Poster # K-124

PHARMACOKINETICS OF INTRAVENOUS AND ORAL PTK796, A NEW AMINOMETHYLCYCLINE ANTIBIOTIC

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ABSTRACT

Background: PTK796 is a novel semi-synthetic compound related to the tetracyclines and specifically derived from minocycline. It has activity against MRSA and pathogens expressing tetracycline resistance. PTK796 is being developed for clinical use with both intravenous (IV) and oral (PO) administration. The current proposed therapeutic dose is 100 mg IV or 300 mg PO administered once daily.

Methods: The pharmacokinetics of PTK796 were evaluated in the following studies:

- Study 1: Single ascending dose of IV PTK796 in healthy males, 25-600 mg (n=5-6 in each dose group, total n=41)
- Study 2: Crossover study, single dose of IV (100 mg) and oral (300 mg) PTK796 in 16 healthy males or females
- Study 3: Single dose of IV PTK796 in 6 healthy males and 6 females, 100 mg.

Plasma PTK796 concentrations were quantified by a validated LC-MS/MS method with a lower limit of quantitation of 20.0 ng/mL.

Results: Intravenous administration of PTK796 exhibited three-compartment pharmacokinetics, with a rapid initial distribution phase and a large volume of distribution of 300-430 L. The terminal half life of PTK796 was about 18 h and clearance was 11.4 L/h. PTK796 exhibited dose-proportional increases in AUC over the dose range 25-600 mg following IV administration. After oral administration, PTK796 was rapidly absorbed with a median T_{max} of 1.8 h (range 1.0 to 3.0 h). The median AUC_{0-24h} after 300 mg PTK796 PO was 5.66 µg*h/mL compared to 5.71 µg*h/mL after 100 mg IV. Based on the median AUC calculation, the oral bioavailability of PTK796 was 33%. In Study 3, the AUC_{0-24h} in females was 7.18±1.03 µg*h/mL and 5.61±0.19 µg*h/mL in males. PTK796 was well tolerated after single IV or PO doses.

Conclusions: PTK796 has dose-proportional pharmacokinetics after intravenous administration. The 100 mg IV and 300 mg PO doses produce comparable exposures. The long half life supports once-daily dosing.

BACKGROUND

- Bacterial resistance to the existing array of antibiotics is a serious health concern necessitating the need for novel antibacterial compounds.
- PTK796 is a novel semi-synthetic compound prepared by chemical modification of minocycline; its physicochemical properties and mechanism of action are similar to minocycline. However, PTK796 has activity against pathogens expressing the two most common mechanisms of tetracycline resistance.
  - Active efflux pumps which transport the drug out of the cell
  - Ribosomal protection proteins which block drug attachment to the ribosome and thereby allow protein synthesis to continue
- PTK796 has activity against gram positive organisms (including MRSA), atypical organisms, and some gram negative organisms.
- PTK796 is being developed for clinical use for both intravenous (IV) and oral (PO) adminsitration.

METHODS

- The pharmacokinetics and safety of PTK796 were evaluated in three Phase I clinical studies (**Table 1**).
- Determination of PTK796 was by LC-MS/MS method (lower limit of quantification=20.0 ng/mL).
- All the studies were conducted in accordance with ICH-GCP guidelines.

Table 1. *Study design*

Study Number	Title	Number of subjects dosed	Doses administered (mg)
Study 1	A Placebo-Controlled, Randomized, Double-Blind, Phase I Study in Healthy Male Subjects to Investigate the Safety, Tolerability and Pharmacokinetics of Ascending Single and Multiple Intravenous Doses of PTK796	55 (41 received PTK796 and 14 received placebo)	25, 50, 100, 200, 300, 400, 600 (IV)
Study 2	A Phase I Study to Evaluate the Pharmacokinetics and Safety of Three Dose Levels of Oral PTK796 Tosylate Salt and Determine the Bioequivalence of the Proposed Therapeutic Dose in Healthy Young Subjects	42 (40 received PTK796 and 02 received placebo); Part B: 16 received PTK796	*Part A: 300, 250 (PO) Part B: 100, 300 (IV and PO)
Study 3	A Placebo-Controlled, Randomized, Double-Blind, Phase I Study to Investigate the Safety, Tolerability and Pharmacokinetics of a Single Intravenous and a Single Oral Dose of PTK796 in Healthy Young Male and Healthy Young Female Subjects	32 (24 received PTK796 and 08 received placebo)	100 (IV) and 200 PO

