

# ORAL TOREZOLID PHOSPHATE IN THE TREATMENT OF SEVERE CSSSI IN PATIENTS WITH SYSTEMIC SIGNS OF INFECTION: A PHASE 2 DOSE RANGING STUDY

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## INTRODUCTION

Torezolid (TR-700) is the active moiety of the prodrug torezolid phosphate (TR-701), a second generation oxazolidinone with 4- to 16-fold greater activity than linezolid against gram-positive species. The objective of this analysis was to review the clinical and microbiological outcome rates of the more severe cases of complicated skin and skin structure infections (cSSSI) including large abscesses, cellulitis and wound infections treated with oral TR-701 once daily (QD), 200 mg, 300 mg, or 400 mg at the end of therapy (EOT) and test of cure (TOC) visits in the modified intent-to-treat (MITT) and the clinically evaluable (CE) patient populations. In line with latest regulatory recommendations, severe cSSSI was defined as having systemic signs or symptoms of infection (>38°C oral temperature, > 10,000 mm<sup>3</sup> white blood cells, or > 10% bands) or lymphatic involvement adjacent to the primary lesion, and a lesion measurement of at least 10 cm greater at baseline.

## STUDY DESIGN

This was a Phase 2 dose-ranging, randomized, double-blind study of oral TR-701 in adult patients diagnosed with cSSSI. The study was conducted at 12 sites in the United States. Patients were randomized 1:1:1 to 200 mg, 300 mg or 400 mg oral TR-701 once-a-day for 5-7 days. Patients were evaluated at Screening/Day 1, 2, 3, and 5 (if applicable), and at End of Therapy (EOT), Test of Cure (TOC; 7-14 days post treatment) and Late Follow-Up (LFU; 21-28 days post treatment). Patients were evaluated for clinical response by the investigator at EOT and TOC and for clinical relapse at LFU. Microbiological samples were to be obtained from the cSSSI site at baseline and then any follow-up visits if medically indicated.

### Key inclusion criteria

- Males or females ≥ 18 to 75 years old;
- Diagnosed with cSSSI requiring oral antimicrobial therapy that had at least one of the following: Severe Abscess, Surgical Wound or Post-Traumatic Wound, Deep Cellulitis;
- Presence of 2 or more local symptoms including: erythema, heat/warmth, pain/tenderness, swelling and/or induration, fluctuance, requirement for drainage of discharge PLUS at least 1 systemic sign of infection: Oral temperature >38°C within previous 24 hours, WBC count >10,000/mm<sup>3</sup>, >10% immature neutrophils, OR lesion size ≥5 cm in its longest dimension; suspected or confirmed infection due to a gram-positive organism.

### Key exclusion criteria

- Uncomplicated SSSI;
- cSSSI infections requiring gram-negative coverage;
- More than 24 hours of antibiotic administration within 96 hours prior to randomization for the treatment of the current infection, unless patient is considered a failure of at least 48 hours of previous treatment that was not linezolid;
- Immunocompromised patients.

## PATIENT POPULATIONS

A total of 82 of the 188 patients that received study drug met the criteria for severe cSSSI as defined above. There were 53 patients diagnosed with severe abscess, 15 with cellulitis, and 4 with wound infections included. Of the total patients enrolled, 84% had systemic signs of infection and 16% had lymphatic involvement in the absence of systemic signs of infection. Lesion sizes ranged from 10 cm to 46 cm.

The statistical populations were defined as:

- Clinically Modified Intent to Treat (cMITT; N=82): patients with a diagnosis of severe cSSSI and had at least one dose of study drug
- Clinically Evaluable (CE; N=73): patients that received at least 3 days of therapy, completed an outcome assessment at TOC, and had no confounding events or factors
- Microbiological Intent to Treat (mMITT; N=67): patients included in cMITT who also had at least 1 gram-positive bacterial cSSSI pathogen
- Microbiologically Evaluable (ME; N=59): patients included in CE who also had at least 1 gram-positive bacterial cSSSI pathogen

## RESULTS

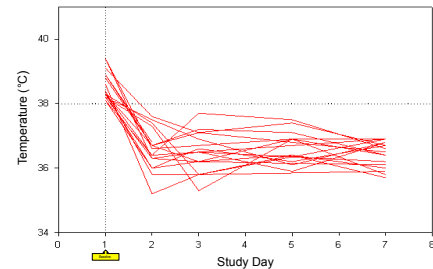
Patients were well balanced across dosage groups including age, gender, and race.

TABLE 1. Baseline Demographics (cMITT Population)

Parameter	200 mg N = 27	300 mg N = 26	400 mg N = 29	ALL N = 82
<b>Age</b>				
Mean	36	34	36	35
Min, Max	18, 60	19, 68	19, 58	18, 68
<b>Gender</b>				
Female	8 (30%)	9 (35%)	9 (31%)	26 (32%)
Male	19 (70%)	17 (65%)	20 (69%)	56 (68%)
<b>Race</b>				
White	24 (89%)	22 (85%)	20 (69%)	66 (81%)
Black	3 (11%)	4 (15%)	8 (28%)	15 (18%)
Asian	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Pacific Islander	0 (0%)	0 (0%)	1 (3%)	1 (1%)

Of the 82 patients included in this sub-group, 15 patients had an elevated temperature at baseline. All of these patients were afebrile by study Day 2 (see Figure 1).

