



# Cefepime–Taniborbactam: A Novel Cephalosporin/ $\beta$ -Lactamase Inhibitor Combination

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## Abstract

Taniborbactam (formerly known as VNRX-5133) is a novel bicyclic boronate  $\beta$ -lactamase inhibitor of serine  $\beta$ -lactamases (SBLs) [Ambler classes A, C, and D] and metallo- $\beta$ -lactamases (MBLs) [Ambler class B], including NDM and VIM, but not IMP. Cefepime–taniborbactam is active in vitro against most isolates of carbapenem-resistant *Enterobacterales* (CRE) and carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), including both carbapenemase-producing and carbapenemase-non-producing CRE and CRPA, as well as against multidrug-resistant (MDR), ceftazidime-avibactam-resistant, meropenem-vaborbactam-resistant, and ceftolozane-tazobactam-resistant *Enterobacterales* and *P. aeruginosa*. The addition of taniborbactam to cefepime resulted in a  $> 64$ -fold reduction in MIC<sub>90</sub> compared with cefepime alone for a 2018–2021 global collection of  $> 13,000$  clinical isolates of *Enterobacterales*. In the same study, against  $> 4600$  *P. aeruginosa*, a fourfold MIC reduction was observed with cefepime–taniborbactam, compared with cefepime alone. Whole genome sequencing studies have shown that resistance towards cefepime–taniborbactam in *Enterobacterales* arises due to the presence of multiple resistance mechanisms, often in concert, including production of IMP, PBP3 alterations, permeability (porin) defects, and upregulation of efflux pumps. In *P. aeruginosa*, elevated cefepime–taniborbactam MICs are also associated with the presence of multiple, concurrent mechanisms, most frequently IMP, PBP3 mutations, and upregulation of efflux pumps, as well as AmpC (PDC) overexpression. The pharmacokinetics of taniborbactam are dose proportional, follow a linear model, and do not appear to be affected when combined with cefepime. Taniborbactam's approximate volume of distribution ( $V_d$ ) at steady state is 20 L and the approximate elimination half-life ( $t_{1/2}$ ) is 2.3 h, which are similar to cefepime. Furthermore, like cefepime, taniborbactam is primarily cleared renally, and clearance corresponds with renal function. Pharmacodynamic studies (in vitro and in vivo) have reported that cefepime–taniborbactam has bactericidal activity against various  $\beta$ -lactamase-producing Gram-negative bacilli that are not susceptible to cefepime alone. It has been reported that antimicrobial activity best correlated with taniborbactam exposure (area under the curve). A phase III clinical trial showed that cefepime–taniborbactam (2 g/0.5 g administered as an intravenous infusion over 2 h) was superior to meropenem for the treatment of complicated urinary tract infection (cUTI), including acute pyelonephritis, caused by *Enterobacterales* species and *P. aeruginosa* while demonstrating similar safety compared with meropenem. The safety and tolerability of taniborbactam and cefepime–taniborbactam has been reported in one pharmacokinetic trial, and in two pharmacokinetic trials and one phase III clinical trial, respectively. Cefepime–taniborbactam appears to be well tolerated in both healthy subjects and patients. Headache and gastrointestinal upset are the most common drug-related adverse effects associated with cefepime–taniborbactam use. Cefepime–taniborbactam will likely have a role in the treatment of infections proven or suspected to be caused by MDR Gram-negative bacteria, including *Enterobacterales* and *P. aeruginosa*. In particular, it may be useful in the treatment of infections caused by isolates that harbor an MBL (NDM, VIM) enzyme, although further clinical data are needed. Additional safety and efficacy studies may support indications for cefepime–taniborbactam beyond cUTI.

Extended author information available on the last page of the article

## Key Points

Taniborbactam is a novel bicyclic boronate,  $\beta$ -lactamase inhibitor that displays *in vitro* activity against Ambler class A, B, C, and D enzymes. Taniborbactam is in clinical development in combination with the  $\beta$ -lactam cefepime. Taniborbactam differs from the inhibitors in recently approved  $\beta$ -lactam/ $\beta$ -lactamase inhibitor (BL-BLI) combinations (ceftazidime-avibactam, imipenem-relebactam, meropenem-vaborbactam) because it inhibits Ambler class B metallo- $\beta$ -lactamases (MBLs), including VIM and NDM, but not IMP.

Cefepime–taniborbactam is active *in vitro* against most isolates of carbapenem-resistant *Enterobacteriales* (CRE) and carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), including both carbapenemase-producing and carbapenemase-non-producing CRE and CRPA, as well as against multidrug-resistant (MDR), ceftazidime-avibactam-resistant, meropenem-vaborbactam-resistant, and ceftolozane-tazobactam-resistant *Enterobacteriales* and *P. aeruginosa*.

Cefepime–taniborbactam is administered at 2 g/0.5 g intravenously every 8 h (assuming normal renal function), with a prolonged infusion time to help maximize pharmacodynamic target attainment.

In a phase III clinical trial treating patients with complicated urinary tract infections, including acute pyelonephritis, due to *Enterobacteriales* species and *P. aeruginosa*, cefepime–taniborbactam was found to be superior to meropenem, while also demonstrating similar safety compared with meropenem. Development of cefepime–taniborbactam for the treatment of hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia is planned.

## 1 Introduction

Widespread use of  $\beta$ -lactams has contributed to the emergence of  $\beta$ -lactam-resistant and multidrug-resistant (MDR) Gram-negative bacilli primarily through the selection of pathogenic strains that produce  $\beta$ -lactamases (*Enterobacteriales*) or carry other resistance mechanisms such as outer membrane permeability changes, efflux pumps, and/or penicillin-binding protein (PBP) alterations [1, 2].  $\beta$ -Lactamases are classified into two structural groups. Serine- $\beta$ -lactamases (SBLs) use serine as a nucleophile to hydrolyze the  $\beta$ -lactam ring, and comprise Ambler class A, C, and D enzymes. Metallo- $\beta$ -lactamases (MBLs) include one or two zinc atoms

in their active site, are classified as Ambler class B enzymes, and hydrolyze almost all  $\beta$ -lactams, including carbapenems, cephalosporins, and penicillins, but not aztreonam (monobactam). MBL incidence is increasing worldwide [1]. Current treatment options for MBL-positive Gram-negative pathogens are limited and some are associated with toxicities (aminoglycosides, polymyxins). The inhibitors in recently approved  $\beta$ -lactam/ $\beta$ -lactamase inhibitor (BL-BLI) combinations other than aztreonam-avibactam (i.e., ceftazidime-avibactam, imipenem-relebactam, meropenem-vaborbactam, cefepime/enmetazobactam) do not inhibit MBLs [3–5]. A BL-BLI combination that includes an inhibitor active against all four Ambler classes, such as taniborbactam (VNRX-5133), would be an important addition to our therapeutic armamentarium [2, 3]. Table 1 summarizes newer, currently marketed BL-BLI combinations as well as those in clinical development. The current review will focus solely on cefepime–taniborbactam, which is currently in phase III of clinical development.

Cefepime is a fourth-generation cephalosporin with activity against both Gram-positive and Gram-negative bacteria, including *Pseudomonas aeruginosa* [6, 7]. Cefepime's chemical structure prevents hydrolysis by chromosomal AmpC-type  $\beta$ -lactamases and generates greater stability than earlier cephalosporins or penicillins against some other  $\beta$ -lactamases [6]. Cefepime resistance is observed in carbapenem-resistant *Enterobacteriales* (CRE) and carbapenem-resistant *P. aeruginosa* (CRPA) carrying both serine-based carbapenemases and MBLs, as well as among cephalosporin-resistant (extended-spectrum  $\beta$ -lactamase [ESBL]-producing) *Enterobacteriales* and *P. aeruginosa* [6, 8]. Cefepime is being studied in combination with taniborbactam, with the aim of protecting cefepime against ESBLs and carbapenemases, both serine carbapenemases (e.g., KPC, OXA-48-like) and MBLs [2, 9].

Taniborbactam is a novel bicyclic boronate  $\beta$ -lactamase inhibitor with *in vitro* activity against Ambler class A, B, C, and D enzymes [3, 10–13]. Taniborbactam differs from the inhibitors in most recently approved BL-BLI combinations (ceftazidime-avibactam, imipenem-relebactam, and meropenem-vaborbactam) because it inhibits MBLs, including VIM and NDM, but not IMP [2, 8]. Cefepime–taniborbactam is active *in vitro* against most isolates of CRE and CRPA, including many isolates that harbor a carbapenemase enzyme, as well as against MDR, ceftazidime-avibactam-resistant, meropenem-vaborbactam-resistant, ceftolozane-tazobactam-resistant and MDR *Enterobacteriales* and *P. aeruginosa* [8, 11]. A randomized, non-inferiority phase III clinical trial (CERTAIN-1) demonstrated the clinical efficacy and safety of cefepime–taniborbactam for the treatment of complicated urinary tract infection (cUTI), compared with meropenem [14].

**Table 1** Recently approved and phase III  $\beta$ -lactam/ $\beta$ -lactamase inhibitor combinations

| Drug                           | Drug class | FDA           |                                                                                             | EMA           |                                                                                                                      | Development phase | References |
|--------------------------------|------------|---------------|---------------------------------------------------------------------------------------------|---------------|----------------------------------------------------------------------------------------------------------------------|-------------------|------------|
|                                |            | Approval year | Indication                                                                                  | Approval year | Indication                                                                                                           |                   |            |
| Ceftazidime–avibactam          | BL/BLI     | 2015<br>2018  | cIAI in combination with metronidazole and cUTI (including pyelonephritis)<br>HABP and VABP | 2016          | cIAI in combination with metronidazole, cUTI, HABP, and VABP<br>Gram-negative aerobic organisms when limited options | –                 | [69]       |
| Imipenem/cilastatin–relebactam | CP/BLI     | 2019          | cUTI, cIAI with limited options, HABP and VABP                                              | 2021          | HABP, VABP, and BSI, possibly secondary to pneumonia, when limited options                                           | –                 | [11]       |
| Meropenem–vaborbactam          | CP/BLI     | 2017          | cUTI                                                                                        | 2018          | cUTI, cIAI, HABP, and VABP when limited options                                                                      | –                 | [11]       |
| Aztreonam–avibactam            | BL/BLI     | –             |                                                                                             | 2024          | cIAI, HABP, VABP, cUTI, and infections due to aerobic Gram-negative organisms with limited treatment options         | –                 |            |
| Cefepime–enmetazobactam        | BL/BLI     | 2024          | cUTI                                                                                        | 2024          | cUTI, HABP                                                                                                           | –                 | [11]       |
| Cefepime–taniborbactam         | BL/BLI     | –             | –                                                                                           | –             | –                                                                                                                    | Phase III         | [11]       |
| Cefepime–zidebactam            | BL/BLI     | –             | –                                                                                           | –             | –                                                                                                                    | Phase III         | [11]       |
| Cefepime–nacubactam            | BL/BLI     | –             | –                                                                                           | –             | –                                                                                                                    | Phase III         | –          |
| Aztreonam–nacubactam           | BL/BLI     | –             | –                                                                                           | –             | –                                                                                                                    | Phase III         | –          |

*BL*  $\beta$ -lactam, *BLI*  $\beta$ -lactamase inhibitor, *FDA* United States Food and Drug Administration, *EMA* European Medicines Agency, *BSI* bloodstream infection, *cIAI* complicated intra-abdominal infection, *CP* carbapenem, *cUTI* complicated urinary tract infection, *HABP* hospital-acquired bacterial pneumonia, *VABP* ventilator-associated bacterial pneumonia

Venatorx Pharmaceuticals (Malvern, PA, USA) is developing cefepime–taniborbactam as a potential treatment for adult patients with cUTI, including pyelonephritis caused by susceptible Gram-negative microorganisms. In February 2024, the US Food and Drug Administration (FDA; we are not aware of the European Medicines Agency [EMA] position on this matter) issued a Complete Response Letter (CRL) and requested additional chemistry, manufacturing, and controls, as well as related data to cefepime–taniborbactam [15]. No clinical safety or efficacy issues were identified and there is no requirement for further clinical data or trials. In the near future, cefepime–taniborbactam is expected to be studied as a potential treatment option for hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP).

This article reviewed the existing published literature for cefepime–taniborbactam, including chemistry, mechanisms of action, mechanisms of resistance, microbiology, pharmacokinetics, pharmacodynamics, efficacy and safety, results from animal studies, and human clinical trials. Publications were identified by a standard comprehensive search (up to February 2024) of PubMed using the key words ‘cefepime’ and ‘taniborbactam’ or ‘VNRX-5133’, ‘boronate inhibitors’, and ‘ $\beta$ -lactam/ $\beta$ -lactamase inhibitors’. Results were supplemented with manuscripts and posters obtained from Venatorx Pharmaceuticals (<https://venatorx.com/manuscript/cefepime-taniborbactam/>) and were reviewed by at least three authors.

## 2 Chemistry

Cephalosporins have a four-membered  $\beta$ -lactam ring fused to a six-membered dihydrothiazine ring with protective side chains added at positions C3 and C7 [16, 17]. Cefepime's C7 side chain is a 2-amino-thiazolyl-acetamido substituted with an oxymino group, identical to the C7 side chain of cefotaxime and ceftriaxone, and further substituted with a 2-carboxypropan-2-yloxyimino moiety for ceftazidime [16]. Unlike other extended-spectrum cephalosporins, cefepime is a zwitterionic oxymino  $\beta$ -lactam due to a quaternary positively charged nitrogen atom in the cephem nucleus (Fig. 1a). The zwitterionic charge allows for rapid penetration through porin channels, thus promoting bactericidal activity against Gram-negative and Gram-positive pathogens [18].

Taniborbactam's discovery as a synthetic non- $\beta$ -lactam bicyclic boronate  $\beta$ -lactamase inhibitor [19, 20] with a *N*-(2-aminoethyl) cyclohexylamine side chain is well described (Fig. 1b) [3]. Avibactam and relebactam are both bicyclic diazabicyclooctane (DBO) derivatives and vaborbactam is a monocyclic boronate (Fig. 1c–e) [21, 22]. Monocyclic (vaborbactam) and bicyclic (taniborbactam)

boronates mimic tetrahedral intermediates of SBL and MBL catalysis [4]. Vaborbactam is inactive against MBLs and OXA-48-like serine carbapenemases [4].

## 3 Mechanism of Action

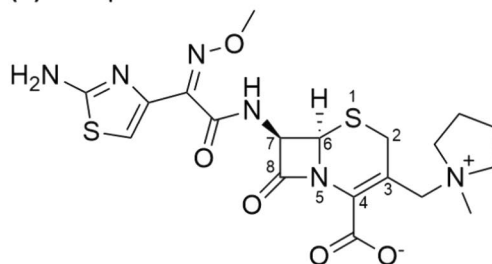
Like other  $\beta$ -lactams, cefepime inhibits peptidoglycan synthesis by covalently binding to PBPs; however, cefepime differs from earlier-generation cephalosporins because it displays a high affinity for both PBP2 and PBP3 of *Enterobacteriales* [6, 23]. PBPs are essential for the cross-linking of peptidoglycan in bacterial cell wall synthesis; their inhibition results in cell lysis [23, 24].

SBLs hydrolyze  $\beta$ -lactams via formation of a covalent bond between an active-serine nucleophile and a  $\beta$ -lactam ring, while MBLs use zinc ions to form a nucleophilic hydroxide via a non-covalent mechanism to hydrolyze a  $\beta$ -lactam ring [25]. The combination of a  $\beta$ -lactamase inhibitor with a  $\beta$ -lactam is a common strategy for overcoming  $\beta$ -lactamase-mediated resistance [3].

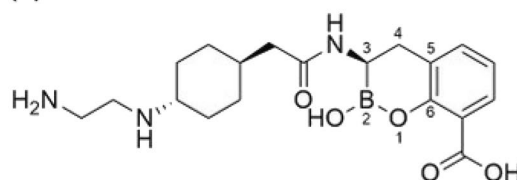
Taniborbactam acts as a reversible covalent inhibitor of SBLs with prolonged binding to the active site with slow

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

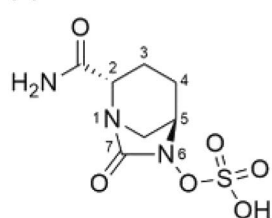
(a) Cefepime



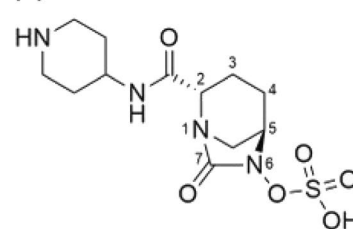
(b) Taniborbactam



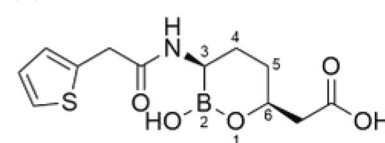
(c) Avibactam



(d) Relebactam



(e) Vaborbactam



dissociation [10, 13, 23]. For MBLs, taniborbactam acts as a competitive inhibitor of di-zinc active sites in subclass B1 MBLs [10, 13, 23]. Various X-ray diffraction crystallography studies have been performed to investigate the binding of taniborbactam to  $\beta$ -lactamases [3, 19, 25]. These high-resolution studies of binding between taniborbactam and SBLs such as CTX-M-15 and OXA-10 revealed that the boron atom of taniborbactam covalently binds to the catalytic Ser70 of the  $\beta$ -lactamase [3, 25]. The boron atom contains one hydroxyl group that is located in the oxyanion hole, thus mimicking the acylation tetrahedral intermediate [3, 25]. For MBLs such as NDM-1 and VIM-2, the tetrahedral boron of taniborbactam binds to the active-site zinc atom (Zn-1), thus mimicking the tetrahedral intermediate following the nucleophilic attack of the  $\beta$ -lactam carbonyl by the hydroxide anion [3, 25]. The second active-site zinc atom (Zn-2) gets extensively coordinated by the carboxylate and phenolic oxygen atoms [31]. Additionally, both bicyclic and tricyclic forms were observed in high-resolution structures,

suggesting that boronate-based inhibitors can adapt multiple forms when interacting with different enzymes to potentially allow for more potent inhibition [3, 19]. Taniborbactam exhibits activity towards both SBLs and MBLs, due to its ability to mimic the tetrahedral intermediates involved in substrate hydrolysis for both these types of enzymes [3, 25].

