

Results of the Phase 2 Study in Complicated Skin and Skin Structure Infections Following IV and Oral Step Down Therapy

*Robert D. Arbeit, J. A. Roberts, A. R. Forsythe, S. M. Johnston, F. Seyedi, M. Pukshansky and S.K. Tanaka
Paratek Pharmaceuticals Inc., Boston MA

ABSTRACT

Background

PTK 0796 (PTK) is the first aminomethylcyclohexane in clinical development. A multicenter Phase 2 randomized, investigator blinded, comparative trial in complicated skin and skin structure infections (cSSSI) was completed in January 2008. Patients with cSSSI who required initial intravenous (IV) therapy and met inclusion and exclusion criteria were enrolled at 11 centers in the US and were randomized to receive either PTK (100mg Q24h IV with 200mg Q24h oral step-down) or linezolid (LZD) (600mg Q12h IV with 600mg Q12h oral step-down).

Results

The ITT populations (111 received PTK, 108 received LZD) were comparable in terms of enrollment criteria, disease severity, co-morbidities, and demographics. Mean duration of total treatment and of IV and oral therapy did not differ between PTK (9.9, 4.3, 5.6 days respectively) and LZD (9.7, 4.3, 5.4 days, respectively). The efficacy (clinical success) of PTK was 88.3% for the ITT population compared to 75.9% for LZD. In the clinically evaluable population, the clinical success rates were 98% and 93.2% for PTK and LZD, respectively. Bacterial pathogens were cultured at baseline from ~74% of each treatment group; over 50% had MRSA. Among the microbiologically evaluable patients, there were 2 failures in the PTK group, none was associated with MRSA and 4 failures in the LZD group, 2 of which were associated with MRSA. PTK was well tolerated. There were no discontinuations due to adverse events (AEs) for PTK (vs 2 for LZD) and no drug-related serious AE in either group. In both treatment groups the most common drug-related AEs were gastrointestinal (12 PTK vs 13 LZD). GI events associated with PTK were observed almost entirely during oral therapy, were mild, and did not result in discontinuation of therapy. There were no observed differences between the treatment groups in hematology or serum chemistry parameters.

Conclusions

Based on these results, PTK 0796 is advancing to Phase 3 trials.

INTRODUCTION

PTK 0796 is the first antibiotic of a new class of compounds, the aminomethylcyclohexanes, which are semi-synthetic compounds related to the tetracyclines. *In vitro* PTK 0796 has excellent activity against a broad range of aerobic and anaerobic organisms, including gram-positive, gram-negative and atypical bacteria. In animal models, PTK 0796 has demonstrated efficacy against clinically important pathogens, including MRSA and multi drug resistant *S. pneumoniae*.

The targeted indications for PTK 0796 encompass serious acute bacterial infections, either prompting or occurring during hospitalization. These include complicated skin and skin structure infection (cSSSI), diabetic foot infections, community- and hospital-acquired pneumonia and intra-abdominal infection. Clinical development of PTK 0796 includes both intravenous and oral formulations and thus offers the potential both for initial parenteral therapy in seriously ill patients as well as the option for subsequent oral “step-down” treatment.

This report presents the results of a recently completed Phase 2 study of PTK 0796 oral and IV formulations in the treatment of adults with cSSSI.

GENERAL STUDY DESIGN

PTK 0796-CSS1-0702 was a randomized (1:1), controlled, evaluator-blinded Phase 2 study comparing PTK 0796 and linezolid (Zyvox™). Subjects were initially treated with study drug IV (PTK 0796 100 mg q24h or linezolid 600 mg q12h) and could be switched to oral therapy (PTK 0796 200 mg q24h or linezolid 600 mg q12h) at Investigator’s discretion. The expected total duration of treatment (IV and oral) was up to 14 days. If the Investigator considered that a subject required gram-negative coverage, the pharmacist provided aztreonam to linezolid-treated subjects and placebo infusions to PTK 0796 subjects.

