F1-353

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

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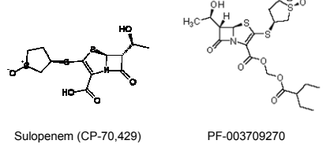
ABSTRACT

- **Background** PF-03709270 is a novel oral prodrug of sulopenem (sulopenem), a parenteral penem antibiotic being developed for hospital and community infections. Upon oral absorption, PF-03709270 is expected to be hydrolyzed, yielding active sulopenem. The PK/pharmacodynamic determinant of efficacy for 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 µg/mL and 1 µg/mL, respectively.
- Methods Nine healthy subjects received single doses of PF-03709270 (400 to 2000 mg), and a placebo in a 4-way crossover design. In a subsequent 3-way crossover study, 4 subjects received 600 mg of PF-03709270 alone and in combination with 500 and 1000 mg of probenecid. Safety was assessed by adverse event (AE), vital signs, heart rate, blood pressure, ECG, cardiac telemetry and safety lab monitoring. sulopenem plasma concentration-time data were analyzed by non-compartmental methods usingWinNonlin v.3.2 (Pharsight®, Mountain View, CA).
- **Results** There were no discontinuations, serious or severe AEs, or significant ECG or lab abnormalities. All AEs were mild. sulopenem systemic exposure following PF-03709270 single doses increased in a dose dependent manner. The apparent terminal half-life (t1/2) of sulopenem was dose independent. At a dose of 2000 mg, PF-03709270 produced sulopenem mean plasma exposures above the MIC targets of 0.5µg/mL for 5.98 hrs, and above 1 µg/mL for 4.82 hrs. Co-administration of 500 and 1000 mg of probenecid with PF-03709270 increased the total mean AUC of sulopenem by 33.8 and 65.1%, respectively, when compared to PF-03709270 administered alone.
- **Conclusions** Oral PF-03709270 produced good exposures of sulopenem in terms of Time above MIC. Co-administration of probenecid increased the exposure and t1/2 of sulopenem. PF-03709270 was safe and well tolerated in both studies.

INTRODUCTION

- Sulopenem (sulopenem) is a broad spectrum, parental β-lactam parental penem antibiotic that is being developed for the treatment of infections associated with common hospital and community pathogens.
- sulopenem is active against common respiratory pathogens including penicllin resistant *Strep. pneumoniae*, fastidious gram negative bacteria including *Enterobactriaceae* including ESBL producing and quinolone resistant strains, and certain clinically relevant anaerobes.
- Minimum inhibitory concentrations (MIC_{90}) of sulopenem against common community and hospital (susceptible) pathogens are 0.5 µg/mL and 1 µg/mL respectively. It is not effective against methicillin resistant *Staph. aureus* or *pseudomonas* spp[1].
- "Time over MIC" or the time duration for which the plasma free drug concentrations remain above MIC values for susceptible pathogens is commonly known PK/PD determinant of efficacy for beta-lactams and penems. *In vitro* studies (poster A-054) in immune-competent and immune-suppressed suggested that for sulopenem a free T>MIC of ~20% is adequate for efficacy. For a dosing interval of 12-hours, this value translates into ~2.4 hours.
- Sulopenem, in daily doses up to 2 g, was evaluated in Phase 2 studies in a variety of hospital and community infections in Japan in early 1990s and appeared to have acceptable efficacy and safety.
- Like penems, sulopenem is not orally bioavailable. An oral ester prodrug of sulopenem, PF-03709270 has been developed (Figure 1). Once absorbed, it is expected to rapidly release sulopenem in the blood circulation.

FIGURE 1



Sulopenem (CP-70,429) PF-003709270

- In an in-house Phase 1, healthy subject clinical pharmacology study, following single escalating doses of sulopenem administered as 1-hour IV infusion, exposure (C_{max} and AUC_{last}) increased in more than proportional manner (7 fold change in dose resulting in 11 fold change in AUC). The mean apparent $T_{1/2}$ was dose independent. Doses ≥ 400 mg provided mean plasma concentrations of sulopenem, above the target of 1.0 µg/mL for at least 2.7 hours. (Table 1, Data on File, Pfizer Inc.).

