

HUMAN PHARMACOKINETICS OF THE PRODRUG TR-701 AND TR-700, ITS ACTIVE MOIETY, AFTER MULTIPLE ORAL DOSES OF TR-701, A NOVEL OXAZOLIDINONE

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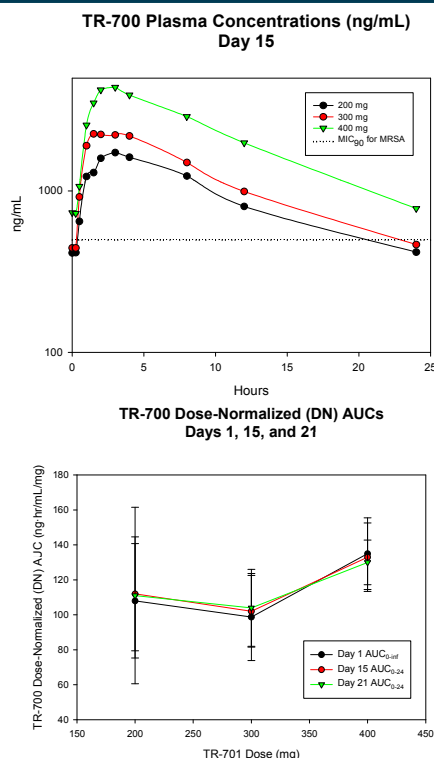
INTRODUCTION

TR-701 is a novel oxazolidinone prodrug antibiotic rapidly converted *in vivo* by phosphatases to the active moiety, TR-700. TR-700 is 4- to 8-fold more potent *in vitro* and *in vivo* than linezolid against all Gram-positive bacteria including multi-drug resistant strains.

STUDY DESIGN

A Phase 1 randomized, double-blind, placebo- and active comparator- (linezolid) controlled dose escalation, safety, and pharmacokinetic (PK) study of TR-701 was conducted in healthy volunteers. The study was conducted at the Covance Phase 1 Research Unit (CRU) in Madison, WI. Cohorts of 10 subjects (8 active and 2 placebo) received either 200, 300, or 400 mg QD TR-701, or 600 mg BID linezolid for 21 days. Subjects were confined to the CRU for 25 days. Plasma and urine PK analyses were performed for subjects in all dose groups on Days 1, 15, and 21.

DATA



PHARMACOKINETICS OF TR-700 AND LINEZOLID

Human Pharmacokinetic Parameters Cohort Means (n=8) Days 1 and 15 (SD)

Parameter	TR-701 200 mg QD		TR-701 300 mg QD		TR-701 400 mg QD		Linezolid 600 mg BID	
	Day 1	Day 15 ^b	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15
C_{max} (µg/mL)	1.8 (1.2)	1.8 (0.4)	2.1 (0.5)	2.5 (0.4)	4.2 (0.8)	4.5 (0.9)	12.2 (3.0)	14.6 (4.6)
C_{min} (µg/mL)	0.3 (0.1)	0.4 (0.2)	0.4 (0.1)	0.5 (0.2)	0.7 (0.2)	0.8 (0.2)	1.7 (1.4)	4.9 (3.3)
T_{max} (median hrs) (range)	3.0 (1.5-4.0)	3.0 (2.0-4.0)	2.0 (1.5-4.0)	1.8 (1.5-4.0)	4.0 (1.0-4.0)	3.0 (2.0-8.0)	1.0 (0.4-1.5)	1.5 (1.0-4.0)
t_{1/2} (hrs)	11.1 (1.2)	10.2 (2.0)	10.1 (1.4)	9.4 (1.2)	8.0 (1.2)	8.4 (1.0)	3.8 (1.7)	4.7 (1.3)
AUC (µg·hr/mL) 0-inf Day 1 / 0-tau Day 15	21.6 (6.5)	22.5 (6.5)	29.6 (7.5)	30.7 (6.1)	54.0 (8.2)	53.2 (7.9)	78.1 (31.6)	108.9 (42.7)
AUC CV%	30	29	25	20	15	15	40	39
Accumulation Ratio (AUC Day 15 / AUC Day 1)	1.04		1.04		0.99		1.39	
CL/F^a (liters/hr)	10.0 (2.8)	9.5 (2.7)	10.6 (2.4)	10.1 (1.8)	7.6 (1.1)	7.7 (1.1)	8.7 (3.1)	6.4 (2.7)
Vz/F^a (liters)	155 (29)	143 (51)	155 (37)	136 (23)	86 (13)	92 (18)	43 (11)	43 (11)

^aBased upon TR-701 Dose, ^bSteady-state Day 15 and Day 21 PK results were comparable

SUMMARY RESULTS

- ◆ Mean C_{max} and AUC values for TR-700 increased in approximately dose-proportional manner after both single and steady-state administration
- ◆ Elimination half-life for TR-700 ranged between 8-11.1 hrs, approximately 2-fold longer than linezolid
- ◆ Plasma concentrations of TR-700 were maintained at >0.5 µg/mL (the MIC₉₀ for MRSA and VRE) for >60% of the 24-hr dosing interval at 200 and 300 mg TR-701, and the entire interval at 400 mg
- ◆ TR-701 was not detected in plasma at these dose levels
- ◆ Less than 1% of the TR-701 dose was excreted in urine as either TR-701 or TR-700

CONCLUSIONS

- ◆ TR-700 shows a favorable PK profile as compared to linezolid and supports doses of 200, 300, and 400 mg in Phase 2 clinical trials
- ◆ TR-700 has a PK profile consistent with once-a-day administration of TR-701
- ◆ The lower variability in systemic exposure and no accumulation of TR-700 versus linezolid should translate into a more predictable safety profile for TR-701
- ◆ Day 1 pharmacokinetics of TR-700 are predictive of repeat administration of TR-701 at steady state
- ◆ The volume of distribution is 2 to 3 times higher than for linezolid
- ◆ The key pharmacodynamic driver for the efficacy of oxazolidinones is AUC/MIC. The value for TR-701 at 200 mg QD (22.5/0.5=45) is greater than for linezolid at 600 mg BID (109/4=27.3)