BOS-228 (formerly LY828, Novartis) is a potent new generation monobactam antibiotic active against carbapenem-resistant Enterobacteriaceae (CRE), a CDC Urgent Threat and WHO Critical Threat when resistance is caused by the production of serine beta-lactamases (SBLs) and/or metallo beta-lactamases (MBLs). Monobactams are important antibiotics due to their intrinsic stability to MBLs. Existing first generation monobactams such as aztreonam have limited clinical utility against MBL-producing CRE because they are susceptible to serine BLs that are often co-expressed in clinical isolates [1]. BOS-228 was identified in a medicinal chemistry program undertaken to generate monobactams with enhanced stability to SBLs. Thus, BOS-228 is differentiated from not just monobactams, but all currently approved beta-lactams in that it represents a potential single agent therapy effective against CRE that express both SBLs and MBLs. BOS-228 has completed Phase 1 clinical trials [2]. BOS-228 was licensed to Boston Pharmaceuticals in late-2018 and will be advanced to late development clinical trials.

RESULTS

BOS-228 showed potent in vitro activity against CRE, with MIC<sub>90</sub> values of 0.5/1 µg/mL for all CRE isolates (Table 2, Table 3).

The MIC<sub>90</sub> value was 1 µg/mL for isolates producing MBL or serine (KPC) carbapenemases, and 2 µg/mL for isolates producing OXA-48-like enzymes (Table 1).

Based on MIC<sub>90</sub> values, BOS-228 was the most potent agent tested against CRE, including MBL-positive isolates and those carrying multiple carbapenemases, regardless of carbapenemase type (Table 2, Figure 2).

Unlike ceftazidime-avibactam, BOS-228 exhibited in vitro activity against MBL-producers, including NDM, IMP and VIM, inhibiting 97.5% of variants at an MIC of ≤0.03 µg/mL (Table 2, Figure 3).

CONCLUSIONS

BOS-228 demonstrated potent in vitro activity against CRE, including KPC-, MBL-, and OXA-producing isolates.

BOS-228 also retained activity against CRE with resistance mediated by non-carbapenemase mechanisms, presumably including permeability defects.

BOS-228, as a novel single agent monobactam, has potential to treat Enterobacteriaceae infections including those caused by MBL- and SBL-expressing CRE.

REFERENCES


Table 1. Distribution of resistance mechanisms among carbapenem-resistant Enterobacteriaceae (CRE) by species

Table 2. In vitro activity of BOS-228 and comparator antimicrobials against 850 carbapenemase-producing CRE