

In a phase 2 complicated skin and soft tissue infections (cSSTI) trial outcomes assessed early in the course of therapy were consistent with outcomes assessed 10-17 days after completing therapy for patients treated with either omadacycline (OMC; PTK796) or linezolid

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Abstract

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ABSTRACT

Background: A successful phase 2 program studying OMC has been completed that suggested efficacy comparable to linezolid, thus supporting progression to a phase 3 program in patients with serious skin infections. Because of an evolving concern that assessing outcome 10-17 days after completing therapy for cSSTI may poorly correlate with historical trial data used to establish treatment effect of antibacterials in this disease, the early responses in patients with cSSTI randomized to either OMC or linezolid were further assessed.

Methods: A post-hoc analysis was conducted that was aimed at defining: 1) incidence of cessation of spread of infection (no increase in either maximum length or width of infection site inflammation) and absence of fever (core body temp <38.2 C) 1-3 days (24-72 hours) after starting therapy and 2) reduction of lesion size during the treatment course.

Results: In OMC and linezolid-treated patients respectively, the clinical response rates 10-17 days after completing therapy were 88.3% (98/111) and 75.9% (82/108) [95% CI for the difference: 1.9, 22.9] in the ITT (intent-to-treat) population, 98.0% (98/100) and 93.2% (82/88) [95% CI for the difference: -1.7, 11.3] in the CE (clinically evaluable) population. The incidence of cessation of lesion size increase and absence of fever at day 1-3 in OMC and linezolid-treated patients, respectively, was 96.8% and 94.4% in the ITT and 96.4% and 93.8% in the CE population. In ITT patients for whom complete data on lesion size were available, mean reduction of maximal lesion dimension was greater for patients treated with OMC than those treated with linezolid evaluated following 24-72 hrs of therapy (31.8%; SE 4.6% for OMC and 6.7%; SE 15.1% for linezolid) and upon completion of therapy (81.1%; SE 3.4% and 63.2%; SE 5.8%). Among ITT subjects who received no systemic antibiotics prior to enrollment, mean reductions were 28.3% (SE 5.1%) for OMC-treated and -6.9% (SE 25.4%) for linezolid-treated patients after 24-72 hrs of therapy. At the end of treatment, mean reduction of lesion size in these patients was 82.7% (SE 4.3%) for OMC-treated and 63.0% (SE 8.0%) for linezolid-treated patients.

Conclusions: Consistent with outcomes assessed 10-17 days after completing therapy, outcome assessed early in the course of therapy with OMC compared favorably to that of linezolid. This phase 2 experience strongly supports continued development of OMC as a treatment of patients with serious skin infections.

INTRODUCTION

Omacycline (OMC or PTK796) is the first antibiotic of a new class of compounds, the aminomethylcyclines, which are semi-synthetic compounds related to the tetracyclines. The tetracyclines comprise a family of antimicrobials which include tetracycline, doxycycline, and minocycline. These agents are well-tolerated, have a broad-spectrum of antimicrobial activity, including gram-positive, gram-negative, anaerobic and atypical bacteria, and have proven effective in the treatment of a variety of bacterial infections involving the respiratory tract, skin and skin structure, urinary tract, and intra-abdominal sites. When first introduced into clinical practice in the 1950's-60's, the tetracyclines were an important component of the antibiotic armamentarium. Although these agents have continued to be used widely, it has only been recently that agents in this class have been developed to address the emergence of antibiotic drug resistance among both gram-positive and gram-negative bacteria.

Two recent developments raise the specter that currently available antibiotics may become even less useful for treatment of infections caused by gram-positive organisms. The first is the emergence of vancomycin resistance in *Enterococcus* species and the subsequent transfer of those resistance elements to *S. aureus*. The second important development is the emergence of methicillin-resistant *S. aureus* which is quickly becoming a predominant cause of staphylococcal infections in both hospital and community settings.

OMC is a broad spectrum antibiotic that is being developed in both parenteral and oral formulations. It has been shown to have potent activity *in vitro* against the two major causes of multi-drug resistant gram-positive bacterial infections: enterococci and staphylococci. OMC is prepared by chemical modification of minocycline and has similar physicochemical properties. However, it has an extended antibacterial spectrum that includes potentially clinically significant activity against tetracycline-resistant pathogens. OMC is active both *in vitro* and in animals against gram-positive and other bacteria expressing either tetracycline resistance. In addition, the drug is active in the presence of resistance to other antibiotics including methicillin, vancomycin, erythromycin, and ciprofloxacin.

The targeted indications for OMC encompass a range of serious acute bacterial infections, including those prompting, or occurring during, hospitalization and requiring parenteral antibiotics. These include complicated skin and skin structure infection and community-acquired pneumonia.

The *in vivo* activity of OMC has been demonstrated in multiple animal models of infection using common pathogens. Based on the dose required for protection against death or for effective reduction of bacterial load (typically >2 log CFU reduction), OMC was, in most cases, as or more potent and effective than currently available antibiotics (e.g., minocycline, vancomycin, linezolid).

