

## ABSOLUTE ORAL BIOAVAILABILITY AND INTRAVENOUS PHARMACOKINETICS OF TOREZOLID PHOSPHATE IN HEALTHY SUBJECTS



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### INTRODUCTION

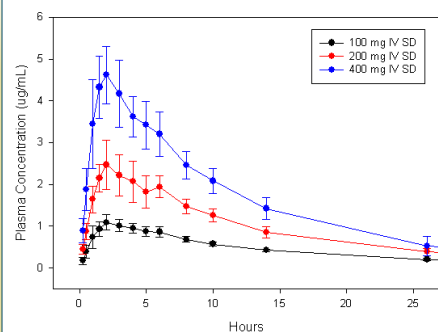
Torezolid phosphate (TR-701 FA) is a novel oxazolidinone prodrug antibiotic that is rapidly converted to the microbiologically active molecule torezolid (TR-700). TR-700 is active against gram-positive bacteria, including linezolid- and methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci. To further characterize intravenous TR-701 FA, a randomized, double-blind, placebo-controlled, single-dose escalation, bioavailability, safety, tolerability, and pharmacokinetic study was performed in healthy subjects. Single doses were escalated from 100 to 200 to 400 mg/day. Absolute bio-availability was assessed following a single 200 mg dose of TR-701 FA in tablet and infusion formulations.

### METHODS

Three cohorts of 12 subjects each (9 active and 3 placebo) received a single dose of placebo or 100, 200, or 400 mg intravenous TR-701 FA in one of three possible regimens: 1) in 500 mL of saline infused over 2 hours, 2) in 250 mL of saline infused over 2 hours or, 3) in 250 mL of saline infused over 1 hour. For the absolute bioavailability determination, a cohort of 8 subjects received the following treatments in a cross-over design: a single 1-hour infusion of 200 mg TR-701 FA in 250 mL saline and, 2) a single dose of one 200 mg TR-701 FA tablet administered with 240 mL water.

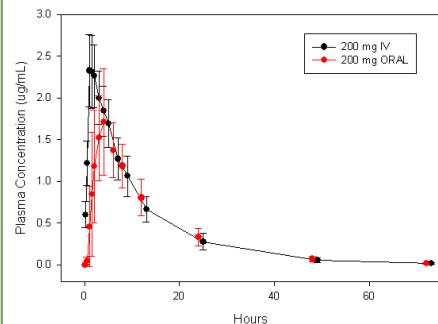
### SINGLE DOSE PLASMA CONCENTRATIONS

**Mean TR-700 Plasma Concentrations Following Single Dose (SD) 100, 200 and 400 mg IV Doses of TR-701 FA**



### BIOAVAILABILITY ASSESSMENT

**Mean TR-700 Plasma Concentrations Following 200 mg TR-701 FA Oral vs IV Dose**



### DATA

Mean (SD) Plasma TR-700 Parameter Data	Single Ascending Dose		
	IV TR-701 FA 100 mg QD n = 9	IV TR-701 FA 200 mg QD n = 9	IV TR-701 FA 400 mg QD n = 9
$C_{max}$ (µg/mL)	1.16 (0.19)	2.62 (0.58)	5.13 (0.79)
DN $C_{max}$ (µg/mL)/(mg)	14.18 (2.27)	15.96 (3.52)	14.97 (15.60)
$T_{max}$ (median hr) (range)	1.92 (1.08 – 2.25)	2.17 (0.92 – 2.33)	2.10 (0.92 – 2.50)
$AUC_{0-t}$ (µg*hr/mL)	17.02 (1.66)	29.99 (10.34)	58.19 (11.38)
$AUC_{0-inf}$ (µg*hr/mL)	17.36 (1.77)	32.58 (8.30)*	58.70 (11.59)
DN $AUC_{0-inf}$ (µg*hr/mL)/(mg)	0.212 (0.022)	0.199 (0.051)*	0.178 (0.035)
CL (L/hr)	4.77 (0.51)	5.41 (1.75)*	5.79 (1.06)
$V_{ss}$ (L)	74.46 (9.42)	67.07 (15.34)*	67.46 (12.16)
$t_{1/2}$ (hr)	13.36 (1.14)	11.05 (0.76)*	11.31 (1.23)

\*n = 8

### BIOAVAILABILITY

Mean (SD) TR-700 PK Parameter Data	200 mg IV TR-701 FA n = 8	200 mg Oral TR-701 FA n = 8
$C_{max}$ (µg/mL)	2.48 (0.41)	1.91 (0.44)
$T_{max}$ (median hr) (range)	1.17 (0.93 – 3.00)	3.50 (1.50 – 8.02)
$AUC_{0-t}$ (µg*hr/mL)	28.71 (6.01)	26.33 (5.88)
$AUC_{0-inf}$ (µg*hr/mL)	29.02 (6.14)	26.67 (6.03)
CL or CL/F (L/hr)	5.92 (1.50)	6.52 (1.89)
$t_{1/2}$ (hr)	11.39 (2.00)	11.06 (2.12)
F %	NA	91.7 (6.8)

Dose dependent CL, CL/F, and F were adjusted for TR-700 by molecular adjustment to TR-701

### RESULTS

- After single dose administration, mean  $C_{max}$  and  $AUC_{0-inf}$  values for TR-700 increased in a linear and proportional manner to TR-701 FA dose levels ranging from 100 to 400 mg (1.16 to 5.13 µg/mL and 17.36 to 58.70 µg\*hr/mL, respectively).
- TR-700 systemic clearance (CL) and volume of distribution ( $V_{ss}$ ) were not affected by TR-701 FA dose levels after IV administration.
- The prodrug TR-701 FA was only detected above the limit of quantitation (5 ng/mL) during the infusion, and for a maximum of 4 hours after infusion.
- The absolute bioavailability of TR-700 from the TR-701 FA tablet was 91.7% with low interpatient variability observed.

### CONCLUSIONS

- The absolute bioavailability of TR-700 from TR-701 FA tablets was 91.7%, demonstrating TR-701 FA is rapidly and completely converted to the active moiety and absorbed.
- These results indicate dosage adjustments between IV and oral administration of TR-701 FA will not be necessary.