

ABSOLUTE BIOAVAILABILITY OF TR-701 FA AND PHARMACOKINETICS AFTER SINGLE AND MULTIPLE DOSE INTRAVENOUS ADMINISTRATION IN HEALTHY ADULT SUBJECTS

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INTRODUCTION

TR-701 Free Acid (FA) is a novel oxazolidinone prodrug antibiotic of the active moiety TR-700, currently being developed for both intravenous (IV) and oral administration for the treatment of acute bacterial skin and skin structure infections (ABSSSI). TR-701 FA 200 mg QD has been selected as the therapeutic dose for ABSSSI.

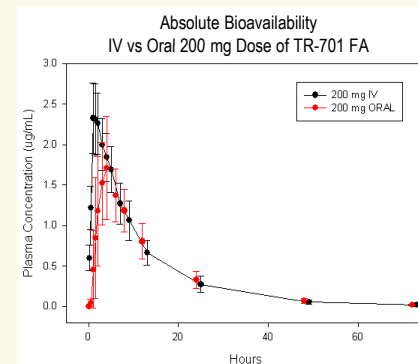
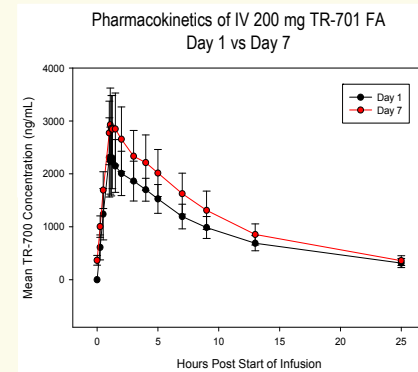
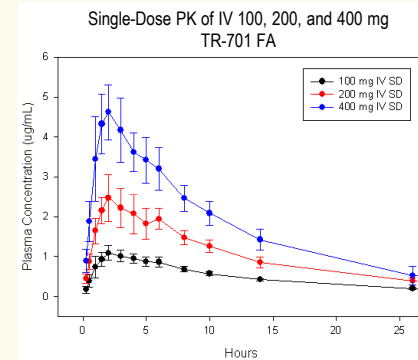
STUDY DESIGN

A randomized, double-blind, placebo-controlled, single- and multiple-dose study was performed to determine the pharmacokinetics (PK) of IV TR-701 FA in healthy adults. Single-dose (SD) cohorts of 12 subjects each were escalated from 100 to 200 to 400 mg IV. A multiple-dose (MD) cohort of 10 subjects (8 active and 2 placebo) received daily IV infusions of 200 mg TR-701 FA infused over one hour in 250 cc of sterile saline for up to 7 days. In a separate, open label absolute bioavailability (Fabs) cohort, 8 subjects received TR-701 FA 200 mg IV over one hour in 250 cc of saline and a 200 mg tablet of TR-701 FA in 240 cc of water in a cross-over design.

RESULTS

The SD mean C_{max} and AUC_{0-inf} values for TR-700 increased in a linear and proportional manner to TR-701 FA dose levels of 100 to 400 mg (1.16 to 5.13 $\mu\text{g/mL}$ and 17.36 to 58.70 $\mu\text{g}\cdot\text{hr/mL}$, respectively). A slight increase in MD mean C_{max} and $t_{1/2}$ values were observed on Day 7 compared to Day 1, however, TR-700 AUC_{0-24} and systemic clearance (CL) values were similar between single and multiple dosing indicating a lack of accumulation. TR-700 concentrations were generally similar on Day 7 compared to Day 1 at the 200 mg dose level. TR-700 CL and volume of distribution (V_{ss}) were not affected by TR-701 FA dose levels after IV administration. The Fabs of TR-700 from TR-701 FA 200 mg tablets was 91.7%.

DATA



TR-700 Parameter Means (SD) After Single Dose Administration of TR-701 FA IV

TR-700 Parameter Means (SD)	TR-701 FA IV 100 mg	TR-701 FA IV 200 mg	TR-701 FA IV 400 mg
C_{max} ($\mu\text{g/mL}$)	1.16 (0.18)	2.62 (0.58)	5.13 (0.79)
T_{max} (hrs) MEDIAN (RANGE)	1.92 (1.08-2.25)	2.17 (0.92-2.33)	2.10 (0.92-2.50)
$t_{1/2}$ (hrs)	13.4 (1.14)	11.0 (0.76)	11.3 (1.23)
AUC_{0-inf} ($\mu\text{g}\cdot\text{hr/mL}$)	17.36 (1.77)	32.58 (8.30)	58.70 (11.59)
CL (liters/hr)	4.77 (0.51)	5.41 (1.75)	5.79 (1.06)
V_{ss} (liters)	74.5 (9.42)	67.1 (15.3)	67.5 (12.2)

TR-700 Plasma Parameter Means (SD) After Multiple Dose (7 Days) Administration of TR-701 FA IV 200 mg QD

	Day 1	Day 7
C_{max} ($\mu\text{g/mL}$)	2.34 (0.64)	3.01 (0.66)
T_{max} (hr) [MEDIAN (min-max)]	1.08 (0.92-1.50)	1.17 (0.92-1.50)
$t_{1/2}$ (hr)	9.33 (1.5)	12.4 (1.25)
AUC_{0-24} ($\mu\text{g}\cdot\text{hr/mL}$)	22.29 (4.24)	29.19 (6.22)
Linearity Ratio (AUC_{0-24} Day 7 / AUC_{0-inf} Day 1)	1.1	
CL (liters/hr)	6.37 (1.19)	5.87 (1.41)
V_{ss} (liters)	77.6 (15.9)	80.1 (21.0)

Absolute Bioavailability of Oral TR-701 FA Tablet Relative to IV TR-701 FA

Parameter (Units)	N	Test Mean (200 mg FA Oral Tablet)	Reference Mean (200 mg FA IV)	Test/Reference	90% Confidence Interval
AUC_{0-inf} ($\text{ng}\cdot\text{hr/mL}$)	8	25972	28393	91.47 ^a	(86.81, 96.38)
Fabs %	8	--	--	91.7 ^b	--

^a Ratio of parameter means for natural log transformed parameter (expressed as a percent). Natural log transformed ratios transformed back to the linear scale.
^b Arithmetic mean value

CONCLUSIONS

Following IV infusion, TR-701 FA is rapidly and completely converted to TR-700.

Day 1 pharmacokinetics of TR-700 are predictive of steady state PK.

IV TR-701 FA at 200 mg QD for 7 days showed no accumulation over time.

PK data support a once-daily dosing regimen for IV TR-701 FA.

The absolute bioavailability of the active moiety TR-700 with a 200 mg TR-701 FA tablet was 91.7%.

Dosage adjustments between IV and oral administration of TR-701 FA will not be necessary.

ACKNOWLEDGMENTS

We wish to acknowledge the staff at the Covance Clinical Research Unit in Madison, WI for their conduct of this clinical trial.