Tables 2 and 3 display available published data for  $IC_{50}$  (half maximal inhibitory concentration; the lower the concentration the greater the binding and expected inhibition) and  $K_i$  (inhibitory dissociation constant, the lower the concentration the more potent the inhibitor is) values for a variety of Ambler class enzymes for taniborbactam compared with recently marketed  $\beta$ -lactamase inhibitors (avibactam, relebactam, vaborbactam). The focus in Tables 2 and 3 is on data from inhibitor head-to-head comparative studies, although at times comparative inhibitor data were not available, thus some variability in the data occur. Taniborbactam shows either similar or increased activity when compared with avibactam, relebactam, and vaborbactam

**Table 2**  $IC_{50}$  values for taniborbactam and comparator  $\beta$ -lactamase inhibitors against various  $\beta$ -lactamase enzymes

| $\beta$ -Lactamase | $\beta$ -Lactamase inhibitor |                   |                   |             | References  |
|--------------------|------------------------------|-------------------|-------------------|-------------|-------------|
|                    | $IC_{50}$ ( $\mu$ M)         |                   |                   |             |             |
|                    | Taniborbactam                | Avibactam         | Relebactam        | Vaborbactam |             |
| Class A            |                              |                   |                   |             |             |
| CTX-M-15           | 0.01                         | 0.003             | NA                | 0.42        | [3]         |
| KPC-2              | 0.03                         | 0.06              | $0.082 \pm 0.017$ | 0.1         | [3, 70]     |
| SHV-5              | 0.0004                       | 0.013             | 0.36              | 0.44        | [3, 21]     |
| TEM-116            | 0.12                         | NA                | NA                | 6           | [19]        |
| Class B1           |                              |                   |                   |             |             |
| IMP-1              | 2.51/39.8                    | > 100             | > 100             | > 100       | [3, 19, 70] |
| NDM-1              | 0.19                         | > 100             | > 100             | > 100       | [3, 70]     |
| VIM-1              | 0.0079                       | NA                | NA                | 398         | [19, 70]    |
| VIM-2              | 0.0005, 0.026                | > 100             | NA                | > 100       | [3, 19]     |
| Class B2           |                              |                   |                   |             |             |
| CphA               | 2.51                         | NA                | NA                | 631         | [19]        |
| Class B3           |                              |                   |                   |             |             |
| L1                 | > 10                         | NA                | NA                | 336         | [19]        |
| Class C            |                              |                   |                   |             |             |
| AmpC <sup>a</sup>  | 0.301                        | NA                | 0.47              | 5           | [19, 21]    |
| CMY-2              | 0.007                        | 0.007             | NA                | 0.22        | [3]         |
| P99 AmpC           | 0.03                         | 0.016             | $0.026 \pm 0.007$ | 0.09        | [3, 70]     |
| PDC-3              | $0.016 \pm 0.002$            | $0.049 \pm 0.005$ | NA                | NA          | [71]        |
| PDC-88             | $0.022 \pm 0.002$            | $0.061 \pm 0.007$ | NA                | NA          | [71]        |
| Class D            |                              |                   |                   |             |             |
| OXA-1              | 0.16                         | 0.04              | NA                | 7.9         | [3]         |
| OXA-10             | 0.234                        | NA                | NA                | > 400       | [19]        |
| OXA-48             | 0.42, 0.537                  | 0.55              | $0.18 \pm 0.05$   | 25, 38.8    | [3, 19, 70] |

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

<sup>a</sup>Wild-type AmpC (PDC-1) in *P. aeruginosa*

**Table 3**  $K_i$  values for taniborbactam and comparator  $\beta$ -lactamase inhibitors against various  $\beta$ -lactamase enzymes

|          | $\beta$ -Lactamase inhibitor $K_i$ (nanomolar) |                           |                           |                           | References           |
|----------|------------------------------------------------|---------------------------|---------------------------|---------------------------|----------------------|
|          | Taniborbactam                                  | Avibactam                 | Relebactam                | Vaborbactam               |                      |
| Class A  |                                                |                           |                           |                           |                      |
| CTX-M-14 | $1.2 \pm 0.5$                                  | $0.41 \pm 0.13$           | $10 \pm 3$                | $33 \pm 13$               | <a href="#">[5]</a>  |
| CTX-M-15 | $2.6 \pm 0.1$                                  | $0.18 \pm 0.08$           | $24 \pm 1$                | $30 \pm 4$                | <a href="#">[5]</a>  |
| KPC-2    | $32 \pm 0.009$                                 | $11 \pm 3$                | $40 \pm 8$                | $56 \pm 15$               | <a href="#">[5]</a>  |
| SHV-5    | $3 \pm 0.2$                                    | NA                        | NA                        | NA                        | <a href="#">[10]</a> |
| SHV-12   | $0.15 \pm 0.03$                                | $0.24 \pm 0.07$           | $36 \pm 6$                | $21 \pm 4$                | <a href="#">[5]</a>  |
| TEM-10   | $2.8 \pm 0.8$                                  | $1.4 \pm 0.4$             | $48 \pm 7$                | $140 \pm 40$              | <a href="#">[5]</a>  |
| Class B1 |                                                |                           |                           |                           |                      |
| IMP-1    | $> 2 \times 10^4$                              | $> 1.6 \times 10^5$       | $> 1.6 \times 10^5$       | $> 1.6 \times 10^5$       | <a href="#">[5]</a>  |
| IMP-26   | $> 2 \times 10^4$                              | $> 1.6 \times 10^5$       | $> 1.6 \times 10^5$       | $> 1.6 \times 10^5$       | <a href="#">[5]</a>  |
| NDM-1    | $4.5 \pm 1.3$                                  | $> 1.6 \times 10^5$       | $> 1.6 \times 10^5$       | $> 1.6 \times 10^5$       | <a href="#">[5]</a>  |
| VIM-1    | $31 \pm 3$                                     | $> 1.6 \times 10^5$       | $> 1.6 \times 10^5$       | $> 1.6 \times 10^5$       | <a href="#">[5]</a>  |
| Class B3 |                                                |                           |                           |                           |                      |
| L1       | $1.7 \times 10^4$                              | NA                        | NA                        | NA                        | <a href="#">[5]</a>  |
| Class C  |                                                |                           |                           |                           |                      |
| P99      | $2.4 \pm 0.5$                                  | $10 \pm 2$                | $14 \pm 2$                | $35 \pm 15$               | <a href="#">[5]</a>  |
| PDC1     | 22                                             | 56                        | 78                        | NA                        | <a href="#">[5]</a>  |
| Class D  |                                                |                           |                           |                           |                      |
| OXA-23   | $> 2 \times 10^4$                              | $1.7 \pm 0.4 \times 10^3$ | NA                        | $6.6 \pm 1.1 \times 10^3$ | <a href="#">[5]</a>  |
| OXA-48   | $6.1 \pm 0.7$                                  | $36 \pm 10$               | $1.8 \pm 0.1 \times 10^3$ | $1.4 \pm 0.5 \times 10^4$ | <a href="#">[5]</a>  |

$K_i$  inhibitory dissociation constant, NA data not available

against various class A, C, and D  $\beta$ -lactamases. Additionally, taniborbactam displays activity against subclass B1 MBLs (NDM and VIM, but not IMP or subclass B3 L1-type enzymes).

## 4 Mechanisms of Resistance

Cefepime resistance in *Enterobacterales* is most often due to the production of ESBLs and less frequently due to carbapenemases; whereas in *P. aeruginosa*, cefepime resistance frequently occurs due to upregulation of efflux pumps and increased production of chromosomal AmpC enzyme (PDC, *Pseudomonas*-derived cephalosporinase) [6]. Both CLSI and EUCAST lowered the cefepime susceptibility breakpoints in recent years to prevent ESBL-producing isolates of *Escherichia coli*, *Klebsiella pneumoniae*, *Klebsiella oxytoca*, and *Proteus mirabilis* from being reported as cefepime susceptible, thus limiting potential treatment failures [6]. Combining cefepime and taniborbactam frequently lowers the cefepime MIC for isolates containing SBLs and MBLs, including CTX-M, KPC, OXA-48-like, NDM, and VIM enzymes, as well as for MDR, ceftazidime-avibactam-resistant, meropenem-vaborbactam-resistant, and ceftolozane-tazobactam-resistant *Enterobacterales* and *P. aeruginosa* [8, 10].

Combinations of mechanisms of resistance are commonly present in rare isolates of *Enterobacterales* and *P. aeruginosa* identified with elevated cefepime–taniborbactam MICs. Whole genome sequencing (WGS) studies of *Enterobacterales* showed there are multiple potential mechanisms associated with cefepime–taniborbactam MICs  $\geq 16$  mg/L; these include production of IMP carbapenemases, PBP3 alterations, permeability (porin) defects, and upregulation of efflux pumps [8, 26, 27]. WGS studies identified mutations in porin proteins such as OmpA, OmpR, OmpK35, and OmpK36 in *K. pneumoniae* isolates that were associated with elevated cefepime–taniborbactam MICs, and concomitantly carried NDM-1 or NDM-5, CTX-M-15, and one or more class D enzymes [8, 26]. Although taniborbactam displays activity against NDM-1 and VIM-1, Le Terrier et al. reported that NDM-9/NDM-30 and VIM-83 (which differ from NDM-1 and VIM-1 by one single amino acid substitution) are not inhibited by taniborbactam. Crystallography data by Drusin et al. revealed that the substitution of Glu149 for a Lys residue in NDM-9 resulted in reduced affinity and activity of taniborbactam [22]. Mutations in ramR, OmpK36, and blaKPC-3 are responsible for resistance in *K. pneumoniae* for other  $\beta$ -lactam/ $\beta$ -lactamase combinations such as ceftazidime-avibactam, imipenem-relebactam, and meropenem-vaborbactam [10,

28]. Satapoomin et al. identified that the aforementioned mutations, in association with an additional mutation in OmpK35 and production of OXA-232, conferred reduced susceptibility to cefepime–taniborbactam [28].

*Pseudomonas* spp. can acquire both enzymatic (e.g.,  $\beta$ -lactamase) and non-enzymatic mechanisms of antimicrobial resistance [29]. Increased production of PDC limits the activity of ceftazidime, and upregulated efflux pumps (meropenem) and OprD (imipenem) mutations limit the utility of carbapenems [29]. WGS studies identified multiple resistance mechanisms occurring simultaneously in *P. aeruginosa* with elevated cefepime–taniborbactam MICs, such as IMP production, PBP3 mutations, upregulation of efflux pumps, and AmpC (PDC) overexpression [8, 26].

In summary, resistance towards cefepime–taniborbactam is due to the presence of multiple resistance mechanisms produced by Gram-negative bacteria [26]. Further strains need to be studied for more information about specific resistance mechanisms that may limit the utility of cefepime–taniborbactam for treating MDR Gram-negative organisms [26].

## 5 Microbiology

Tables 4 and 5 compare the *in vitro* activities of cefepime alone, cefepime–taniborbactam, ceftazidime–avibactam, imipenem–relebactam, and meropenem–vaborbactam against Gram-negative bacilli with different phenotypes and genotypes (specific  $\beta$ -lactamases and other resistance mechanisms) [3, 5, 8, 9, 26, 27, 29–37]. The data shown in the tables are modal MICs generated from comparing all published *in vitro* studies of cefepime–taniborbactam and comparators that were conducted using reference methods [38]. The precise number of tested isolates was different for each agent as not all agents (other than cefepime/taniborbactam) were tested in each study. Percentage susceptibilities were not listed for the various agents as the primary purpose of these tables is a comparative MIC analysis of cefepime/taniborbactam to cefepime, as well as selective BL–BLI combinations.

Cefepime–taniborbactam demonstrated significant activity against *Enterobacterales* spp., resulting in a > 64-fold reduction in MIC compared with cefepime alone. Specifically, for MBL-, ESBL-, and KPC-producing *Enterobacterales*, taniborbactam lowered the cefepime MIC by > 2- to > 64-fold. Against cefepime-resistant *Enterobacterales*, the addition of taniborbactam to cefepime resulted in > 16-fold reduction in MIC. Additionally, taniborbactam enhanced cefepime activity against both carbapenemase-positive and carbapenemase-negative CRE (Table 4). Against *P. aeruginosa*, a fourfold reduction in MIC was observed with cefepime–taniborbactam, compared with cefepime alone. Cefepime alone and cefepime–taniborbactam display greater

activity against *Enterobacterales* than *P. aeruginosa*, similar to most other  $\beta$ -lactams and their respective BL–BLI combinations (Table 4). Limited data show that taniborbactam decreases cefepime MIC<sub>50</sub> and MIC<sub>90</sub> values by four to eightfold against *Stenotrophomonas maltophilia*, and has minimal effect on cefepime against *Acinetobacter baumannii*. Compared with ceftazidime–avibactam, imipenem–relebactam, and meropenem–vaborbactam, cefepime–taniborbactam displayed similar, enhanced (two to fourfold increase) or significantly enhanced (> 4-fold) *in vitro* activity against Gram-negative aerobes.

Karlowsky et al. evaluated the *in vitro* activity of cefepime–taniborbactam versus a large collection of *Enterobacterales* and *P. aeruginosa* clinical isolates obtained from patients evaluated at hospitals in 56 countries between 2018 and 2020. Utilizing a breakpoint of  $\leq 16$  mg/L, these investigators reported that cefepime–taniborbactam inhibited 99.7% of all *Enterobacterales* isolates, including > 97% of isolates with MDR and ceftolozane–tazobactam-resistant phenotypes;  $\geq 90\%$  of isolates with meropenem-resistant, difficult-to-treat resistant (DTR), meropenem–vaborbactam-resistant, and ceftazidime–avibactam-resistant phenotypes; 100% of VIM-positive, AmpC-positive, and KPC-positive isolates; 98.7% of ESBL-positive isolates; 98.8% of OXA-48-like-positive isolates; and 84.6% of NDM-positive isolates [8]. Utilizing the cefepime–taniborbactam breakpoint of  $\leq 16$  mg/L, 97.4% of all *P. aeruginosa* isolates were susceptible, including  $\geq 85\%$  of isolates with meropenem-resistant, MDR, and meropenem–vaborbactam-resistant phenotypes; > 75% of isolates with DTR, ceftazidime–avibactam-resistant, and ceftolozane–tazobactam-resistant phenotypes; and 87.4% of VIM-positive isolates [8].

Table 5 displays the activity of cefepime–taniborbactam and comparators against specific  $\beta$ -lactamases produced by *Enterobacterales* and *P. aeruginosa* [5, 6, 10, 28, 32, 39–44]. The data in Table 5 primarily display comparative activity versus engineered isogenic strains, and also for characterized clinical strains. MIC<sub>50</sub> and MIC<sub>90</sub> values are typically not relevant when agents are tested for small numbers of isolates (< 10). Taniborbactam significantly increased *in vitro* activity of cefepime against *Enterobacterales* spp. producing ESBLs (2- to 2048-fold MIC reduction), and Ambler class B (2- to 1024-fold MIC reduction), Ambler class C (2- to 1024-fold MIC reduction), and Ambler class D (2- to 256-fold MIC reduction)  $\beta$ -lactamases. The large range in MIC fold reduction of cefepime/taniborbactam compared with cefepime designates that more genotypes need to be tested to obtain a full and complete picture of the activity of cefepime/taniborbactam, especially versus CRE genotypes. Additionally, taniborbactam enhanced the activity of cefepime against *P. aeruginosa* producing ESBLs (8-fold MIC reduction), and Ambler class B (2- to 32-fold MIC reduction), Ambler class C (4- to 64-fold MIC reduction), and Ambler class D

