

IMPROVED PHARMACOKINETICS OF THE NOVEL OXAZOLIDINONE ANTIBIOTIC TOREZOLID PHOSPHATE COMPARED TO LINEZOLID IN HEALTHY SUBJECTS

K. A. Muñoz¹, C. Bethune², J. Bohn², R. Wright², P. Bien¹, P. Prokocimer¹
¹Trius Therapeutics, San Diego, CA; ²Covance Inc, Madison, WI



INTRODUCTION

Torezolid phosphate (TR-701) is a novel oxazolidinone prodrug that is rapidly converted to the microbiologically-active molecule torezolid (TR-700). TR-700 is active against gram-positive organisms. TR-701 is about to undergo Phase 3 trials for acute bacterial skin and skin structure infections.

OBJECTIVES

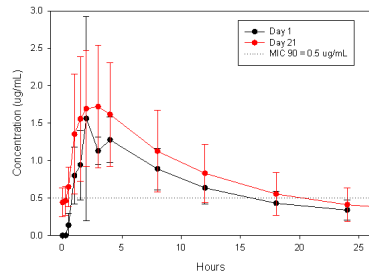
To compare the pharmacokinetics and safety of the therapeutic dose of TR-701 and the currently label-approved dose of linezolid after multiple dosing in healthy adults.

METHODS

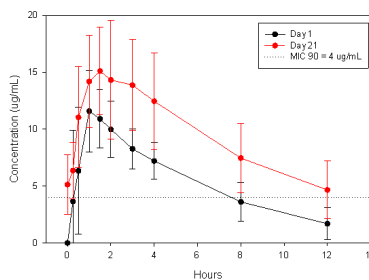
A multiple-dose study was performed to determine the pharmacokinetics of the prodrug TR-701 and its active moiety, TR-700, compared to linezolid in healthy adults. Each cohort of 10 subjects (8 active and 2 placebo) received oral doses of 200 mg TR-701 once-a-day or twice daily oral doses of 600 mg linezolid for 21 days.

PK FIGURES

Mean Plasma Concentrations TR-700 (µg/mL) TR-701 200 mg QD



Mean Plasma Concentrations Linezolid (µg/mL) Linezolid 600 mg BID



DATA

Human Pharmacokinetic Parameters Cohort Means (SD) Days 1 and 21

Parameter	TR-701 200 mg QD n = 8		LINEZOLID 600 mg BID n = 8	
	Day 1	Day 21	Day 1	Day 21
C_{max} (µg/mL)	1.79 (1.25)	1.92 (0.86)	12.19 (3.00)	16.52 (4.59)
C_{min} (µg/mL)	0.34 (0.13)	0.44 (0.19)	1.69 (1.40)	5.13 (2.61)
T_{max} (median hr) (range)	3.02 (1.5, 4.05)	1.50 (0.25, 4.0)	1.00 (0.35, 1.50)	1.50 (0.50, 4.00)
t_{1/2} (hr)	11.1 (1.20)	14.7 (2.34)	3.80 (1.67)	5.75 (1.15)
AUC_{0-inf} (µg·hr/mL)	21.61 (6.54)	NA	78.07 (31.61)	NA
AUC_{0-tau} (µg·hr/mL)	16.71 (3.80)	22.13 (10.10)	65.90 (19.17)	114.57 (38.15)
Linearity Ratio (AUC _{0-tau} Day 21/AUC _{0-inf} Day 1)	0.97 (0.35)		1.47 (0.26)	
CL/F (liters/hr)	7.48 (2.12)	6.63* (2.05)	8.73 (3.09)	5.76 (1.89)
Vz/F (liters)	117 (21.9)	131* (31.6)	42.9 (11.2)	46.1 (12.7)

*N = 7
 tau = 24 hours for TR-701 and tau = 12 hours for linezolid

RESULTS

- Following oral administration of TR-701 capsules at 200 mg QD for 21 days, the pharmacokinetics of TR-700 after a single dose of TR-701 well predicted the exposure after repeat administration (linearity ratio = 0.97).
- Steady-state concentrations of TR-700 were achieved by 3 days of repeat administration of TR-701.
- Mean TR-700 C_{max} and AUC values were similar between Day 1 and Day 21 while linezolid mean C_{max} and AUC values increased after multiple dosing.
- There was no evidence of accumulation of TR-700, while linezolid showed a 47% increase in the extent of exposure from Day 1 to Day 21.
- Mean TR-700 oral clearance (CL/F) values decreased 11%, compared to a decrease of 34% observed for linezolid after 21 days of repeat administration.
- Mean half-life (t_{1/2}) values for TR-700 were over 2-fold greater than those observed with linezolid.

CONCLUSIONS

- After multiple dosing with TR-701 or linezolid for 21 days, TR-700 exhibited consistent exposure without accumulation.
- Linezolid exposure increased after repeat administration.
- Both drugs were safe and well-tolerated.