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O1060 Pharmacokinetics-pharmacodynamics of the novel beta-lactamase inhibitor GT-055 in combination with the siderophore cephalosporin GT-1

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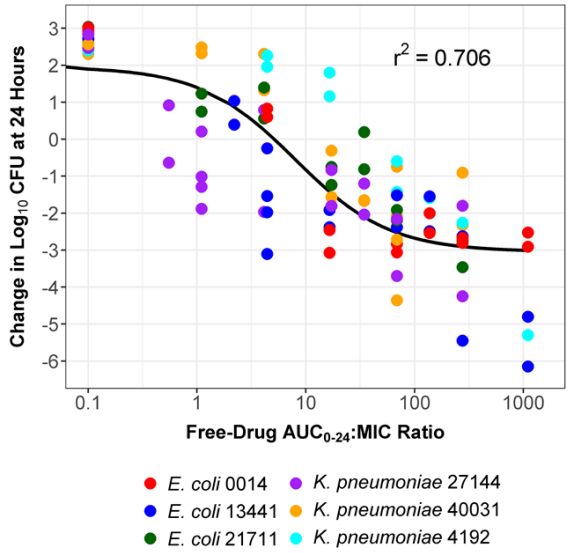
Background: GT-055 (formerly LCB18-055) is a novel beta-lactamase inhibitor (BLI) with *in vitro* activity against a variety of beta-lactamase enzymes. When GT-055 is paired with the novel siderophore cephalosporin, GT-1 (formerly LCB10-0200), the BLI has been shown to improve the *in vitro* activity up to 8-fold against a variety of Gram-negative organisms including Enterobacteriaceae. The objective of the studies described herein was to identify the pharmacokinetic-pharmacodynamic (PK-PD) index associated with the efficacy of GT-055, as well as determine the magnitude of the PK-PD index associated with net bacterial stasis, 1- and 2-$\log_{10}$ colony forming unit (CFU) reductions from baseline.

Materials/methods: 24 hour one-compartment *in vitro* infection models were utilized in all studies. GT-055 dose-fractionation (DFS) and dose-ranging studies (DRS) were conducted utilizing GT-1 doses of 1 or 2 g administered every 8 hours (q8h). One isolate was evaluated in the DFS, for which total daily doses of GT-055 (0.09, 0.38, 0.75, and 1.5 g) were fractionated into regimens administered every 4, 6, 8, or 12 hours. In the DRS, six Enterobacteriaceae isolates known to express a variety of beta-lactamase enzymes were exposed to GT1 (2g q8h) in combination with a range of GT-055 doses (0.008 to 2 g q8h). Data from the DFS and DRS were pooled and relationships between change in $\log_{10}$ CFU/mL from baseline at 24 hours and GT-055 area under the concentration time curve (AUC), maximum concentration (C_{max}) and percent time above a variety of concentration thresholds (%T>Ct), were determined.

Results: The data generated in the DFS suggested both GT-055 AUC:GT1 minimum inhibitory concentration (MIC) (potentiated at a 1:1 ratio of beta-lactam:BLI) ratio, and %T> GT-055 Ct of 0.75 mg/L, describe the efficacy of GT-055 well. AUC:MIC ratio was the best predictor of GT-055 efficacy across the pooled Enterobacteriaceae panel evaluated in the DRS with values of 4.13, 13.7, and 57.2 associated with net bacterial stasis, 1- and 2-$\log_{10}$ CFU/mL reductions from baseline at 24 hours, respectively.

Conclusions: Results of GT-1 + GT-055 *in vitro* studies provided insight about the activity of the inhibitor when utilized in combination with GT-1 and will serve to guide future studies.


Change in Log10 CFU at 24 Hours
3
2
1
0
-1
-2
-3
-4
-5
-6
r2 = 0.706
0.1
1
10
100
1000
Free-Drug AUC0-24:MIC Ratio
E. coli 0014
E. coli 13441
E. coli 21711
K. pneumoniae 27144
K. pneumoniae 40031
K. pneumoniae 4192