*Part A: Parallel-Group Randomized; Part B: Placebo Controlled, Randomized, Crossover
Only Part B of Study 2 and IV data from Study 3 are presented.

RESULTS

Pharmacokinetics

- PTK796 exhibited rapid distribution from the central compartment, followed by a second distribution phase after approximately 6 h following the start of IV infusion.
- The terminal elimination half-life was ~18 h (**Figure 1**) [Study 1].
- Total apparent clearance remained relatively constant across the dose range studied and volume of distribution (Vd) was large (333-640 L) suggesting considerable extravascular distribution (**Table 2**).

Figure 1. *Mean PTK796 plasma concentrations versus time by dose (logarithmic plot)*

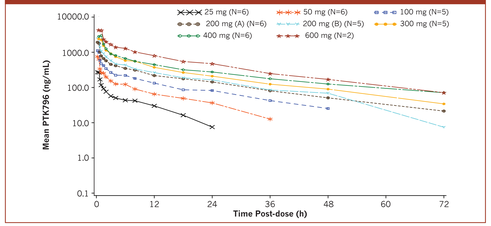


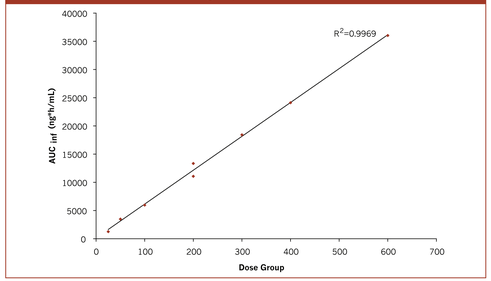
Table 2. *Summary of mean (SD) pharmacokinetic parameters after intravenous dosing of PTK796*

PTK796 Group (mg)	C_{max} (ng/mL)	AUC_{0-24} (ng•h/mL)	AUC_{0-inf} (ng•h/mL)	$t_{1/2}$ (h)	CL (L/h)	Vd (L)
Dose Administered Over 30 Minutes						
25 (N=6)	280 (58.7)	915 (183.4)	1260 (296.0)	11.7 (3.4)	20.9 (5.3)	333 (38.7)
50 (N=6)	789 (347.5)	2384 (575.8)	3484 (1422.5)	20.5 (20.5)	15.8 (4.5)	380 (191.3)
100 (N=5)	1130 (346.0)	4319 (847.9)	5958 (812.5)	14.1 (2.8)	17.1 (2.5)	353 (114.0)
200 (A) (N=6)	2008 (798.2)	7504 (1766.5)	11068 (2534.2)	18.7 (4.1)	18.8 (4.0)	506 (152.8)
200 (B) (N=5)	2602 (364.1)	9073 (1269.9)	13336 (2031.7)	19.0 (4.5)	15.3 (2.3)	412 (84.0)
Dose Administered Over 60 Minutes						
300 (N=5)	2459 (681.2)	12835 (2718.5)	18421 (3377.6)	19.3 (3.5)	16.7 (3.1)	467 (118.9)
400 (N=6)	3206 (711.3)	14709 (2160.5)	24118 (3814.8)	26.0 (4.5)	17.0 (2.9)	640 (163.7)
600 (N=2)	4511 (113.6)	24919 (914.0)	36023 (2404.9)	17.1 (0.1)	16.7 (1.1)	411 (30.1)

200 (A): received 0.5 mg/mL
200 (B): received 1 mg/mL

- Pharmacokinetics was linear over the entire dose range (25 mg - 600 mg) as assessed by AUC, indicating dose proportionality (**Figure 2**).

