P 694

Safety and efficacy of PTK 0796 (Omadacycline) as treatment of complicated skin and soft tissue infection (cSSTI)

PARATEK PHARMACEUTICALS

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ABSTRACT

Background Having completed phase 1 and 2 clinical programs, PTK 0796, an aminomethylcycline, broad-spectrum antibacterial agent active against all the leading causes of cSSTI including methicillin-resistant *Staphylococcus aureus* (MRSA), has begun assessment in phase 3 trials.

Methods A randomized (1:1), controlled, evaluator-blind, stratified by infection type, trial comparing PTK 0796 (100mg iv; 300mg po QD) to linezolid (LZD; 600mg iv/po BID) was designed to establish non-inferiority between treatment arms regarding efficacy based on clinical assessment immediately after (EOT), and 10-17 days after (TOC) completing therapy in the intent-to-treat (ITT) and clinically evaluable (CE) populations. Subjects were given iv therapy initially with an option to transition to oral formulations of either PTK 0796 or LZD. Moxifloxacin (400 mg QD) was added to LZD treatment if infection due to Gram-negative bacteria was suspected.

Results The trial was administratively stopped to address alignment with a new FDA guidance on ABSSSI, after 143 of the planned 790 subjects were enrolled. Subjects enrolled at 6 sites with 140 and 127 qualifying for the ITT and CE populations, respectively. A total of 44 (65%) PTK 0796 and 48 (67%) LZD subjects had cellulitis and 14 (21%) PTK 0796 subjects and 14 (19%) LZD subjects (19%) had wound infections. The mean and median duration of therapy were 10.1 and 10.0 days for PTK 0796 and 9.9 and 9.5 days for LZD subjects. MRSA was the most frequently isolated pathogen and success in the CE population occurred in 96.2% (25/26) with PTK 0796 and 93.5% (29/31) with LZD treatment. There were comparable numbers of treatment emergent adverse events (56;82.4% in PTK 0796 and 58;80.6% in LZD) and study-drug related adverse events (41;60.3% in PTK 0796 and 41;56.9% in LZD) across treatment arms. The most common adverse events reported involved the gastrointestinal system and the most common of these was nausea, reported by 18 PTK 0796 and 19 LZD treated subjects.

Conclusions Results of this phase 3 trial experience are consistent with those of the phase 2 clinical program that also involved patients with cSSTI and showed comparable efficacy and overall safety/tolerability between PTK 0796 and LZD. Although stopped before meeting planned enrolment goals, results in the CE population met the protocol-defined criteria of a 10% margin to conclude non-inferiority between treatments.

INTRODUCTION

PTK 0796 is the first antibiotic of a new class of compounds, the aminomethylcyclines, which are semi-synthetic compounds related to the tetracyclines. In addition to activity against tetracycline-susceptible organisms, PTK 0796 is active both *in vitro* and in animals against Gram-positive pathogens expressing tetracycline resistance. The drug is also active in the presence of resistance to other antibiotics including methicillin, vancomycin, erythromycin, and ciprofloxacin. Thus, PTK 0796 represents a potentially important option in the treatment of resistant pathogens that are becoming an increasing problem.

The targeted indications for PTK 0796 encompass a range of serious acute bacterial infections, either prompting or occurring during hospitalization. Currently, these include complicated skin and skin structure infection and community-acquired pneumonia.

The study was designed to compare the safety and efficacy of PTK 0796 with linezolid (Zyvox®) in the treatment of adults with complicated skin and skin structure infections (cSSSI).

STUDY DESIGN

This was a randomized (1:1), stratified, controlled, evaluator-blinded Phase 3 study comparing PTK 0796 and linezolid (Zyvox™) for the treatment of adults with complicated skin and skin structure infections. All patients had four scheduled evaluations: at Enrollment (Baseline); at End of IV Treatment; at End of Treatment; and at 10 to 17 days after the last dose of treatment (Test of Cure Evaluation).

