A Phase 1, Randomized, Open-label, Crossover Study In Healthy Subjects Under Fasting Conditions of Orally Administered Sulopenem Etzadroxil Alone or with Probenecid to Determine the Pharmacokinetics of Sulopenem

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ABSTRACT

Background: Antimicrobial resistance to available oral antibiotics is becoming progressively more common, precipitating the need for additional treatment options as step-down from initial intravenous (IV) therapy as well as for treatment of infections in the community. Sulopenem (CP-70,429) is a thiopenem antibiotic active against quinolone non-susceptible and ESBL-producing Enterobacteriaceae. As the key pharmacokinetic-pharmacodynamic variable correlating with efficacy for penem antibiotics is time above minimum inhibitory concentration (T>MIC), we examined the utility of probenecid, an OAT-1 inhibitor of β-lactam excretion, on the pharmacokinetic (PK) parameters for the oral prodrug of sulopenem, sulopenem etzadroxil.

Methods: Twelve healthy males and females received a single oral dose of 500 mg sulopenem etzadroxil as powder in bottle either alone or co-administered with a single oral dose of probenecid 500 mg in a crossover design with a washout period of 6 days. All doses were administered under fasting conditions. Blood samples for plasma PK analysis were collected and PK parameters for sulopenem, the parent compound of sulopenem etzadroxil, were determined.

Results:

Treatment	N	Sulopenem Parameter (Day 1; mean)			
		C_{max} (ng/mL)	$AUC_{0\text{-}INF}$ (hr*ng/mL)	T>MIC (0.5 µg/mL) [hr]	T>MIC (0.5 µg/mL) [%, 12 hr interval]
500 mg sulopenem etzadroxil	10	1928	3871	2.8	23.3
500 mg sulopenem etzadroxil + 500 mg probenecid	11	1929	4964	3.6	30.2

Conclusions: Probenecid increases the AUC of sulopenem by 28% in the fasted state and extends the mean time over MIC.

INTRODUCTION

- Sulopenem is a thiopenem antibiotic being developed for the treatment of infections caused by multi-drug resistant bacteria
  - Has potent activity against Enterobacteriaceae
    - Including those with ESBLs or AmpC-type β-lactamases, and those that are quinolone non-susceptible
  - Has an intravenous and oral formulation
  - Being developed for the treatment of urinary tract infection and complicated intra-abdominal infection
  - Exerts bactericidal activity through inhibition of bacterial cell wall synthesis by binding to penicillin-binding proteins
- Probenecid competitively inhibits the renal tubular secretion of β-lactam antibacterial agents
  - safely been used with other β-lactam antibiotics to reduce their dose or dosing frequency when used to treat infections in humans
  - Co-administration of probenecid with sulopenem etzadroxil demonstrated an increase in the exposure of sulopenem in a Phase 1 study
- This single dose cross over study evaluated the PK, tolerability and safety of the oral pro-drug sulopenem etzadroxil 500 mg administered either alone or with probenecid under fasted conditions to assess its effect on the PK of sulopenem

METHODS

- This study was a randomized, open label, single-dose, crossover study of sulopenem etzadroxil, with or without co-administration of probenecid, in the fasted state.
- Twelve healthy male and female subjects were randomized to receive a single dose of either sulopenem etzadroxil 500 mg powder for oral suspension alone or sulopenem etzadroxil 500 mg powder for oral suspension co-administered with 500 mg of probenecid in a tablet in a cross over design with a washout period of 6 days.
- 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.
- The following PK parameters for sulopenem were determined using WinNonlin v 6.3: Cmax, Tmax, AUC_{last}, $AUC_{0\text{-}\infty}$, $t_{1/2}$, CL/F, and time above $MIC_{0.5}$ µg/mL.
- Safety was assessed using vital signs, clinical laboratory measurements and adverse event data.

RESULTS

Table 1: Demographics of Healthy Volunteers in Study

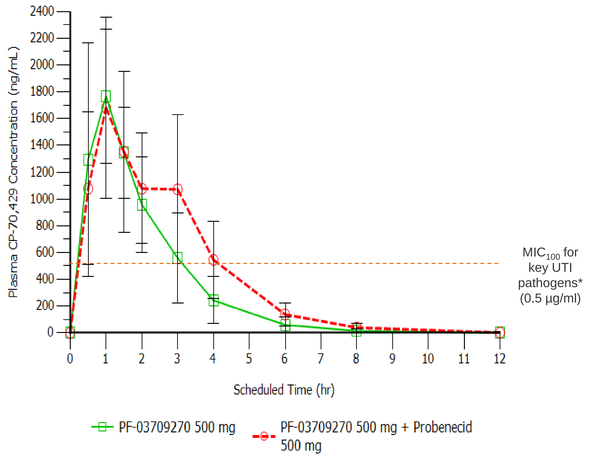
Characteristic		Results N=11
Mean Age (years, ± SD)		42.0 ± 13.9
Min, Max		20, 59
Gender, n (%)		
	Female	4 (36.4)
	Male	7 (63.6)
Race, n (%)		
	African American	7 (65.6)
	White	4 (36.4)
Height (cm)		
	Mean (SD)	172.0 (9.6)
	Min, Max	155.0, 183.0
Weight (kg)		
	Mean (SD)	80.3 (12.3)
	Min, Max	61.3, 104.8
BMI (kg/m2)		
	Mean (SD)	27.2 (3.9)
	Min, Max	20.3, 32

RESULTS

Table 2: Summary of Sulopenem PK Parameters

Treatment	N	Sulopenem Parameter (Day 1; mean)				
		C_{max} (ng/mL)	$AUC_{0\text{-}INF}$ (hr*ng/mL)	CL/F (L/hr)	T>MIC (0.5 µg/mL) [hr]	T> MIC (0.5 µg/mL) [%, 12 hr interval]
Sulopenem etzadroxil 500 mg	10	1928	3886	136.3	2.8	23.3
Sulopenem etzadroxil 500 mg + Probenecid 500 mg	11	1929	4977	108.4	3.6	30.2

Figure 1: Effect of Probenecid on the PK of Sulopenem



*Key UTI pathogens are *E. coli, K. pneumoniae, K. oxytoca* and *P. mirabilis*

Table 3: Summary of Adverse Events

	Sulopenem Etzadroxil 500 mg N = 10 n (%)	Sulopenem Etzadroxil 500 mg + Probenecid 500 mg N = 11 n (%)
All TEAEs	2 (20.0)	0
Related TEAEs	0	0
Mild TEAEs	2 (20.0)	0
Moderate TEAEs	0	0
Severe TEAEs	0	0
Serious AEs	0	0
TEAEs Leading to Discontinuation of Study Drug	0	0

CONCLUSIONS

- Probenecid increases the AUC of sulopenem
  - By 28% in the fasted state
- Probenecid extends the mean time over MIC for sulopenem in the plasma
  - At 0.5 µg/mL, the $MIC_{100\%}$ for sulopenem against key UTI pathogens, probenecid improves mean target attainment by approximately 7%
- Sulopenem etzadroxil with or without co-administration of probenecid is well tolerated
- These data support the further formulation development of sulopenem and probenecid in a combination tablet formulation