The Novel β-lactamase Inhibitor ETX2514 Restores Sublactam Activity against Recent, Globally Diverse Clinical Isolates of Acinetobacter baumannii calcoaceticus Complex Isolates

S. McLeod1, M. Huband2, Y. Edah3, R. Tommasi1, and A. Miller1
1Entasis Therapeutics, Waltham, MA, USA and 2JMI Laboratories, North Liberty, IA USA

Background
ETX2514 is a novel, diazabicyclooctenone β-lactamase inhibitor with broad-spectrum activity against class A, C and D serine β-lactase containing (ABC) organisms. ETX2514, combined with sublactam (SUL-ETX2514) is currently in clinical development for the treatment of infections caused by Acinetobacter baumannii calcoaceticus complex (ABC) organisms. ABC can cause severe infections that are especially difficult to treat due to drug resistance and lack of effective treatments. Multiple public health agencies have highlighted ABC infections as among the most urgent threats to global health due to the rapid rise in resistance caused by β-lactamase producers.

Methods
The minimum inhibitory concentration (MIC) for each strain was determined following Clinical and Laboratory Standards Institute (CLSI) guidelines, and data analysis was performed using CLSI testing criteria. ETX2514-SUL was tested as a selection of sublactam in the presence of a fixed concentration of ETX2514. ETX2514 is a novel, diazabicyclooctenone BLI from a series of diazabicyclooctene β-lactamase inhibitors (DABIOs) currently in Phase 3 clinical development for the treatment of antibiotic-resistant infections caused by ABC. ETX2514 is a novel BLI with antibacterial activity against ABC isolates from China and Latin America was performed at JMI laboratories. The addition of ETX2514 decreased the sulbactam MIC90 from 64 to 2 mg/L against the Chinese isolates, which exhibited high levels of resistance to other antibiotics, including 78% ipemipenem (IPM)-resistance. The addition of ETX2514 decreased the sulbactam MIC90 from >64 to 8 mg/L.

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Results
ETX2514-SUL was highly active against these diverse collections of ABC isolates, regardless of their resistance determinants. The addition of 4 mg/L ETX2514 to SUL-ETX2514 increased the sublactam MIC90 to 2 mg/L, against all ABC isolates, which exhibited high levels of resistance to other antibiotics, including 78% IPM-resistance. The addition of ETX2514 decreased the sulbactam MIC90 from >64 to 8 mg/L. The activity of ETX2514-SUL was also measured against the A. baumannii complex panel from the CDC & FDA Antibiotic Resistance Isolate Bank. A. baumannii complex panel was obtained from the CDC & FDA Antibiotic Resistance Isolate Bank.


Conclusions
ETX2514-SUL demonstrated potent antibacterial activity against geometrically diverse, recent, multidrug-resistant ABC isolates. These data support the continued development of ETX2514-SUL as a promising new agent for the treatment of antibiotic-resistant infections caused by ABC.

55 A. baumannii were collected during 2017 from ten medical centers in six Latin American countries (Argentina, Brazil, Chile, Costa Rica, Mexico and Panama). Isolates represent a variety of infection types including bloodstream (n=23), pneumonia in hospitalized patients (n=66), and skin and soft tissue (n=12).

ETX2514 Restores Sublactam Activity against A. baumannii Colonized from China

101 A. baumannii were collected during 2013 from Chinese medical centers in 7 cities (Hankou, Hangzhou, Jinan, Shanghai, Shenyang and Wuhan and Zhengzhou). Isolates represent a variety of infection types including bloodstream (n=23), pneumonia in hospitalized patients (n=66), and skin and soft tissue (n=12).

ETX2514 Restores Sublactam Activity against A. baumannii Colonized from Latin America

The A. baumannii baumannii Panel was obtained from the CDC and FDA Antibiotic Resistance (AR) isolate bank. This panel is comprised of 41 sequenced multidrug-resistant ABC organisms that were chosen to represent a diversity of antimicrobial susceptibilities.

References

Conclusion
ETX2514 restored sublactam antibacterial activity against a collection of recent ABC clinical isolates from China and Latin America with MIC90 values of 2 mg/L and 0.5 mg/L, respectively. This panel represents sublactam antibacterial activity against the multidrug-resistant CDC & FDA ARIs isolate Panel. These data support further development of ETX2514 in combination with sublactam for the treatment of infections caused by multidrug-resistant A. baumannii.