Patients were stratified at study entry by type of infection (i.e., wound infection, cellulitis, major abscess). Enrolment of patients with major abscess was limited to 20% Patients were initially treated with study drug IV and then switched to oral therapy at the discretion of the Investigator. The expected duration of IV treatment was 4-7 days; the expected total duration of treatment (IV and oral) was up to 14 days. The study was double-blinded during the IV treatment phase and Evaluator-blinded during the oral treatment phase. ***The primary hypothesis was evaluated by analysis of the clinical success rates in the intent-to-treat (ITT) and clinically evaluable (CE or per protocol)*** . The two analyses were treated as co-primary. The 95% confidence intervals were to be calculated for the difference in success rates between the two treatment groups for each population. If the lower limit of the 95% confidence interval for [PTK 0796 – linezolid] was greater than or equal to –10% for both endpoints, then the hypothesis that PTK 0796 is non-inferior to linezolid would be supported. Should the lower limit of the 95% confidence interval exceed 0% then the superiority of PTK 0796 over linezolid would be supported. With 790 subjects randomized 1:1 with required distribution among infection types, there would be 395 subjects in each treatment group for the total ITT population and at least 316 subjects with cellulitis and wound infection only. A comparator success rate of 75% was assumed in the ITT population (where non-evaluable subjects were failures) and 85% in the CE population. With an evaluability rate of 85% and a two-sided significance level of 0.05, the study would have ~90% power for each of the co-primary endpoints.

The study was designed to align with the 1998 FDA guidance on developing antimicrobial drugs for the treatment of complicated skin and skin structure infections (1). After the study was initiated, FDA modified its guidance for the conduct of studies for this indication. This modification included changes in criteria defining the disease indication (cSSSI to acute bacterial skin and skin structure infections (ABSSSI)) as well as focus of the primary efficacy endpoint to an early response assessment rather than a test of cure assessment. With these major modifications, the trial design did not align with the FDA's guidance for trials aimed at supporting the approval of an antibiotic for treatment of ABSSSI. As a result, the trial was administratively terminated after having enrolled 143 of the planned 790 subjects.

RESULTS

Patients were enrolled in this study between April 2009 and March 2010 in 6 US sites. The trial was stopped after 17% (140/790) of the planned sample size was enrolled. The following characteristics of patients enrolled were noted:

- The mean age of patients randomized into PTK 0796 was 5.5 years older than linezolid-treated patients (~70% of linezolid-treated patients were < 44 years of age compared to 56% in the PTK 0796-treatment arm).
- Approximately 20% of patients enrolled were Hep C seropositive (10-fold higher incidence than estimated in the general popoulation).
- More than 1/3 (35.3%) of PTK 0796 treated patients had infections involving the lower extremity. This compared to <25% (23.6%) in the linezolid treatment arm.

Table 1. Demographics and baseline characteristics

	PTK 0796 N=68	Linezolid N=72
Mean age in years + SD	**41.7 + 14.61**	**36.2 + 12.53**
Age category: ≥18 to ≤44; n (%)	38 (55.9)	51 (70.8)
>44 to ≤64; n (%)	26 (38.2)	20 (27.8)
>64; n (%)	4 (5.9)	1 (1.4)
Sex		
Male	42	51
Female	26	21
Race		
Caucasian	56	61
Black	7	7
Hepatitis C seropositive		
n (%)	16 (23.5)	14 (19.4)
Type of qualifying infection		
Wound infection	14 (20.6)	14 (19.4)
Cellulitis	44 (64.7)	48 (66.7)
Major abscess	10 (14.7)	10 (13.9)
Primary location of qualifying infection		
Head and neck	6 (8.8)	5 (6.9)
Chest/Thorax (below neck to umbilicus)	4 (5.9)	4 (5.6)
Abdomen/Buttocks/Upper Thigh (umbilicus to mid-thigh)	17 (25.0)	15 (20.8)
Right upper extremity (shoulder to fingertips)	10 (14.7)	16 (22.2)
Left upper extremity (shoulder to fingertips)	7 (10.3)	15 (20.8)
Right lower extremity (below mid-thigh to toes)	13 (19.1)	6 (8.3)
Left lower extremity (below mid-thigh to toes)	11 (16.2)	11 (15.3)
Primary cause of infection		
None apparent	33 (48.5)	41 (56.9)
Trauma	11 (16.2)	9 (12.5)
Surgery	1 (1.5)	1 (1.4)

EFFICACY ANALYSES

Clinical success in both the ITT and CE analysis populations were comparable across treatment arms when measured at either the EOT or TOC evaluation.

