# Identification and Susceptibility of Pathogens Isolated from Patients with Complicated Skin and Skin Structure Infections (cSSSI): Results of a PTK796 (PTK) Phase 2 Clinical Trial


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## ABSTRACT


**Background** Paratek conducted a randomized, investigator-blinded Phase 2 clinical trial in adults with cSSSI comparing PTK (100mg IV/200mg oral, QD) with linezolid (LZD) (600mg IV/600 mg oral, Q12h). LZD was supplemented with aztreonam when gram negative infection was suspected. A total of 234 patients were enrolled.

**Methods** Patient enrollment isolates were identified and tested at a central laboratory. MICs were determined by broth microdilution using dried panels. Analysis was based on the Clinically Evaluable (CE) population with a pathogen isolated at enrollment (ME).

**Results** The predominant pathogen isolated was *S. aureus* (SA). 67 patients in the PTK arm were clinical successes with 80 isolates of SA (56.3% MRSA) and 59 isolates from 45 clinical successes (67.8% MRSA) in the LZD arm. $MIC_{90}$s for MRSA and MSSA from each treatment arm were 0.25 µg/ml (PTK) and 2.0 µg/ml (LZD). Other pathogens in the PTK clinical success group included β-hemolytic strep (4 pts, mixed cultures), Gram negative bacteria (5 pts, 4 mixed), *E. faecalis* (2pts, one mixed), *S. hemolyticus* (1pt, mixed), and *S. constellatus* (1pt, only pathogen). In the LZD clinical success group other pathogens included Gram negatives (4 pts , 3 mixed), *E. faecium* (1pt, mixed), and *S. constellatus* (2 pts, only pathogen). There were only two clinical failures in the PTK arm, both MSSA (PTK MIC = 0.25 and 0.5 µg/ml, mixed cultures) and three in the LZD arm, 2 MRSA (LZD MIC = 2µg/ml, 1 mixed) and one MSSA (LZD MIC = 2µg/ml, only pathogen).

**Conclusions** PTK exhibited excellent efficacy in the Phase 2 trial compared to LZD (CE Success 98% vs 93.2% respectively and ME Success 97.4% vs 93.7%, respectively). *S. aureus* was the predominant pathogen at enrollment (93.3% from PTK and 87.3% from LZD) the majority of which were MRSA. Susceptibility to PTK and LZD did not differ between MRSA and MSSA and did not differ between treatment arms.


## INTRODUCTION

PTK796 is a novel aminomethylcycline currently in worldwide development by Paratek Pharmaceuticals and Novartis Pharmaceuticals. PTK796 is a member of the tetracycline family and exhibits excellent *in vitro* activity and efficacy in animal infection models. PTK796 is active against the most common pathogens associated with skin and skin structure infections, most notably community acquired MRSA and beta-hemolytic streptococci. PTK796 overcomes tetracycline resistance common to these pathogens, either tetracycline efflux or ribosomal protection. Paratek Pharmaceuticals conducted a Phase 2 clinical trial in complicated skin and skin structure infection from July 2007 through January 2008. The study was a randomized, investigator blinded study comparing intravenous and oral PTK796 to linezolid in the treatment of complicated skin and skin structure infections (1).

## STUDY DESIGN

The Phase 2 trial was an investigator blinded evaluation in which patients with qualifying infections and clinical status were randomized to receive either 100 mg PTK796 intravenously QD or 600 mg linezolid intravenously BID. In cases suspected of being caused by Gram negative pathogens, patients received, in blinded fashion), either placebo (saline) infusions (PTK796 treatment group) or aztreonam (linezolid treatment group). Following the intravenous course and at the decision of the principal investigator, patients were discharged with either 200 mg oral PTK796 QD or 600mg linezolid, BID.

Patient demographics were well balanced between the two treatment groups. As shown in Table 1 the types of infection were similar between groups although infections tended to be larger and more severe in the PTK796 treatment group(1). Clinical outcome are shown in Table 2.

