# Examining the antimicrobial activity of cefepime-taniborbactam (formerly cefepime/VNRX-5133) against *Burkholderia* species isolated from cystic fibrosis patients in the United States

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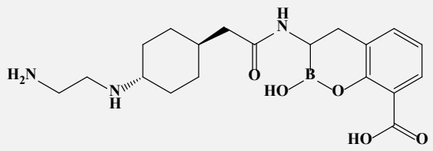
## Abstract

**Background:** *Burkholderia cepacia* complex (Bcc), a group of >20 related species, and *B. gladioli* are opportunistic human pathogens that cause chronic infections in people with cystic fibrosis (CF) or compromised immune systems. Ceftazidime and trimethoprim-sulfamethoxazole are first-line agents used to treat infections due to *Burkholderia* spp. However, these species have developed resistance to many antibiotics, including first-line therapies. β-lactam resistance in *Burkholderia* species is largely mediated by PenA-like chromosomal class A β-lactamases. A novel investigational β-lactam/β-lactamase inhibitor combination, cefepime-taniborbactam (formerly cefepime/VNRX-5133) demonstrates potent antimicrobial activity against gram-negative bacteria producing class A, B, C, and D β-lactamases. The activity of cefepime-taniborbactam was investigated against Bcc and *B. gladioli*; moreover, the biochemical activity of taniborbactam against the PenA1 carbapenemase was evaluated.
**Methods:** CLSI-based agar dilution antimicrobial susceptibility testing using cefepime and cefepime combined with taniborbactam at 4 mg/L was conducted against a curated panel of 150 *Burkholderia* species obtained from the *Burkholderia cepacia* Research Laboratory and Repository. Isolates were recovered from respiratory specimens from 150 different individuals with CF receiving care in 68 cities throughout 36 states within the United States. PenA1 was purified for steady-state kinetic assays.
**Results:** The addition of taniborbactam shifted cefepime MICs towards the provisionally susceptible range against this highly drug-resistant collection of *Burkholderia* species; the $MIC_{50}$ decreased by 4-fold from 32 µg/mL to 8 µg/mL. Based on our previous analysis of first-line agents in this strain panel, cefepime-taniborbactam was similarly active compared to ceftazidime and trimethoprim-sulfamethoxazole, with 39%, 36%, and 37% of isolates resistant or provisionally resistant, respectively. Taniborbactam demonstrated potent inactivation of the *B. multivorans* PenA1 with a $K_{i\ app}$ value of 0.40 ± 0.04 µM that is comparable to the previously reported value for avibactam ($K_{i\ app}$ = 0.5 µM).
**Conclusions:** The addition of taniborbactam lowered cefepime MICs overall against highly drug-resistant *Burkholderia* species. Cefepime-taniborbactam had similar coverage within the strain set compared to first-line agents, ceftazidime and trimethoprim-sulfamethoxazole. Taniborbactam was a potent inactivator of PenA1. Cefepime-taniborbactam may be beneficial as a potential alternative to first-line agents against *Burkholderia* spp.

## Background

- Ceftazidime and trimethoprim-sulfamethoxazole are first-line agents used to treat infections caused by the *Burkholderia cepacia* complex (Bcc) and *B. gladioli.*
- Bcc and *B. gladioli* possess a PenA-like chromosomal class A β-lactamase, which largely contributes towards β-lactam resistance among these organisms.
- β-Lactamases are enzymes that hydrolyze β-lactam antibiotics, and inactivate them, making the drug ineffective.
- Taniborbactam (formerly VNRX-5133) is a novel boronic acid β-lactamase inhibitor that is in development in combination with cefepime. (1)

**Taniborbactam (VNRX-5133)**



**Goal:** Determine the antimicrobial activity of cefepime-taniborbactam against a panel of 150 Bcc and *B. gladioli* and determine the inhibitory potency of taniborbactam against PenA1 from *B. multivorans* ATCC 17616.

## Results

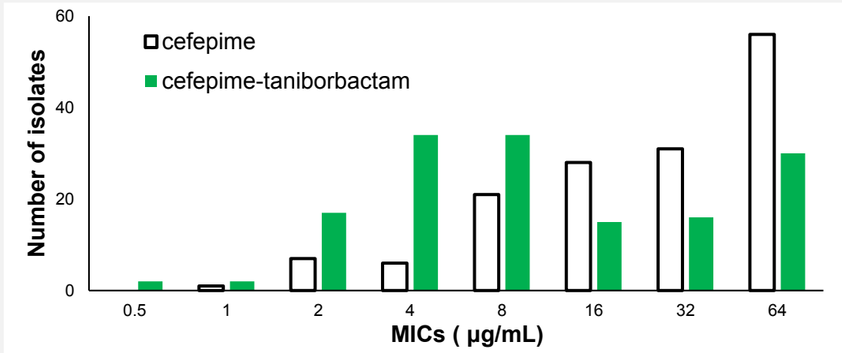



**Figure 1.** Agar dilution susceptibility testing results for cefepime alone (white bars) compared to cefepime combined with taniborbactam (green bars). The addition of taniborbactam reduced the cefepime $MIC_{50}$ from 32 µg/mL to 8 µg/mL.

