

INTRODUCTION

Community-acquired MRSA has become an epidemic in the United States and has become a major public health issue requiring new treatment options.¹ Tedizolid formerly known as torezolid (TR-700) is the active moiety of the prodrug tedizolid phosphate (TR-701), an oxazolidinone with 4-16 fold greater activity than linezolid against gram-positive species including MRSA, and has a favorable PK profile allowing once-daily dosing, while retaining activity against linezolid-resistant strains.²

At the time this Phase 2 was conducted, the indication was complicated skin and skin structure infections (cSSSI) with a primary endpoint of Investigator Assessed Clinical Outcome at the Test of Cure Visit. In August 2010, the FDA issued draft guidance³ for developing antibiotics in the treatment of ABSSSI which recommends a primary endpoint of cessation of spread and resolution of fever at the 48-72 Hours Visit. The Phase 2 data was re-evaluated using the new FDA definitions of response to therapy, and the analysis is presented here.

METHODS

This is a retrospective analysis to compare the outcomes of the study using criteria defined in the old and the new FDA guidance. In line with the current FDA ABSSSI guidance, response to therapy was assessed looking at cessation of spread of lesion and resolution of fever (<38°C) at the Day 3 visit (48 hours).

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 tedizolid once daily 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).

Key inclusion criteria

Males or females ≥ 18 to 75 years old; diagnosed with cSSSI requiring oral antimicrobial therapy that had at least 1 of the following: a) abscess (with ≥ 2 cm induration or required incision and drainage), b) surgical wound or post-traumatic wound, or c) 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 mm³, >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 cSSSI; cSSSI infections requiring gram-negative coverage, or suspected to be caused by gram-negative organisms; 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.

RESULTS

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

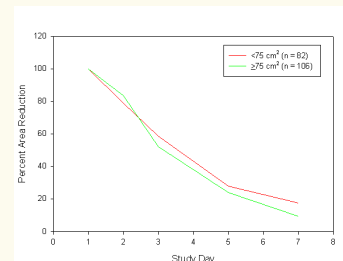
TABLE 1: Demographics

Parameter	All Patients N=188
Age	
Mean (SD)	36.4 (12.1)
Min, Max	18.0, 68.0
Gender	
Female	66 (35.1%)
Male	122 (64.9%)
Race	
White	140 (74.5%)
Black	45 (23.9%)
Asian	1 (0.5%)
Pacific Islander	1 (0.5%)
Other	1 (0.5%)
ABSSSI Diagnosis	
Infected Wound	11 (5.9%)
Cellulitis	33 (17.6%)
Severe Abscess	144 (76.6%)
Regional and/or Systemic Signs of Infection	107 (56.9%)
Area (cm²)	
Mean (SD)	177.7 (219.3)
Min, Max	7.0, 1656.0
< 75 cm ²	72 (38.3%)
≥ 75 cm ²	116 (61.7%)

Cessation of spread of lesion: by Day 3 (48 hrs), 172/181 (95%) patients showed no increase in size of lesion from baseline (median size: 11 cm). There was no difference in response by dose regimen. Patients with baseline lesion surface area (length x width) ≥ 75 cm² had similar response to therapy at the Day 3 visit.

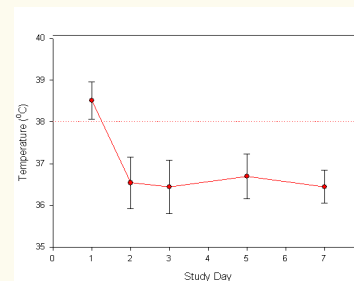
RESULTS CONTINUED

FIGURE 1: Response of Lesion Area for Patients with a Baseline Lesion Surface Area ≥ 75 cm² and < 75 cm²



Fever: All 19 patients with fever at screening were afebrile within 24 hours and the effect remained sustained thereafter.

FIGURE 2: Fever Response to Therapy (mean temperature, n=19)



COMPARISON TO CLINICAL OUTCOMES

A comparison was done looking at the investigator's outcome at EOT and TOC versus the newer definition of responder using a programmatic outcome. The programmatic outcome of responder at the Day 3 visit is defined as cessation of spread of the lesion at Day 3 (at least no increase) and afebrile (≤ 37.6°C) at Day 3.

TABLE 2: Comparison of Phase 2 TR-701 Results in ABSSSI Using Two Assessment Methods: Investigator's Outcome and Programmatic Outcome

Criteria	Old Guidance		New Guidance
	Investigator's Outcome	Investigator's Outcome	Programmatic Outcome
	Clinical Success	Clinical Success	Responder
Time of Assessment	End of Therapy (EOT)	Test of Cure (TOC)	Day 3 of Therapy
ITT	92.0% (173/188)	87.8% (165/188)	90.4% (170/188)
CE	96.6% (170/176)	95.7% (157/164)	NA

CONCLUSIONS

- Cessation of spread of lesion and fever respond rapidly to tedizolid therapy by Day 3.
- Early assessment of markers of infection can be considered for an early decision to either change antibiotics therapy or predict a favorable outcome allowing early patient discharge.

REFERENCES

1. Moran G, Krishnadasan A, Gorwitz R, Fosheim G, McDougal L, Carey R, Talan D, for the EMERGENCY ID Net Study group. Methicillin-resistant *S. aureus* infections among patients in the Emergency department. *New Engl J Med.* 2006; 355 (7):666-674.
2. Shaw KJ, Poppe S, Schaadt R, Brown-Driver V, Finn J, Pillar CM, Shinabarger D, and Zurenko G. In vitro activity of TR-700, the antibacterial moiety of the prodrug TR-701, against linezolid-resistant strains. *AAC.* 2008; 52(12): 4442-7.
3. Guidance for Industry Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment. Draft Guidance. August 2010.