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## Population Pharmacokinetic Modeling of TP-434, a Novel Fluorocycline, Following Single and Multiple Dose Administration

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### Abstract/Introduction

**Background:** A multiple ascending dose (MAD) study was completed for TP-434. TP-434 was administered for 10 days at doses of 0.5 mg/kg QD over 30 minutes, 1.5 mg/kg QD over 30 minutes, 1.5 mg/kg QD over 1 hour and 1 mg/kg BID over 1 hour. In each cohort, 6 subjects received TP-434 and 2 subjects received placebo. Plasma and urinary TP-434 samples were collected throughout the study. This analysis aimed to describe the pharmacokinetics (PK) of TP-434, confirm previously determined PK and select dosing regimens for further investigation.

**Methods:** Population PK analyses were done with ADAPT 5 (maximum likelihood expectation maximization) using plasma and urinary data collected for each group. Standard model discrimination criteria were used to determine the best model. Two-, three- and four-compartment models were tested. Results were then compared to those obtained from single ascending dose (SAD) data.

**Results:** The PK of TP-434 was described by a 4-compartment model with linear elimination. Mean parameters (% intersubject variability) were Vc = 12.2 L (10.9%), CLnr = 11.5 L/h (23.0%), Vp1 = 16.6 L (2.28%), CLd1 = 29.9 L/h (21.2%), Vp2 = 188 L (15.4%), CLd2 = 4.90 L/h (46.7%), Vp3 = 103 L (9.56%), CLd3 = 21.2 L/h (29.4%) & CLr = 2.05 L/h (15.7%). Based on the MAD study, steady-state volume of distribution was 320 L and mean half-life was around 48 hours. Residual variability for plasma and urinary data was 14.0% and 21.5%, respectively. Results were similar to those reported following SAD administration & daily doses  $\geq 1.5$  mg/kg were predicted to be effective for organisms with MIC  $\leq 2$   $\mu$ g/ml.

**Conclusion:** The multiple dose PK of TP-434 was well-described by a 4-compartment model. Results are in line with those previously determined using SAD data and indicate dose linearity. The doses predicted to cover all pathogens with MICs  $\leq 2$   $\mu$ g/ml will be tested in a Phase 2 trial for treatment of complicated intra-abdominal infections.

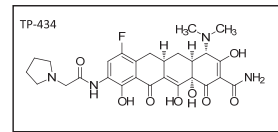
#### Background

- TP-434 (Figure 1) is a novel fluorocycline being developed by Tetraphase Pharmaceuticals.
- The potency and spectrum of TP-434 warrants its further development as a new treatment option for serious nosocomial infections, including intra-abdominal, skin, and respiratory infections.
- A single ascending dose (SAD) study was recently completed in healthy volunteers.
- Population pharmacokinetic (PK) analyses were performed throughout the conduct of the SAD study in order to describe the disposition of TP-434 using an appropriate model.
- Simulations were performed with this model to determine what dosing regimens should be further evaluated in a multiple ascending dose (MAD) setting.

#### Objectives

- To describe the PK of TP-434 following single dose administration.
- To predict multiple-dose PK of TP-434 based on SAD study results.
- To characterize the PK of TP-434 following multiple dose administration and confirm previously determined results.

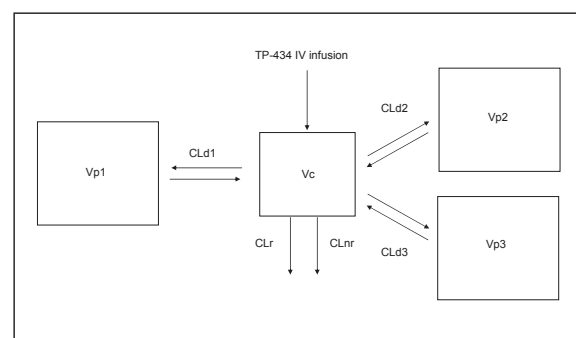
Figure 1. Chemical Structure of TP-434



#### Final Model for Single and Multiple-Dose Administration

- The final model selected to describe the plasma PK of TP-434 was a 4-compartment model with linear elimination, as depicted in Figure 2.
- A mixed additive and proportional error model was used for residual variability.

Figure 2. Final PK Model for TP-434



CLd1: Distributional clearance between central and peripheral compartment 1, CLnr: non-renal clearance, CLr: renal clearance, Vc: central volume of distribution, Vp1: Peripheral volume of distribution of TP-434 (1<sup>st</sup> compartment)

### Methods

Table 1: Study Designs

| Study | Total number of healthy subjects enrolled | TP-434 Dosing Regimens*   | Treatment Duration | Sampling Schedule*   |       |
|-------|---|---|--------------------|--|-------|
|       |   |   |                    | Plasma   | Urine |
| SAD   | 56  | 0.5 mg/kg IV infused over 30 minutes<br>1.5 mg/kg IV infused over 30 minutes<br>1.5 mg/kg IV infused over 1 hour<br>1 mg/kg BID over 1 hour | Single dose        | Pre-dose, 0.25, 0.5, 1, 2, 4, 8, 16, 32, 64, 128, 256, 512, 1024, 2048, 4096, 8192, 16384, 32768, 65536, 131072, 262144, 524288, 1048576, 2097152, 4194304, 8388608, 16777216, 33554432, 67108864, 134217728, 268435456, 536870912, 1073741824, 2147483648, 4294967296, 8589934592, 17179869184, 34359738368, 68719476736, 137438953472, 274877906944, 549755813888, 1099511627776, 2199023255552, 4398046511104, 8796093022208, 17592186044416, 35184372088832, 70368744177664, 140737488355328, 281474976710656, 562949953421312, 1125899906842624, 2251799813685248, 4503599627370496, 9007199254740992, 18014398509481984, 36028797018963968, 72057594037927936, 144115188075855872, 288230376151711744, 576460752303423488, 1152921504606846976, 2305843009213693952, 4611686018427387904, 9223372036854775808, 18446744073709551616, 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