Inclusion criteria included:

- 18 to 80 years of age
- Signed informed consent
- Effective birth control or non-childbearing potential
- Negative pregnancy test
- Qualifying complicated skin and skin structure infection

Patient exclusion criteria included:

- Nursing
- Previously treated under this protocol
- Allergy to study antibiotics
- Received investigational drug within 1 month
- History of chronic liver cirrhosis
- ALT exceeding 2x ULN during week prior to enrollment
- Total bilirubin exceeding ULN during week prior to enrollment
- Total body weight <40kg or >150kg
- Known to be HIV positive and meets CDC criteria for AIDS
- Life expectancy less than 3 months
- Requires hemodialysis or peritoneal dialysis
- Creatinine clearance (calculated) <30mL/min
- Absolute neutrophil count <500/uL
- Hypotension (supine systolic BP<90mmHg) and perfusion abnormalities
- Requires ‘pressors’ to maintain blood pressure and/or adequate tissue perfusion
- Received potentially effective systemic antibiotic within 48hrs
- Has an infecting pathogen known to be intermediate or resistant to study antibiotics
- Has confirmed or suspected non-infectious skin disorder that may interfere with evaluations
- Any concomitant condition that would interfere with evaluation or completion of the study

There were four scheduled evaluations during the study: Enrollment, End of IV Treatment, End of Treatment, and Test of Cure (10-17 days after last treatment).

RESULTS

Study Population and Demographics

A total of 234 patients were enrolled in the study; patient disposition by study population is shown in Table 1.

Table 1. Patient Disposition

Subpopulations	PTK 0796	Linezolid
All Randomized	118	116
Intent-to-treat ^a	111 (100%)	108 (100%)
Modified ITT ^b	84 (75.7%)	78 (72.2%)
Clinically Evaluable ^c	100 (90.1%)	88 (81.5%)
Microbiologically Evaluable ^d	77 (69.4%)	63 (58.3%)
Safety Population ^e	111 (100%)	108 (100%)

a. Intent-to-treat (ITT), all subjects (as randomized) who received at least one dose of study drug.
b. Modified ITT (mITT), all ITT subjects who had a bacterial pathogen isolated at Enrollment.
c. Clinically Evaluable (CE), all ITT subjects who met specific criteria, particularly received no additional antibiotics during the study and were seen for Test-of-Cure as required.
d. Microbiologically Evaluable (ME), all CE subjects who had a bacterial pathogen isolated at Enrollment.
e. Safety population, all ITT subjects as treated. PTK 0796 group includes all subjects who received any PTK 0796 regardless of randomization; Linezolid includes only subjects who received linezolid as study drug regardless of randomization.

At Enrollment subjects in both treatment groups were similar with respect to patient demographics (Table 2), type of infection (Table 3), severity of infection (Figure 1, Table 4) and co-morbidities (Table 5).

Table 2. Patient Demographics (ITT population)

Characteristic	Measure	PTK 0796 (n=111)	Linezolid (n=108)
Sex	Male	66 (59.5%)	57 (52.8%)
Ethnicity	Hispanic	38 (34.2%)	53 (49.1%)
	Non Hispanic	73 (65.8%)	55 (50.9%)
Race	Caucasian	97 (87.4%)	99 (91.7%)
	Black	8 (7.2%)	6 (5.6%)
	Asian	4 (3.6%)	1 (0.9%)
	Other	2 (1.8%)	2 (1.8%)
	Age (Years)	18-44	51 (45.9%)
	45-64	50 (45.0%)	48 (44.4%)
	≥ 65	10 (9.0%)	10 (9.3%)
Weight (Kg)	Mean (range)	84.2 (45-144)	85.0 (51-152)
BMI (Kg/M ²)	Mean (range)	28.8 (17-48)	29.3 (19-52)

Table 3. Type of Infection (ITT population)

Type of Infection	PTK 0796 (n = 111)	Linezolid (n = 108)
Injury (incl. trauma, surgery, bites, burns*)	21	17
Major Abscess†	73	72
Lower extremity ulcer	9	9
Cellulitis with comorbidity	8	10

* Burns of less than 5% of body surface area.
† Among PTK 0796 subjects with major abscess, 84% had lesions ≥5 cm (maximal dimension).

