

# TR-701 (DA-7218) is Significantly More Potent than Linezolid in Skin and Soft Tissue Models of Infection

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## Abstract

### Background:

Skin and soft tissue infections (SSTIs) are a common cause of morbidity in both community and hospital acquired infections. In this study, the efficacy of TR-701 (DA-7218), a novel oxazolidinone prodrug, and linezolid were evaluated in both the thigh and air pouch models of MRSA infection.

### Methods:

For the thigh infection model, mice were rendered neutropenic by IP injection of cyclophosphamide. Infections were initiated by injecting  $10^8$  CFU of log phase MRSA strain M126 into the right thigh of each mouse. TR-701 or linezolid were dosed by oral gavage 2 hrs post infection with 5, 10 and 20 mg/kg once- or twice-daily for either one or two days. Thighs were removed and viable counts were determined. For the air pouch model, mice were injected with 5 mL of air into the loose connective dorsal tissue. After 24 hrs, 2 mL of  $10^6$  CFU of MRSA M126 in 5% mucin were inoculated into each pouch. Treatments with TR-701 or linezolid began immediately after infection at 5, 10 and 20 mg/kg once- or twice-daily for either one or two days. Viable counts were determined after aspiration of the pouch fluid at either 24 or 48 hrs after the first treatment and compared to control mice.

### Results:

The doses required for reducing the CFU of MRSA in the thigh model were 5 mg/kg for TR-701 and 20 mg/kg for linezolid, respectively. TR-701 demonstrated a 0.9 to 2.5 greater log reduction in cfu/thigh and a 0.8 to 5 greater log reduction in CFU/mL in an air pouch, on a dose per dose comparison versus linezolid whether compounds were dosed once- or twice-daily for two days.

### Conclusions:

In two mouse models of SSTI infection (thigh and air pouch), TR-701 was found to be significantly more potent than linezolid against an MRSA strain, whether dosed once- or twice daily for either 1 or 2 days.

## Methods

### Thigh infection model

Male ICR mice were rendered neutropenic by intraperitoneal (IP) administration of cyclophosphamide. MRSA M126 was grown in tryptic soy agar medium. The organisms were collected and suspended in saline to the appropriate concentration. Bacterial suspensions (0.1 mL) containing approximately  $4.5 \times 10^8$  CFU/mL were inoculated into right thigh of mice. TR-701 (DA-7218) and linezolid were administered orally 2 hour post infection with 5, 10, and 20 mg/kg once-daily or twice-daily for either one or two days. The thighs were removed at each time point and homogenized in 10 mL of 0.9% saline. The viable bacterial counts in the thigh homogenates were determined.

### Air pouch model

Air pouches were induced in ICR mice by injecting 5 mL of sterile filtered air into loose connective dorsal tissue. Bacterial suspensions of MRSA M126 were prepared in saline containing 5% bacteriological mucin. After 24 hours, bacterial suspensions (2 mL) containing approximately  $10^6$  CFU/mL were inoculated into each pouch. Oral treatments with TR-701 (DA-7218) and linezolid began immediately after infection at 5, 10, and 20 mg/kg once- or twice-daily for either one or two days. The infected pouch fluids were collected just before treatment and at each time points. Viable counts were determined after aspiration of the pouch fluid and compared to control mice.

## Results

### Thigh infection model (Table 1 and Fig. 1)

- All doses tested for reducing the viable counts in a thigh were 5 mg/kg for TR-701 (DA-7218) and 20 mg/kg for linezolid.
- Treatment with TR-701 (DA-7218) gave significantly lower CFU counts of MRSA than linezolid using either once- or twice-daily dosing for either one or two days at all doses examined.

### Air pouch model (Table 2 and Fig. 2)

- The doses required for reducing the viable counts in the pouch fluid were 5 mg/kg for TR-701 (DA-7218) and 10 mg/kg for linezolid.
- Treatment with TR-701 (DA-7218) gave significantly lower CFU counts of MRSA than linezolid using either once- or twice-daily dosing for two days at all doses examined.

Table 1. Efficacy of TR-701 (DA-7218) and linezolid in a murine thigh infection model.

