warrant future study. There has been a focus on the combination of ceftaroline and avibactam for cases of diabetic foot ulcer and polymicrobial wound infection. [50] This combination would potentially provide effective activity for anaerobic bacteria, drug resistant Gram-negative bacteria, and methicillin-resistant staphylococci simultaneously. [50, 51] Ceftaroline-avibactam was studied in cUTI in a phase II study that was recently completed (ClinicalTrials.gov Identifier: NCT01281462). Likewise, there is promising *in vitro* data utilizing the combination of aztreonam and avibactam. This combination resulted in a reduction in carbapenem MIC for carbapenem-resistant Enterobacteriaceae including MBL-containing pathogens was reduced. [4, 11, 52] The hypothesis is that MBL producing pathogens, often concurrently produce extended spectrum or AmpC β-lactamases, which can be inhibited by avibactam while aztreonam intrinsically evades hydrolysis by MBLs and can thereby still exert an antimicrobial effect.[4, 52]

6. Conclusion

All three agents do share common features and limited treatment experience. Limited trials have shown comparable clinical outcomes to comparators. However, randomized data from patients with carbapenem-resistant bacterial infections is not yet available. In addition, more widespread use in the future will undoubtedly lead to increasing rates of resistance development, as has already been shown for avibactam. As such, it will be the responsibility of the clinical community to ensure both judicious use and determine the optimal settings in which to employ these new agents. A renewed focus on combining antimicrobial stewardship and infection control measures in conjunction with medicinal therapy may offer the greatest benefit in prolonging the lifespan of these therapeutic options. [6]

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Key points

- Three novel β-lactamase inhibitors are discussed in this review: avibactam, vaborbactam, and relebactam.
- Current clinical studies have focused primarily on their co-formulation with β-lactams; ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-relebactam.
- These β-lactamase inhibitors have activity against class A and C β-lactamases, including carbapenemases of the *Klebsiella pneumoniae* carbapenemase (KPC) family.
- Most clinical studies with results to date have involved non-pathogen-specific common infectious syndromes such as complicated urinary tract infection and complicated intra-abdominal infection.

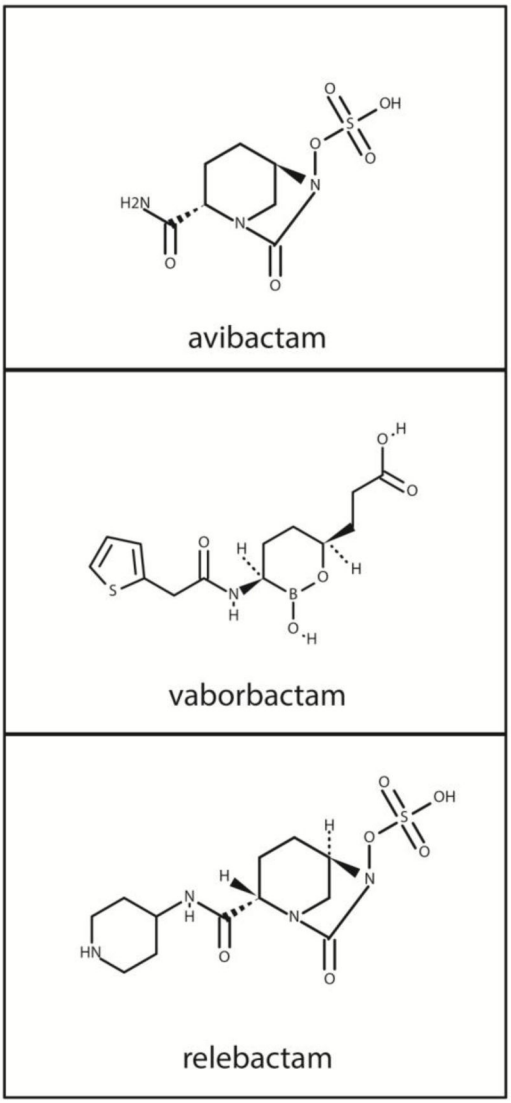

Figure 1.
Chemical structures of avibactam, vaborbactam and relebactam

Table 1

Activities of avibactam, vaborbactam and relebactam against various classes of β-lactamases. TBD: To be determined.

