Pharmacokinetics / Pharmacodynamics of Finafloxacin in the Murine Thigh Infection Model with S. aureus and E. coli

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Abstract

Background: Finafloxacin (FIN), a novel fluorquinolone (FQ) in clinical development, has the unique property of being active under acidic conditions, unlike other marketed FQs. Since local acidic environments are a hallmark of bacterial infection, FIN may offer an advantage over existing agents in treating these infections. This study was performed to determine the PK/PD parameter that best correlates to FIN efficacy. Methods: Doses for FIN and other FQs were determined at pH 5.0 and 7.2. Panel 2 (S. aureus) was chosen because of prior studies showing pH 5.0 selective activity. In vivo studies were performed in neutropenic, thigh-infected animals. The dose vs. change in log CFU/thigh relationship vs. administered dose was determined. PK was performed in neutropenic, thigh-infected animals. The dose vs. change in log CFU/thigh relationship vs. administered dose was determined. PK/PD parameter that best correlates to FIN efficacy. Conclusion: Finafloxacin (FIN) is in the region of those described for other fluorquinolones in Gram-negative organisms (> 60). The preliminary PK/PD target of an AUC/MIC of 88.1 for E. coli is in the region of those described for other fluorquinolones in Gram-negative organisms (> 60). Further testing is warranted with a larger dose set to more accurately define the magnitude of the PK/PD parameter which describes the in vivo efficacy of FIN.

Methods and Materials

Base Panel 1: Structure of Finafloxacin

- FIN was administered by the same route used for the PK and dose-ranging studies (q24h, q12h and q6h) in order to determine PK parameters (Cmax, AUC, T>MIC) in neutropenic, thigh-infected animals. The dose vs. change in log CFU/thigh relationship vs. administered dose was determined. PK was performed in neutropenic, thigh-infected animals. The dose vs. change in log CFU/thigh relationship vs. administered dose was determined. PK/PD parameter that best correlates to FIN efficacy. Conclusion: Finafloxacin (FIN) is in the region of those described for other fluorquinolones in Gram-negative organisms (> 60). The preliminary PK/PD target of an AUC/MIC of 88.1 for E. coli is in the region of those described for other fluorquinolones in Gram-negative organisms (> 60). Further testing is warranted with a larger dose set to more accurately define the magnitude of the PK/PD parameter which describes the in vivo efficacy of FIN.

References


Acknowledgments

This study was funded and supported by Merlion Pharma GmbH, Berlin, Germany. Financial support was provided by an unrestricted educational grant from Avanos Medical, Inc., a division of Johnson & Johnson. The authors wish to thank the efforts and support of Dr. Kukula of UNTHSC for technical assistance. The authors would like to acknowledge Phung Nguyen, Jessica Pierce and Maciej Labischinski for technical assistance.

Summary and Conclusions

- FIN is 4- to 16-fold more active than the other fluorquinolones by MIC testing at pH 5 – 6.
- FIN exhibited a good correlation for the pharmacokinetic parameter of AUC/MIC and %T>MIC.
- FIN exhibited a good correlation between total administered dose and antibacterial effect against both E. coli and S. aureus in the murine thigh infection model.
- The PK/PD parameter which best predicts FIN efficacy in this model was AUC/MIC, closely followed by %T>MIC. These parameters are also used to describe the clinical efficacy of marketed fluorquinolones and could also be utilized to set target exposures in the clinical evaluation of FIN.
- The preliminary PK/PD target of an AUC/MIC of 88.1 for E. coli is in the region of those described for other fluorquinolones in Gram-negative organisms (> 60).
- Further testing is warranted with a larger dose set to more accurately define the magnitude of the PK/PD parameter which describes the in vivo efficacy of FIN.