

In vitro Activity of TR-700 (Torezolid) and Linezolid against Gram-positive Clinical Isolates from a Phase 2 Complicated Skin Clinical Trial

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Revised Abstract

Background: TR-700 (Torezolid), the active form of the prodrug TR-701, is an investigational oxazolidinone with potent activity against resistant gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA). Currently, TR-701 is undergoing clinical development for the treatment of serious gram-positive bacterial infections, including those caused by MRSA. This study examines the *in vitro* activity of TR-700 and linezolid (LZD) against gram-positive pathogens encountered during a recently completed Phase 2 complicated skin and skin structure infection (cSSSI) clinical trial.

Methods: A total of 196 isolates consisting of 183 gram-positive cocci (160 *S. aureus*, 7 coagulase-negative staphylococci [CoNS], 13 viridans group streptococci [VGS], and 3 beta-hemolytic streptococci [BHS]) were obtained at baseline from patients enrolled in a Phase 2, multi-center, randomized, double-blind study of oral TR-701 in the treatment of cSSSI in adults in the US. Susceptibility to TR-700 and LZD were determined by broth microdilution according to CLSI guidelines.

Results: *S. aureus* was the most frequently encountered baseline pathogen at 81.6%, followed by VGS (6.6%) and CoNS (3.6%). TR-700 had an MIC₅₀ and MIC₉₀ of 0.25 µg/mL against both MSSA and MRSA isolates relative to the MIC₅₀ of 1 µg/mL and MIC₉₀ of 2 µg/mL observed with LZD. CoNS TR-700 MICs ranged from 0.12-0.25 µg/mL, lower than LZD which had an MIC range of 0.5-1 µg/mL. Against VGS, TR-700 had an MIC₅₀ and MIC₉₀ of 0.25 µg/mL, relative to the MIC₅₀ of 0.5 µg/mL and MIC₉₀ of 1 µg/mL seen with LZD. 3 BHS (2 *S. agalactiae*, 1 *S. pyogenes*) had TR-700 MICs of 0.25, 0.25, and 0.12 µg/mL relative to MICs of 1, 0.5 and 0.5 µg/mL for LZD.

Conclusions: TR-700 had potent activity against baseline gram-positive cocci isolated during a cSSSI clinical trial, and its activity profile was not altered against MRSA, the most frequently encountered pathogen. Based on MIC₅₀/MIC₉₀s, TR-700 was 4-fold more potent than LZD against recovered gram-positive clinical isolates.

Background

TR-700 (Torezolid), the active moiety of the phosphate prodrug TR-701, has potent activity against commonly encountered resistant gram-positive cocci, including methicillin-resistant *Staphylococcus aureus* (MRSA). Based on its activity profile, TR-701 is currently undergoing clinical development for the treatment of serious gram-positive infections. The safety and efficacy of two doses of TR-701 for the treatment of complicated skin and skin structure infections (cSSSI) was evaluated in a recently completed phase II clinical trial. This study reports the *in vitro* activity profile of TR-700 against gram-positive cocci isolated during the course of this trial relative to linezolid, an in class comparator.

Methods

A total of 196 isolates were obtained at baseline from patients enrolled in a phase II, multi-center, randomized, double-blind study of oral TR-701 in the treatment of cSSSI in adults in the US. Of the baseline isolates collected, 183 were gram-positive cocci (160 *S. aureus*, 7 coagulase-negative staphylococci [CoNS], 13 viridans group streptococci [VGS], and 3 beta-hemolytic streptococci). All isolates received throughout the trial period were centrally tested against TR-700 and linezolid by broth microdilution according to CLSI guidelines (M7-A8; M100-S18). With regards to CoNS, *S. epidermidis* were excluded from MIC analysis.

Results

Table 1. Frequency of baseline pathogens from clinical trial

Organism	n	%
<i>Staphylococcus aureus</i>	160	81.6
Coagulase negative staphylococci	7	3.6
<i>Corynebacterium</i> spp.	3	1.5
<i>Enterococcus avium</i>	1	0.5
<i>Klebsiella pneumoniae</i>	5	2.6
<i>Micrococcus species</i>	1	0.5
<i>Morganella morganii</i>	1	0.5
<i>Proteus mirabilis</i>	1	0.5
<i>Pseudomonas aeruginosa</i>	1	0.5
<i>Streptococcus agalactiae</i>	2	1.0
<i>Streptococcus pyogenes</i>	1	0.5
Viridans streptococci	13	6.6
Total	196	100

