# A Phase 1 Study to Assess the Pharmacokinetics of Sulopenem Etzadroxil (PF-03709270)

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## ABSTRACT

**BACKGROUND:** Sulopenem etzadroxil is a pro-drug of sulopenem (CP-70,429) designed to enhance its bioavailability. A Phase 1 study was performed to evaluate the effect of food and probenecid on the pharmacokinetics, safety and tolerability of sulopenem etzadroxil.

**METHODS**: This study is a randomized, double blinded (investigator and subject blinded, sponsor-open), placebo-controlled, multiple dose study in healthy volunteers of PF-03709270, with or without co-administration of probenecid, in fed or fasted state. Subjects were dosed twice a day for 6 days and once on Day 7. For the treatment groups dosed in the fed state, subjects were dosed approximately 30 minutes after the start of their meal. Pharmacokinetic sampling was done in 8 subjects per treatment group.

**RESULTS:**

| Treatment | Fed / Fasted | Descriptive Statistic | Parameter (Day 1) | | | |
|---|---|---|---|---|---|---|
| | | | Cmax (ng/mL) | $AUC_{TAU}$ (hr*ng/mL) | T>MIC (0.5µg/ml) [hr] | T> MIC (0.5 µg/ml) [%] |
| **500 mg PF-03709270** | Fasted | Mean | 1770.000 | 3683.093 | 2.660 | 22.2 |
| | | SD | 529.474 | 728.892 | | |
| | | Median | 1720.00 | 3478.43 | | |
| | | CV% | 29.9 | 19.8 | 15.0 | |
| | | | | | | |
| **500 mg PF-03709270** | Fed | Mean | 1869.875 | 4545.342 | 3.127 | 26.1 |
| | | SD | 741.019 | 1131.901 | | |
| | | Median | 1725.00 | 4509.96 | | |
| | | CV% | 39.6 | 24.9 | 27.9 | |
| . | | | | | | |
| **500 mg PF-03709270 + 500 mg probenecid** | Fasted | Mean | 1773.750 | 3952.865 | 3.063 | 25.5 |
| | | SD | 465.463 | 893.698 | | |
| | | Median | 1830.00 | 4238.98 | | |
| | | CV% | 26.2 | 22.6 | 23.2 | |
| | | | | | | |
| **500 mg PF-03709270 + 500 mg probenecid** | Fed | Mean | 1690.000 | 6396.538 | 5.364 | 44.7 |
| | | SD | 576.517 | 1415.977 | | |
| | | Median | 1500.00 | 6301.46 | | |
| | | CV% | 34.1 | 22.1 | 41.9 | |

**CONCLUSIONS**: Both food and probenecid increase the absorption of PF-03709270 and consequently serum levels of sulopenem. The combination of food and probenecid further increases serum exposures of sulopenem and all significantly prolong the T>MIC for sulopenem. These data will help inform PKPD modelling in selection of a dose for Phase 3 studies.

## INTRODUCTION

Sulopenem is a penem β-lactam antibiotic which is being developed for the treatment of infections caused by multi-drug resistant bacteria. Sulopenem has potent activity against species of the Enterobacteriaceae that encode ESBLs or AmpC-type β-lactamases that confer resistance to third generation cephalosporins, exerts bactericidal activity through inhibition of bacterial cell wall synthesis by binding to penicillin-binding proteins and is available as intravenous and oral pro-drug formulations.

This multiple dose study evaluated the PK, tolerability and safety of the oral pro-drug PF 03709270 in multiple doses of 500 mg administered twice daily for 7 days under either fed or fasted conditions, and with or without co-administration of probenecid.

## METHODS

This study was a randomized, double blinded, placebo-controlled, multiple dose study of PF-03709270, with or without co-administration of probenecid, in the fed or fasted state. Subjects were randomized and treated for 7 days in a Phase 1 unit. Plasma concentrations of sulopenem were measured pre-dose, and at 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 hours respectively post dosing. Urine was collected on Day 1 in the following intervals: 0-2, 2-4, 4-6, 6-8, 8-12 hours post dosing, and on Day 7 at 0-6, 6-12 and 12-24 hours post-dose.

## RESULTS

**Table 1. Demographics**

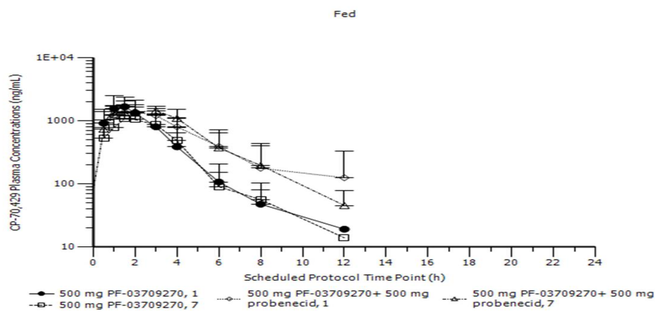
| Variable | PF-03709270 500 mg | | | | Placebo |
|---|---|---|---|---|---|
| | Fed | | Fasted | | Fed/Fasted |
| | + Probenecid | No Probenecid | + Probenecid | No probenecid | +/- Probenecid |
| N | 16 | 16 | 16 | 16 | 64 |
| Age (years) | | | | | |
| Mean (SD) | 35.9 (11.7) | 39.1 (13.7) | 37.0 (10.0) | 34.6 (10.7) | 36.5 (10.2) |
| Min, Max | 24, 59 | 20, 58 | 26, 59 | 20, 55 | 20, 60 |
| Sex, n (%) | | | | | |
| Female | 1 (6.3) | 2 (12.5) | 1 (6.3) | 0 | 0 |
| Male | 15 (93.8) | 14 (87.5) | 15 (93.8) | 16 (100) | 64 (100) |
| Race, n (%) | | | | | |
| African American | 14 (87.5) | 11 (68.8) | 13 (81.3) | 12 (75.0) | 43 (67.2) |
| White | 2 (12.5) | 5 (31.3) | 3 (18.8) | 4 (25.0) | 20 (31.3) |
| Asian | 0 | 0 | 0 | 0 | 1 (1.6) |
| Height (cm) | | | | | |
| Mean (SD) | 177.3 (7.0) | 175.2 (11.3) | 176.8 (7.0) | 178.1 (7.3) | 177.0 (6.8) |
| Min, Max | 165.0, 194.0 | 159.0, 198.0 | 165.0, 195.0 | 165.0, 195.0 | 163.0, 194.0 |
| Weight (kg) | | | | | |
| Mean (SD) | 80.7 (11.19) | 83.5 (13.29) | 86.3 (11.09) | 82.9 (9.22) | 83.6 (11.36) |
| Min, Max | 63.6, 98.8 | 58.9, 117.6 | 67.6, 102.3 | 62.8, 94.9 | 60.6, 110.0 |