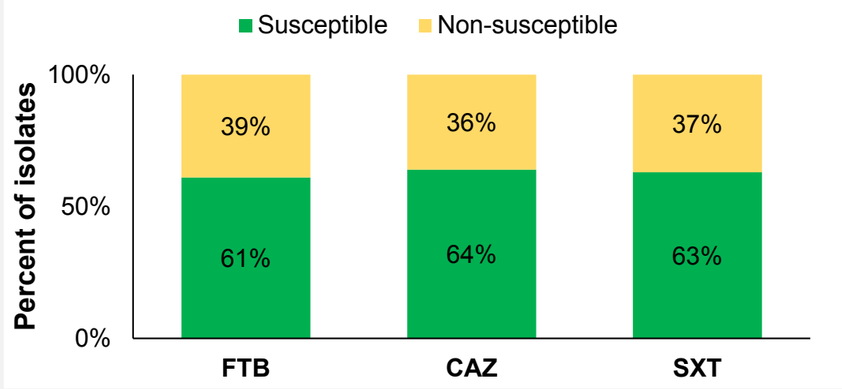



**Figure 2.** Comparison of the percentage of isolates that are susceptible (green) and non-susceptible (yellow) to cefepime-taniborbactam (FTB), ceftazidime (CAZ) (2), and trimethoprim-sulfamethoxazole (SXT) (2). Breakpoints for FTB for Bcc are not established, thus *Pseudomonas aeruginosa* breakpoints for FEP were provisionally used (S ≤ 8; non-S ≥ 16) for FTB. The CLSI breakpoints for CAZ and SXT against Bcc are S ≤ 8; non-S ≥ 16 and S ≤ 2/38; non-S ≥ 4/76, respectively. S = susceptible

**Table 1.** Steady-state inhibitor kinetic values against *B. multivorans* PenA1

| Parameter | Taniborbactam | Avibactam [2] |
|---|---|---|
| $K_{i\ app}$ | 400 ± 40 nM | 500 ± 50 nM |
| $k_2/K$ | 8.8 ± 1.1 × $10^4$ $M^{-1}s^{-1}$ | 2 ± 1 × $10^6$ $M^{-1}s^{-1}$ |
| $k_{off}$ | 2 ± 1 × $10^{-4}$ $s^{-1}$ | 2 ± 1 × $10^{-3}$ $s^{-1}$ |
| $t_{1/2}$ | 58 min | 5.8 min |

Individual data points were collected in triplicate, while all experiments were completed at a minimum in duplicate. Nitrocefin was used as the reporter substrate at a fixed concentration of 100 µM.

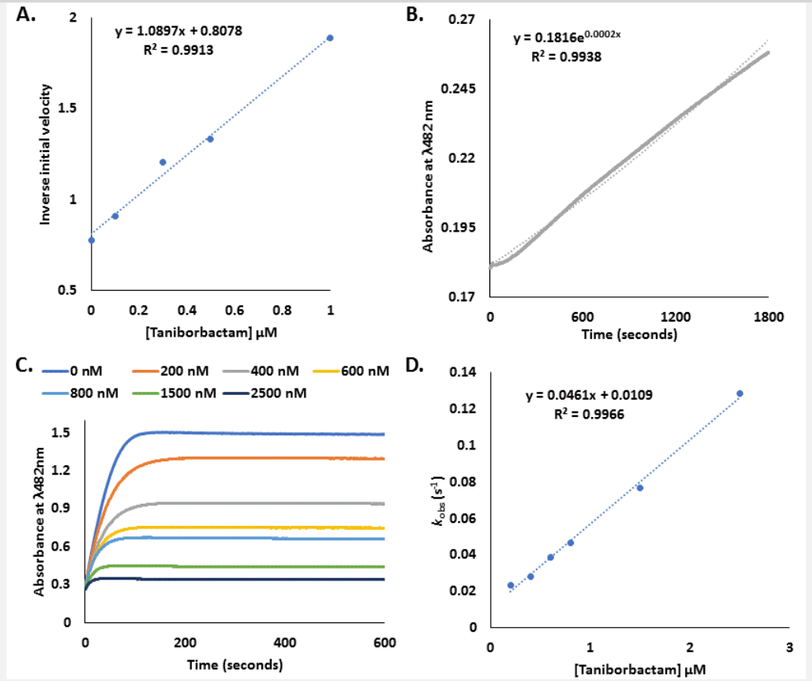



**Figure 4.** Steady-state kinetics of PenA1 and TAN, where nitrocefin was used as a reporter substrate at a fixed concentration of 100 µM. **A.** Determination of $K_{i\ app}$ for PenA1 and taniborbactam (TAN). **B.** Determination of $k_{off}$ for PenA1 and TAN; 10× $K_{i\ app}$ of TAN for PenA1 was used. **C.** Inhibition of PenA1 activity over time at varying [TAN]. **D.** Plots in panel C were fit to equation 1 to obtain $k_{obs}$; the slope of the line represents the $k_2/K$ value of TAN for PenA1.

## Conclusions

- The addition of taniborbactam to cefepime lowered cefepime MIC against Bcc and *B. gladioli.* Taniborbactam was a potent inactivator of PenA1.
- Provisional susceptibility rates for cefepime-taniborbactam were similar to susceptibility rates for ceftazidime and trimethoprim-sulfamethoxazole against Bcc and *B. gladioli*.
- Cefepime-taniborbactam possesses promising potential to be an alternative treatment for infections caused by Bcc and *B. gladioli.*

## References

**1.** Hamrick JC, et al. 2020. *VNRX-5133 (Taniborbactam), a broad-spectrum inhibitor of serine- and metallo-β-lactamases, restores activity of cefepime in Enterobacterales and Pseudomonas aeruginosa.* Antimicrob Agents Chemother 64.
**2.** Papp-Wallace, K.M., et al., *Overcoming an extremely drug resistant (XDR) pathogen: Avibactam restores susceptibility to ceftazidime for Burkholderia cepacia complex isolates from cystic fibrosis patients.* ACS Infect Dis, 2017. **3**(7): p. 502-511.

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