FIGURE 1: Temperature Measured On-therapy in Patients Febrile at Baseline



In patients with WBC counts that are elevated at baseline (≥ 10,000 cells/mm<sup>3</sup>), almost all patients (95%) had a >1000 cell/mm<sup>3</sup> decrease by Day 3 (see Table 2).

TABLE 2: Changes in White Blood Cell Count from Baseline to Day 3, N\*(%)

WBC Count at Baseline (cells/mm <sup>3</sup> )	An Increase	0-<500 Decrease	500-<1000 Decrease	1000-<3000 Decrease	3000-<5000 Decrease	>5000 Decrease	Below 10,000
≥ 10,000 (n=62)	0	2 (3.2%)	1 (1.6%)	13 (21.0%)	15 (24.2%)	31 (50.0%)	50 (80.6%)
<10,000 (n=15)*	0	1 (6.7%)	1 (13.3%)	7 (46.7%)	5 (33.3%)	0 (0.0%)	NA

\*Patients with baseline and Day 3 values included (77 of 82)

Maximum lesion size (including erythema) declined steadily on therapy in all treatment groups (see Figures 2, 3, and 4).

FIGURE 2: Maximum Lesion Size in Patients Randomized to TR-701 200 mg

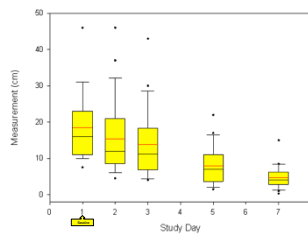


FIGURE 3: Maximum Lesion Size in Patients Randomized to TR-701 300 mg

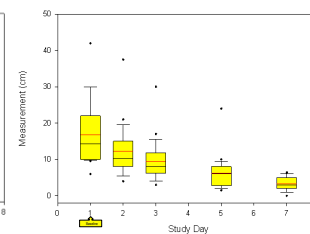
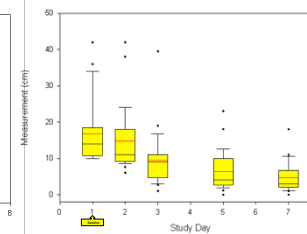


FIGURE 4: Maximum Lesion Size in Patients Randomized to TR-701 400 mg



Boundary of the box closest to zero indicates the 25<sup>th</sup> percentile, the black line within the box marks the median, the red line the mean, and the boundary of the box farthest from zero indicates the 75<sup>th</sup> percentile. Error bars above and below the box indicate the 10<sup>th</sup> and 90<sup>th</sup> percentiles, dots are <10<sup>th</sup> or >90<sup>th</sup> percentile.

## CLINICAL OUTCOMES

The clinical cure rates ranged from 93% to 100% at EOT and from 89% to 100% at TOC in the cMITT population. In the CE population cure rates ranged from 96% to 100% at EOT and at TOC (see Table 3).

TABLE 3. Cure Rates at EOT and TOC in cMITT and CE Populations

Population	200 mg	300 mg	400 mg
<b>cMITT*</b>			
EOT	25/27 (93%)	26/26 (100%)	27/29 (93%)
TOC	24/27 (89%)	26/26 (100%)	26/29 (90%)
<b>CE</b>			
EOT	23/24 (96%)	23/23 (100%)	25/26 (96%)
TOC	22/23 (96%)	23/23 (100%)	25/26 (96%)

## MICROBIOLOGICAL OUTCOMES

A total of 61 patients of this sub-group had *S. aureus* as the baseline pathogen, the majority of which was MRSA (15% MSSA, 85% MRSA). The microbiological outcome was 100% eradication for all pathogens in the ME population.

TABLE 4. Rates of *Staphylococcus aureus* Isolated at Baseline

Pathogen	200 mg	300 mg	400 mg
<b><i>Staphylococcus aureus</i></b>			
MRSA	21 (81%)	17 (83%)	23 (91%)
MSSA	4 (19%)	3 (17%)	2 (9%)

## CONCLUSIONS

All doses provided a rapid improvement in clinical signs and symptoms of severe cSSSI.

All doses investigated proved to be equally effective in patients with severe cSSSI.

These results in conjunction with PK-PD simulations support 200 mg once daily to be the lowest effective dose for selection in the Phase 3 pivotal cSSSI studies.<sup>1,2</sup>

## REFERENCES

- Prokocimer P, Bien P, Munoz KA, Bohn J, Wright R, Bethune C. Human pharmacokinetics of the prodrug TR-701 and TR-700, its active moiety, after multiple oral doses of 200 to 400 mg TR-701, a novel oxazolidinone. ICAAC 2008; Abstract F1-2064.
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