**Table 4** In vitro activity (MIC, mg/L) of cefepime–taniborbactam and comparators against Gram-negative aerobes

| Gram-negative aerobes                                                                                                                | Cefepime          |                                | Cefepime–taniborbactam <sup>a</sup> |                   |                                |                                | Cefepime–<br>taniborbactam MIC<br>fold reduction <sup>c</sup> | Ceftazidime–<br>avibactam |                                | Imipenem–<br>relebactam        |                                | Meropenem–<br>vaborbactam      |                                |                                |
|--------------------------------------------------------------------------------------------------------------------------------------|-------------------|--------------------------------|-------------------------------------|-------------------|--------------------------------|--------------------------------|---------------------------------------------------------------|---------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|
|                                                                                                                                      | MIC <sub>50</sub> |                                | Range                               |                   | MIC <sub>50</sub>              | MIC <sub>90</sub> <sup>b</sup> |                                                               | Range                     | MIC <sub>50</sub>              | MIC <sub>90</sub> <sup>b</sup> | MIC <sub>50</sub>              | MIC <sub>90</sub> <sup>b</sup> | MIC <sub>50</sub>              | MIC <sub>90</sub> <sup>b</sup> |
|                                                                                                                                      | MIC <sub>50</sub> | MIC <sub>90</sub> <sup>b</sup> | Range                               | MIC <sub>50</sub> | MIC <sub>90</sub> <sup>b</sup> | Range                          |                                                               | MIC <sub>50</sub>         | MIC <sub>90</sub> <sup>b</sup> | MIC <sub>50</sub>              | MIC <sub>90</sub> <sup>b</sup> | MIC <sub>50</sub>              | MIC <sub>90</sub> <sup>b</sup> | MIC <sub>50</sub>              |
| <i>Acinetobacter baumannii</i> .<br>Cefiderocol non-susceptible <sup>d</sup><br>Carbapenem-resistant <sup>e</sup> ,<br>NDM producers | 2                 | 4                              | 1–32                                | 2                 | 4                              | 1–32                           | –                                                             | 4                         | 16                             | NA                             | NA                             | NA                             | NA                             |                                |
|                                                                                                                                      | 256               | 256                            | ≤ 0.25 to > 256                     | 64                | 128                            | ≤ 0.125 to > 128               | 2                                                             | NA                        | NA                             | 64                             | 128                            | 32                             | 64                             |                                |
|                                                                                                                                      | > 128             | > 128                          | > 128                               | > 128             | > 128                          | > 128                          | –                                                             | > 128                     | > 128                          | NA                             | NA                             | NA                             | NA                             |                                |
| Carbapenem-resistant <sup>e</sup> ,<br>OXA producers                                                                                 | 32                | 64                             | 4 to > 128                          | 32                | 64                             | 4 to > 128                     | –                                                             | 64                        | > 128                          | NA                             | NA                             | NA                             | NA                             |                                |
| <i>Burkholderia cepacia</i> complex and<br><i>Burkholderia gladioli</i>                                                              | 32                | 64                             | 1–64                                | 8                 | 64                             | 0.5–64                         | –                                                             | NA                        | NA                             | NA                             | NA                             | 2                              | 8                              |                                |
| <i>Citrobacter freundii</i><br><i>Elizabethkingia meningoseptica</i><br><i>Enterobacter cloacae</i> complex                          | ≤ 0.25            | 2                              | ≤ 0.25 to > 16                      | 0.03              | 0.12                           | ≤ 0.008 to > 16                | 16                                                            | NA                        | NA                             | NA                             | NA                             | NA                             | NA                             |                                |
|                                                                                                                                      | 16                | 32                             | 16–32                               | 4                 | 4                              | 2–8                            | 8                                                             | 64                        | 64                             | NA                             | NA                             | NA                             | NA                             |                                |
|                                                                                                                                      | ≤ 0.25            | 16                             | ≤ 0.25 to > 16                      | 0.06              | 0.5                            | ≤ 0.008 to > 16                | 32                                                            | NA                        | NA                             | NA                             | NA                             | NA                             | NA                             |                                |
| Carbapenemase producers                                                                                                              | > 32              | > 32                           | 2 to > 32                           | 1                 | 8                              | 0.5–32                         | > 4                                                           | > 32                      | > 32                           | 4                              | 16                             | 4                              | 32                             |                                |
| NDM producers                                                                                                                        | > 128             | > 128                          | 32 to > 128                         | 2                 | 8                              | 0.06–64                        | > 16                                                          | > 128                     | > 128                          | NA                             | NA                             | 64                             | 64                             |                                |
| <i>Enterobacteriales</i> spp.                                                                                                        | ≤ 0.25            | > 16                           | ≤ 0.25 to > 16                      | 0.06              | 0.25                           | ≤ 0.008 to > 16                | > 64                                                          | ≤ 0.012                   | 0.5                            | NA                             | NA                             | ≤ 0.06                         | 0.12                           |                                |
| Carbapenemase-positive CRE <sup>f</sup>                                                                                              | 32                | > 32                           | ≤ 0.25 to > 32                      | 1                 | 8                              | ≤ 0.016–32                     | > 4                                                           | 4                         | > 16                           | 1                              | 8                              | 8                              | > 16                           |                                |
| Carbapenemase-negative CRE <sup>f</sup>                                                                                              | > 32              | > 32                           | 1 to > 32                           | 2                 | 8                              | 2–8                            | > 4                                                           | 1                         | 4                              | 0.25                           | 1                              | 1                              | 4                              |                                |
| Cefepime-resistant <sup>g</sup>                                                                                                      | > 64              | > 64                           | 16 to > 64                          | 1                 | 4                              | 0.008–32                       | > 16                                                          | 1                         | 8                              | 0.25                           | 4                              | ≤ 0.06                         | 8                              |                                |
| Cefiderocol non-susceptible <sup>d</sup>                                                                                             | 256               | 256                            | ≤ 0.25 to > 256                     | 16                | 128                            | ≤ 0.125 to > 128               | 2                                                             | NA                        | NA                             | 8                              | 64                             | 16                             | 64                             |                                |
| DTR <sup>h</sup>                                                                                                                     | NA                | NA                             | NA                                  | 1                 | 16                             | 0.016 to > 16                  | NA                                                            | 4                         | > 16                           | NA                             | NA                             | 8                              | > 16                           |                                |
| ESBL producers                                                                                                                       | > 16              | > 16                           | ≤ 0.25 to > 16                      | 0.12              | 1                              | 0.008 to > 16                  | > 16                                                          | 0.25                      | 1                              | NA                             | NA                             | ≤ 0.06                         | 0.12                           |                                |
| KPC producers                                                                                                                        | > 32              | > 32                           | 8 to > 32                           | 1                 | 4                              | 0.016–8                        | > 8                                                           | 2                         | 8                              | 0.125                          | 0.5                            | 0.25                           | 2                              |                                |
| MBL producers                                                                                                                        | > 32              | > 32                           | 2 to > 32                           | 1                 | 16                             | 0.03 to > 16                   | > 2                                                           | > 32                      | > 32                           | > 32                           | > 64                           | > 32                           | > 32                           |                                |
| MDR <sup>i</sup>                                                                                                                     | NA                | NA                             | NA                                  | 0.25              | 4                              | 0.016 to > 16                  | NA                                                            | 0.5                       | > 16                           | NA                             | NA                             | ≤ 0.06                         | > 16                           |                                |
| Meropenem non-susceptible <sup>j</sup>                                                                                               | > 16              | > 16                           | 0.5 to > 16                         | 1                 | 8                              | 0.016 to > 16                  | > 2                                                           | 4                         | > 16                           | NA                             | NA                             | 8                              | > 16                           |                                |
| NDM producers                                                                                                                        | > 32              | > 32                           | 16 to > 32                          | 0.5               | 4                              | ≤ 0.06 to > 32                 | > 8                                                           | > 32                      | > 32                           | > 32                           | > 64                           | > 32                           | > 32                           |                                |
| VIM producers                                                                                                                        | 32                | > 32                           | > 32                                | 1                 | 8                              | 0.03–16                        | > 4                                                           | > 32                      | > 32                           | 16                             | 64                             | 16                             | 32                             |                                |
| <i>Escherichia coli</i>                                                                                                              | ≤ 0.25            | > 16                           | ≤ 0.25 to > 16                      | 0.03              | 0.12                           | ≤ 0.008 to > 16                | > 128                                                         | NA                        | NA                             | NA                             | NA                             | NA                             | NA                             |                                |
| Carbapenemase producers                                                                                                              | 32                | > 32                           | ≤ 0.25 to > 32                      | 0.25              | 8                              | ≤ 0.06–16                      | > 4                                                           | ≤ 0.25                    | > 32                           | 1                              | 32                             | 0.5                            | > 32                           |                                |
| Cefiderocol non-susceptible <sup>d</sup> with<br>PBP3 modification                                                                   | 256               | 256                            | ≤ 0.25 to > 256                     | 64                | 128                            | ≤ 0.125 to > 128               | 2                                                             | NA                        | NA                             | 16                             | 32                             | 32                             | 64                             |                                |
| NDM producers                                                                                                                        | > 128             | > 128                          | 64 to > 128                         | 16                | 32                             | 0.25–64                        | > 4                                                           | > 128                     | > 128                          | NA                             | NA                             | 64                             | 128                            |                                |
| <i>Klebsiella oxytoca</i>                                                                                                            | ≤ 0.25            | 1                              | ≤ 0.25 to > 16                      | 0.03              | 0.06                           | ≤ 0.008–4                      | 16                                                            | NA                        | NA                             | NA                             | NA                             | NA                             | NA                             |                                |
| <i>Klebsiella pneumoniae</i>                                                                                                         | ≤ 0.25            | > 16                           | ≤ 0.25 to > 16                      | 0.06              | 1                              | ≤ 0.008 to > 16                | > 16                                                          | NA                        | NA                             | NA                             | NA                             | NA                             | NA                             |                                |
| Carbapenemase producers                                                                                                              | > 32              | > 32                           | ≤ 0.25 to > 32                      | 0.5               | 4                              | ≤ 0.06–16                      | > 8                                                           | 1                         | 32                             | 1                              | 4                              | 1                              | 8                              |                                |

Table 4 (continued)

| Gram-negative aerobes                       | Cefepime          |                                | Cefepime–taniborbactam <sup>a</sup> |                   |                                | Cefepime–<br>taniborbactam MIC<br>fold reduction <sup>c</sup> | Ceftazidime–<br>avibactam |                   | Imipenem–<br>relebactam        |                   | Meropenem–<br>vaborbactam      |                   |                                |
|---------------------------------------------|-------------------|--------------------------------|-------------------------------------|-------------------|--------------------------------|---------------------------------------------------------------|---------------------------|-------------------|--------------------------------|-------------------|--------------------------------|-------------------|--------------------------------|
|                                             | MIC <sub>50</sub> | MIC <sub>90</sub> <sup>b</sup> | Range                               | MIC <sub>50</sub> | MIC <sub>90</sub> <sup>b</sup> |                                                               | Range                     | MIC <sub>50</sub> | MIC <sub>90</sub> <sup>b</sup> | MIC <sub>50</sub> | MIC <sub>90</sub> <sup>b</sup> | MIC <sub>50</sub> | MIC <sub>90</sub> <sup>b</sup> |
| NDM producers                               | 128               | > 128                          | 32 to > 128                         | 4                 | 64                             | 0.5–128                                                       | > 2                       | > 128             | > 128                          | NA                | NA                             | 64                | > 128                          |
| <i>Proteus mirabilis</i>                    | ≤ 0.25            | 16                             | ≤ 0.25 to > 16                      | 0.06              | 0.25                           | ≤ 0.008–8                                                     | 64                        | NA                | NA                             | NA                | NA                             | NA                | NA                             |
| <i>Pseudomonas aeruginosa</i>               | 4                 | 32                             | ≤ 0.12 to > 32                      | 2                 | 8                              | ≤ 0.06 to > 32                                                | 4                         | 2                 | 8                              | NA                | NA                             | 0.5               | 16                             |
| Carbapenemase-positive CRPA <sup>k</sup>    | ≥ 32              | ≥ 32                           | 4 to ≥ 32                           | 8                 | > 32                           | 1 to > 32                                                     | –                         | > 16              | > 16                           | NA                | NA                             | > 16              | > 16                           |
| Carbapenemase-negative CRPA <sup>k</sup>    | NA                | NA                             | NA                                  | 8                 | 16                             | 1 to > 16                                                     | NA                        | 8                 | > 16                           | NA                | NA                             | 16                | > 16                           |
| Cefepime-resistant <sup>l</sup>             | 32                | > 32                           | 16 to > 32                          | 8                 | 16                             | 0.5 to > 32                                                   | > 2                       | 8                 | > 16                           | NA                | NA                             | 16                | > 16                           |
| Cefiderocol non-susceptible <sup>d</sup>    | 32                | 256                            | ≤ 0.25 to > 256                     | 32                | 128                            | ≤ 0.125 to > 128                                              | 2                         | NA                | NA                             | 2                 | 32                             | 8                 | 64                             |
| DTR <sup>g</sup>                            | NA                | NA                             | NA                                  | 8                 | > 32                           | 1 to > 32                                                     | NA                        | > 16              | > 16                           | NA                | NA                             | 16                | > 16                           |
| MDR non-carbapenemase producer <sup>m</sup> | 16                | ≥ 128                          | 1 to ≥ 128                          | 8                 | ≥ 128                          | 1 to ≥ 128                                                    | –                         | 16                | ≥ 128                          | 2                 | 8                              | 16                | 32                             |
| MDR KPC producers <sup>m</sup>              | ≥ 128             | ≥ 128                          | ≥ 128                               | 16                | ≥ 128                          | 4 to ≥ 128                                                    | –                         | 8                 | 32                             | 16                | ≥ 128                          | ≥ 128             | ≥ 128                          |
| MDR MBL producers <sup>m</sup>              | ≥ 128             | ≥ 128                          | 16 to ≥ 128                         | 64                | ≥ 128                          | 4 to ≥ 128                                                    | –                         | 64                | ≥ 128                          | ≥ 128             | ≥ 128                          | 32                | ≥ 128                          |
| MBL                                         | NA                | NA                             | NA                                  | 8                 | > 32                           | 1 to > 32                                                     | NA                        | > 16              | > 16                           | NA                | NA                             | > 16              | > 16                           |
| MDR <sup>m</sup>                            | 32                | ≥ 128                          | 1 to ≥ 128                          | 16                | ≥ 128                          | 1 to ≥ 128                                                    | –                         | 16                | ≥ 128                          | 4                 | ≥ 128                          | 16                | ≥ 128                          |
| VIM-producing                               | 32                | > 32                           | 4 to > 32                           | 8                 | 32                             | 1 to > 32                                                     | –                         | > 16              | > 16                           | NA                | NA                             | > 16              | > 16                           |
| <i>Serratia marcescens</i>                  | ≤ 0.25            | 2                              | ≤ 0.25 to ≥ 16                      | 0.06              | 0.25                           | 0.016 to > 16                                                 | 8                         | NA                | NA                             | NA                | NA                             | NA                | NA                             |
| <i>Stenotrophomonas maltophilia</i>         | 32                | 64                             | 1–128                               | 4                 | 16                             | 0.5–16                                                        | 4                         | 16                | 128                            | NA                | NA                             | NA                | NA                             |

Adapted from references [3, 5, 8, 9, 26, 27, 29–37]

CRE carbapenem-resistant *Enterobacteriaceae*, CRPA carbapenem-resistant *Pseudomonas aeruginosa*, ESBL extended-spectrum  $\beta$ -lactamase, DTR difficult-to-treat-resistant, KPC *Klebsiella pneumoniae* carbapenemase, MBL metallo- $\beta$ -lactamase, MDR multidrug-resistant, MIC minimum inhibitory concentration, MIC<sub>50</sub> minimum concentration (mg/L) to inhibit growth of 50% of isolates, MIC<sub>90</sub> minimum concentration (mg/L) to inhibit growth of 90% of isolates, NA data not available, – indicates no reduction

<sup>a</sup>Fixed taniborbactam concentration of 4 mg/L<sup>b</sup>MIC<sub>90</sub> not calculated when there were fewer than 10 isolates<sup>c</sup>Fold reductions calculated using MIC<sub>90</sub> values, or MIC<sub>50</sub> values if MIC<sub>90</sub> data not available; represents a reduction in cefepime MIC values with the addition of taniborbactam<sup>d</sup>Cefiderocol MIC ≥ 1 mg/L<sup>e</sup>Carbapenem resistance based on meropenem MIC > 4 mg/L<sup>f</sup>CRE defined as resistance to meropenem (MIC ≥ 4 mg/L)<sup>g</sup>Cefepime MIC ≥ 16 mg/L<sup>h</sup>DTR defined as isolates intermediate or resistant to fluoroquinolones, all  $\beta$ -lactams, including carbapenems and piperacillin-tazobactams, but excluding ceftazidime-avibactam, ceftolozane-tazobactam, and meropenem-vaborbactam<sup>i</sup>MDR defined as resistant to at least one agent from ≥ 3 antimicrobial classes<sup>j</sup>Meropenem MIC > 1 mg/L<sup>k</sup>CRPA defined as resistant to meropenem and/or imipenem (MIC ≥ 8 mg/L)<sup>l</sup>Cefepime MIC > 8 mg/L<sup>m</sup>MDR defined as multiclonal isolates that harbored MBLs, SBLs, PBP mutations, other non-enzymatic resistance mechanisms

**Table 5** In vitro activity (MIC, mg/L) of ceftipime–taniboractam and comparators against *Enterobacteriales* and *Pseudomonas aeruginosa* carrying specific  $\beta$ -lactamases

| Organism                      | Ambler class | β-lactamase enzyme                                     | n   | Cefepime                       |                                | Cefepime–taniboractam          |                                | MIC fold reduction <sup>b</sup> | Ceftazidime–avibactam          |                                | Meropenem–vaborbactam          |                                |
|-------------------------------|--------------|--------------------------------------------------------|-----|--------------------------------|--------------------------------|--------------------------------|--------------------------------|---------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|
|                               |              |                                                        |     | MIC <sub>50</sub> <sup>c</sup> | MIC <sub>90</sub> <sup>d</sup> | MIC <sub>50</sub> <sup>c</sup> | MIC <sub>90</sub> <sup>d</sup> |                                 | MIC <sub>50</sub> <sup>c</sup> | MIC <sub>90</sub> <sup>d</sup> | MIC <sub>50</sub> <sup>c</sup> | MIC <sub>90</sub> <sup>d</sup> |
| <i>Citrobacter freundii</i>   |              |                                                        |     |                                |                                |                                |                                |                                 |                                |                                |                                |                                |
| A, C                          |              | TEM-1, AmpC                                            | 1   | 0.5                            | NA                             | ≤ 0.016                        | NA                             | ≤ 0.016                         | 32                             | 0.12                           | NA                             | NA                             |
| A, C                          |              | TEM-163, AmpC                                          | 1   | 8                              | NA                             | ≤ 0.016                        | NA                             | ≤ 0.016                         | 256                            | 0.25                           | NA                             | NA                             |
| B                             |              | NDM-1                                                  | 1   | 32                             | NA                             | 4                              | NA                             | 4                               | 8                              | NA                             | NA                             | NA                             |
| A, B                          |              | CTX-M-15, NDM-1                                        | 2   | > 256                          | NA                             | 8                              | NA                             | 2–8                             | > 32                           | NA                             | NA                             | NA                             |
| A, B, C                       |              | CTX-M-14, NDM-1, CMY-79                                | 1   | 64                             | NA                             | 0.06                           | NA                             | 0.06                            | > 1024                         | > 256                          | NA                             | NA                             |
| <i>Enterobacter cloacae</i>   |              |                                                        |     |                                |                                |                                |                                |                                 |                                |                                |                                |                                |
| A                             |              | CTX-M-15                                               | 1   | ≥ 256                          | NA                             | 1                              | NA                             | 1                               | ≥ 256                          | 1                              | NA                             | NA                             |
| A                             |              | KPC                                                    | 1   | ≥ 256                          | NA                             | 1                              | NA                             | 1                               | ≥ 256                          | 2                              | NA                             | NA                             |
| A                             |              | TEM-1                                                  | 1   | 4                              | NA                             | 0.12                           | NA                             | 0.12                            | > 32                           | 1                              | NA                             | NA                             |
| B                             |              | NDM-1                                                  | 1   | 128                            | NA                             | 8                              | NA                             | 8                               | 16                             | NA                             | NA                             | NA                             |
| A, B                          |              | CTX-M-15, NDM-1                                        | 2   | > 256                          | NA                             | 8                              | NA                             | 4–8                             | > 32                           | NA                             | NA                             | NA                             |
| A, B, D                       |              | TEM-1, NDM-1, OXA-1, KLUY-1, PBP3 modification (N570S) | 1   | > 256                          | NA                             | > 128                          | NA                             | > 128                           | > 2                            | NA                             | NA                             | NA                             |
| B                             |              | VIM-1                                                  | 1   | 128                            | NA                             | 4                              | NA                             | 4                               | 32                             | ≥ 64                           | NA                             | NA                             |
| A, B                          |              | CTX-M-9, VIM-1                                         | 3   | 16                             | NA                             | ≤ 0.125                        | NA                             | ≤ 0.125–2                       | 128                            | NA                             | NA                             | NA                             |
| D                             |              | OXA-48                                                 | 1   | 128                            | NA                             | 0.5                            | NA                             | 0.5                             | 256                            | 1                              | NA                             | NA                             |
| <i>Enterobacteriales</i> spp. |              |                                                        |     |                                |                                |                                |                                |                                 |                                |                                |                                |                                |
| A                             |              | CTX-M-1                                                | 393 | NA                             | NA                             | 0.12                           | 1                              | 0.016–8                         | NA                             | 0.25                           | 1                              | ≤ 0.06                         |
| A                             |              | CTX-M-9                                                | 73  | NA                             | NA                             | 0.06                           | 0.12                           | 0.016–4                         | NA                             | ≤ 0.12                         | 0.5                            | ≤ 0.06                         |
| A                             |              | SHV ESBL                                               | 23  | NA                             | NA                             | 0.06                           | 0.25                           | 0.03–1                          | NA                             | 0.5                            | 2                              | ≤ 0.06                         |
| C                             |              | AmpC                                                   | 34  | NA                             | NA                             | 0.06                           | 2                              | 0.016–2                         | NA                             | 0.25                           | 2                              | ≤ 0.06                         |
| D                             |              | OXA-48                                                 | 297 | > 32                           | > 32                           | 1                              | 4                              | 0.06–32                         | > 8                            | 0.5                            | 1                              | 16                             |
| –                             |              | PFN OmpK36                                             | 137 | NA                             | NA                             | 2                              | 32                             | 2–32                            | NA                             | 4                              | > 64                           | > 64                           |
| –                             |              | NF OmpK36                                              | 62  | NA                             | NA                             | 2                              | 8                              | 2–8                             | NA                             | 4                              | > 64                           | > 64                           |
| <i>Escherichia coli</i>       |              |                                                        |     |                                |                                |                                |                                |                                 |                                |                                |                                |                                |
| A                             |              | CTX-M-2                                                | 1   | 128                            | NA                             | 0.25                           | NA                             | 0.25                            | 512                            | 0.5                            | NA                             | NA                             |
| A                             |              | CTX-M-15                                               | 3   | > 64                           | NA                             | 0.125                          | NA                             | 0.06–0.125                      | 512                            | 0.5                            | NA                             | ≤ 0.03                         |
| A                             |              | KPC                                                    | 2   | 128                            | NA                             | 1                              | NA                             | 0.06–1                          | 128                            | 1                              | NA                             | NA                             |
| A                             |              | KPC-2                                                  | 1   | 4                              | NA                             | ≤ 0.125                        | NA                             | ≤ 0.125                         | 32                             | 0.5                            | NA                             | ≤ 0.125                        |
| A                             |              | KPC-3                                                  | 1   | 8                              | NA                             | ≤ 0.125                        | NA                             | ≤ 0.125                         | 64                             | 0.5                            | NA                             | ≤ 0.125                        |
| A                             |              | PER-1                                                  | 1   | 8                              | NA                             | ≤ 0.125                        | NA                             | ≤ 0.125                         | 64                             | 16                             | NA                             | ≤ 0.125                        |
| A                             |              | PER-6                                                  | 1   | > 256                          | NA                             | ≤ 0.125                        | NA                             | ≤ 0.125                         | 2048                           | 64                             | NA                             | ≤ 0.125                        |
| A                             |              | TEM-1, CTX-M                                           | 1   | ≥ 256                          | NA                             | 0.12                           | NA                             | 0.12                            | > 2048                         | 1                              | NA                             | NA                             |