TABLE 1: MEAN (± SD*) PHARMACOKINETIC PARAMETERS OF SULOPENEM FOLLOWING SINGLE ASCENDING INTRAVENOUS DOSES OF SULOPENEM IN HEALTHY ADULT SUBJECTS**

Dose (mg)	C_{max} (µg/mL)	AUC_{last} h.µg/mL	AUC_{inf} h.µg/mL	CL (L/h)	V_{ss} (L)	$T_{1/2}$ (h)	T> 1.0 µg//Ml (h)
400	11.6 ± 3.4	14.1 ± 3.0	14.2 ± 3.0	29.2 ±6.0	23.1 ±5.4	0.89 ± 0.24	2.73 ±0.57
800	23.7 ± 4.4	29.5 ± 4.8	29.7 ± 4.8	27.6 ±4.3	22.5 ±4.6	1.27 ± 0.40	3.35 ±0.23
1600 (MTD)* **	50.9 ± 7.5	71.5 ± 14.2	71.7 ± 14.3	23.0 ±4.0	20.6 ±3.3	1.16 ± 0.20	4.85 ±0.79
2400	88.0 ± 15.6	121 ± 23.4	121 ± 23.5	20.6 ±4.5	20.0 ±3.7	1.20 ± 0.16	5.76 ±0.73
2800	111 ± 12.7	157 ± 21.5	157 ± 21.9	18.2 ±2.7	17.5 ±2.3	1.15 ± 0.26	6.28 ±1.1

*SD: Standard deviation

** Eight subjects were randomized to each dose group except for 2400 mg dose group with 12 subjects

***MTD: Maximum tolerated dose; nausea and vomiting were the dose limiting adverse events; 1 subject each at 2400mg and 2800 mg dose reported severe vomiting. All other AEs were mild to moderate and mostly related to GI tract

  - Sulopenem, together with its oral prodrug, PF-03709270, is intended to offer IV to oral therapy for treating a variety of infections including community acquired pneumonia, health care associated pneumonia, complicated urinary tract infections, complicated intra-abdominal infections, pelvic inflammatory disease, complicated skin and skin structure infections, diabetic foot infection and gonorrhea, caused by susceptible pathogens
- Oral penem, PF-03709270, could potentially be the only oral option available for ESBL producing and quinolone resistant gram negative pathogens
- The option of IV-to-oral switch or initiating therapy with an oral penem in a hospital setting could minimize hospital stay thereby reducing overall treatment costs and improving productivity
- The broad spectrum of activity coupled with lack of anti-pseudomonal activity of sulopenem also provides a potential opportunity for the use of the oral penem, PF-03709270, in community settings
- As with some other beta-lactams, probenecid, a uricosuric agent, may also be co-administered with the PF-03709270 to reduce renal clearance (major elimination pathway of sulopenem) and increase systemic exposure of sulopenem, if necessary for infections that may require higher exposures

OBJECTIVES

- To evaluate pharmacokinetics, safety and tolerability of escalating doses of PF-03709270, the oral prodrug of sulopenem, sulopenem in healthy adult subjects
- To evaluate the pharmacokinetics, safety and tolerability of PF-03709270 when administered in combination with probenecid in healthy adult subjects

METHODS

- Nine healthy adult subjects received single escalating doses of PF-03709270, and a placebo in a randomized, investigator- and subject-blind (sponsor open), 4-way crossover design study. Each subject received 3 escalating doses of PF-03709270 in the range of 400 mg to 2000 mg in a fasted state. There was a wash period 7-14 days between two successive dosing periods.
- In a subsequent randomized, open label, 3-way cross over design study, four healthy adult subjects received 600 mg of PF-03709270 alone (with placebo) and in combination with 500 mg and 1000 mg of probenecid in a fasted state. All subjects were confined to Pfizer Clinical Research Unit for at least 24 hours following drug administration for monitoring of safety and tolerability. PK samples were collected predose and at periodic intervals up to 12 hours post dosing.
- **Pharmacokinetic Assessment:** sulopenem plasma concentrations were assessed using high performance liquid chromatography with tandem mass spectrometry (HPLC/MS/MS) method with a dynamic range of 25 ng.mL to 5000 ng/mL. PF-03709270 blood concentrations were assessed in the first study using HPLC/MS/MS method with a dynamic range of 1 ng/mL and 50 ng/mL. Formic acid (a PF-03709270 breakdown product) plasma concentrations were assessed in the first study utilizing a ion chromatography method with a dynamic range of 1.0 to 100 µg/mL. sulopenem plasma concentration-time data were analyzed by non-compartmental methods usingWinNonlin v.3.2 (Pharsight®, Mountain View, CA).
- **Safety and Tolerability Assessment:** This included physical examination, vital signs (blood pressure and heart rate), electrocardiogram, continuous cardiac telemetry, safety clinical laboratory tests, and adverse event (AE) monitoring.

RESULTS

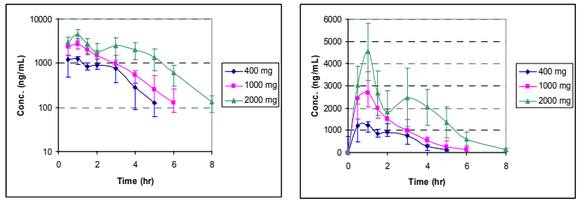
Pharmacokinetic Results

- All the 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 0.76 and 1.10 hours. Following single oral doses of 400 mg and 1000 mg, on an average, plasma concentrations of sulopenem remained above 0.5 µg/mL for at least 3 hours. Following 1000 mg dose, on an average, plasma concentrations of sulopenem remained above 1 µg/mL for at least 2.5 hours (Figures 2 & 3). No significant levels of prodrug, PF-03709270 or its breakdown byproduct, formate were detected in this study.