Figure 1. MIC distribution of TR-700 and linezolid against staphylococci

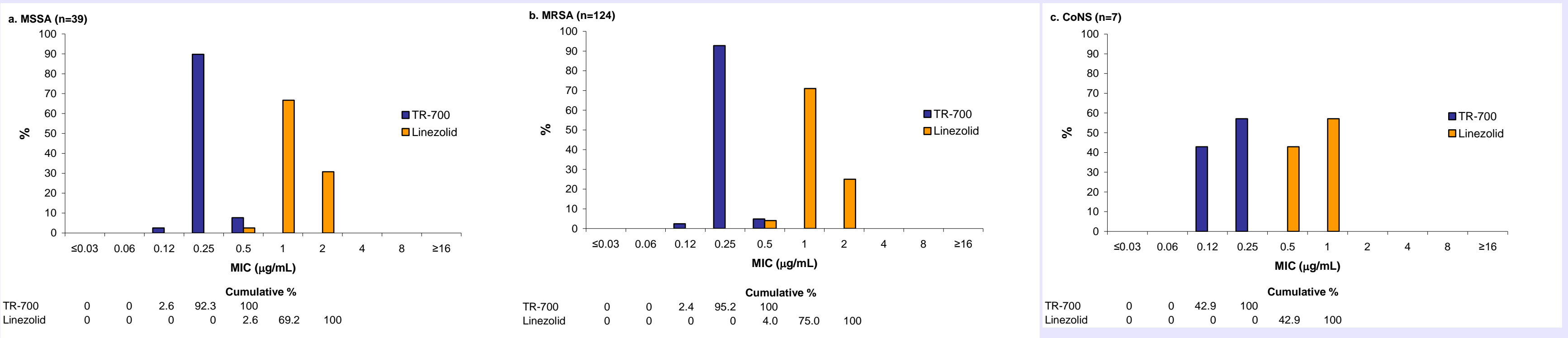


Table 2. Antimicrobial activity of TR-700 and linezolid against staphylococci

Organism	Agent	Phenotype ^a	Total n	Range	MIC (µg/mL)			nS	%S	nl	%l	nR	%R
					Mode	MIC ₅₀	MIC ₉₀						
<i>S. aureus</i>	TR-700	All	163	0.12-0.5	0.25	0.25	0.25	— ^b	—	—	—	0	0
		MSSA	39	0.12-0.5	0.25	0.25	0.25	—	—	—	—	0	0
	Linezolid	All	163	0.5-2	1	1	2	163	100	0	0	0	0
		MSSA	39	0.5-2	1	1	2	39	100	0	0	0	0
CoNS	TR-700	All	7	0.12-0.25	NA ^c	NA	NA	—	—	—	—	0	0
		Linezolid	7	0.5-1	NA	NA	NA	7	100	0	0	0	0

^aMSSA/ MRSA, methicillin susceptible/ resistant *S. aureus*

^bCLSI MIC breakpoints not available for interpretation

^cNA, not applicable: n <10

Table 3. Antimicrobial activity of TR-700 and linezolid against viridans group streptococci

Agent	Total n	Range	MIC (µg/mL)			nS	%S	nl	%l	nR	%R
			Mode	MIC ₅₀	MIC ₉₀						
TR-700	15	0.03-0.25	0.25	0.25	0.25	— ^a	—	—	—	0	0
Linezolid	15	0.12-1	1	0.5	1	15	100	0	0	0	0

^aCLSI MIC breakpoints not available for interpretation

•*S. aureus* was the most frequently encountered baseline pathogen at 81.6%, followed by VGS (6.6%) and CoNS (3.6%) (Table 1).

•Of the *S. aureus* isolates, 76% were MRSA.

•TR-700 had an MIC₅₀ and MIC₉₀ of 0.25 µg/mL against both methicillin-susceptible *S. aureus* (MSSA) and MRSA isolates relative to the MIC₅₀ of 1 µg/mL and MIC₉₀ of 2 µg/mL observed with linezolid (Table 2).

•Against MSSA and MRSA, TR-700 MICs were two-doubling dilutions lower than linezolid. TR-700 MICs ranged from 0.12 to 0.5 µg/mL and linezolid MICs ranged from 0.5 to 2 µg/mL for both MSSA and MRSA (Figure 1a-b).

•TR-700 MICs ranged from 0.12 to 0.25 µg/mL and linezolid MICs ranged from 0.5 to 1 µg/mL against CoNS (Table 2, Figure 1c).

