DISCLOSURES

This project began with federal funds from the National Institute of Allergy and Infectious Diseases, National Institutes of Health, Department of Health and Human Services, under Contract No. HHSN272201300019C, and The Wellcome Trust under Award No. 360G-Wellcome-101999/Z/13/Z, and continues with federal funds from the Department of Health and Human Services; Office of the Assistant Secretary for Preparedness and Response, Biomedical Advanced Research and Development Authority, under Contract No. HHSO100201900007C.
INTRODUCTION
Taniborbactam is a novel β-lactamase-based broad-spectrum β-lactamase inhibitor that displays activity against several β-lactamases and most metallo-β-lactamases (Ambler Classes A, B, C, and D) [1]. Taniborbactam restores the activity of cefepime against cephalosporin- and carbapenem-resistant Enterobacterales with Pseudomonas aeruginosa. The activity of the investigational combination cefepime-taniborbactam and comparator agents was evaluated against a global collection of clinical isolates of Enterobacterales and P. aeruginosa defined with β-lactamase carriage.

MATERIALS & METHODS
13,731 Enterobacterales and 4,619 P. aeruginosa isolates collected from 56 countries in 2018-2020 were a part of this study. MICs of cefepime with taniborbactam fixed at 4 mg/L and comparators were determined by the ISO 20776-1:2019 method [2] and interpreted using 2021 EUCAST breakpoints [3]. The MICs of cefepime-taniborbactam were determined to be ≤0.12 mg/L for Enterobacterales and ≤1 mg/L for P. aeruginosa. Organisms with cefepime-taniborbactam MIC ≤1 mg/L were classified as susceptible, ≤4 mg/L as intermediate (I), and ≥8 mg/L as resistant (R) to cefepime-taniborbactam. MBL (n=229) and OXA-48-like (n=168) with 100% (MIC ≤1 mg/L) and 98.2% (MIC ≤4 mg/L) of the organisms inhibited at ≤8 mg/L, respectively (Table 1 and Figure 3). For the ESBLs, the % inhibited at ≤8 mg/L was 99.3%. The addition on taniborbactam to cefepime shifted the mode of the MIC distribution against non-IMP carbapenemase-carrying P. aeruginosa from 8 mg/L for cefepime alone (Figure 3).

RESULTS
• Against Enterobacterales carrying carbapenemes (n=627), cefepime-taniborbactam was the most active agent tested, with 90.7% of isolates inhibited at ≤8 mg/L (95.2% inhibited at ≤16 mg/L) and an MIC₅₀ of 8 mg/L (Table 1 and Figure 1).

• The ability of taniborbactam to inhibit MBLs was clearly evident when the MIC of taniborbactam was ≤8 mg/L, 76.0% of the population was inhibited at the provisional breakpoint of ≤8 mg/L (87.6% inhibited at ≤16 mg/L), a far greater proportion than the comparator carbapenem (n=34) with 6.2% (MIC ≤8 mg/L).

• Cefepime-taniborbactam was also the most active agent examined versus Enterobacterales harboring the seer-carbapenemases KPC (n=207) and OXA-48-like (n=168) with 100% (MIC ≤4 mg/L) and 98.2% (MIC ≤4 mg/L) of the organisms inhibited at ≤8 mg/L, respectively (Table 1 and Figure 3). For the ESBLs, the % inhibited at ≤8 mg/L was 98.8%.

• The provisional breakpoint of 8 mg/L was fixed for acquisition of β-lactamase genes by PCR and genome sequencing, while those with defined β-lactamase activity were assigned to ESBL and/or AmpC-type enzymes. ESBLs (n=534) possessing cefepime-taniborbactam MIC ≤16 mg/L were tested against cefepime and cefepime-taniborbactam.

• Cefepime and cefepime-taniborbactam MIC value frequency distribution against carbapenemase-carrying P. aeruginosa (n=216) is presented in Figure 2. The addition of taniborbactam to cefepime greatly enhances its in vitro activity against both Enterobacterales and P. aeruginosa carrying seer- and metallo-β-lactamases. These findings support the continued development of cefepime-taniborbactam as a potential new therapeutic agent for use against Gram-negative pathogens resistant to currently available antimicrobial agents.

CONCLUSIONS
The addition of taniborbactam to cefepime has been shown to enhance its in vitro activity against both Enterobacterales and P. aeruginosa carrying seer- and metallo-β-lactamases. These findings support the continued development of cefepime-taniborbactam as a potential new therapeutic agent for use against Gram-negative pathogens resistant to currently available antimicrobial agents.

REFERENCES

Table 1. In vitro activity of cefepime-taniborbactam and comparator agents against molecularly characterized isolates of Enterobacterales and P. aeruginosa

<table>
<thead>
<tr>
<th>Carbapenemase</th>
<th>Organism/Genotype</th>
<th>MIC ₅₀ (mg/L)</th>
<th>Percent susceptible (%)</th>
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</table>
| CT            | Organisms with cefepime-taniborbactam MIC ≤1 mg/L were classified as susceptible, ≤4 mg/L as intermediate (I), and ≥8 mg/L as resistant (R) to cefepime-taniborbactam. MBL (n=229) and OXA-48-like (n=168) with 100% (MIC ≤1 mg/L) and 98.2% (MIC ≤4 mg/L) of the organisms inhibited at ≤8 mg/L, respectively (Table 1 and Figure 3). For the ESBLs, the % inhibited at ≤8 mg/L was 99.3%. The addition on taniborbactam to cefepime shifted the mode of the MIC distribution against non-IMP carbapenemase-carrying P. aeruginosa from 8 mg/L for cefepime alone (Figure 3).

Figure 1. Cefepime and cefepime-taniborbactam MIC value frequency distribution against carbapenemase-carrying Enterobacterales (n=627). Cefepime-taniborbactam was the most active agent tested, with 90.7% of isolates inhibited at ≤8 mg/L (95.2% inhibited at ≤16 mg/L) and an MIC₅₀ of 8 mg/L (Table 1 and Figure 1).

Figure 2. Percentage of isolates from various Enterobacterales genotypes susceptible to cefepime-taniborbactam and comparator agents. Cefepime-taniborbactam is the most active agent tested, with 90.7% of isolates inhibited at ≤8 mg/L (95.2% inhibited at ≤16 mg/L) and an MIC₅₀ of 8 mg/L (Table 1 and Figure 1).