Table 5 (continued)

| Organism                       | Ambler class | $\beta$ -lactamase enzyme                 | n  | Cefepime                       |                                | Cefepime–taniborbactam         |                                | MIC fold reduction <sup>b</sup> | Ceftazidime–avibactam          |                                | Meropenem–vaborbactam          |                                |
|--------------------------------|--------------|-------------------------------------------|----|--------------------------------|--------------------------------|--------------------------------|--------------------------------|---------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|
|                                |              |                                           |    | MIC <sub>50</sub> <sup>c</sup> | MIC <sub>90</sub> <sup>d</sup> | MIC <sub>50</sub> <sup>c</sup> | MIC <sub>90</sub> <sup>d</sup> |                                 | MIC <sub>50</sub> <sup>c</sup> | MIC <sub>90</sub> <sup>d</sup> | MIC <sub>50</sub> <sup>c</sup> | MIC <sub>90</sub> <sup>d</sup> |
| B                              |              | IMP-1                                     | 3  | 16                             | NA                             | 16                             | 16–64                          | –                               | > 128                          | NA                             | 32                             | NA                             |
| B                              |              | IMP-2                                     | 1  | 16                             | NA                             | 16                             | 16                             | –                               | NA                             | NA                             | NA                             | NA                             |
| B                              |              | IMP-4                                     | 1  | 16                             | NA                             | 16                             | 16                             | –                               | NA                             | NA                             | NA                             | NA                             |
| B                              |              | NDM                                       | 2  | ≥ 256                          | NA                             | 2                              | 32 to ≥ 256                    | ≥ 128                           | ≥ 64                           | NA                             | NA                             | NA                             |
| B                              |              | NDM-1                                     | 3  | 64                             | NA                             | 0.5                            | 16–256                         | 128                             | > 64                           | NA                             | 32                             | NA                             |
| B                              |              | NDM-2                                     | 1  | 8                              | NA                             | 0.25                           | 8                              | 32                              | NA                             | NA                             | NA                             | NA                             |
| B                              |              | NDM-5                                     | 3  | 16                             | NA                             | 0.5                            | 8–512                          | 32                              | > 128                          | NA                             | 16                             | NA                             |
| B                              |              | NDM-5, PBP3 modification (YRIN)           | 5  | > 256                          | NA                             | 64                             | 128 to > 256                   | > 4                             | NA                             | NA                             | 32                             | NA                             |
| B                              |              | NDM-7                                     | 3  | 8                              | NA                             | 0.5                            | 8–512                          | 16                              | > 128                          | NA                             | 2                              | NA                             |
| B                              |              | NDM-9                                     | 3  | 16                             | NA                             | 16                             | 16                             | –                               | > 128                          | NA                             | 4                              | NA                             |
| B                              |              | NDM-14                                    | 1  | 32                             | NA                             | 0.5                            | 32                             | 64                              | NA                             | NA                             | NA                             | NA                             |
| B                              |              | VIM-1                                     | 3  | 32                             | NA                             | 2                              | 16–128                         | 16                              | > 128                          | NA                             | 4                              | NA                             |
| A, B                           |              | CTX-M-15, NDM-5, PBP3 modification (YRIN) | 6  | > 256                          | NA                             | 64                             | > 256                          | > 4                             | NA                             | NA                             | 64                             | NA                             |
| B, C                           |              | NDM-5, CMY-145                            | 3  | > 64                           | NA                             | 32                             | > 64                           | > 2                             | > 256                          | NA                             | NA                             | NA                             |
| B, C                           |              | NDM-5, CMY-42, PBP3 modification (YRIN)   | 10 | 256                            | 256                            | 16                             | 256 to > 256                   | 16                              | NA                             | NA                             | NA                             | NA                             |
| C                              |              | CMY-2                                     | 1  | 1                              | NA                             | ≤ 0.125                        | 1                              | 8                               | 2                              | NA                             | ≤ 0.125                        | NA                             |
| C                              |              | CMY-42                                    | 1  | 4                              | NA                             | ≤ 0.125                        | 4                              | 32                              | 4                              | NA                             | ≤ 0.125                        | NA                             |
| D                              |              | OXA-18                                    | 1  | 1                              | NA                             | ≤ 0.125                        | 1                              | 8                               | 1                              | NA                             | ≤ 0.125                        | NA                             |
| D                              |              | OXA-48                                    | 7  | 32                             | NA                             | 0.12                           | 0.25–128                       | > 256                           | 0.25                           | NA                             | NA                             | NA                             |
| <i>Enterobacter hormaechei</i> |              |                                           |    |                                |                                |                                |                                |                                 |                                |                                |                                |                                |
| B, D                           |              | NDM-1, OXA-16, ACT-16                     | 1  | 32                             | NA                             | 0.5                            | 32                             | 64                              | > 256                          | NA                             | NA                             | NA                             |
| <i>Klebsiella oxytoca</i>      |              |                                           |    |                                |                                |                                |                                |                                 |                                |                                |                                |                                |
| A                              |              | KPC                                       | 1  | 32                             | NA                             | 0.25                           | 32                             | 128                             | 16                             | NA                             | NA                             | NA                             |
| A, C                           |              | TEM-1, CMY-2                              | 1  | 4                              | NA                             | 0.06                           | 4                              | > 64                            | 1                              | NA                             | NA                             | NA                             |

Table 5 (continued)

| Organism                      | Ambler class                           | β-lactamase enzyme | n  | Cefepime                       |                                | Cefepime-taniborbactam         |                                | MIC fold reduction <sup>b</sup> | Ceftazidime-avibactam          |                                | Meropenem-vaborbactam          |                                |        |
|-------------------------------|----------------------------------------|--------------------|----|--------------------------------|--------------------------------|--------------------------------|--------------------------------|---------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|--------|
|                               |                                        |                    |    | MIC <sub>50</sub> <sup>c</sup> | MIC <sub>90</sub> <sup>d</sup> | MIC <sub>50</sub> <sup>c</sup> | MIC <sub>90</sub> <sup>d</sup> |                                 | MIC <sub>50</sub> <sup>c</sup> | MIC <sub>90</sub> <sup>d</sup> | MIC <sub>50</sub> <sup>c</sup> | MIC <sub>90</sub> <sup>d</sup> |        |
| <i>Klebsiella pneumoniae</i>  |                                        |                    |    |                                |                                |                                |                                |                                 |                                |                                |                                |                                |        |
| A                             | KPC                                    |                    | 10 | ≥ 256                          | ≥ 256                          | 32 to ≥ 256                    | 0.5                            | 1                               | 0.06–1                         | ≥ 256                          | 4                              | NA                             | NA     |
| A                             | KPC-2                                  |                    | 1  | 32                             | NA                             | 32                             | 0.125                          | NA                              | 0.125                          | 256                            | 0.125                          | NA                             | ≤ 0.03 |
| A                             | KPC-3                                  |                    | 3  | 64                             | NA                             | 64 to > 64                     | 0.5                            | NA                              | 0.12–0.5                       | 128                            | 1                              | NA                             | 0.25   |
| A                             | SHV-18                                 |                    | 1  | 1                              | NA                             | 1                              | 0.25                           | NA                              | 0.25                           | 4                              | 0.5                            | NA                             | ≤ 0.03 |
| A                             | SHV-1, TEM-1                           |                    | 1  | 16                             | NA                             | 16                             | 0.12                           | NA                              | 0.12                           | > 128                          | 2                              | NA                             | NA     |
| A, B                          | SHV-11, CTX-M-15, NDM-1                |                    | 1  | 128                            | NA                             | 128                            | 2                              | NA                              | 2                              | 64                             | ≥ 64                           | NA                             | NA     |
| A, B, D                       | CTX-M-15, SHV-11, TEM-1B, NDM-5, OXA-1 |                    | 1  | 64                             | NA                             | NA                             | 0.25                           | NA                              | 0.25                           | 256                            | > 256                          | NA                             | NA     |
| A, C                          | SHV-12, TEM-1, AmpC                    |                    | 1  | 8                              | NA                             | 8                              | 0.03                           | NA                              | 0.03                           | > 256                          | 1                              | NA                             | NA     |
| B                             | NDM                                    |                    | 4  | ≥ 256                          | NA                             | 128 to ≥ 256                   | 0.5                            | NA                              | 0.5–4                          | ≥ 512                          | ≥ 64                           | NA                             | NA     |
| B                             | VIM-1                                  |                    | 1  | > 64                           | NA                             | > 64                           | 1                              | NA                              | 1                              | > 64                           | > 64                           | NA                             | 8      |
| C                             | AmpC                                   |                    | 1  | 16                             | NA                             | 16                             | 0.06                           | NA                              | 0.06                           | > 256                          | 4                              | NA                             | NA     |
| D                             | OXA-48                                 |                    | 9  | 32                             | NA                             | 8–128                          | 0.25                           | NA                              | 0.06–0.25                      | 128                            | 0.5                            | NA                             | NA     |
| A, D                          | KPC-3, OXA-232, OmpK35, OmpK36         |                    | 1  | > 256                          | NA                             | > 256                          | 8                              | NA                              | 8                              | 32                             | NA                             | NA                             | NA     |
| <i>Proteus mirabilis</i>      |                                        |                    |    |                                |                                |                                |                                |                                 |                                |                                |                                |                                |        |
| B                             | NDM-5                                  |                    | 1  | 8                              | NA                             | 8                              | 0.12                           | NA                              | 0.12                           | > 64                           | 128                            | NA                             | NA     |
| <i>Pseudomonas aeruginosa</i> |                                        |                    |    |                                |                                |                                |                                |                                 |                                |                                |                                |                                |        |
| A                             | KPC-2                                  |                    | 2  | > 64                           | NA                             | > 64 to > 256                  | 8                              | NA                              | 4–8                            | > 8                            | 8                              | NA                             | 32     |
| A                             | GES                                    |                    | 51 | NA                             | NA                             | NA                             | 8                              | 16                              | 1 to > 32                      | NA                             | 8                              | > 16                           | > 16   |
| A                             | VEB                                    |                    | 21 | NA                             | NA                             | NA                             | 8                              | 8                               | 4–8                            | NA                             | > 16                           | > 16                           | > 16   |
| B                             | NDM-1                                  |                    | 1  | > 256                          | NA                             | > 256                          | 64                             | NA                              | 64                             | > 4                            | > 128                          | NA                             | 64     |
| B                             | NDM-5                                  |                    | 1  | > 256                          | NA                             | > 256                          | 64                             | NA                              | 64                             | > 4                            | > 128                          | NA                             | 32     |
| B                             | NDM-7                                  |                    | 1  | > 256                          | NA                             | > 256                          | 64                             | NA                              | 64                             | > 4                            | > 128                          | NA                             | 64     |
| B                             | NDM-9                                  |                    | 1  | > 256                          | NA                             | > 256                          | > 128                          | NA                              | > 128                          | > 2                            | > 128                          | NA                             | 64     |
| B                             | SPM-1                                  |                    | 1  | > 256                          | NA                             | > 256                          | 16                             | NA                              | 16                             | > 16                           | 128                            | NA                             | 32     |
| B                             | VIM-1                                  |                    | 1  | > 256                          | NA                             | > 256                          | 128                            | NA                              | 128                            | > 2                            | > 128                          | NA                             | 64     |
| B                             | VIM-2                                  |                    | 1  | 128                            | NA                             | 128                            | 4                              | NA                              | 4                              | 32                             | 128                            | NA                             | 32     |
| B                             | VIM-5                                  |                    | 1  | 128                            | NA                             | 128                            | 128                            | NA                              | 128                            | –                              | NA                             | NA                             | > 128  |
| C                             | CMY-2                                  |                    | 1  | 128                            | NA                             | 128                            | 16                             | NA                              | 16                             | 8                              | 128                            | NA                             | 0.5    |
| C                             | CMY-42                                 |                    | 1  | 128                            | NA                             | 128                            | 2                              | NA                              | 2                              | 64                             | 64                             | NA                             | 0.5    |
| C                             | PDC-222 <sup>e</sup>                   |                    | 1  | 8                              | NA                             | 8                              | 2                              | NA                              | 2                              | 4                              | 8                              | NA                             | NA     |
| C                             | PDC-477 <sup>e</sup>                   |                    | 1  | 16                             | NA                             | 16                             | 4                              | NA                              | 4                              | 4                              | 32                             | NA                             | NA     |
| C                             | PDC-483 <sup>e</sup>                   |                    | 1  | 256                            | NA                             | 256                            | 4                              | NA                              | 4                              | 64                             | 16                             | NA                             | NA     |
| D                             | OXA-2 <sup>e</sup>                     |                    | 2  | 8                              | NA                             | 4–8                            | 8                              | NA                              | 4–8                            | –                              | 4                              | NA                             | NA     |

**Table 5** (continued)

| Organism                   | Ambler class | $\beta$ -lactamase enzyme | <i>n</i> | Cefepime                       |                                | Cefepime–taniborbactam         |                                | MIC fold reduction <sup>b</sup> | Ceftazidime-avibactam          |                                | Meropenem-vaborbactam          |                                |
|----------------------------|--------------|---------------------------|----------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|---------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|
|                            |              |                           |          | MIC <sub>50</sub> <sup>c</sup> | MIC <sub>90</sub> <sup>d</sup> | MIC <sub>50</sub> <sup>c</sup> | MIC <sub>90</sub> <sup>d</sup> |                                 | MIC <sub>50</sub> <sup>c</sup> | MIC <sub>90</sub> <sup>d</sup> | MIC <sub>50</sub> <sup>c</sup> | MIC <sub>90</sub> <sup>d</sup> |
| <i>Serratia marcescens</i> | D            | OXA-10 <sup>e</sup>       | 2        | 32                             | NA                             | 8                              | NA                             | 4                               | 8                              | NA                             | NA                             | NA                             |
|                            | D            | OXA-14 <sup>e</sup>       | 3        | 64                             | NA                             | 16                             | NA                             | 4                               | 128                            | NA                             | NA                             | NA                             |
|                            | D            | OXA-23                    | 1        | 32                             | NA                             | 16                             | NA                             | 2                               | 1                              | NA                             | 8                              | NA                             |
| A, C                       |              | SHV-12, TEM-1, AmpC,      | 2        | 4                              | NA                             | 0.06                           | NA                             | > 64                            | 0.5                            | NA                             | NA                             | NA                             |

Adapted from references [5, 8, 10, 28, 32, 39–44]

*ESBL* extended-spectrum  $\beta$ -lactamase, *KPC Klebsiella pneumoniae* carbapenemase, MIC<sub>50</sub> minimum concentration (mg/L) to inhibit growth of 50% of isolates, MIC<sub>90</sub> minimum concentration (mg/L) to inhibit growth of 90% of isolates, *n* number of isolates, NA data not available, *PFN* partially functional, *OmpK35 Klebsiella* outer membrane porin 35, *OmpK36 Klebsiella* outer membrane porin 36, *PFN* partially functional, – indicates no reduction

<sup>a</sup>Fixed taniborbactam concentration of 4 mg/L<sup>b</sup>Fold reductions calculated using MIC<sub>50</sub> values, or MIC<sub>90</sub> when available; represents reduction in cefepime MIC values with the addition of taniborbactam<sup>c</sup>Actual MIC recorded for *n* of 1; median MIC recorded for fewer than 10 isolates<sup>d</sup>MIC<sub>90</sub> not calculated when there were fewer than 10 isolates<sup>e</sup>Isolates resistant to ceftolozane-tazobactam (MIC >4 mg/L) and/or ceftazidime-avibactam (MIC >8 mg/L)

(2- to 4-fold MIC reduction)  $\beta$ -lactamases. Against *A. baumannii*, taniborbactam decreased cefepime MICs by two to eightfold against various isolates that produced Ambler classes A, B, and D enzymes.

As displayed in Table 5, cefepime–taniborbactam displayed similar, enhanced (two to fourfold increase) or significantly enhanced (> 4 fold) in vitro activity against isolates producing one or more enzymes of each of the four Ambler classes compared with ceftazidime-avibactam. It demonstrated similar, enhanced (two to fourfold increase) or significantly enhanced (> 4 fold) in vitro activity against *Enterobacterales* and *P. aeruginosa* isolates harboring Ambler class B and D enzymes compared with meropenem-vaborbactam. The majority of isolates with elevated cefepime–taniborbactam MICs likely contained multiple mechanisms of resistance other than  $\beta$ -lactamase production, such as overexpression of efflux pumps and porin alterations, as discussed in the mechanisms of resistance section.

## 6 Pharmacokinetics

The pharmacokinetics (PK) of intravenous cefepime are well described. Cefepime demonstrates linear PK with a volume of distribution ( $V_d$ ) of 16.6–19.3 L and a serum half-life ( $t_{1/2}$ ) of 2.0–2.3 h in healthy adults ( $n = 31$ , ~20–44 years of age, ~74 kg, normal renal function) [45]. The total clearance (CL) of cefepime is 7.4–9.1 L/h with over 80% eliminated unchanged in the urine [45]. Compared with adults, the PK of cefepime in children ( $n = 31$ ) is characterized by a larger  $V_d$  ( $0.4 \pm 0.2$  L/kg) and shorter  $t_{1/2}$  ( $1.8 \pm 0.6$  h) [46]. The protein binding of cefepime in plasma is estimated at 20% [47]. Although, initial in vitro studies reported protein binding values of 14–19% [48, 49], a study of clinical samples from hospitalized patients, including those in intensive care ( $n = 36$ ), observed variable protein binding ranging from 0.8 to 48.4% (median 38.6%) [50].

