PHARMACOKINETICS (PK), SAFETY AND TOXICITY OF SINGLE ORAL DOSES OF PF-03709270, WITH AND WITHOUT ADMINISTRATION OF PROBENECID

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INTRODUCTION

Sulopenem (sulopenem) is a broad spectrum, parental penem antibiotic that is being developed for hospital and community infections. Upon oral absorption, PF-03709270 is expected to be hydrolyzed, yielding active sulopenem. The Phosphorylase Magnus demonstrates efficacy of oral penems, i.e., Time above minimum inhibitory concentration (MIC) correlates with its efficacy. The target MIC values for sulopenem efficacy in community and hospital infections are 0.5 g/mL and 1 g/mL, respectively.

Methods: Three healthy subjects received single doses of PF-03709270 (400 mg, 1000 mg, and 2000 mg) in a 4-way crossover design. In a subsequent 3-way crossover study, 4 subjects received 600 mg of PF-03709270 alone or in combination with 500 mg and 1000 mg of probenecid. Safety was assessed via clinical examination, vital signs, urine, and stool collections, and serum chemistry and hematology tests.

RESULTS (Continued)

- No Effect of Probencid Co-administration: Co-administration of 500 and 1000 mg probenecid with PF-03709270 increased the total mean AUC of sulopenem by 33.8% and 65.1%, respectively, when compared with placebo co-administration. The inter-individual variability in the 500 mg group was higher compared to the 1000 mg probenecid group. A dose related increase in apparent elimination half life was also observed in this group. A 50 mg dose of PF-03709270 administered with or without probenecid did not result in plasma concentrations above 1.0 µg/mL for at least 3.6 hours on an average. Probencid co-administration prolonged the Time the MIC above was administered.

EFFECT OF PROBENECID (500 & 1000 MG) ON EXPOSURE PARAMETERS CMAX AND AUC OF SULOPENEM FOLLOWING COADMINISTRATION WITH 800 MG PF-03709270

FIGURE 4

RESULTS

- All subjects who received active treatment were analyzed for PK.
- PF-03709270 single dose escalation study: The systemic exposure to sulopenem increased in a dose related manner. The apparent terminal half-life of sulopenem was dose independent and varied between 3.9 and 11.9 hours. Following oral single doses of 400 mg and 1000 mg, an average, plasma concentrations of sulopenem remained above 0.5 µg/mL for at least 3 hours. Following 1000 mg dose, an average, plasma concentrations of sulopenem remained above 1 µg/mL for at least 2.8 hours (Figures 2 and 3). It has significant levels of binding, PF-03709270 or its breakdown byproducts, were detected in this study.

FIGURE 2

PK FOR SULOPENEM FOLLOWING DOSES OF 400MG, 1000MG, AND 2000MG OF PF-03709270 (N=4)

CONCLUSIONS

- PF-03709270, when administered in single oral doses of 400 mg to 2000 mg was well tolerated in healthy adult subjects.

- On an average, oral administration of 400 mg and 1000 mg doses of PF-03709270 maintained plasma concentrations for at least 4 hours above 0.5 µg/mL, and 1 µg/mL target plasma concentrations, respectively, thereby meeting the MIC >MIC-2 and >MIC-4 endpoints of PF-03709270 with 2% Time the MIC above was administered. Further work on PK/PD modeling phases will be reported in a future study.

REFERENCES