Figure 1. Infection Characteristics and Severity (ITT population)

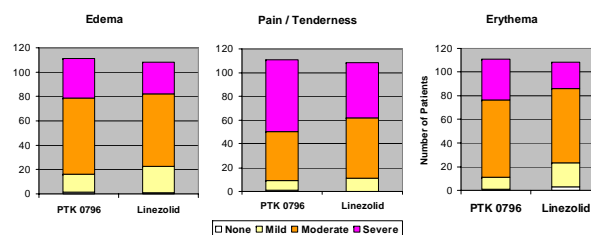


Table 4. Maximal dimensions of infections (ITT population)

Type of Infection	PTK 0796 ^a (n=111)	Linezolid ^a (n=108)
Major Abscesses ^b	10 (6 – 16)	7.8 (4.1 – 13)
Infected Injury	10.5 (4 – 31)	7 (3 – 19.5)
Cellulitis with co-morbidity	20 (12 – 31)	18 (3.3 – 33)

a. Median (IQR) in centimeters
b. Includes surrounding cellulitis

The treatment groups were also well balanced for co-morbidities, including a substantial number of patients with HCV (Table 5).

Table 5. Comorbid Conditions (ITT population)

Condition ^a	PTK 0796 (n=111)	Linezolid (n=108)
Hepatitis C seropositive	46 (41%)	40 (37%)
Substance Abuse	41 (37%)	36 (33%)
Diabetes Mellitus	27 (24%)	20 (19%)
Cardiovascular Disease ^b	35 (32%)	38 (35%)

a. Hepatitis C seropositive confirmed by serology; other conditions based on patient medical histories.
b. Includes coronary artery or peripheral vascular disease

Treatment

Duration of treatment, both by IV route and overall, similar for both groups (Table 6).

Table 6. Duration of treatment (ITT population)

Route	PTK 0796 ^a (n=111)	Linezolid ^a (n=108)
IV	4 (2 – 6)	3 (2 – 6)
Total (IV plus oral)	10 (8 – 12)	10 (7 – 13)

a. median (IQR)

Clinical Efficacy

PTK 0796 and linezolid demonstrated comparable efficacy across all four study populations (ITT, mITT, CE, ME) (Table 7).

In the ITT and mITT populations, a number of patients failed to return for test of cure visits or failed to return within the prescribed timeframe for the test of cure visits. This disproportionately and negatively affected the success rate in the Intent to Treat and modified ITT populations for linezolid, although overall efficacy was comparable between PTK 0796 and linezolid.

Table 7. Summary of Clinical Outcome by Population

Population	PTK 0796 n (%)	Linezolid n (%)	Difference (95% CI) ^a
ITT	N=111	N=108	
Success	98 (88.3)	82 (75.9)	12.4 (1.9, 22.9)
Failure ^b	13 (11.7)	26 (24.1)	
Clinical failure	2 (1.8)	6 (5.6)	
Non-evaluable	11 (9.9)	20 (18.5)	
MITT	N=84	N=78	
Success	75 (89.3)	59 (75.6)	13.6 (1.4, 25.9)
Failure ^b	9 (10.7)	19 (24.4)	
Clinical failure	2 (2.4)	4 (5.1)	
Non-evaluable	7 (8.3)	15 (19.2)	
Clinically Evaluable	N=100	N=88	
Success	98 (98.0)	82 (93.2)	4.8 (-1.7, 11.3)
Failure ^b	2 (2.0)	6 (6.8)	
Microbiologically Evaluable	N=77	N=63	
Success	75 (97.4)	59 (93.7)	3.8 (-4.0, 11.5)
Failure ^b	2 (2.6)	4 (6.3)	

a. [PTK 0796 – linezolid], 95% confidence interval using a normal approximation to the binomial distribution with continuity correction.
b. In the ITT and MITT populations, non-evaluable subjects were included as Failures; non-evaluable subjects were excluded from the CE and ME populations and Failure was restricted to Clinical Failures.

Microbiology

MRSA was the most frequent primary pathogen isolated in both PTK 0796 and linezolid groups (Table 8).