The pulmonary penetration of cefepime was described in a study by Boselli et al. [51]. Similar cefepime concentrations were observed in the plasma (mean 13.5  $\mu$ g/mL) and epithelial lining fluid (ELF; mean 14.1  $\mu$ g/mL) of critically ill patients receiving 2000 mg of cefepime (infusion time [ $t'$ ] 0.5 h) followed by 4000 mg daily as a continuous infusion for nosocomial pneumonia ( $n = 20$ ) [51]. Lodise et al., studied the penetration of cefepime into the cerebrospinal fluid (CSF) of patients who had an external ventriculostomy and nosocomial pneumonia being treated with 2000 mg of cefepime ( $t'$  0.5 h) every 12 h ( $n = 7$ ) [52]. Based on the ratio of area under the concentration–time curves (AUC) in CSF to plasma, the median penetration of cefepime in CSF was 7.8% (interquartile range 3–22%).

The PK of cefepime have been characterized in special populations, such as the critically ill [47]. Nicasio et al.,

**Table 6** Pharmacokinetics of intravenous taniborbactam administered with and without cefepime

| Study (year of publication)<br>Patient description [reference]  | Subject demographics:<br>No. of M/F subjects;<br>mean age; mean body weight <sup>g</sup> | Renal function<br>(description)<br>CrCl or eGFR <sup>a</sup>                | Taniborbactam dose<br>(intravenous, 2 h infusion) | $C_{max}$ (mg/L)         | AUC <sup>b</sup> (mg · h/L) | CL <sub>Total</sub> (L/h) | CL <sub>Renal</sub> (L/h) |
|-----------------------------------------------------------------|------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------|---------------------------------------------------|--------------------------|-----------------------------|---------------------------|---------------------------|
| Asempa et al. (2023)<br>Healthy adults [55]                     | 14/6; 34.8 y; 72.8 ± 14.0 kg                                                             | 115.7 ± 26.2 mL/min                                                         | 500 mg q8h × 3 doses <sup>c</sup>                 | 24.1 ± 4.1               | 81.9 ± 13.9                 | 6.3 ± 1.0                 | NA                        |
| Dowell et al. (2021)<br>Healthy adults [56]                     | 4/2; 27.0 ± 5.3 y; 75.0 ± 16.6 kg                                                        | NA                                                                          | 62.5 mg × 1 dose                                  | 3.4 ± 0.6                | 11.3 ± 1.5                  | 5.6 ± 0.8                 | NA                        |
|                                                                 | 5/1; 31.8 ± 8.9 y; 86.9 ± 16.9 kg                                                        |                                                                             | 125 mg × 1 dose                                   | 5.0 ± 0.7                | 20.3 ± 2.8                  | 6.2 ± 0.8                 | NA                        |
|                                                                 | 5/1; 28.7 ± 6.3 y; 77.4 ± 9.1 kg                                                         |                                                                             | 250 mg × 1 dose                                   | 11.5 ± 1.6               | 41.1 ± 7.8                  | 6.3 ± 1.1                 | NA                        |
|                                                                 | 3/3; 27.3 ± 5.0 y; 82.0 ± 10.0 kg                                                        |                                                                             | 500 mg × 1 dose                                   | 22.7 ± 2.6               | 82.5 ± 7.6                  | 6.1 ± 0.5                 | 3.9 ± 0.6                 |
|                                                                 | 4/2; 35.0 ± 6.5 y; 91.1 ± 14.4 kg                                                        |                                                                             | 1000 mg × 1 dose                                  | 43.3 ± 6.4               | 156.5 ± 24.6                | 6.5 ± 1.0                 | 5.0 ± 0.8                 |
|                                                                 | 3/3; 34.5 ± 4.6 y; 70.4 ± 17.2 kg                                                        |                                                                             | 1500 mg × 1 dose                                  | 71.8 ± 11.7              | 263.4 ± 46.9                | 5.9 ± 1.1                 | 3.9 ± 0.7                 |
|                                                                 | 8/1; 32.2 ± 7.9 y; 84.7 ± 13.8 kg                                                        |                                                                             | 250 mg q8h × 28 doses                             |                          |                             |                           |                           |
|                                                                 |                                                                                          |                                                                             | Day 1                                             | 10.5 ± 1.9               | 34.4 ± 5.9                  | NA                        | NA                        |
|                                                                 |                                                                                          |                                                                             | Day 10                                            | 11.2 ± 1.8               | 41.6 ± 6.3                  | 6.2 ± 1.0                 | 5.2 ± 0.9                 |
|                                                                 | 4/5; 26.7 ± 5.7 y; 73.6 ± 12.1 kg                                                        |                                                                             | 500 mg q8h × 28 doses                             |                          |                             |                           |                           |
|                                                                 |                                                                                          |                                                                             | Day 1                                             | 25.8 ± 3.9               | 81.9 ± 12.0                 | NA                        | NA                        |
|                                                                 |                                                                                          |                                                                             | Day 10                                            | 26.5 ± 3.4               | 89.1 ± 12.3                 | 5.7 ± 0.7                 | 5.3 ± 0.8                 |
|                                                                 | 3/6; 30.6 ± 9.2 y; 76.0 ± 18.8 kg                                                        |                                                                             | 750 mg q8h × 28 doses                             |                          |                             |                           |                           |
|                                                                 |                                                                                          |                                                                             | Day 1                                             | 39.1 ± 9.3               | 119.1 ± 21.4                | NA                        | NA                        |
|                                                                 |                                                                                          |                                                                             | Day 10                                            | 38.8 ± 7.1               | 139.5 ± 30.1                | 5.6 ± 1.2                 | 5.2 ± 1.5                 |
| Dowell et al. (2022)<br>Adults with varying renal function [57] | 6/2; 49 ± 11 y; 87.0 ± 13.7 kg                                                           | Normal (CrCl ≥ 90)<br>131.0 ± 25.8 mL/min                                   | 500 mg × 1 dose <sup>c</sup>                      | 22.0 ± 2.5               | 83.6 ± 9.5                  | 5.8 ± 0.7                 | 4.4 ± 0.8 <sup>d</sup>    |
|                                                                 | 3/3; 58 ± 7 y; 84.6 ± 15.3 kg                                                            | Mild impairment<br>(eGFR 60–89)<br>74.6 ± 7.9 mL/min/1.73m <sup>2</sup>     | 500 mg × 1 dose <sup>c</sup>                      | 22.8 ± 5.2               | 97.4 ± 11.2                 | 5.0 ± 0.7                 | 4.2 ± 1.0                 |
|                                                                 | 3/3; 62 ± 11 y; 81.4 ± 20.1 kg                                                           | Moderate impairment<br>(eGFR 30–59)<br>36.1 ± 5.2 mL/min/1.73m <sup>2</sup> | 500 mg × 1 dose <sup>c</sup>                      | 26.9 ± 6.5               | 225 ± 50.6                  | 2.1 ± 0.5                 | 1.6 ± 0.3                 |
|                                                                 | 3/3; 60 ± 12 y; 78.3 ± 20.2 kg                                                           | Severe impairment<br>(eGFR < 30)<br>22.5 ± 9.4 mL/min/1.73m <sup>2</sup>    | 500 mg × 1 dose <sup>c</sup>                      | 27.9 ± 6.1               | 445 ± 352.9                 | 1.1 ± 0.8                 | 0.8 ± 0.9                 |
|                                                                 | 7/0; 48 ± 11 y; 87.5 ± 12.7 kg                                                           | Receiving hemodialysis<br>6.1 ± 1.3 mL/min/1.73m <sup>2</sup>               | 500 mg × 1 dose <sup>c,e</sup>                    | 37.7 ± 27.8 <sup>f</sup> | 2003 ± 642.9 <sup>f</sup>   | 0.25 ± 0.07 <sup>f</sup>  | NA                        |

Data are expressed as mean ± standard deviation where possible

AUC area under the concentration-time curve,  $CL_{Renal}$  renal clearance,  $CL_{Total}$  total body clearance,  $C_{max}$  maximum plasma concentration,  $CrCl$  creatinine clearance,  $eGFR$  estimated glomerular filtration rate, M/F male/female, NA data not available, q8h every 8 h, y years

<sup>a</sup>CrCl reported in mL/min and eGFR reported in mL/min/1.73 m<sup>2</sup>

<sup>b</sup>AUC from time zero to infinity for single doses and over a dosing interval for multiple doses

<sup>c</sup>Coadministered with cefepime 2000 mg

<sup>d</sup> $n = 7$ , one subject was excluded as the urine sample was missed

<sup>e</sup>Dose administered post-dialysis

<sup>f</sup>Values reported for the off-dialysis period

conducted a population PK study of cefepime in critically ill adults with ventilator-associated pneumonia [53]. Patients ( $n = 32$ ,  $57 \pm 21$  years of age,  $84 \pm 23$  kg, creatinine clearance [CrCl]  $101 \pm 41$  mL/min) received 2000 mg of cefepime ( $t' 3$  h) every 8 h (renally adjusted). The final PK model included CrCl as a covariate for drug elimination ( $k_e$ ) and body weight as a covariate for  $V_d$ . The mean population values for total CL and  $V_d$  were  $7.6 \pm 3.3$  L/h and  $0.26 \pm 0.19$  L/kg, respectively. More recently, Alshaer et al. published a population PK model for cefepime in critically ill children ( $n = 36$ ,  $3.9 \pm 4.7$  years of age,  $16 \pm 16$  kg, CrCl  $68 \pm 39$  mL/min) and adults ( $n = 644$ ,  $55 \pm 19$  years of age,  $85 \pm 33$  kg, CrCl  $111 \pm 73$  mL/min) [54]. The cefepime doses were 50 mg/kg ( $t' 0.5$  h) every 8 h for children and 2000 mg ( $t' 0.5$  h or 3–4 h) every 8 h or 6000 mg daily as a continuous infusion for adults (renally adjusted and accompanied by therapeutic drug monitoring). The final model incorporated body weight as a covariate for  $V_d$ , and CrCl, and age as a covariate for  $k_e$ . The population value for  $V_d$  was  $18.3 \pm 10.4$  L, while the  $k_e$  was  $0.37 \pm 0.29$  h<sup>-1</sup> in adults and  $1.22 \pm 0.73$  h<sup>-1</sup> in children.

The PK of taniborbactam administered with and without cefepime were described in three published studies (Table 6) [55–57]. Of note, a previous investigation of cefepime and taniborbactam did not observe changes in the PK of either agent when administered in combination [58]. Asempa et al. investigated the PK, including pulmonary disposition, of cefepime–taniborbactam (2000 mg/500 mg [ $t' 2$  h] every 8 h for three doses) in healthy adults [55]. Blood samples ( $n = 8$ ) were collected with the last dose. Total taniborbactam concentrations were measured in all samples, whereas free concentrations were also measured in samples collected at the end of infusion. ELF samples were collected via bronchoalveolar lavage at the end of infusion and at 4, 6, and 8 h ( $n = 5$  at each time). The mean taniborbactam plasma maximum concentration ( $C_{max}$ ) was  $24.1 \pm 4.1$  mg/L and AUC from time zero to 8 h ( $AUC_8$ ) was  $81.9 \pm 13.9$  mg · h/L. The protein binding of taniborbactam was negligible (0–0.7%). The  $V_d$  at steady state,  $t_{1/2}$ , and total CL were  $20.3 \pm 3.0$  L,  $2.3 \pm 0.3$  h, and  $6.3 \pm 1.0$  L/h, respectively. The concentrations of taniborbactam in ELF decreased over time from  $3.9 \pm 1.0$  mg/L at 2 h to  $0.3 \pm 0.3$  mg/L at 8 h. The concentrations in alveolar macrophages remained relatively constant ( $12.4 \pm 6.9$  mg/L at 2 h and  $14.9 \pm 2.9$  mg/L at 8 h). The  $AUC_8$  in ELF and alveolar macrophages was 13.8 mg h/L and 106 mg h/L, respectively, whereas the  $AUC_8$  ratio compared with plasma was 0.17 for ELF and 1.29 for alveolar macrophages.

Dowell et al., investigated the PK of single- and multiple-dose regimens of taniborbactam in healthy adults [56]. The single-dose studies included six doses ranging from 62.5 to 1500 mg ( $t' 2$  h). As detailed in Table 6, there were

proportional (dose-dependent) increases in the mean  $C_{max}$  and  $AUC_{\infty}$ . The multiple-dose regimens included 250, 500, and 750 mg ( $t' 2$  h) of taniborbactam every 8 h for 28 doses (10 days). Overall, the plasma concentrations were similar on Days 1 and 10. For the clinical dose of 500 mg every 8 h, the mean  $C_{max}$  and  $AUC_8$  on Day 10 were  $26.5$  mg/L  $\pm$   $3.4$  mg/L and  $89.1 \pm 12.3$  mg · h/L, respectively. The total taniborbactam CL (single-dose studies) was 5.6–6.5 L/h, with a renal CL of 3.9–5.0 L/h.

Another study by Dowell et al. investigated the PK of single-dose cefepime–taniborbactam (2000 mg/500 mg [ $t' 2$  h]) in those with varying degrees of renal function (Table 6) [57]. Renal function was categorized as normal (CrCl  $\geq 90$  mL/min), mild impairment (estimated glomerular filtration rate [eGFR] 60–89 mL/min/1.73 m<sup>2</sup>), moderate impairment (eGFR 30–59 mL/min/1.73 m<sup>2</sup>), severe impairment (eGFR  $< 30$  mL/min/1.73 m<sup>2</sup>), and receiving hemodialysis. As expected, the total cefepime CL decreased with declining renal function, i.e.,  $5.7 \pm 0.8$  L/h (normal),  $4.6 \pm 0.5$  L/h (mild),  $2.1 \pm 0.5$  L/h (moderate), and  $1.2 \pm 0.8$  L/h (severe). The effects of renal function on total taniborbactam CL were similar, specifically,  $5.8 \pm 0.7$  L/h (normal),  $5.0 \pm 0.7$  L/h (mild),  $2.1 \pm 0.5$  L/h (moderate), and  $1.1 \pm 0.8$  L/h (severe). Participants receiving chronic intermittent high-flux hemodialysis (4 h duration) received the cefepime–taniborbactam dose post-dialysis (6 h after the initiation of dialysis). The total cefepime and taniborbactam CL<sub>off-dialysis</sub> were  $0.43 \pm 0.07$  L/h and  $0.25 \pm 0.07$  L/h, respectively. The CL<sub>on-dialysis</sub> was  $1.23 \pm 0.22$  L/h for cefepime and  $0.58 \pm 0.13$  L/h for taniborbactam. Although the authors concluded that further study is required, they suggested that renal adjusted dosing for cefepime–taniborbactam may be similar to that recommended for cefepime alone.

## 7 Pharmacodynamics

The in vitro pharmacodynamics of cefepime–taniborbactam were investigated by Noel et al. in a one-compartment dilutional model of  $\beta$ -lactamase-producing (CTX-M, KPC, AmpC, and OXA-48) *Enterobacteriales* ( $n = 4$ ) [59]. Isolates demonstrated cefepime MICs of  $> 4$  to  $> 128$  mg/L and cefepime–taniborbactam MICs of 0.5–8 mg/L. To characterize the pharmacodynamics, a human simulated regimen of cefepime (2000 mg [ $t' 2$  h] every 8 h) was administered with various doses of taniborbactam. The latter included continuous infusions with steady-state concentrations of 0.003–10 mg/L and intermittent dosing once, twice, or three times daily. Antimicrobial activity correlated best with taniborbactam exposure (AUC, thus AUC/MIC). The AUC from time zero to 24 h ( $AUC_{24}$ ) associated with bacteriostasis and  $\geq 1\text{-log}_{10}$  kill at 24 h

ranged from 4.0 to 5.8 mg h/L and 4.4 to 11.2 mg h/L, respectively.

The in vivo pharmacodynamics of cefepime–taniborbactam were also evaluated in two murine infection models by Abdelraouf et al. [60, 61]. The first study was conducted in a neutropenic murine thigh infection model using cefepime-resistant *Enterobacteriales* expressing ESBLs, AmpC  $\beta$ -lactamases, and/or carbapenemases and *P. aeruginosa* expressing AmpC  $\beta$ -lactamases and/or carbapenemases [60]. Three mice per group were tested for in vivo efficacy studies. A bacterial inoculum of  $\sim 10^6$  colony-forming units (CFUs) was injected into each thigh 2 h prior to treatment. A human-simulated regimen of cefepime (2000 mg [ $t'$  2 h] every 8 h) was administered alone and in combination with taniborbactam 1 or 5 mg/kg/day as one, two, or four doses over 24 h against KPC-producing *K. pneumoniae* ( $n = 1$ ; cefepime MIC of  $> 512$  mg/L, cefepime–taniborbactam MIC of 2 mg/L) and KPC-producing *P. aeruginosa* ( $n = 1$ ; cefepime MIC of  $> 512$  mg/L, cefepime–taniborbactam MIC of 4 mg/L). The authors noted that the frequency of taniborbactam dosing did not correlate with the potentiation of cefepime activity, and hence that taniborbactam  $fAUC/MIC$  predicted efficacy in combination with cefepime. In taniborbactam dose-ranging studies, at least 1- $\log_{10}$  bacterial kill of *Enterobacteriales* ( $n = 26$ ; cefepime MIC of 256 to  $> 512$  mg/L, cefepime–taniborbactam MIC of 0.06–16 mg/L) and *P. aeruginosa* ( $n = 4$ ; cefepime MIC of 256 to  $> 512$  mg/L, cefepime–taniborbactam MIC of 2–16 mg/L) was associated with taniborbactam  $fAUC_{24}/MICs$  of 2.62 and 0.46, respectively. Importantly, the simulated clinical dose of cefepime–taniborbactam (2000 mg/500 mg [ $t'$  2 h] every 8 h) achieved  $\geq 1$ - $\log_{10}$  kill for all isolates tested ( $n = 30$ ). Another study by Abdelraouf and Nicolau was conducted in a neutropenic murine model of pneumonia [61]. ESBL-, AmpC- and/or carbapenemase-producing isolates of *Enterobacteriales* and *P. aeruginosa* were tested. Six mice per group were intranasally inoculated with 50  $\mu$ L of a bacterial suspension containing  $10^7$  CFUs/mL 2 h prior to treatment. A human-simulated regimen equivalent to cefepime (2000 mg [ $t'$  4 h] every 8 h) was administered alone and in combination with a human-simulated regimen equivalent to 7.8, 31.25, 62.5, and 500 mg of taniborbactam over 24 h. For the *Enterobacteriales* isolates ( $n = 8$ ), bacteriostasis and 1- $\log_{10}$  kill were associated with a median taniborbactam  $fAUC_{24}/MIC$  of 0.96 and 4.03, respectively. For *P. aeruginosa* ( $n = 4$ ), bacteriostasis and 1- $\log_{10}$  kill were observed at a median  $fAUC_{24}/MIC$  of 1.35 and 3.02, respectively. The simulated dose of cefepime–taniborbactam 2000 mg/500 mg ( $t'$  4 h) every 8 h achieved  $> 1$ - $\log_{10}$  kill for all isolates and  $> 2$ - $\log_{10}$  kill for 14/18 isolates.

