

HUMAN PHARMACOKINETICS OF TR-700 AFTER ASCENDING SINGLE ORAL DOSES OF THE PRODRUG TR-701, A NOVEL OXAZOLIDINONE ANTIBIOTIC

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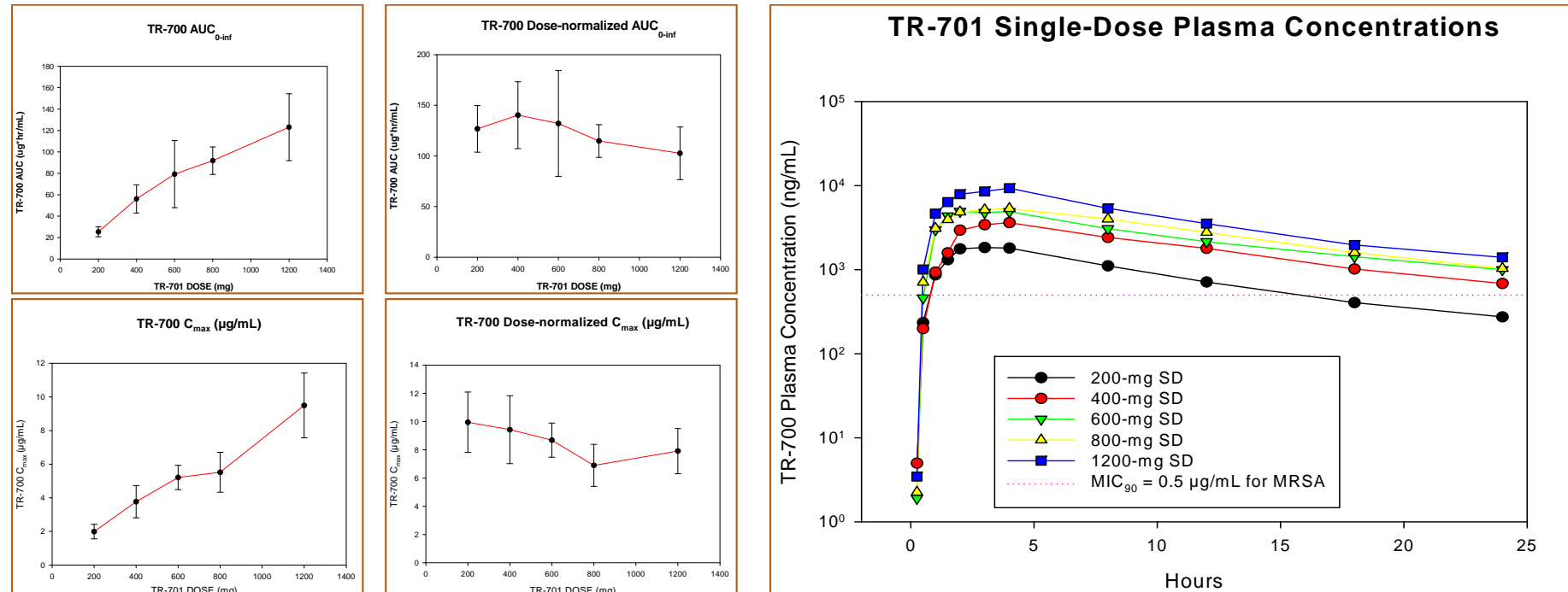
INTRODUCTION

The prodrug TR-701 is a novel oxazolidinone antibiotic that is rapidly converted *in vivo* by phosphatases, to the active molecule TR-700. TR-700 is 4- to 8-fold more potent *in vitro* and *in vivo* than linezolid against Gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE), as well as Gram-negative bacteria including *Mycobacterium tuberculosis* and *Legionella pneumophila*.

STUDY DESIGN

A randomized, double-blind, placebo-controlled, ascending single-dose study was performed to assess the safety, tolerability and pharmacokinetics (PK) of TR-701 and TR-700 in healthy adult subjects. Cohorts of 8 subjects (6 active and 2 placebo) received single oral doses of 200, 400, 600, 800, or 1200 mg TR-701 after a 10-hr fast. Plasma and urine concentrations of TR-701 and TR-700, were determined by Covance Bioanalytical Laboratory Services, Inc. using a validated analytical procedure (LC-MS/MS). Written informed consent was obtained from all subjects prior to any study-specific procedures were carried out.

DATA



TR-700 Parameter Means (SD)	TR-701 200 mg QD	TR-701 400 mg QD	TR-701 600 mg QD	TR-701 800 mg QD	TR-701 1200 mg QD
C_{max} (µg/mL)	2.0 (0.4)	3.8 (1.0)	5.2 (0.7)	5.5 (1.2)	9.5 (1.9)
T_{max} (median hours) (RANGE)	3 (1-4)	3.5 (2-4)	2.5 (2-4)	4 (2-8)	4 (2-4)
t_{1/2} (hours)	11.2 (3.6)	10.8 (0.8)	11.4 (2.6)	10.6 (1.3)	10.4 (1.4)
AUC_{0-infinity} (µg·hr/mL)	25.4 (4.6)	56.1 (13.2)	79.3 (31.3)	91.8 (12.9)	123.1 (31.2)
CL/F¹ (mL/min)	8.1 (1.5)	7.4 (1.6)	8.8 (4.0)	8.9 (1.3)	10.4 (3.0)
Vz/F¹ (liters)	128 (31)	116 (24)	134 (31)	135 (19)	154 (39)

¹Based upon TR-701 dose

SUMMARY RESULTS & CONCLUSIONS

- ◆ TR-701 is rapidly converted to TR-700
- ◆ TR-700 plasma concentrations were above the MIC₉₀ (0.5 µg/mL) for MRSA and VRE for an average of 15.3 hrs at 200 mg, and for greater than 24 hrs at doses of 400 mg and above
- ◆ For TR-700, mean t_{1/2} values ranged from 10.4-11.4 hrs and median T_{max} values ranged from 2.5-4 hrs
- ◆ Mean C_{max} and AUC_{0-inf} for TR-700 increased in a linear and approximately dose-proportional manner from 200-1200 mg
- ◆ TR-701 was only detected above the 5 ng/mL limit of quantitation in a single subject in the 1200-mg cohort from 0.25-3 hrs (range 5.9-16.9 ng/mL)
- ◆ Less than 1% of the TR-701 dose was excreted in urine as either TR-701 or TR-700
- ◆ Single-doses of TR-701 were well-tolerated up to 1200 mg with no significant clinical or laboratory abnormalities
- ◆ These PK data support a once-daily dosing regimen for TR-701