FIGURE 2

PK FOR SULOPENEM FOLLOWING DOSES OF 400MG, 1000MG, AND 2000MG OF PF-03709270 (N=6)

Mean (±SD) concentration-time profiles for sulopenem following oral doses of PF-03709270

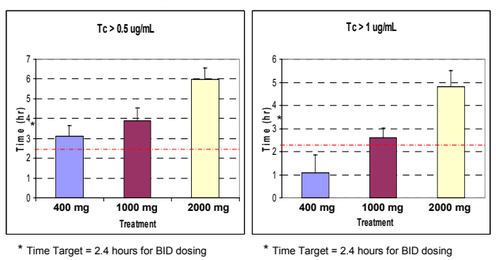


Mean (±SD) PK Parameters

Dose	Cmax [ng/mL]	Tmax [hr]	AUClast [hr*ng/mL]	T1/2 (hr)	Estimated F [%]	Tc > 0.5 ug/mL [hr]	Tc > 1 ug/mL [hr]
400	**1464.33**	**1.17**	**3454.63**	**0.84**	**33.58**	**3.10**	**1.10**
	(442.26)	(0.93)	(670.40)	(0.16)	(6.52)	(0.55)	(0.76)
1000	**2860.00**	**0.83**	**6421.50**	**1.00**	**23.83**	**3.91**	**2.59**
	(570.33)	(0.41)	(1208.30)	(0.17)	(4.48)	(0.63)	(0.44)
2000	**4666.67**	**1.33**	**13131.24**	**1.10**	**20.13**	**5.98**	**4.82**
	(1180.69)	(0.82)	(2100.97)	(0.62)	(3.22)	(0.56)	(0.69)

FIGURE 3

TIME ABOVE CRITICAL CONCENTRATION FOR SULOPENEM FOLLOWING DOSES OF 400MG, 1000MG AND 2000MG OF PF-03709270 (N=6) (HISTOGRAM BARS ± SD)



* Time Target = 2.4 hours for BID dosing

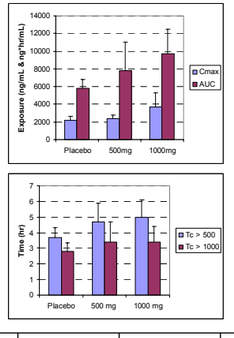
* Time Target = 2.4 hours for BID dosing

RESULTS (Continued)

- Effect of Probenecid Co-administration: Co-administration of 500 and 1000 mg probenecid with PF-0307290 increased the total mean AUC_{last} 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 study, a 600 mg dose of PF-0370-9270 administered with or without probenecid was able to maintain plasma concentrations above 1 µg/mL for at least 2.8 hours, on an average. Probenecid co-administration prolonged the Time over MIC by about 20-30%. (Figure 4).

FIGURE 4

EFFECT OF PROBENECID (500 & 1000 MG) ON EXPOSURE PARAMETERS CMAX AND AUC OF SULOPENEM FOLLOWING CO-ADMINISTRATION WITH 600 MG PF-03709270



	Cmax (ng/mL)	AUC (hr*ng/mL)	Half-life (hr)	Tc > 500ng (hr)	Tc > 1000ng (hr)
Placebo	2207 ± 406	5830 ± 1002	0.82 ± 0.06	3.7 ± 0.62	2.8 ± 0.56
500mg	2380 ± 412	7814 ± 3196	0.99 ± 0.15	4.7 ± 1.2	3.4 ± 1.3
1000mg	3670 ± 1613	9726 ± 2732	1.41 ± 0.18	5.0 ± 11.2	3.4 ± 0.99

Tc: Target plasma concentrations

Safety and Tolerability:

- There were no deaths, serious adverse events or discontinuations due to AEs reported in this study. Treatment related AEs included abdominal pain, diarrhea, nausea, dysguesia and headache. All AEs were mild in severity. No clinically significant changes in vital signs, telemetry, ECGs or safety clinical laboratory test findings were reported.

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 and 1000 mg doses of PF-03709270 maintained sulopenem plasma concentrations for at least 2.4 hours above 0.5 µg/mL and 1 µg/mL target plasma concentrations, respectively. thereby making of BID dosing regimens of PF-0370,9270 with 20% Time over MIC coverage a feasible option. For further work on PK/PD modeling please refer to poster # A-034)
- Co-administration of PF-03709270 with probenecid was well tolerated and increased the plasma exposure and Time over MIC for CP-70429. Hence, this combination could be developed as a potential treatment option for infections that may require higher plasma concentrations

REFERENCE

1) Minamimura *et al*, Antimicrobial Agents and Chemotherapy, July 1993, P. 1547-1551.