**Table 2. Effect of Food on PK of Sulopenem**

| PK Parameter | Fasted | | Fed | | Fed/Fasted | | |
|---|---|---|---|---|---|---|---|
| | GM | SD | GM | SD | GMR | 90% CI | rMSE |
| $C_{max}$ (ng/mL) | 1289.4 | 497.3 | 1179.4 | 273.3 | 0.92 | 69 - 122 | 0.102 |
| $AUC_{tau}$ (hr*ng/mL) | 2626.3 | 480.8 | 3706.4 | 903.1 | 1.41 | 116 - 171 | 0.212 |
| $TAMIC_{0.5}$ (hours) | 2.1 | 0.3 | 2.9 | 0.8 | 1.38 | 109 - 168 | 0.247 |

AUCtau = area under the concentration time curve from time 0 to 12 hours; CI = confidence intervals; Cmax = maximum observed concentration; GM = geometric means; GMR = ratio of geometric means; rMSE = Square root of the residual error from the model; SD = standard deviation; TAMIC0.5 = time above minimum inhibitory concentration of 0.5 µg/mL

**Figure 1. Effect of Probenecid on PK of Sulopenem**




**Urine Concentrations**: Urinary concentrations of sulopenem were measured in fed and fasted conditions, with and without co-administration of probenecid, and demonstrated that urinary concentrations far exceeded plasma concentrations of sulopenem (50-100 times) and stayed above $MIC_{90}$ values for a duration of 8-12 hours after dosing.

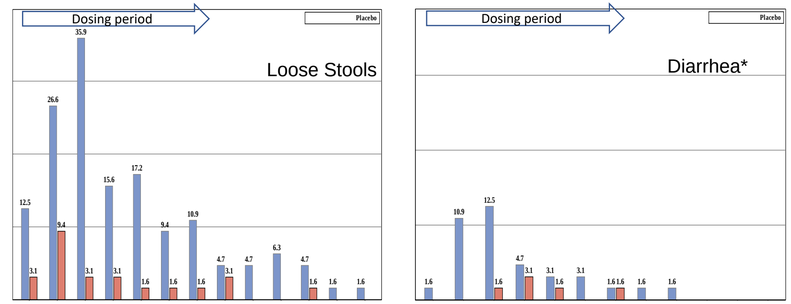
## RESULTS

**Table 3. Overview of Adverse Events**

| Variable | PF-03709270 500 mg | | | | Placebo |
|---|---|---|---|---|---|
| | Fed | | Fasted | | Fed/Fasted |
| Number of Patients with: | + Probenecid | No Probenecid | + Probenecid | No Probenecid | +/- Probenecid |
| | N=16 | N=16 | N=16 | N=16 | N=64 |
| | n (%) | n (%) | n (%) | n (%) | n (%) |
| Adverse events (AE) | 12 (75.0) | 10 (62.5) | 12 (75.0) | 13 (81.3) | 25 (39.1) |
| Treatment emergent AE (TEAE) | 12 (75.0) | 10 (62.5) | 12 (75.0) | 13 (81.3) | 24 (37.5) |
| Drug-Related TEAE | 10 (62.5) | 8 (50.0) | 11 (68.8) | 13 (81.3) | 18 (28.1) |
| Serious TEAE | 0 | 0 | 0 | 0 | 0 |
| TEAE Leading to Premature Discontinuation | 1 (6.3) | 0 | 0 | 0 | 0 |
| Diarrhea* | 2 (12.5) | 2 (12.5) | 2 (12.5) | 3 (18.8) | 2 (3.1) |

*Diarrhea defined as having 3 or more episodes of diarrhea in 1 day or having 2 or more episodes of diarrhea per day for 2 consecutive days

**Figure 2. Duration of Loose Stools/Diarrhea***




*Diarrhea defined as having 3 or more episodes of diarrhea in 1 day or having 2 or more episodes of diarrhea per day for 2 consecutive days

## CONCLUSIONS

- Both food and probenecid individually increased serum levels of sulopenem.
- The combination of food and probenecid further increased serum exposures of sulopenem.
- Probenecid, food, or the combination of both, all significantly prolonged the T>MIC for sulopenem.
- Urine concentrations of sulopenem far exceeded those in plasma and were sustained above the $MIC_{90}$ for 8-12 hours post-dose.
- Diarrhea, the most common AE reported, was mild, self-limited and not associated with discontinuation of treatment.

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