Figure 2. *Linear regression for dose proportionality for mean AUC_{0-inf} following a single dose of PTK796 – all dose groups*



- A comparison of IV and orally administered PTK796 pharmacokinetic parameters are given in **Table 3** [Study 2, Part B].
- After oral administration, PTK796 was rapidly absorbed as indicated by T_{max} <2.0 h.
- Based on the median AUC_{inf} comparison, the oral bioavailability of PTK796 was estimated to be approximately 33%.

Table 3. *Summary statistics for principal pharmacokinetic parameters*

Parameter (units)	Dose of PTK796	Mean	Geometric mean	Median	Range (Min-Max)
C_{max} (µg/mL)	300 mg PO (n=16)	0.65	0.59	0.56	0.25-1.34
	100 mg IV (n=16)	1.01	0.96	1.02	0.42-1.54
$AUC_{(0-t)}$ (µg.h/mL)	300 mg PO (n=16)	5.35	5.13	5.50	2.27-8.24
	100 mg IV (n=16)	6.44	6.23	5.97	4.07-9.65
$AUC_{(0-inf)}$ (µg.h/mL)	300 mg PO (n=13)	7.76	7.53	8.04	5.22-12.28
	100 mg IV (n=13)	8.95	8.55	8.08	5.71-16.27
T_{max} (h)	300 mg PO (n=16)	1.94	-	2.00	0.50-4.00
	100 mg IV (n=16)	0.75	-	0.55	0.55-3.07

- After single IV administration, female subjects had ~20% higher AUC compared to male subjects (**Table 4**) [Study 3].

Table 4. *PTK796 exposure by Sex for Young Subjects after IV administration of 100 mg PTK796 (Geometric mean, n=6)*

Route	Geometric Least Squares Mean (GLSM)					
	Parameter	Male	Female	Ratio of GLSM Male/Female	90% C.I. of Ratio of GLSM	P-value*
IV	C_{max} (ng/mL)	1130.35	1203.78	0.94	(0.72, 1.22)	0.670
	AUC_{24} (h.ng/mL)	5593.27	7104.88	0.79	(0.71, 0.88)	0.003
	AUC_{inf} (h.ng/mL)	8478.42	10952.51	0.77	(0.67, 0.89)	0.008

*From ANOVA model with sex as main effect.

Safety

- Across studies, no serious adverse events were reported and none of the subjects discontinued due to adverse events (AEs).
- All AEs were mild in intensity and resolved by the end of the study.
  - Study 1
    - The most commonly reported AEs were related to procedural complications, primarily reports of cannula site reaction: 22% (n=9) in PTK796 group and 7% (n=1) in the placebo group.
    - Five subjects had one or more elevated ALT values assessed by the investigator as clinically significant and considered drug-related. Peak ALT levels ranged from 1.9 to 3.8×Upper Limit of Normal. All 5 subjects were in the 3 highest dose groups (i.e., 300 (n=1), 400 (n=2) and 600 mg (n=2)). In four of the five subjects, ALT values declined to normal range by the end of the study. In one subject ALT values declined steadily, after the subject abstained from alcohol.
  - Study 2
    - Nausea was the most frequent AE (n=4; 25%) observed in Part B following oral administration of PTK796, however no case was reported following IV administration.
  - Study 3
    - In the IV group, four subjects had a total of seven AEs, of which only one (dysphoria) was considered to be drug-related by the investigator.

CONCLUSIONS

- PTK796 showed dose-proportional pharmacokinetics after intravenous administration. The 100 mg IV and 300 mg PO doses produced comparable total exposures.
- The terminal elimination half life supports once-daily dosing.
- PTK796 administered intravenously and orally was well tolerated.

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