	TEM/SHV (Class A)	**CTX-M (Class A)**	**AmpC (Class C)**	***K. pneumoniae* carbapenemase (Class A)**	**OXA (Class D)**	**IMP/VIM (Class B)**
Avibactam	YES	YES	YES	YES	YES	NO
Vaborbactam	YES	YES	YES	YES	NO	NO
Relebactam	YES	YES	YES	YES	TBD	NO

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Table 2

Clinical studies on ceftazidime-avibactam

Avibactam			
Study	**Population and Design**	**Primary Outcome Result**	**Limitations**
Vazquez et al. [19]	Phase II: 135 hospitalized patients with cUTI Randomized 1:1 to ceftazidime-avibactam (500mg/125mg every 8 hours) or imipenem/cilastatin 500 mg every 6 h) for a total of 7–14 days	Favorable clinical response at test-of-cure: 19/27 (70.4%) ceftazidime-avibactam vs. 25/35 (71.4%) imipenem comparator Study drug observed difference, −1.1% (95% CI: −27.2 to 25%)	Ceftazidime/avibactam dose for normal renal function is: 2.5 gm (4:1 ratio – including 2 g ceftazidime and 0.5gm avibactam). Study design with lower dose administered than recommended
Lucasti et al. [20]	Phase II: 135 hospitalized patients with cIAI Randomized 1:1 to ceftazidime-avibactam (2000mg/500mg every 8 hours) plus metronidazole (500mg every 8 hours) or meropenem (1,000 mg) every 8h for a total of 5–14 days	Favorable clinical response at test-of-cure: 62/68 (91.2%) ceftazidime-avibactam vs. 71/76 (93.4%) meropenem comparator Study drug observed difference, −2.2% (95% CI: −20.4% to 12.2%)	>80% of patients with low APACHE scores Subset of patients (e.g. >45% with appendicitis) may have been cured without any antibiotics
Wagenlehner et al. [21]	Phase III: 1033 hospitalized adults with suspected or microbiologically confirmed cUTI Randomized 1:1 to ceftazidime-avibactam (2000 mg/500 mg every 8 hours) or doripenem (500 mg every 8 hours) – treatment duration 10–14 days with possible oral antibiotic switch after ≥5 days study drug	Patient-reported symptomatic resolution at day 5: 276/393 (70.2%) avibactam vs 276/417 (66.2%) doripenem Difference, 4.0% (95% CI: −2.39% to 10.42%) Combined symptomatic resolution/microbiological eradication at test of cure (TOC): 280/393 (71.2%) avibactam vs 269/417 (64.5%) doripenem Difference non-inferiority, 6.7% (95% CI: 0.3% to 13.12%) All organism susceptibility 311/400 (77.8%)ceftazidime-avibactam vs. 297/419 (70.9%) doripenem -- significance in favor of avibactam	Evaluated patient population 393 avibactam and 417 doripenem (total 810 of 1033 randomized patients) Despite overall organism susceptibility higher to combination ceftazidime-avibactam in comparison to doripenem; in ceftazidime non-susceptible subset test-of-cure similar at (62.7%) ceftazidime-avibactam and (60.7%) doripenem Patients with a creatinine clearance ≤30 mL/minute or on dialysis were excluded
Mazuski et al. [22]	Phase III: 1066 hospitalized adults with cIAI Randomized, 1:1 double-blinded comparison of ceftazidime-avibactam (2000mg/500mg every 8 hours) plus metronidazole (500mg every 8 hours) with meropenem (1000mg every 8 hours, 30 minute infusion)	Ceftazidime-avibactam plus metronidazole was noninferior to meropenem across Clinical cure rate: microbiologically modified intention-to-treat at test-of-cure: Ceftazidime-avibactam plus metronidazole 337/413 (81.6%) and meropenem 349/410 (85.1%) Difference, non-inferiority, −3.5% (95% CI: −8.64 to 1.58% Clinical cure rate for ceftazidime resistant infection: Ceftazidime-avibactam plus metronidazole 39/47 (83.0%) and meropenem 55/64 (85.9%) Difference, non-inferiority, −3.0 (95%CI: −17.89 to 10.60%)	Majority of patients with appendicitis > 80% of patients with an APACHE II score of ≤10 Low incidence of bacteremia (4.2% ceftazidime-avibactam, 2.7% meropenem) Patients with a creatinine clearance ≤30 mL/minute or on dialysis were excluded
Carmeli et al. [24]	Phase III, pathogen-specific: 333 patients with cUTI or cIAI caused by ceftazidime-resistant Enterobacteriaceae or *P. aeruginosa* Randomized, open-label; 1:1 ceftazidime-avibactam (2000mg/500mg every 8 hours) vs. best available therapy	Clinical cure at test-of-cure: 140/154 (91%, 95% CI 85.6%–94.7%)) ceftazidime-avibactam vs. 135/148 (91%, 95% CI 85.9%–95.0%) best available therapy	Open label No inferential statistics performed