**Table 1. Characteristics of Infections (ITT)**

| Type of Infection | N | Median (cm) Maximum Dimension (range) | N | Median (cm) Maximum Dimension (range) |
|---|---|---|---|---|
| | PTK796 | | Linezolid | |
| Major Abscess | 73 | 10 (6-16) | 72 | 7.8 (4.1-13) |
| Injury | 21 | 10.5 (4-31) | 17 | 7 (3-19.5) |
| Cellulitis | 8 | 20 (12-31) | 10 | 18 (3.3-33) |
| Lower Extremity Ulcer | 9 | 3.5 (1.2-10) | 9 | 2.5 (1 – 28) |

**Table 2. Derivation of Patient Population**

| Population[1] | Treatment Group | Total # Patients | Patients by Clinical Outcome[2] | |
|---|---|---|---|---|
| | | | Success | Failure |
| ITT | PTK796 | 111 | 98 | 2 |
| | Linezolid | 108 | 82 | 6 |
| mITT | PTK796 | 84 | 75 | 2 |
| | Linezolid | 78 | 59 | 4 |
| Clinically Evaluable | PTK796 | 100 | 98 | 2 |
| (CE) | Linezolid | 88 | 82 | 6 |
| Microbiologically | PTK796 | 77 | 75 | 2 |
| Evaluable (ME) | Linezolid | 63 | 59 | 4 |
| ME w/ | PTK796 | 71 | 69 | 2 |
| Susceptibility (MES) | Linezolid | 49 | 46 | 3 |

[1]ITT= All patients enrolled and treated; mITT=All patients with at least one pathogen isolated at baseline; CE=all ITT patients completing all clinical evaluations; ME = all CE pts with at least one pathogen at baseline; ME w/Susceptibility= All ME with central laboratory MIC testing.

[2]Patients not completing evaluations for administrative reasons have been excluded .

## MICROBIOLOGY METHODS

Qualified samples of infected tissue were processed by local clinical microbiology laboratories. Isolated organisms were sent to a central laboratory for definitive identification and susceptibility testing. Susceptibility to PTK796 was determined using dried MIC panels (TREK Diagnostics, Cleveland, OH ) previously shown to perform comparably to standard reference methods. Linezolid, oxacillin, and aztreonam susceptibilities were determined using commercially available methods. The Primary population for this report is the clinically evaluable population for which there was at least one pathogen at baseline for which an MIC was determined. In some cases, there were multiple isolates with slightly different MICs that were included in the analyses.

## RESULTS

As shown in Table 3, *Staphylococcus aureus* was the most frequently isolated pathogen (67/71 patients in the PTK796 treatment group and 45/49 in the linezolid treatment group. It was most often the sole pathogen isolated, but did occur in mixed infections.

**Table 3. Types of Pathogens at Baseline**

| Organism | Number of Isolates | |
|---|---|---|
| | PTK796 (71 patients, 67 with *S. aureus*) | Linezolid ( 49 patients, 45 with *S.aureus*) |
| MRSA | 45 | 40 |
| MSSA | 35 | 19 |
| β-hemolytic Streptococci | 5 | 2 |
| *Enterococcus* sp | 4 | 1 |
| Other Gram + Cocci | 2 | 1 |
| Gram Negative Bacilli | 14 | 5 |

The susceptibility of the isolates to study antibiotics is shown in Table 4. PTK796 exhibited potent activity against *S. aureus* regardless of whether the organism was MRSA or MSSA.

**Table 4. Susceptibility of *S. aureus* to study antibiotics**

| Organism | Treatment Group | # Isolates | Antibiotics | MIC (µg/ml) | | |
|---|---|---|---|---|---|---|
| | | | | MIC Range | $MIC_{50}$ | $MIC_{90}$ |
| *S. aureus* | PTK796 | 80 | PTK796 | 0.12-2 | 0.12 | 0.25 |
| | | | Linezolid | 1-4 | 2 | 2 |
| | Linezolid | 59 | PTK796 | 0.12-1 | 0.25 | 0.25 |
| | | | Linezolid | 1-4 | 2 | 2 |
| MSSA | PTK796 | 35 | PTK796 | 0.12-2 | 0.25 | 0.5 |
| | | | Linezolid | 1-4 | 2 | 2 |
| | Linezolid | 19 | PTK796 | 0.12-0.25 | 0.12 | 0.25 |
| | | | Linezolid | 1-4 | 2 | 4 |
| MRSA | PTK796 | 45 | PTK796 | 0.12-0.5 | 0.12 | 0.25 |
| | | | Linezolid | 1-2 | 2 | 2 |
| | Linezolid | 40 | PTK796 | 0.12-1 | 0.12 | 0.25 |
| | | | Linezolid | 1-2 | 2 | 2 |

The distribution of PTK and linezolid MICs for *S. aureus* are shown in Figure 1a and 1b.