The in vitro pharmacodynamics of humanized plasma exposures of cefepime–taniborbactam were also evaluated in a hollow fiber infection model [62, 63]. These studies

used high inocula,  $> 10^7$  or  $> 10^8$  CFUs of cefepime-non-susceptible *Enterobacteriales* or *P. aeruginosa*, and demonstrated that the simulated clinical dose (2000 mg/500 mg [ $t'$  2 or 4 h] every 8 h) was associated with resistance prevention. In one study simulating the 2 h infusion dose, cefepime–taniborbactam achieved at least 3- $\log_{10}$  kill within 8 h and prevented regrowth of resistant subpopulations for 7 days against *Enterobacteriales* and *P. aeruginosa* isolates ( $n = 9$ ) producing SBL and/or MBL with cefepime–taniborbactam MICs ranging from 0.25 to 8 mg/L [62]. In a second study evaluating the 4 h infusion dose, humanized cefepime–taniborbactam exposures were efficacious against all SBL- and/or MBL-producing *K. pneumoniae* or *P. aeruginosa* strains ( $n = 8$ ; cefepime–taniborbactam MIC range 0.5–8 mg/L) and suppressed the emergence of resistance over the 4-day study duration [63].

## 8 Animal Studies

Animal studies have been conducted to assess the in vivo efficacy of cefepime–taniborbactam against infections caused by  $\beta$ -lactamase-producing Gram-negative bacilli using neutropenic murine urinary tract, pulmonary, and thigh infection models. Table 7 summarizes the available data from animal studies to date, comparing the reduction in bacterial inoculum resulting from cefepime and cefepime–taniborbactam exposure.

Lasko et al. evaluated the in vivo efficacy of cefepime–taniborbactam using a neutropenic murine cUTI model with 18 cefepime-resistant isolates, including *Enterobacteriales* ( $n = 9$ ), *P. aeruginosa* ( $n = 3$ ), and *S. maltophilia* ( $n = 6$ ) [64]. The isolates possessed various  $\beta$ -lactamases, including AmpC, ESBL, KPC, and OXA-48 (Table 7). Female CD-1 mice (six per group) were inoculated into the kidney with 0.05 mL of bacterial suspension ( $10^8$  CFUs/mL). Three hours post bacterial inoculation, saline, cefepime, and cefepime–taniborbactam were administered subcutaneously and a change in  $\log_{10}$  CFUs was evaluated at 48 h relative to 0 h. In vivo efficacy was assessed via change in  $\log_{10}$  CFUs/kidney reduction from 48-h controls. A cefepime human-simulated plasma regimen (HSR) was administered at 8 mg/kg at 0 h, followed by 4.5 mg/kg every 8 h, and cefepime–taniborbactam HSR was administered at 15/7.5 mg/kg at 0 h, followed by 7.5/3.75 mg/kg every 8 h over a 48-h period. The  $\log_{10}$  reduction in CFU/kidney was comparable between the cefepime and saline-treated control group, indicating the cefepime treatment was ineffective. However, cefepime–taniborbactam was associated with a  $> 4$   $\log_{10}$  CFU/kidney reduction for *Enterobacteriales* isolates, compared with control groups. Among all *P. aeruginosa* isolates (cefepime–taniborbactam MICs 4–16 mg/L), cefepime–taniborbactam resulted in a  $6.50 \pm 0.26$

**Table 7** Animal studies of cefepime–taniborbactam

| Study (year of publication) [reference]    | Animal/infection model | <i>n</i>    | Antimicrobial agent                    | Dose                                                           | Organism [cefepime MIC, cefepime–taniborbactam MIC, mg/L] ( $\beta$ -Lactamase[s] present) | Cefepime log <sub>10</sub> increase or reduction | Cefepime–taniborbactam log <sub>10</sub> increase or reduction |
|--------------------------------------------|------------------------|-------------|----------------------------------------|----------------------------------------------------------------|--------------------------------------------------------------------------------------------|--------------------------------------------------|----------------------------------------------------------------|
| Abdelraouf et al. (2020) <sup>a</sup> [60] | Mouse/thigh            | 3 per group | Cefepime HSR or Cefepime–taniborbactam | 2 g IV q8h ( <i>t'</i> 2 h)<br>2/0.5 g IV q8h ( <i>t'</i> 2 h) | <i>E. coli</i> EC481 [>512, 0.125] <sup>b</sup> (CTX-M-15)                                 | 2.43 ± 0.51 increase                             | 1.78 ± 0.09 reduction                                          |
|                                            |                        |             |                                        |                                                                | <i>E. cloacae</i> ECL124 [>512, 8] <sup>b</sup> (TEM-OSBL, CTX-M-15, ACT-7)                | 3.04 ± 0.81 increase                             | 1.06 ± 0.15 reduction                                          |
|                                            |                        |             |                                        |                                                                | <i>K. pneumoniae</i> KP329B [512, 0.25] <sup>b</sup> (SHV-11, SHV-5, OXA-9, KPC-2, TEM-1)  | 1.77 ± 0.56 increase                             | 1.61 ± 0.23 reduction                                          |
|                                            |                        |             |                                        |                                                                | <i>K. pneumoniae</i> KP510 [256, 0.06] <sup>b</sup> (CTX-M-11, SHV-11, DHA-1, TEM-1A)      | 0.00 ± 0.37 increase                             | 1.54 ± 0.62 reduction                                          |
|                                            |                        |             |                                        |                                                                | <i>K. pneumoniae</i> KP569 [>512, 4] <sup>b</sup> (OXA-48, CTX-M-15)                       | 3.58 ± 0.23 increase                             | 1.44 ± 0.24 reduction                                          |
|                                            |                        |             |                                        |                                                                | <i>K. pneumoniae</i> KP575 [>512, 2] <sup>b</sup> (KPC)                                    | 2.51 ± 0.38 increase                             | 1.92 ± 0.33 reduction                                          |
|                                            |                        |             |                                        |                                                                | <i>K. pneumoniae</i> KP579 [>512, 16] <sup>b</sup> (SHV-11, TEM-1, CTX-M-15, OXA-48)       | 3.52 ± 0.16 increase                             | 2.03 ± 0.67 reduction                                          |
|                                            |                        |             |                                        |                                                                | <i>K. pneumoniae</i> KP580 [>512, 8] <sup>b</sup> (SHV-OSBL, TEM-OSBL, CTX-M-15, OXA-48)   | 3.13 ± 0.15 increase                             | 1.40 ± 0.24 reduction                                          |
|                                            |                        |             |                                        |                                                                | <i>K. pneumoniae</i> KP583 [>512, 4] <sup>b</sup> (SHV-32, TEM-1, CTX-M-15, OXA-48)        | 3.64 ± 0.20 increase                             | 1.68 ± 0.22 reduction                                          |
|                                            |                        |             |                                        |                                                                | <i>K. pneumoniae</i> KP585 [512, 8] <sup>b</sup> (KPC)                                     | 1.06 ± 0.66 increase                             | 1.95 ± 0.43 reduction                                          |

**Table 7** (continued)

| Study (year of publication) [reference] | Animal/infection model | <i>n</i> | Antimicrobial agent | Dose | Organism [cefepime MIC, cefepime–tazobactam MIC, mg/L] ( $\beta$ -Lactamase[s] present)        | Cefepime log <sub>10</sub> increase or reduction | Cefepime–tazobactam log <sub>10</sub> increase or reduction |
|-----------------------------------------|------------------------|----------|---------------------|------|------------------------------------------------------------------------------------------------|--------------------------------------------------|-------------------------------------------------------------|
|                                         |                        |          |                     |      | <i>K. pneumoniae</i> KP679 [>512, 4] <sup>b</sup><br>(OXA-232, OXA-9, TEM-1A, CTX-M-15, OXA-1) | 3.24 $\pm$ 0.79 increase                         | 2.73 $\pm$ 0.50 reduction                                   |
|                                         |                        |          |                     |      | <i>K. pneumoniae</i> KP 686 [>512, 1] <sup>b</sup><br>(KPC-3, OXA-9, TEM-1A, SHV-11)           | 1.27 $\pm$ 0.93 increase                         | 2.53 $\pm$ 0.37 reduction                                   |
|                                         |                        |          |                     |      | <i>K. pneumoniae</i> KP731 [>512, 1] <sup>b</sup><br>(SHV-11, TEM-1, KPC-3)                    | 1.94 $\pm$ 1.26 increase                         | 2.99 $\pm$ 0.59 reduction                                   |
|                                         |                        |          |                     |      | <i>K. pneumoniae</i> KP732 [>512, 1] <sup>b</sup><br>(SHV-OSBL, TEM-OSBL, KPC-2)               | 2.33 $\pm$ 0.51 increase                         | 2.13 $\pm$ 0.22 reduction                                   |
|                                         |                        |          |                     |      | <i>K. pneumoniae</i> KP734 [>512, 2] <sup>b</sup><br>(KPC-3)                                   | 1.87 $\pm$ 0.56 increase                         | 1.60 $\pm$ 0.16 reduction                                   |
|                                         |                        |          |                     |      | <i>K. pneumoniae</i> KP735 [>512, 2] <sup>b</sup><br>(KPC-2)                                   | 1.27 $\pm$ 0.69 increase                         | 2.79 $\pm$ 0.24 reduction                                   |
|                                         |                        |          |                     |      | <i>K. pneumoniae</i> KP736 [>512, 1] <sup>b</sup><br>(SHV-11, CTX-M-55, OXA-48)                | 3.45 $\pm$ 0.44 increase                         | 1.43 $\pm$ 0.06 reduction                                   |
|                                         |                        |          |                     |      | <i>K. pneumoniae</i> KP737 [>512, 2] <sup>b</sup><br>(SHV-OSBL, CTX-M-15, OXA-48)              | 3.72 $\pm$ 0.16 increase                         | 1.71 $\pm$ 0.21 reduction                                   |
|                                         |                        |          |                     |      | <i>K. pneumoniae</i> KP738 [>512, 4] <sup>b</sup><br>(KPC-3)                                   | 2.96 $\pm$ 0.36 increase                         | 1.57 $\pm$ 0.42 reduction                                   |
|                                         |                        |          |                     |      | <i>K. pneumoniae</i> KP739 [>512, 8] <sup>b</sup><br>(SHV-11, TEM-1, CTX-M-15, OXA-48)         | 3.55 $\pm$ 0.20 increase                         | 2.36 $\pm$ 0.39 reduction                                   |

**Table 7** (continued)

| Study (year of publication) [reference]    | Animal/infection model | <i>n</i>    | Antimicrobial agent                | Dose                                                           | Organism [cefepime MIC, cefepime–taniborbactam MIC, mg/L] ( $\beta$ -Lactamase[s] present)      | Cefepime log <sub>10</sub> increase or reduction | Cefepime–taniborbactam log <sub>10</sub> increase or reduction |
|--------------------------------------------|------------------------|-------------|------------------------------------|----------------------------------------------------------------|-------------------------------------------------------------------------------------------------|--------------------------------------------------|----------------------------------------------------------------|
|                                            |                        |             |                                    |                                                                | <i>K. pneumoniae</i> KP740 [ $>512$ , 8] <sup>b</sup><br>(SHV-OSBL, TEM-OSBL, CTX-M-15, OXA-48) | 3.33 $\pm$ 0.23 increase                         | 1.35 $\pm$ 0.26 reduction                                      |
|                                            |                        |             |                                    |                                                                | <i>K. pneumoniae</i> KP742 [ $>512$ , 8] <sup>b</sup><br>(SHV-11, TEM-1, CTX-M-15, OXA-48)      | 3.70 $\pm$ 0.24 increase                         | 1.97 $\pm$ 0.37 reduction                                      |
|                                            |                        |             |                                    |                                                                | <i>K. pneumoniae</i> KP743 [ $>512$ , 8] <sup>b</sup><br>(SHV-11, TEM-1, CTX-M-15, OXA-48)      | 3.58 $\pm$ 0.27 increase                         | 1.50 $\pm$ 0.92 reduction                                      |
|                                            |                        |             |                                    |                                                                | <i>K. pneumoniae</i> KP744 [ $>512$ , 4] <sup>b</sup><br>(SHV-32, TEM-1, CTX-M-15, OXA-48)      | 3.53 $\pm$ 0.32 increase                         | 2.00 $\pm$ 0.32 reduction                                      |
|                                            |                        |             |                                    |                                                                | <i>P. aeruginosa</i> PSA1593 [ $>512$ , 4] <sup>b</sup><br>(KPC)                                | 2.45 $\pm$ 0.41 increase                         | 1.19 $\pm$ 0.26 reduction                                      |
|                                            |                        |             |                                    |                                                                | <i>P. aeruginosa</i> PSA1672 [ $>512$ , 2] <sup>b</sup><br>(AmpC overexpression)                | 3.56 $\pm$ 0.26 increase                         | 2.75 $\pm$ 0.00 reduction                                      |
|                                            |                        |             |                                    |                                                                | <i>P. aeruginosa</i> PSA1679 [256, 16] <sup>b</sup><br>(AmpC overexpression)                    | 2.97 $\pm$ 0.25 increase                         | 2.14 $\pm$ 0.26 reduction                                      |
|                                            |                        |             |                                    |                                                                | <i>P. aeruginosa</i> PSA1681 [ $>512$ , 8] <sup>b</sup><br>(AmpC overexpression)                | 3.29 $\pm$ 0.27 increase                         | −2.57 $\pm$ 0.43 reduction                                     |
|                                            |                        |             |                                    |                                                                | <i>E. coli</i> EC747 [512, 2] <sup>b</sup><br>(KPC)                                             | ~1.5 increase                                    | ~2.2 reduction                                                 |
|                                            |                        |             |                                    |                                                                | <i>E. coli</i> EC753 [ $>512$ , 2] <sup>b</sup><br>(CTX-M-15) <sup>c</sup>                      | ~2.7 increase                                    | ~3.8 reduction                                                 |
| Abdelraouf et al. (2023) <sup>a</sup> [61] | Mouse/pulmonary        | 6 per group | Cefepime or Cefepime–taniborbactam | 2 g IV q8h ( <i>t'</i> 4 h)<br>2/0.5 g IV q8h ( <i>t'</i> 4 h) |                                                                                                 |                                                  |                                                                |

**Table 7** (continued)

| Study (year of publication) [reference] | Animal/infection model | <i>n</i> | Antimicrobial agent | Dose | Organism [cefepime MIC, cefepime–tazobactam MIC, mg/L] ( $\beta$ -Lactamase[s] present)              | Cefepime log <sub>10</sub> increase or reduction | Cefepime–tazobactam log <sub>10</sub> increase or reduction |
|-----------------------------------------|------------------------|----------|---------------------|------|------------------------------------------------------------------------------------------------------|--------------------------------------------------|-------------------------------------------------------------|
|                                         |                        |          |                     |      | <i>E. coli</i> EC755 [ $>512$ , 16] <sup>b</sup> (CTX-M-15, EC-TYPE, OXA-1, TEM-1) <sup>c,d</sup>    | ~2.3 increase                                    | ~3.9 reduction                                              |
|                                         |                        |          |                     |      | <i>E. cloacae</i> ECL108 [ $>512$ , 2] <sup>b</sup> (KPC-2, ACT-7, CTX-M-15, OXA-1, TEM-1B)          | ~1.6 increase                                    | ~1.6 reduction                                              |
|                                         |                        |          |                     |      | <i>K. pneumoniae</i> KP647 [ $>512$ , 0.12] <sup>b</sup> (KPC-3)                                     | ~2.4 increase                                    | ~2.3 reduction                                              |
|                                         |                        |          |                     |      | <i>K. pneumoniae</i> KP679 [ $>512$ , 4] <sup>b</sup> (OXA-232, OXA-9, TEM-1A, CTX-M-15, OXA-1)      | ~2.3 increase                                    | ~2.2 reduction                                              |
|                                         |                        |          |                     |      | <i>K. pneumoniae</i> KP681 [ $>512$ , 1] <sup>b</sup> (CTX-M-15, OXA-1, OXA-232, SHV-1) <sup>e</sup> | ~2. increase                                     | ~2.5 reduction                                              |
|                                         |                        |          |                     |      | <i>K. pneumoniae</i> KP731 [ $>512$ , 1] <sup>b</sup> (SHV-11, TEM-1, KPC-3)                         | ~2.5 increase                                    | ~2.6 reduction                                              |
|                                         |                        |          |                     |      | <i>P. aeruginosa</i> PSA1711 [128, 16] <sup>b</sup> (PDC-103, KPC-2)                                 | ~2.2 increase                                    | ~2.4 reduction                                              |
|                                         |                        |          |                     |      | <i>P. aeruginosa</i> PSA1714 [4, 32] <sup>b</sup> (PDC-1)                                            | ~1.9 increase                                    | ~2.6 reduction                                              |
|                                         |                        |          |                     |      | <i>P. aeruginosa</i> PSA1715 [4, 16] <sup>b</sup> (PDC-5)                                            | ~2.5 increase                                    | ~2.5 reduction                                              |
|                                         |                        |          |                     |      | <i>P. aeruginosa</i> PSA1844 [ $>512$ , 2] <sup>b</sup> (KPC-2, PDC-42)                              | ~2.9 increase                                    | ~2.3 reduction                                              |

**Table 7** (continued)

| Study (year of publication) [reference] | Animal/infection model | <i>n</i>    | Antimicrobial agent                | Dose                                                                                                                         | Organism [cefepime MIC, cefepime–taniborbactam MIC, mg/L] ( $\beta$ -Lactamase[s] present)          | Cefepime log <sub>10</sub> increase or reduction | Cefepime–taniborbactam log <sub>10</sub> increase or reduction |
|-----------------------------------------|------------------------|-------------|------------------------------------|------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|--------------------------------------------------|----------------------------------------------------------------|
| Lasko et al. <sup>f</sup> (2022) [64]   | Mouse/urinary tract    | 6 per group | Cefepime or Cefepime–taniborbactam | 8 mg/kg SC $\times$ 1, then 4.5 mg/kg q8h SC $\times$ 6<br>15/7.5 mg/kg SC $\times$ 1, then 7.5/3.75 mg/kg SC q8h $\times$ 6 | <i>E. coli</i> EC720 [ $>512$ , 16] <sup>b</sup> (CTX-M-15, OXA-1)                                  | ~2.3 increase                                    | ~3.9 reduction                                                 |
|                                         |                        |             |                                    |                                                                                                                              | <i>E. coli</i> EC748 [512, 2] <sup>b</sup> (ESC-35, OXA-1, KPC-3)                                   | ~1.8 increase                                    | ~2.2 reduction                                                 |
|                                         |                        |             |                                    |                                                                                                                              | <i>E. cloacae</i> ECL124 [ $>512$ , 8] <sup>b</sup> (TEM-OSBL, CTX-M-15, ACT-7)                     | ~1.6 increase                                    | ~1.8 reduction                                                 |
|                                         |                        |             |                                    |                                                                                                                              | <i>K. pneumoniae</i> KP579 [ $>512$ , 16] <sup>b</sup> (SHV-11, TEM-1, CTX-M-15, OXA-48)            | ~2.7 increase                                    | ~1.9 reduction                                                 |
|                                         |                        |             |                                    |                                                                                                                              | <i>K. pneumoniae</i> KP744 [ $>512$ , 4] <sup>b</sup> (SHV-32, TEM-1, CTX-M-15, OXA-48)             | ~0.9 increase                                    | ~2.5 reduction                                                 |
|                                         |                        |             |                                    |                                                                                                                              | <i>P. aeruginosa</i> PSA1681 [ $>512$ , 8] <sup>b</sup> (OXA-486, PDC-8, OXA-10, CTX-M-2)           | ~2.5 increase                                    | ~3.0 reduction                                                 |
|                                         |                        |             |                                    |                                                                                                                              | <i>K. pneumoniae</i> KP390 [512, 0.06] <sup>b</sup> (KPC)                                           | ~0.25 reduction                                  | ~4.6 reduction                                                 |
|                                         |                        |             |                                    |                                                                                                                              | <i>E. cloacae</i> ECL123 [ $>512$ , 0.5] <sup>b</sup> (TEM-OSBL, CTX-M-15, ACT-New Variant, OXA-48) | ~0.40 reduction                                  | ~6.2 reduction                                                 |
|                                         |                        |             |                                    |                                                                                                                              | <i>K. pneumoniae</i> KP905 [ $>512$ , 1] <sup>b</sup> (KPC-3, SHV-11, TEM-1b, OMPK35)               | ~0 reduction                                     | ~4.9 reduction                                                 |