Dose (mg/kg/day)	Dosing regimen <sup>b</sup>	Log Reduction of CFU/thigh <sup>a</sup>			
		TR-701 (DA-7218)		Linezolid	
		24h	48h	24h	48h
5	BID	3.45	2.10	1.07	0.08
10	BID	2.99	4.01	0.97	1.48
20	BID	3.75	4.35	2.21	2.83
5	QD	2.68	2.31	0.82	1.45
10	QD	2.82	2.92	1.03	1.90
20	QD	3.44	4.36	2.28	2.05

<sup>a</sup> Values are log reduction in CFU/thigh from vehicle control group.  
<sup>b</sup> Abbreviations: BID = twice-daily dosing; QD = once-daily dosing.

Fig. 1. Antimicrobial efficacy of TR-701 (DA-7218) compared with that of linezolid in a murine thigh infection model.

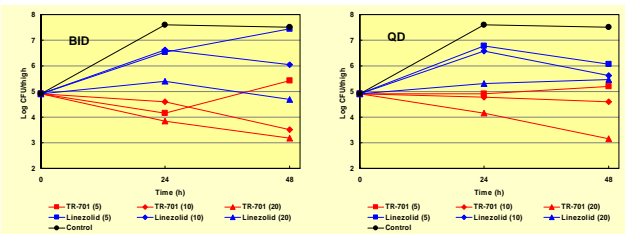
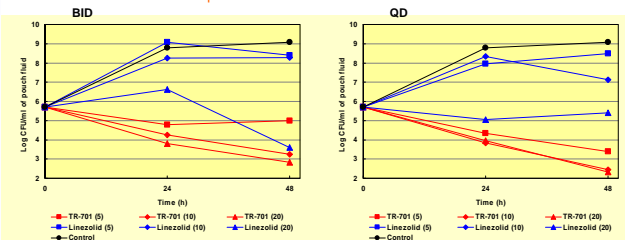


Table 2. Efficacy of TR-701 (DA-7218) and linezolid in a murine air pouch model.

Dose (mg/kg/day)	Dosing regimen <sup>b</sup>	Log Reduction of CFU/mL <sup>a</sup>			
		TR-701 (DA-7218)		Linezolid	
		24h	48h	24h	48h
5	BID	4.00	4.07	-0.29	0.66
10	BID	4.55	5.82	0.55	0.78
20	BID	4.98	6.23	2.16	5.47
5	QD	4.45	5.67	0.83	0.58
10	QD	4.95	6.63	0.44	1.95
20	QD	4.84	6.74	3.73	3.67

<sup>a</sup> Values are log reduction in CFU/thigh from vehicle control group.  
<sup>b</sup> Abbreviations: BID = twice-daily dosing; QD = once-daily dosing.

Fig. 2. Antimicrobial efficacy of TR-701 (DA-7218) compared with that of linezolid in murine air pouch model.



## Conclusions

- TR-701 (DA-7218) was found to be significantly more potent than linezolid against a MRSA strain in both thigh and air pouch infection models.
- TR-701 (DA-7218) showed up to a 2.5 greater log reduction in CFU than linezolid when compounds were dosed once- or twice-daily for either 1 or 2 days.

## Introduction

Skin and soft tissue infections (SSTIs) are a common cause of morbidity in both the community and the hospital acquired infections. SSTIs may be caused by a wide range of pathogens, with *Staphylococcus aureus* recovered from 40% of SSTIs in the SENTRY Antimicrobial Surveillance Program. A large number of antimicrobial agents are available for the treatment of skin infections. Uncomplicated infections such as impetigo, limited cellulitis and infected cysts may be treated effectively with numerous oral agents. However, complicated skin and skin structure infections (cSSSIs), such as extensive cellulitis, diabetic foot ulcers, major abscesses or wound infections, often require aggressive treatment, including intravenous antibiotics. In addition to the well-documented risk of acquiring infections caused by methicillin-resistant *S. aureus* (MRSA) in the hospital setting, there has been a steadily increasing incidence of community acquired MRSA infections causing cSSSIs, necessitating the use of agents such as vancomycin, daptomycin or linezolid. TR-701 (DA-7218) an oxazolidinone antibiotic, is an orally- and intravenously-administered prodrug of the microbiologically-active molecule, TR-700 (DA-7157), with good in vitro activity against gram-positive organisms including MRSA, VRE and PRSP. The present study compared the efficacy of TR-701 (DA-7218) with that of linezolid in two models of SSTI in mice.