**Figure 1a. MIC Distribution for *S. aureus* (PTK796 Treatment Group)**

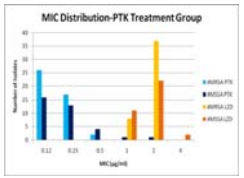
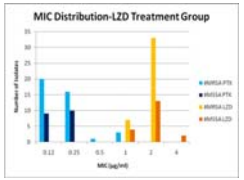



**Figure 1a. MIC Distribution for *S. aureus* (Linezolid Treatment Group)**




There were 2 clinical failures in the PTK796 treatment group and 3 clinical failures in the linezolid treatment group, all with *S. aureus*. In each case there was no indication that susceptibility was a factor in the clinical outcome since MICs were consistent with the entire population (Table 5).

**Table 5. Identification and Susceptibility of *S. aureus* from Clinical Failures at**

| Treatment Group | Patient # | Organism at Baseline | MIC (µg/ml) | |
|---|---|---|---|---|
| | | | PTK796 | Linezolid |
| PTK796 | #1 | MSSA | 0.5 | 2 |
| | #2 | MRSA | 0.25 | 2 |
| Linezolid | #1 | MRSA | 0.5 | 2 |
| | #2 | MSSA | 0.12 | 2 |
| | #3 | MRSA | 0.25 | 2 |

PTK796 was also active *in vitro* against other pathogens isolated as shown in Table 6.

**Table 6a. Susceptibility of Other Pathogens (PTK796 Treatment Group)**

| Organism | # Isolates | MIC Range (µg/ml) | | |
|---|---|---|---|---|
| | | PTK796 | Linezolid | Aztreonam |
| β-hemolytic *Streptococcus*, Group A | 1 | 0.06 | 1 | - |
| β-hemolytic *Streptococcus*, Group B | 2 | 0.06-0.25 | 1-4 | - |
| β-hemolytic *Streptococcus*, Group G | 2 | 0.12-0.25 | 2 | - |
| *S. constellatus* | 1 | 0.015 | 2 | - |
| *E. faecalis* | 4 | 0.06-0.25 | 2-8 | - |
| *S. haemolyticus* | 1 | 1 | 1 | - |
| *C. koseri* | 1 | 1 | - | S |
| *E. cloacae* | 5 | 0.06-4 | - | S |
| *E. coli* | 3 | 0.25-8 | - | S |
| *K. pneumoniae* | 3 | 2-4 | - | S |
| *P. mirabilis* | 1 | 8 | - | S |
| *A. baumanii* | 1 | 0.25 | - | R |

* Aztreonam S≤4, R≥16

**Table 6b. Susceptibility of Other Pathogens (Linezolid Treatment Group)**

| Organism | # Isolates | MIC Range (µg/ml) | | |
|---|---|---|---|---|
| | | PTK796 | Linezolid | Aztreonam (S/I/R) |
| β-hemolytic *Streptococcus*, Group B | 1 | 0.25 | 2 | - |
| β-hemolytic *Streptococcus*, Group G | 1 | 0.25 | 2 | - |
| *S. constellatus* | 2 | 0.03-0.06 | 2 | - |
| *E. faecium* | 1 | 0.06 | 2 | - |
| *C. freundii* | 1 | 8 | - | R |
| *E. cloacae* | 1 | 2 | - | S |
| *E. coli* | 1 | 0.5 | - | S |
| *K. pneumoniae* | 2 | 2-4 | - | S |

* Aztreonam S≤4, R≥16

## CONCLUSION

The Phase 2 evaluation of PTK796 in comparison to linezolid indicated that PTK was safe and well tolerated and appeared to be efficacious compared to linezolid. The most common pathogen isolated was *S. aureus*, the majority of which were MRSA. PTK796 was active against *S. aureus*, with an $MIC_{90}$ of 0.25µg/ml. Only two clinical failures occurred in the PTK796 treated group. In neither case was the infection caused by an organism with elevated PTK796 MIC. There were three failures in the linezolid treated group and none of these isolates had elevated MICs to linezolid to account for the lack of success.

## REFERENCES


[1]Arbeit, Robert D., J.A. Roberts, A.R. Forsythe, S.M. Johnston, F. Seyedi, M. Pukshansky, and S.K. Tanaka. 2008. Safety and Efficacy of PTK 0796: Results of the Phase 2 Study in Complicated Skin and Skin Structure Infections Following IV and Oral Step Down Therapy. Abstract L-1515b. 48th Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington DC.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