Clinical efficacy was similar for both MSSA and MRSA (Table 9).

Table 8. Distribution of baseline pathogens by treatment (mITT)

Pathogen	PTK 0796 (N=84)	Linezolid (N=78)
<i>S. aureus</i> (MRSA)	44 (52.4%)	38 (48.7%)
<i>S. aureus</i> (MSSA)	31 (36.9%)	29 (37.2)
B-Hemolytic Streptococci	7 (8.3%)	2 (2.6%)
Streptococci, other	4 (4.8%)	8 (10.3%)
Enterococci	2 (2.4%)	5 (6.4%)
Gram-positive, other	0	1 (1.3%)
Gram-negative, other	13 (15.5%)	8 (10.3%)
Anaerobes	0	3 (3.8%)

Table 9. Clinical Outcomes by Baseline Pathogen and Treatment (mITT and ME populations) for patients with *S. aureus* by methicillin susceptibility

Pathogen	mITT		ME	
	PTK 0796	Linezolid	PTK 0796	Linezolid
MRSA	N=44	N=38		
Success	42 (95.5%)	30 (78.9%)	100%	93.8%
Failure	0	2		
Non-evaluable	2	6		
MSSA	N=31	N=29		
Success	27 (87.1%)	21 (72.4%)	93.1%	93.1%
Failure	2	2		
Non-evaluable	2	6		

Safety

PTK 0796 was safe and well-tolerated. There were no drug-related SAEs in the PTK 0796 safety population and no patient discontinued PTK 0796 because of an adverse event (compared with two patients in the linezolid group). The incidence and pattern of reported AEs – both overall and drug-related – were similar for both treatment groups.

Table 10. Frequency of subjects with AEs (total and drug-related) by MedRA System Organ Class

System Organ Class	PTK 0796 (N=111)		Linezolid (N=108)	
	Total	Drug Related ^a	Total	Drug Related ^a
No adverse events	65	--	53	--
Cardiac	4	0	4	3
Ear	0	0	2	1
Eye	2	0	1	1
Gastrointestinal	21	12	18	13 ^b
General	11	5	8	4
Hematologic	1	0	2	0
Infection	6	0	9	1
Injury	1	0	1	1
Investigations	7	3	10	8
Metabolism	9	1	7	2
Musculoskeletal	8	0	2	0
Neurologic	12	4	14	7
Psychologic	5	2	6	3
Renal	2	1	2	0
Reproductive	2	0	2	0
Respiratory	3	0	2	0
Skin	12	7	10	6 ^c
Vascular	3	0	1	1

a. Assessed as probably or possibly drug-related by blinded evaluator.
b. Includes 1 patient discontinued due to heartburn.
c. Includes 1 patient discontinued due to rash.

CONCLUSIONS

In this Phase 2 study of over 200 adults with complicated skin and skin-structure infections, the safety and efficacy of PTK 0796 administered by IV and oral routes was comparable to linezolid (Zyvox™).

Based on these results, PTK 0796 is proceeding to Phase 3 trials in cSSSI, diabetic foot infection and moderate to severe community acquired pneumonia (CAP).

REFERENCES

Traczewski MM, Brown SD. PTK 0796: *In vitro* Potency and Spectrum of Activity Compared to Ten other Antimicrobial Compounds. Abstract F-753. In: 43rd ICAAC; Chicago: American Society for Microbiology.

Weir S, Maccone A, Donatelli J, et al. The activity of PTK 0796 against tetracycline resistance. Abstract F-752. In: 43rd ICAAC; Chicago: American Society for Microbiology.

McKenney D, Quinn JM, Jackson CL, et al. Evaluation of PTK 0796 in Experimental Models of Infections Caused by Gram-Positive and Gram-Negative Pathogens. Abstract F-757. In: 43rd ICAAC; Chicago: American Society for Microbiology.

Ladel CH, Endermann R, Broetz-Oesterheld H, Labischinski H. BAY 73-7388 demonstrates greater activity than linezolid in range of murine models of skin and soft tissue infection. Abstract P929. In: 14th ECCMID; Prague, Czech Republic.