Oral Pharmacokinetics and Efficacy of AFN-1252 in a Murine Septicemia Infection Model with S. aureus

Abstract

Objective: AFN-1252 is a novel small molecule inhibitor of FabI, a bacterial fatty acid biosynthesis enzyme. The compound has been discovered by Affinium Pharmaceuticals and is under investigation for the treatment of Gram-positive infections, including hospital and community acquired methicillin-resistant Staphylococcus aureus (MRSA). The current study was performed to evaluate the efficacy of AFN-1252 following oral administration in a mouse septicemia model with S. aureus.

Methods: Female CD-1 mice were infected with a bacterial inoculum of S. aureus Smith resulting in the lethal face infection model with S. aureus. Female 5-6 week old CD-1 mice (18-22 gm) were used in the studies. Mice were challenged by injecting 0.5 ml intraperitoneally of a S. aureus bacterial inoculum suspended in hog gastric mucin. The Time to Cmax and AUC exposure obtained with the Poloxamer formulation were 3 x higher than that achieved with the carboxymethylcellulose formulation of AFN-1252. Analysis of AFN-1252 plasma levels demonstrated that although lower plasma exposure following oral administration than the equivalent dose in CMC, AFN-1252 exhibited ED50 values of 0.29 mg/kg and 0.15 mg/kg in CMC and PLX formulations, respectively, while LNZ exhibited ED50 values of 2.8 - 4.7 mg/kg.

Conclusion: Oral AFN-1252 is highly effective in the lethal S. aureus murine septicemia model and exhibits much greater efficacy than LNZ, supporting the potentiality of AFN-1252 as a therapeutic treatment for bacterial bloodstream infections.

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References