Table 2. Clinical Response in the ITT population at EOT and TOC

Visit Clinical outcome	PTK 0796 N=68 n (%)	Linezolid N=72 n (%)	PTK 0796 - Linezolid Difference (95% CI)
End of treatment (EOT)			
Clinical success	61 (89.7)	66 (91.7)	-2.0 (-12.4, 8.5)
Not Clinical Success (failure + nonevaluable)	7 (10.3)	6 (8.3)	
Clinical failure (failure only)	1 (1.5)	3 (4.2)	
Test of cure (TOC)			
Clinical success	58 (85.3)	64 (88.9)	-3.6 (-15.5, 8.3)
Clinical failure (failure + non-evaluable)	10 (14.7)	8 (11.1)	
Clinical failure (failure only)	2 (2.9)	3 (4.2)	

In addition to observing comparable clinical success rates in the overall CE and ITT analysis populations, success rates for patients characterized by cSSSI subtype (wound, cellulitis, major abscess) were also comparable across treatment arms.

Table 3. Clinical Response in the CE (per-protocol) population at EOT and TOC

Visit Clinical outcome	PTK 0796 Success / Total (%)	Linezolid Success / Total (%)	PTK 0796 - Linezolid Difference (95% CI)
Success at End of treatment			
All cSSSI patients	59/60 (98.3)	64/67 (95.5)	2.8 (-12.4, 8.5)
Wound	13/13 (100)	12/13 (92.3)	
Cellulitis	38/39 (97.4)	44/45 (97.8)	
Major Abscess	8/8 (100)	8/9 (88.9)	
Success at Test of cure			
All cSSSI patients	58/60 (96.7)	64/67(95.5)	1.1 (-6.5, 8.8)
Wound	13/13 (100)	12/13 (92.3)	
Cellulitis	38/39 (97.4)	44/45 (97.8)	
Major Abscess	7/8 (89.5)	8/9 (88.9)	

Clinical success in patients in whom an infecting pathogen was identified was comparable across treatment arms. MRSA was the frequently isolated pathogen. Among patents with MRSA infections, successful clinical response was achieved in 96.2% (25/26) patients treated with PTK 0796 and in 93.5% (29/31) patients treated with linezolid.

Table 4. Clinical Response in the Microbiologically Evaluable Population

	PTK 0796 Eradicated / Total (%)	Linezolid Eradicated / Total (%)	PTK 0796 - Linezolid Difference (95% CI)
All pathogens	47/49 (95.9%)	51/52 (98.1%)	-2.2 (-9.9, 5.6)
Staphylococcus aureus - methicillin susceptible	**17/18 (94.4%)**	**13/13 (100%)**	
Staphylococcus aureus - methicillin resistant	**25/26 (96.2%)**	**29/31 (93.5%)**	

RESULTS (continued)

POST-HOC ANALYSIS: reduction in lesion size

This study was initiated well before the issuance of the August 2010 FDA guidance for study of Acute Bacterial Skin and Skin Structure Infections (ABSSSI) (2) which identified changes in lesion size as central to conclusions about antibiotic effect. However, patients in the trial were scheduled to have the maximal lesion dimension recorded at scheduled study visits (end of IV therapy, EOT, TOC). In some instances, the end of iv therapy occurred during the first 72 hours of therapy. All patients had the maximal lesion dimension measured at baseline. Given the recent interest on assessing progress of lesion size in patients with ABSSSI (lesions >75 cm^2), a post-hoc analysis was done that compared across treatment arms on the changes in maximal lesion dimension . This analysis was focused on patient's whose lesion had a maximal dimension of >10cm to approximate the 75 cm^2 criteria that is evolving as a definition of ABSSSI.