**Table 7** (continued)

| Study (year of publication) [reference] | Animal/infection model | <i>n</i> | Antimicrobial agent | Dose | Organism [cefepime MIC, cefepime–tazobactam MIC, mg/L] ( $\beta$ -Lactamase[s] present)             | Cefepime log <sub>10</sub> increase or reduction | Cefepime–tazobactam log <sub>10</sub> increase or reduction |
|-----------------------------------------|------------------------|----------|---------------------|------|-----------------------------------------------------------------------------------------------------|--------------------------------------------------|-------------------------------------------------------------|
|                                         |                        |          |                     |      | <i>K. pneumoniae</i> KP737 [>512, 2] <sup>b</sup> (SHV-OSBL, CTX-M-15, OXA-48)                      | ~0.25 increase                                   | ~5.3 reduction                                              |
|                                         |                        |          |                     |      | <i>K. pneumoniae</i> KP738 [>512, 4] <sup>b</sup> (KPC-3)                                           | ~0.25 increase                                   | ~5.0 reduction                                              |
|                                         |                        |          |                     |      | <i>E. cloacae</i> ECL124 [>512, 8] <sup>b</sup> (TEM-OSBL, CTX-M-15, ACT-7)                         | ~0.1 reduction                                   | ~4.8 reduction                                              |
|                                         |                        |          |                     |      | <i>K. pneumoniae</i> KP579 [>512, 16] <sup>b</sup> (SHV-11, TEM-1, CTX-M-15, OXA-48)                | ~0.05 reduction                                  | ~4.2 reduction                                              |
|                                         |                        |          |                     |      | <i>E. coli</i> EC774 [>512, 16] <sup>b</sup> (OXA-48, CTX-M-15, PBP3 4-aa (YRIK) insertion)         | ~0.2 increase                                    | ~5.5 reduction                                              |
|                                         |                        |          |                     |      | <i>E. coli</i> EC773 [>512, 16] <sup>b</sup> (CTX-M-15, OXA-1, OXA-181, PBP3 4-aa (YRIN) insertion) | ~0.4 increase                                    | ~4.3 reduction                                              |
|                                         |                        |          |                     |      | <i>P. aeruginosa</i> PSA1602 [512, 4] <sup>b</sup> (KPC-5, OXA-50, PAO)                             | ~0.2 reduction                                   | ~6.3 reduction                                              |
|                                         |                        |          |                     |      | <i>P. aeruginosa</i> PSA1681 [>512, 8] <sup>b</sup> (AmpC)                                          | ~0.05 reduction                                  | ~6.4 reduction                                              |
|                                         |                        |          |                     |      | <i>P. aeruginosa</i> PSA1711 [128, 16] <sup>b</sup> (PDC-103, KPC-2)                                | ~0.2 increase                                    | ~7.0 reduction                                              |
|                                         |                        |          |                     |      | <i>S. maltophilia</i> STM109 [256, 32] <sup>b</sup> (L1, L2)                                        | ~1.4 reduction                                   | ~6.1 reduction                                              |

**Table 7** (continued)

| Study (year of publication) [reference] | Animal/infection model | <i>n</i> | Antimicrobial agent | Dose | Organism [cefepime MIC, cefepime–taniborbactam MIC, mg/L] ( $\beta$ -Lactamase[s] present) | Cefepime log <sub>10</sub> increase or reduction | Cefepime–taniborbactam log <sub>10</sub> increase or reduction |
|-----------------------------------------|------------------------|----------|---------------------|------|--------------------------------------------------------------------------------------------|--------------------------------------------------|----------------------------------------------------------------|
|                                         |                        |          |                     |      | <i>S. maltophilia</i> STM110 [128, 32] <sup>b</sup> (L1, L2)                               | ~0.1 reduction                                   | ~5.2 reduction                                                 |
|                                         |                        |          |                     |      | <i>S. maltophilia</i> STM111 [128, 128] <sup>b</sup> (L1, L2)                              | ~0.05 increase                                   | ~1.6 reduction                                                 |
|                                         |                        |          |                     |      | <i>S. maltophilia</i> STM112 [128, 2] <sup>b</sup> (L1, L2)                                | ~0.5 reduction                                   | ~7.1 reduction                                                 |
|                                         |                        |          |                     |      | <i>S. maltophilia</i> STM113 [128, 1] <sup>b</sup> (L1, L2)                                | ~1.1 reduction                                   | ~6.4 reduction                                                 |
|                                         |                        |          |                     |      | <i>S. maltophilia</i> STM115 [256, 1] <sup>b</sup> (L1, L2)                                | ~0.2 reduction                                   | ~7.7 reduction                                                 |

HSR human simulated plasma regimen, IV intravenous, MIC minimum inhibitory concentration, *n* number of animals, *OmpK35* *Klebsiella* outer membrane porin 35, OSBL original spectrum  $\beta$ -lactamase, *q8h* every 8 h, SC subcutaneous

<sup>a</sup>Study completed over 24 h

<sup>b</sup>Cefepime MIC/cefepime MIC with 4 mg/L taniborbactam

<sup>c</sup>PBP3 mutation characterized by a 4-amino-acid (YRIK) insertion after position 333 and an A413V substitution

<sup>d</sup>G137D substitution in *OmpC* present

<sup>e</sup>*OmpK35* mutation present

<sup>f</sup>Study completed over 48 h

log<sub>10</sub> CFU/kidney reduction, and with *S. maltophilia* isolates (cefepime–taniborbactam MICs 1–32 mg/L), a  $6.47 \pm 0.65$  log<sub>10</sub> CFU/kidney reduction was observed with the addition of cefepime–taniborbactam. Overall, cefepime–taniborbactam resulted in a substantial reduction in bacterial burden against AmpC, ESBL, KPC, and OXA-48 producing *Enterobacteriales*, *P. aeruginosa*, and *S. maltophilia* [64].

In 2020, Abdelraouf et al. evaluated cefepime–taniborbactam in vivo efficacy using a neutropenic thigh model with 26 *Enterobacteriales* isolates and four *P. aeruginosa* isolates possessing various class A, C, and D  $\beta$ -lactamases (Table 7) [60]. Female ICR mice (three per group) received 0.1 mL of 10<sup>7</sup> CFUs/mL intramuscular injections of bacteria into each thigh. Two hours post bacterial inoculation, cefepime HSR alone was administered, as well as in combination with taniborbactam 8.33% HSR (cefepime:taniborbactam, 24:1, a subtherapeutic concentration that will not be discussed)

or 100% HSR taniborbactam (cefepime:taniborbactam, 2:1) over a 24-h period. Dosing schedules were adjusted to maintain similar human exposures to cefepime 2 g every 8 h and taniborbactam 0.5 g every 8 h, both infused over 2 h. Change in log<sub>10</sub> CFU/thigh counts were evaluated at 24 h relative to 0 h controls. Overall, cefepime HSR alone resulted in increased bacterial growth. In contrast, the 2:1 HSR cefepime:taniborbactam combination resulted in a  $\geq 2$  log<sub>10</sub> CFU/thigh reduction in 11 isolates, and  $\geq 1$  log<sub>10</sub> CFU/thigh reduction against the remaining 19 isolates.

In 2023, Abdelraouf et al. evaluated cefepime–taniborbactam in vivo efficacy using a neutropenic pneumonia model with cefepime non-susceptible *Enterobacteriales* (*n* = 13) and *P. aeruginosa* (*n* = 5) strains that harbored various  $\beta$ -lactamases with cefepime–taniborbactam MICs ranging from 0.12 to 16 mg/L [61]. Dosing schedules were

**Table 8** Cefepime–taniborbactam clinical trial summary

| Trial description [reference]                                                                                                                                      | n   | Treatment regimens                                                                                                                                                                 | Primary outcome                                                                                                                                       | Primary outcome results<br>n/N (%)                                 | Secondary outcomes                                                                                                                                                                                                                                                                                                                       | Secondary outcome results<br>n/N (%)                                                                                                                                                                                    |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Phase III, double-blind, randomized trial comparing cefepime–taniborbactam with meropenem in the treatment of cUTI and AP; ClinicalTrials.gov ID: NCT03840148 [14] | 661 | Cefepime–taniborbactam 2 g/0.5 g IV (t' 2 h) q8h × 7 days <sup>a</sup><br><br>Meropenem 1 g IV (t' 0.5 h) q8h × 7 days <sup>a</sup><br><br>Oral stepdown therapy was not permitted | Composite success in the microITT <sup>b</sup> population (microbiologic <sup>c</sup> and clinical <sup>d</sup> ) at test of cure on trial days 19–23 | Cefepime–taniborbactam: 207/293 (70.6)<br>Meropenem: 83/143 (58.0) | microITT: Composite success (microbiologic and clinical success) at the end of treatment <sup>e</sup><br>microITT: Composite success (microbiologic and clinical success) at late follow-up <sup>f</sup><br>Extended microITT <sup>g</sup> : Composite success (microbiologic and clinical success) at the end of treatment <sup>e</sup> | Cefepime–taniborbactam: 261/293 (89.1)<br>Meropenem: 123/143 (86.0)<br><br>Cefepime–taniborbactam: 187/293 (63.8)<br>Meropenem: 74/143 (51.7)<br><br>Cefepime–taniborbactam: 216/305 (70.8)<br>Meropenem: 86/147 (58.5) |

AP acute pyelonephritis, CFUs colony-forming units, cUTI complicated urinary tract infection, IV intravenous, microITT microbiological intention-to-treat, n/N no. of patients meeting the outcome/total no. of patients in the study arm, q8h every 8 h

<sup>a</sup>Duration could be extended to 14 days for patients with bacteremia

<sup>b</sup>Randomized patients who had a positive baseline urine culture with at least 10<sup>5</sup> CFUs/mL of a Gram-negative pathogen against which both cefepime–taniborbactam and meropenem were active in vitro, and with a maximum of two microorganisms identified

<sup>c</sup>Microbiological eradication defined as a reduction in all baseline Gram-negative pathogens in the urine to <10<sup>3</sup> CFUs/mL

<sup>d</sup>Clinical success defined as symptomatic resolution or return to pre-infection baseline of all core signs and symptoms, with no use of additional antibacterial agents for cUTI

<sup>e</sup>Defined as ≤24 h after the last dose of a trial drug

<sup>f</sup>Trial days 28–35 after the initiation of IV therapy with the assigned trial drug

<sup>g</sup>All patients in the microITT group plus patients with a susceptible baseline Gram-negative pathogen to at least one trial drug

adjusted to maintain similar human exposures to cefepime 2 g every 8 h infused over 4 h, and cefepime–taniborbactam 2/0.5 g every 8 h, infused over 4 h. A reduction in  $\log_{10}$  CFU/lung counts was evaluated at 24 h, relative to 0 h. The results of the study showed that the cefepime–taniborbactam HSR regimen produced at least  $> 1 \log_{10}$  kill in all 18 strains, and  $> 2 \log_{10}$  kill in 14/18 strains; thus, demonstrating the in vivo activity of cefepime–taniborbactam against cefepime non-susceptible *Enterobacterales* and *P. aeruginosa*.

In summary, the results of the various neutropenic murine infection studies completed to date show that cefepime–taniborbactam results in greater reduction of bacterial burden in Gram-negative bacilli producing various Ambler class A, C, and D enzymes (with cefepime–taniborbactam MICs  $\leq 16$  mg/L), when compared with cefepime monotherapy. Limited animal study data are available assessing cefepime–taniborbactam in vivo potency against Gram-negative bacilli carrying Ambler class B enzymes.

## 9 Clinical Trials

In the clinical trial section, our focus was phase III, randomized, comparative clinical trials, and not preliminary data from phase II studies. A phase III, double-blind, double-dummy, randomized, non-inferiority trial (CERTAIN-1) compared the efficacy and safety of cefepime–taniborbactam with meropenem for the treatment of hospitalized patients with cUTI, including pyelonephritis (NCT03840148) [14] and is summarized in Table 8. Overall, 661 patients were randomized (2:1) to receive either cefepime–taniborbactam (2 g/0.5 g) intravenously ( $t'$  2 h) every 8 h or meropenem (1 g) intravenously ( $t'$  0.5 h) every 8 h for 7 days with no oral stepdown therapy (Table 8). The treatment duration could be extended up to 14 days at the investigator's discretion for patients with bacteremia related to the infection. Dosing of the study medications was adjusted in patients with renal impairment, and the study medications were discontinued for patients with an eGFR of  $< 30$  mL/min/1.73 m<sup>2</sup>. Patients eligible for inclusion in the study were adults ( $\geq 18$  years of age) with a diagnosis of cUTI or acute pyelonephritis according to regulatory guidances [65] who required intravenous antibacterial therapy as initial treatment. Pyelonephritis patients had pyuria, at least one systemic symptom or sign of infection (e.g., nausea/vomiting, chills, fever  $> 38$  °C), and flank pain or costovertebral angle tenderness. cUTI patients had pyuria, at least one systemic symptom or sign of infection (e.g., nausea/vomiting, chills, fever  $> 38$  °C), at least one local symptom or sign of infection (e.g., dysuria, urinary frequency, urinary urgency or pelvic/suprapubic pain or tenderness), and one

complicating factor. Patients with prostatitis, a perinephric or renal abscess, prior renal transplantation, or a urinary catheter or foreign body (e.g., ureteric stent or nephrostomy tube) that could not be discontinued by study day 5 were excluded. For a detailed list of all exclusion criteria, please refer to the study protocol (available online as supplementary material for reference [14]).

In accordance with FDA and EMA guidance for evaluating drugs for cUTI, the primary outcome was evaluated at test of cure on trial days 19–23 in the microbiologic intention-to-treat (microITT) population, and included both microbiologic success and clinical success (composite success). Clinical success was defined as symptom resolution or return to baseline pre-morbid state, with no new cUTI symptoms, and no need for additional antibacterial therapy for cUTI. Microbiologic success was defined as a reduction in the colony count of the qualifying Gram-negative pathogen recovered at study entry to  $< 10^3$  CFUs/mL in a urine sample obtained at the test-of-cure visit. The microITT population included all randomized patients who had a positive baseline urine culture with at least  $10^5$  CFUs/mL of a qualifying Gram-negative pathogen against which both cefepime–taniborbactam and meropenem were active in vitro, and with a maximum of two microorganisms identified. The microITT population included 436 patients (66% of those enrolled in the trial), with the most common exclusion criterion being the absence of a baseline Gram-negative pathogen. To determine non-inferiority between cefepime–taniborbactam and meropenem, the non-inferiority margin was set at 15% of the lower boundary of the 95% confidence interval (CI: two-sided alpha level of 0.05), with 90% power to assess the primary outcome. If non-inferiority was demonstrated, a pre-specified superiority assessment was then performed. The microITT primary outcome (composite success) was 70.6% ( $n = 207/293$ ) and 58.0% ( $n = 83/143$ ) for the cefepime–taniborbactam and meropenem groups, respectively (Table 8), thus showing cefepime–taniborbactam was superior to meropenem with a treatment difference of 12.6 percentage points (95% CI 3.1–22.2;  $p = 0.009$ ). This was primarily driven by a statistically higher rate of microbiological success among patients randomized to cefepime–taniborbactam (78.2%) relative to meropenem (66.4%). Composite success among subgroups (age, infection type, disease severity, presence of bacteremia or systemic inflammatory response syndrome [SIRS] and renal impairment) at test of cure was consistent with the primary efficacy analysis.

The pathogens at baseline for the microITT group were primarily *Enterobacterales* ( $n = 418$ , 95.9%), including *E. coli* ( $n = 301$ , 69.0%), *K. pneumoniae* ( $n = 60$ , 13.8%), *P. mirabilis* ( $n = 20$ , 4.6%), and *Enterobacter cloacae* complex ( $n = 17$ , 3.9%); 4.1% of baseline pathogens were *P. aeruginosa* ( $n = 18$ ). Of the baseline pathogens in the cefepime–taniborbactam group, 22.5% ( $n = 66$ ) were

cefepime resistant, 25.9% ( $n = 76$ ) were ESBL-producing (defined as pathogens that had an MIC for ceftazidime, aztreonam, or cefepime of  $\geq 2$  mg/L) and 34.1% ( $n = 100$ ) were MDR (defined as non-susceptible to one or more agents in three or more antimicrobial categories). Of the baseline pathogens in the meropenem group, 21% ( $n = 30$ ) were cefepime resistant, 28% ( $n = 40$ ) were ESBL-producing, and 38.5% ( $n = 55$ ) were MDR. At test of cure, when stratified by pathogen, cefepime–taniborbactam had a higher number of patients with microbiological success compared with meropenem, except with *P. aeruginosa* and *K. pneumoniae* for which microbiological success was comparable between treatment arms. Clinical success in the microITT population according to pathogen was similar in both the cefepime–taniborbactam and meropenem groups.