Table 3

Clinical studies on meropenem-vaborbactam.

Vaborbactam			
Study	**Population and Design**	**Result**	**Limitations**
TANGO-1 [33]	Phase 3: 550 hospitalized adults with cUTI Double-blind, randomized 1:1 double dummy active controlled trial comparison of meropenem-vaborbactam (2gm/2gmevery 8 hours) with piperacillin-tazobactam (4gm/0.5gm every 8 hours)	Microbiologically modified intent-to-treat: Success (clinical cure or improvement and microbiologic eradication of baseline bacterial pathogen reduced to < 10^4CFU) at end-of-therapy Meropenem-Vaborbactam 188/192 (98.4%) vs. Piperacillin-tazobactam 171/182 (94.0%) Difference, superiority, 4.5% (95% CI: 0.7 to 9.1%) Microbial Eradication (baseline bacterial pathogen being reduced to < 103CFU) at test-of-cure (follow up visit day 15–19) Meropenem-Vaborbactam 118/178 (66.3%) vs. Piperacillin-tazobactam 102/169 (60.4%) Difference, non-inferior, 5.9% (95%CI: −4.2% to 16.0%)	Awaiting publication of full results Review of organisms will be required Superiority at end-of-therapy did not persist at test-of-cure
TANGO 2 [33]	Phase 3: Target 150 patients for treatment of cUTI, HABP/VABP, or cIAI, or bacteremia with known/suspected carbapenem-resistant Enterobacteriaceae Randomized 2:1 open label comparison of meropenem-vaborbactam with best-available-therapy	Study in progress	Results to follow

Table 4

Clinical studies on imipenem-relebactam.

Relebactam			
Study	**Population and Design**	**Result**	**Limitations**
Lucasti et al. [42]	Phase 2: Adults with cIAI, 351 randomized subjects Randomized 1:1:1 controlled double-blind comparison of: **1** Imipenem-cilastatin (IMI) (500mg every 6 hours) with relebactam (REL) (250mg every 6 hours) **2** Imipenem-cilastatin (500mg every 6 hours) with relebactam (125mg every 6 hours) **3** Imipenem-cilastatin (500mg every 6 hours) with placebo	Primary efficacy endpoint: microbiologically evaluable subjects with favorable clinical response at discontinuation of IV therapy IMI/250mg REL 78/81 (96.3%) vs. IMI/125mg REL 78/81 (98.8%) and IMI/placebo 79/83 (95.2%) Non-inferiority between all groups 36 subjects (13%) with Gram-negative imipenem non-susceptible pathogens: 34 were microbiologically evaluable All had favorable clinical response: (14/14 receiving REL 250mg, 9/9 receiving REL 125 mg, 11/11 receiving IMI alone. 7/40 pathogens isolated which were non-susceptible to imipenem were susceptible to combination IMI/REL	Patients with APACHE > 30 were excluded Patients with baseline renal dysfunction were excluded. Cases high proportion of complicated appendicitis (53%) and cholecystitis (17%) No determination or comment on superiority could be made
Protocol 7655-003 [43]	Phase 2: Adults with cUTI, 302 randomized subjects Multicenter, randomized comparison of Imipenem/relebactam combination vs. Imipenem	Favorable microbiologic response reported in groups of: IMI/REL 250mg (95.5%, N = 67), IMI/REL 125mg (98.6%, N = 71), IMI/placebo (98.7%, N = 75) Non-inferiority between groups	Unpublished data Non-inferiority study