Table 5. Mean (SE) Percent Change in Maximal Lesion Dimension Among ITT Subjects With Baseline Maximal Lesion Dimension of ≥ 10cm

Time Point	PTK 0796		Linezolid	
	N	Mean (SE)	N	Mean (SE)
Enrollment (Maximal Lesion Dim in cm)	62	20.75 (1.3)	63	22.80 (1.4)
Percent Reduction from Enrollment				
EOIV: Subjects Receiving 24-72 Hours of IV	12	-62.3% (4.7%)	12	-56.8% (6.3%)
EOIV	59	-60.4% (2.7%)	59	-62.5% (2.8%)
EOT	60	-81.3% (2.8%)	61	-86.3% (1.9%)
TOC	60	-92.3% (1.7%)	61	-92.5% (1.5%)

- Most patients enrolled (62/68, 91.2% PTK 0796-treated and 63/72 87.5% of linezolid-treated) had lesions with a maximal dimension that was >10cm.
- Percent reduction in lesion size was comparable across treatment arms
- For the subset of patients who had measurements taken 24-72 hrs after starting therapy, the mean percent reduction was 62.3% in PTK 0796-treated and 56.8% in linezolid-treated patients.

PHARMACOKINETIC ANALYSES

Plasma concentrations of PTK 0796 were comparable to those measured in healthy volunteers and phase 2 patients. Plasma concentrations after 300mg oral dosing were comparable to that achieved with 100mg i.v dosing.

Table 6. Omadacycline exposure in cSSTI patients

Infusion	Hours (Nominal) Post Start of Infusion 1	Plasma Concentration ng/mL		
		N	Mean	Std Dev
1	1	46	896.0	1183.4
	3	41	403.2	118.7
	6	32	293.8	103.8
3	24 (1 Hr Prior to Inf 3)	44	136.4	116.1
7	72 (1 Hr Prior to Inf 7)	36	234.9	260.4
1-3 Hours Following Oral Administration		27	399.8	243.3
			AUC_{0-24} hr·ng/ml	
AUC_{0-24} for Infusion 1 (Using Actual Sampling Times for Trapezoidal Rule)*		24	6096.6	3463.2

SAFETY ANALYSES

The overall incidence of adverse events was similar in both treatment groups. The only notable difference favoring comparator was in headache. No subject discontinued study drug due to headache and 12/16 reports of headache in PTK 0796 treated subjects were mild. This observed frequency of headache in PTK 0796 treated subjects is not consistent with that seen in the Phase 2 (CSSI-0702) trial where headache was reported less frequently overall, and occurred more frequently in linezolid than in PTK 0796-treated subjects (6.3%; 7/111 v 8.3% 9/109). The 1 death occurred in a patient with metastatic lung cancer, 14 days after TOC. No SAE reported was considered to be study drug related.

Table 7. Adverse events in PTK 0796 and Linezolid treated patients

	PTK 0796 N=68; n (%)	Linezolid N=72; n (%)
Treatment-emergent AE (TEAE)	56 (82.4)	58 (80.6)
Study drug related TEAE	41 (60.3)	41 (56.9)
AEs leading to study drug discontinuation	2 (2.9)	0
Serious TEAE	3 (4.4)	1 (1.4)
Death	1 (1.5)	0
TEAEs occurring in >10% of patients in either treatment group		
Nausea	18 (26.5)	19 (26.4)
Vomiting	6 (8.8)	11 (15.3)
Diarrhea	3 (4.4)	13 (18.1)
Headache	16 (23.5)	5 (6.9)
Dizziness	7 (10.3)	6 (8.3)

CONCLUSIONS

- Although stopped well short of the planned enrollment, the results in this phase 3 trial are consistent with those reported in the phase 2 cSSSI trial and support the conclusion that PTK 0796 (omadacycline) is not inferior to linezolid as a treatment of patients with serious infections involving the skin and adjacent structures.
- Intravenous and oral formulations of PTK 0796 were well tolerated
- This experience supports the continued development of PTK 0796 for the treatment of patients with serious infectious diseases.

REFERENCES

(1) US FDA. Guidance for industry: Uncomplicated and complicated skin and skin structure infections—developing antimicrobial drugs for treatment. 1998 Jul.

(2) US FDA Center for Drug Evaluation and Research (CDER) "Guidance for Industry: ABSSI: Developing Drugs for Treatment" http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071185.pdf

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