Secondary endpoints included end of treatment (i.e.,  $\leq 24$  h after the last dose of a trial drug) and late follow-up (trial days 28–35) composite (microbiologic and clinical) success in the microITT group, and composite success in the extended microITT group (all patients in the microITT group plus patients with a baseline Gram-negative pathogen against which at least one trial drug was active in vitro) (Table 8). In the microITT population, the composite success at end of treatment was 89.1% ( $n = 261/293$ ) and 86% ( $n = 123/143$ ) for cefepime–taniborbactam and meropenem, respectively (treatment difference, 3.1 percentage points; 95% CI – 3.2 to 10.4). The end-of-treatment microbiologic success was 96.9% ( $n = 284/293$ ) for cefepime–taniborbactam, and 97.2% ( $n = 139/143$ ) for meropenem, and the end-of-treatment clinical success was 90.4% ( $n = 265/293$ ) for cefepime–taniborbactam and 88.8% ( $n = 127/143$ ) for meropenem. The composite success at late follow-up was 63.8% ( $n = 187/293$ ) for cefepime–taniborbactam, compared with 51.7% ( $n = 74/143$ ) for meropenem, with a treatment difference of 12.1 percentage points (95% CI 2.2–21.9). The late follow-up microbiologic success was 70.6% ( $n = 207/293$ ) for cefepime–taniborbactam and 62.9% ( $n = 90/143$ ) for meropenem, and the late follow-up clinical success was 81.2% ( $n = 238/293$ ) for cefepime–taniborbactam and 71.3% ( $n = 102/143$ ) for meropenem. In the extended microITT group, the composite success at test of cure was 70.8% ( $n = 216/305$ ) for cefepime–taniborbactam and 58.5% ( $n = 86/147$ ) for meropenem. Additionally, treatment with cefepime–taniborbactam resulted in composite success among seven of eight patients infected with CRE and eight of nine patients infected with carbapenemase-producing *Enterobacteriales* [66]. It should also be mentioned that no development of resistance was detected during the trial to either cefepime–taniborbactam or meropenem among the baseline pathogens. Based on the primary and secondary endpoint findings, the authors concluded that cefepime–taniborbactam was superior to meropenem for the treatment of

hospitalized patients with cUTI (including patients with acute pyelonephritis).

## 10 Adverse Events

The safety and tolerability of taniborbactam and cefepime–taniborbactam has been reported in one PK trial, and in two PK trials and one phase III clinical trial, respectively (Table 9). A PK study by Dowell et al. reported the safety and tolerability of taniborbactam compared with placebo, after administering a single dose (ascending intravenous doses ranging from 62.5 to 1500 mg [ $t' 2$  h]) in 48 healthy subjects, and as multiple ascending intravenous doses ranging from 250 to 750 mg every 8 h ( $t' 2$  h) over a period of 10 days in 36 healthy subjects (Table 9) [56]. No serious adverse events or deaths were reported, and no subjects withdrew from the study due to treatment-related adverse events. The most common drug-related adverse event reported in subjects receiving taniborbactam was headache. In the single-ascending dose group, two drug-related adverse events occurred; one participant in the taniborbactam 125 mg group experienced nausea, and one participant in the placebo group experienced a headache. Other adverse events reported in the pooled taniborbactam group, which the investigators deemed not related to treatment, included headache, migraine, abdominal pain, vomiting, viral upper respiratory tract infection, arthralgia, back pain, increased blood creatine phosphokinase, and increased hepatic enzymes. In the multiple ascending dose group, treatment-related adverse events in the pooled taniborbactam group included headache, nausea, dizziness, and diarrhea. Other adverse events reported that the investigator deemed not related to treatment with taniborbactam included constipation, dizziness, jaw pain, and phlebitis. Higher doses of taniborbactam were not associated with increased severity or frequency of treatment-related adverse events.

In a phase I PK study by Asempa et al., 20 healthy subjects received an intravenous dose of 2/0.5 g of cefepime–taniborbactam every 8 h ( $t' 2$  h) for a total of three doses [55]. No serious adverse events or deaths were reported and no subjects withdrew from the study due to a treatment-related adverse event. The most common adverse event reported was leukocytosis (experienced by six subjects). Other adverse events reported by two or more participants were headache, erythematous rash, dizziness, chills, hyperbilirubinemia, increased blood creatinine, and increased international normalized ratio.

In another PK study by Dowell et al., 33 healthy subjects with varying degrees of renal impairment ( $n = 8$  with normal renal function,  $n = 18$  with renal impairment and eGFRs ranging from 5.5 to 85 mL/min/1.73 m<sup>2</sup>, and  $n = 7$  receiving hemodialysis), received a single intravenous dose

**Table 9** Treatment-emergent adverse events reported for cefepime–taniborbactam

| Study (year)<br>[reference]             | Dose                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Adverse events reported (n, %)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|-----------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Asempa et al. (2023)<br>[55]            | Cefepime–taniborbactam 2/0.5 g IV<br>( <i>t'</i> 2 h) q8h × 3 doses                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Cefepime–taniborbactam ( <i>n</i> = 20)<br>Leukocytosis (6, 30) <sup>a</sup><br>Headache <sup>b</sup><br>Dizziness <sup>b</sup><br>Erythematous rash <sup>b</sup><br>Chills <sup>b</sup><br>Increased INR <sup>b</sup><br>Hyperbilirubinemia <sup>b</sup><br>Increased creatinine <sup>b</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| CERTAIN-1 Clinical<br>Trial (2024) [14] | Cefepime–taniborbactam 2/0.5 g IV<br>( <i>t'</i> 2 h) q8h × 7 days <sup>c</sup><br>Meropenem 1 g IV ( <i>t'</i> 30 mins) q8h<br>× 7 days <sup>c</sup>                                                                                                                                                                                                                                                                                                                                                                                                                            | Cefepime–taniborbactam ( <i>n</i> = 440)<br>Headache (27, 6.1) <sup>a</sup><br>Diarrhea (18, 4.1) <sup>a</sup><br>Constipation (14, 3.2) <sup>a</sup><br>Hypertension (10, 2.3) <sup>a</sup><br>Nausea (9, 2) <sup>a</sup><br>Abdominal distension (7, 1.6) <sup>a</sup><br>Anemia (7, 1.6) <sup>a</sup><br>Dizziness (7, 1.6) <sup>a</sup><br>Hypokalemia (7, 1.6) <sup>a</sup><br>Phlebitis (6, 1.4) <sup>a</sup><br>Vomiting (6, 1.4) <sup>a</sup><br>Cough (5, 1.1) <sup>a</sup><br>Pyrexia (5, 1.1) <sup>a</sup><br>Increased alanine aminotransferase (4, 0.9) <sup>a</sup><br>Vulvovaginal candidiasis (3, 0.7) <sup>a</sup><br>Discontinuation of trial drug (13, 3) <sup>a</sup><br>Serious adverse events (9, 2) <sup>a</sup><br>Serious adverse events related to trial drug (2, 0.5) <sup>a</sup> |
|                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Meropenem ( <i>n</i> = 217)<br>Headache (8, 3.7) <sup>a</sup><br>Diarrhea (5, 2.3) <sup>a</sup><br>Constipation (3, 1.4) <sup>a</sup><br>Hypertension (2, 0.9) <sup>a</sup><br>Nausea (2, 0.9) <sup>a</sup><br>Abdominal distension (3, 1.4) <sup>a</sup><br>Anemia (3, 1.4) <sup>a</sup><br>Dizziness (1, 0.5) <sup>a</sup><br>Hypokalemia (1, 0.5) <sup>a</sup><br>Phlebitis (1, 0.5) <sup>a</sup><br>Vomiting (1, 0.5) <sup>a</sup><br>Cough (2, 0.9) <sup>a</sup><br>Pyrexia (3, 1.4) <sup>a</sup><br>Increased alanine aminotransferase (5, 2.3) <sup>a</sup><br>Vulvovaginal candidiasis (3, 1.4) <sup>a</sup><br>Discontinuation of trial drug (2, 0.9) <sup>a</sup><br>Serious adverse events (4, 1.8) <sup>a</sup><br>Serious adverse events related to trial drug (0, 0) <sup>a</sup>               |
| Dowell et al. (2021)<br>[56]            | Single-ascending IV dose group:<br>Taniborbactam 62.5 mg IV ( <i>t'</i> 2 h)<br>× 1<br>Taniborbactam 125 mg IV ( <i>t'</i> 2 h)<br>× 1<br>Taniborbactam 250 mg IV ( <i>t'</i> 2 h)<br>× 1<br>Taniborbactam 500 mg IV ( <i>t'</i> 2 h)<br>× 1<br>Taniborbactam 1000 mg IV ( <i>t'</i> 2 h)<br>× 1<br>Taniborbactam 1500 mg IV ( <i>t'</i> 2 h)<br>× 1<br>Multiple-ascending IV dose group:<br>Taniborbactam 250 mg IV ( <i>t'</i> 2 h)<br>q8h × 10 days<br>Taniborbactam 500 mg IV ( <i>t'</i> 2 h)<br>q8h × 10 days<br>Taniborbactam 750 mg IV ( <i>t'</i> 2 h)<br>q8h × 10 days | Taniborbactam <sup>d</sup> ( <i>n</i> = 36)<br>Headache (1, 2.8) <sup>a</sup><br>Migraine (1, 2.8) <sup>a</sup><br>Abdominal pain (1, 2.8) <sup>a</sup><br>Nausea (1, 2.8) <sup>a</sup><br>Vomiting (1, 2.8) <sup>a</sup><br>Viral URTI (1, 2.8) <sup>a</sup><br>Arthralgia (1, 2.8) <sup>a</sup><br>Back pain (1, 2.8) <sup>a</sup><br>Increased blood CPK (1, 2.8) <sup>a</sup><br>Increased hepatic enzymes (1, 2.8) <sup>a</sup><br>Taniborbactam <sup>e</sup> ( <i>n</i> = 27)<br>Headache (3, 11.1) <sup>a</sup><br>Nausea (2, 7.4) <sup>a</sup><br>Constipation (2, 7.4) <sup>a</sup><br>Diarrhea (1, 3.7) <sup>a</sup><br>Dizziness (1, 3.7) <sup>a</sup><br>Jaw pain (1, 3.7) <sup>a</sup><br>Phlebitis (1, 3.7) <sup>a</sup>                                                                        |
|                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Placebo ( <i>n</i> = 12)<br>Headache (2, 16.7) <sup>a</sup><br>Viral upper respiratory tract (1, 8.3) <sup>a</sup><br>Pharyngitis (1, 8.3) <sup>a</sup><br>Arthralgia (1, 8.3) <sup>a</sup><br>Placebo ( <i>n</i> = 9)<br>Headache (2, 22.2) <sup>a</sup><br>Nausea (1, 11.1) <sup>a</sup><br>Dry mouth (1, 11.1) <sup>a</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |

**Table 9** (continued)

| Study (year)<br>[reference]  | Dose                                                       | Adverse events reported (n, %)                                                                                                                                                                                                                                                                            |
|------------------------------|------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Dowell et al. (2022)<br>[57] | Cefepime–taniborbactam 2/0.5 g IV<br>( <i>t</i> ' 2 h) × 1 | Cefepime–taniborbactam ( <i>n</i> = 33)<br>Headache <sup>b</sup><br>Migraine <sup>b</sup><br>Diarrhea <sup>b</sup><br>Upper abdominal pain <sup>b</sup><br>Jaw pain <sup>b</sup><br>Drug withdrawal syndrome (caffeine withdrawal) <sup>b</sup><br><i>Clostridioides difficile</i> infection <sup>b</sup> |

CPK creatine phosphokinase, INR international normalized ratio, IV intravenous, *n* number of participants, URTI upper respiratory tract infection

<sup>a</sup>Number of participants who experienced an adverse event, percentage of participants who experienced an adverse event

<sup>b</sup>Frequency of adverse event not specified

<sup>c</sup>Treatment could be extended up to 14 days in the case of bacteremia

<sup>d</sup>Pooled taniborbactam adverse event incidence across all taniborbactam groups in single-ascending IV dose study

<sup>e</sup>Pooled taniborbactam adverse event incidence across all taniborbactam groups in multiple-ascending IV dose study

of cefepime–taniborbactam 2 g/0.5 g (*t*' 2 h) [57]. Hemodialysis subjects received doses both on and off hemodialysis. No serious adverse events or deaths were reported, and no subject withdrew from the study due to drug-related adverse events. Overall, cefepime–taniborbactam was well-tolerated by subjects and the majority of adverse events reported were mild. Seven subjects in total experienced eight adverse events related to treatment, including headache, migraine, diarrhea, upper abdominal pain, jaw pain, drug withdrawal syndrome (caffeine withdrawal), and *Clostridioides difficile* infection. No adverse events related to hematology, chemistry, urinalysis, or coagulation changes were reported and no evidence of renal toxicity was observed. There was no evident relationship with reduced eGFR or timing of hemodialysis that was associated with an increased incidence or severity of treatment-associated adverse events.

In the CERTAIN-1 phase III clinical trial, cefepime–taniborbactam was compared with meropenem for the treatment of cUTI and acute pyelonephritis [14]. Adverse events during treatment occurred in 35.5% (156/440) of patients in the cefepime–taniborbactam group, and in 29% (63/217) of participants in the meropenem group (Table 9). The most common treatment-emergent adverse events reported in the cefepime–taniborbactam group included headache, diarrhea, constipation, nausea, and hypertension. No participants died in the meropenem group, but one participant died in the cefepime–taniborbactam group following discontinuation of treatment and two subsequent hospitalizations for hypoglycemia; however, the investigator deemed the death was not related to use of the trial drug. There were numerically more treatment-emergent adverse events that led to discontinuation of the study in the cefepime–taniborbactam group compared with

the meropenem group and these discontinuations were heterogenous in nature. Treatment-emergent adverse effects that led to discontinuation of 13 patients in the cefepime–taniborbactam group included gastrointestinal disturbances, generalized edema, infections (coronavirus disease 2019 [COVID-19], endocarditis, gastrointestinal candidiasis, renal abscess, tubo-ovarian abscess), dizziness/nausea related to procedural complications, muscle spasms, urticaria, angioedema, rash, and thrombophlebitis. In the meropenem group, two subjects discontinued the study due to treatment-emergent adverse events, which included tubo-ovarian abscess and urticaria. Despite the numerically higher incidence of discontinuation of the trial due to treatment with cefepime–taniborbactam, the researchers still reported that cefepime–taniborbactam had a similar adverse effect profile to meropenem. The majority of adverse events that occurred across both groups were mild or moderate in nature. Two serious treatment-related adverse events were reported in the cefepime–taniborbactam group (angioedema and gastrointestinal candidiasis), and no serious treatment-related adverse events were reported in the meropenem group.

Overall, cefepime–taniborbactam appears to be well tolerated in both healthy subjects and patients with infectious diseases. The majority of available safety and tolerability studies to date report headache and gastrointestinal upset as the most common drug-related adverse effects associated with cefepime–taniborbactam use, with minimal serious treatment-related adverse events reported. It is important to note that the safety and tolerability data are based on a relatively limited number of patients, thus more safety data are needed from postmarketing surveillance studies.

## 11 Drug Interactions

Currently, minimal data are available on specific drug–drug interactions with cefepime–taniborbactam. It has been reported that taniborbactam is neither a significant inducer nor inhibitor of the cytochrome P450 (CYP) 450 enzymes [67]. Additionally, taniborbactam does not appear to be an inhibitor or substrate of relevant transporters and has no significant hepatic metabolism in isolated hepatocytes [67]. In a phase I study evaluating the PK of taniborbactam in combination with cefepime, the results showed there were no drug–drug interactions when coadministered [58]. The same PK study assessed the coadministration of cefepime–taniborbactam with oral metronidazole, and the results also showed there were no interactions when coadministered [58]. Cefepime administration on its own is involved with few drug–drug interactions. Concomitant use of cefepime with nephrotoxic drugs such as aminoglycosides or high-dose diuretics may require increased monitoring of renal function due to the increased risk of nephrotoxicity [68].

## 12 Place in Therapy

Cefepime–taniborbactam is active *in vitro* against most CRE and CRPA, including both carbapenemase-producing and carbapenemase-non-producing isolates, as well as many MDR, ceftazidime-avibactam-resistant, meropenem-vaborbactam-resistant, and ceftolozane-tazobactam-resistant *Enterobacterales* and *P. aeruginosa* isolates. Cefepime–taniborbactam is the first BL-BLI that possesses activity against MBL-producing isolates (NDM and VIM, not IMP), distinguishing its spectrum of activity from those of recently marketed BL-BLI combinations (ceftazidime-avibactam, imipenem-relebactam, meropenem-vaborbactam, but not the recently approved aztreonam-avibactam, which, unlike the three comparators mentioned, possesses activity versus MBL-producing isolates). Cefepime–taniborbactam administered at 2 g/0.5 g intravenously (*t*' 2 h) every 8 h was found to be superior to meropenem in a phase III study for the treatment of cUTI (including acute pyelonephritis), while demonstrating similar safety compared with meropenem [14]. Cefepime–taniborbactam has been shown to penetrate into ELF and alveolar macrophages in humans [55]. Cefepime–taniborbactam will be studied as a potential treatment option for HABP and VABP in the near future [67]. Even though there are currently no published human studies investigating cefepime–taniborbactam efficacy against HABP and VABP, cefepime–taniborbactam has been shown to have *in vivo* efficacy against cefepime–non-susceptible *Enterobacterales* species and *P. aeruginosa* in a translational murine pneumonia model [61].

Cefepime–taniborbactam is anticipated to play an important role in the treatment of infections caused by MDR Gram-negative bacteria, including *Enterobacterales* and *P. aeruginosa*, that demonstrate phenotypic resistance to cefepime and/or carbapenems. In particular, it may prove useful in the treatment of infections caused by isolates that harbor an MBL (NDM, VIM) enzyme. It may also have a role as an empiric antimicrobial option for patients who have risk factors (e.g., colonized, previous infection, recent antibiotics, immunocompromised, recent travel to an endemic CPE region) for infection with an MDR Gram-negative pathogen. However, it is important to note that the efficacy of cefepime–taniborbactam in the treatment of infections caused by carbapenem-resistant and MBL-producing organisms has not been rigorously assessed in clinical trials [14].

As with all novel BL-BLI agents, care should be taken in addressing dosage regimens in the context of infections that are MDR, and in critically ill patients, where such new agents are highly required, while accounting for host factors that may hamper the optimal target attainment of  $\beta$ -lactams [55, 57]. Lastly, as most cephalosporin-based regimens primarily target PBP3, care should be exerted when sequential treatments are used, as cross resistance arising from PBP3 mutations, although rare, may arise [27, 40]. Thus, we believe that carefully designed safety and efficacy studies are required to determine future indications for cefepime–taniborbactam use beyond cUTI.

## Declarations

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**Authors' contribution** GGZ was involved in the design and concept of the entire manuscript and drafting all sections, and also acted as the senior and corresponding author. CM, SM, and JAK were involved in the design and concept of the entire manuscript and drafting all sections. CKL and SZ were involved in the design and concept of the entire manuscript and drafting the Pharmacokinetic and Pharmacodynamic sections. DR and FS were involved in the design and concept of the entire manuscript and drafting the Chemistry and Microbiology sections. DB was involved in the design and concept of the entire manuscript and drafting the Introduction and Mechanism of Action/Resistance sections. HJA was involved in the design and concept of the entire manuscript and drafting the Microbiology section. PLW was involved in the design and concept of the entire manuscript and drafting the Animal Models section. AW was involved in the design and concept of the entire manuscript and drafting the clinical trials and adverse effects sections. NI was involved in the design and concept of the entire manuscript and drafting the Adverse Effects, Drug Interactions and Place in Therapy sections. NC was involved in the design and concept of the entire manuscript and drafting the Clinical Trials section. DN was involved in the design and concept of the entire manuscript and drafting the Pharmacodynamics section. CT was involved in the design and concept of the entire manuscript and drafting the Place in Therapy section.

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