•Against viridans group streptococci, TR-700 had an MIC₅₀ and MIC₉₀ of 0.25 µg/mL, relative to the MIC₅₀ of 0.5 µg/mL and MIC₉₀ of 1 µg/mL seen with linezolid (Table 3).

•TR-700 MICs ranged from 0.03 to 0.25 µg/mL and linezolid ranged from 0.12 to 1 µg/mL against viridans group streptococci (Figure 2).

•Three beta-hemolytic streptococci (2 *S. agalactiae* and 1 *S. pyogenes*) had TR-700 MICs of 0.25, 0.25, and 0.12 µg/mL relative to MICs of 1, 0.5 and 0.5 µg/mL for linezolid, respectively (Table 4).

Figure 2. MIC distribution of TR-700 and linezolid against viridans group streptococci (VGS) (n=15)

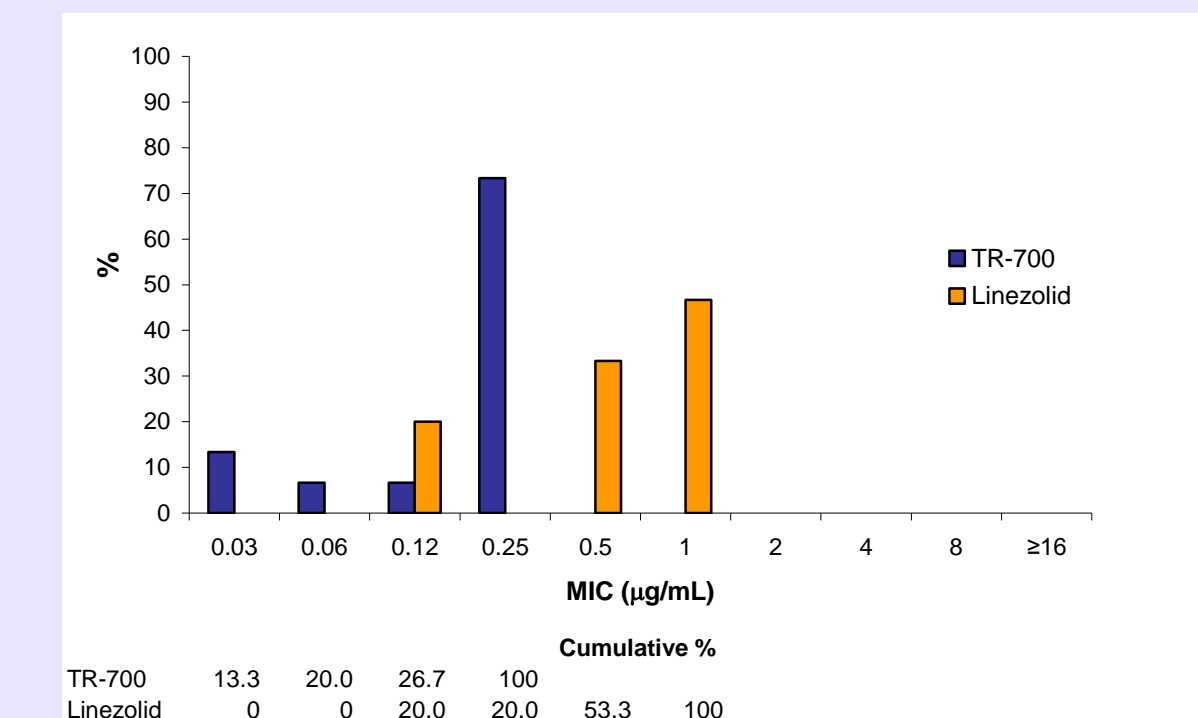


Table 4. Line listing of beta-hemolytic streptococci

Organism	Isolate ID	TR-700		Linezolid	
		MIC (µg/mL)	CLSI interp	MIC (µg/mL)	CLSI interp
<i>S. agalactiae</i>	1852210	0.25	—	1	S
<i>S. agalactiae</i>	1852224	0.25	—	0.5	S
<i>S. pyogenes</i>	2147852	0.12	—	0.5	S

Conclusions

- TR-700 had potent MIC activity against baseline gram-positive cocci isolates during a cSSSI clinical trial.
- The activity profile of TR-700 was not altered against MRSA, the most frequently encountered pathogen.
- Based on MIC₅₀/MIC₉₀s and MIC distributions, TR-700 was 4-fold more potent than linezolid against recovered gram-positive clinical trial isolates.

Acknowledgement

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