STUDY DESIGN

This was a randomized, controlled, evaluator-blinded Phase 2 study comparing OMC and linezolid for the treatment of complicated skin and skin structure infections. Patients were enrolled at eleven sites in the United States. Patients diagnosed as having complicated skin and skin structure infections were randomized on a 1:1 basis to receive either OMC or linezolid. The study was evaluator-blinded. Principal criteria for exclusion included a subject (a) having received an investigational drug within the past one month prior to enrollment, (b) having received greater than 48 hours' treatment with a potentially effective systemic antibiotic immediately prior to the first dose of study drug, or (c) prior enrollment in this protocol.

All subjects were to have four structured evaluations: at Enrollment (Baseline); at End of IV Treatment (EOIV); at End of Treatment; and at 10 to 17 days after last dose of treatment (Test of Cure Evaluation). In addition, the blinded investigator was to see each subject daily while he or she was on IV therapy and once every 3 days while receiving oral treatment to determine whether to continue current treatment, switch from IV to oral therapy, or discontinue treatment.

At each of the four structured evaluations, the blinded investigator assessed the subject, with particular attention to scoring the findings at the primary site of infection and obtaining cultures. Clinical and microbiologic outcomes were to be determined using these assessments. Measurement of lesion size was to be performed at each evaluation.

The protocol-defined primary study objective was to compare the safety and tolerability of OMC and linezolid administered intravenously and orally in adults with complicated skin and skin structure infections. Secondary objectives were to 1) compare the efficacy of OMC and linezolid administered intravenously and orally for the treatment of adults with complicated skin and skin structure infections, and 2) to determine the pharmacokinetics of OMC administered intravenously and orally in a population of adults with complicated skin and skin structure infections.

After the trial was completed, a series of discussions within the infectious diseases and regulatory communities challenged the primary importance of evaluating a patient with cSSTI after completion of antibiotic therapy^{1,2}. Recently, it has been suggested that a more relevant evaluation of antibiotic treatment effect would be found in evaluating the size of a patient's cSSTI infection and the resolution of signs of systemic inflammation during the first days of therapy rather than relying on observations of overall clinical cure 1 to 2 weeks after antibiotic therapy had been completed. Given this proposal, a post hoc evaluation of cSSTI lesion size and of the resolution of elevated body temperature was assessed for the patients completing this phase 2 trial.

RESULTS

Eleven sites, all located in the US, randomized a total of 234 subjects; 219 received at least one dose of study drug. Among the 219 subjects in this ITT population, 188 met criteria of being clinically evaluable (CE), with 162 (74%) having at least one infecting pathogen identified at baseline (ME; microbiologically evaluable population). A total of 67 patients (31 OMC, 36 linezolid) had their EOIV occur 24-72 hours following the start of therapy and were, therefore, eligible for this early response analysis.

Demographics of the ITT population for each of the treatment arms is shown in Table 1. The treatment arms were well-matched for all characteristics, including baseline lesion size.

Table 1. Demography (ITT Population)

		OMC (N=111)	Linezolid (N=108)
Sex [N (%)]:	Male	66 (59.5%)	57 (52.8%)
	Female	45 (40.5%)	51 (47.2%)
Race [N(%)]:	Caucasian	97 (87.4%)	99 (91.7%)
	Black/Other	14 (2.6%)	9 (8.3%)
Age (yrs):	Mean (SD)	44.9 (14.1)	45.8 (13.3)
	Min, Max	19, 81	19, 76
Weight (kg):	Mean (SD)	84.2 (22.0)	85.0 (20.2)
	Min, Max	45, 144	51, 152
BMI (kg/m ²):	Mean (SD)	28.8 (6.9)	29.3 (6.8)
	Min, Max	27.6, 48.5	28.3, 52.2
Lesion Max Linear Dim (cm): N*		102	99
	Mean (SD)	14.9 (13.9)	12.3 (11.8)
	Min, Max	1.5, 96.0	0.5, 52.5
Lesion Max Linear Dim (cm): N* (EOIV at 24-72 hours)		31	36
	Mean (SD)	14.7 (14.4)	11.0 (10.8)
	Min, Max	1.5, 70.0	0.5, 41.0

* Excludes Patients with DFI

RESULTS (continued)

The protocol-defined efficacy outcomes of clinical response at the Test of Cure (TOC) evaluation in the ITT, CE and ME populations are provided in Table 2. Protocol-defined assessments of efficacy in OMC-treated patients compared favorably to that measured in linezolid-treated subjects in each of the three major study populations.

Table 2. Early (24-72 Hour) Clinical Response* Among Patients Following 24-72 Hours of Therapy

Study Population*	OMC		Linezolid	
	N	% Response	N	% Response
ITT	31	96.8	36	94.4
CE	28	96.4	32	93.8
ME	22	95.5	23	95.7

* Defined as cessation of lesion spread and absence of fever (temperature < 38.0° C)
** ITT = Intent-to-Treat, CE=Clinically Evaluable, ME=Microbiologically Evaluable

Post hoc analyses of patients aimed at assessing changes in lesion size during the course of study therapy, by treatment arm, included the following:

- Percent decrease in baseline lesion size by 24-72 hours after starting study therapy
- Percent decrease in baseline lesion size at the completion of study therapy
- Similar analyses for patients who received no systemic antibiotics prior to the study
- Similar analyses for patients with baseline maximal lesion dimension of > 10 cm

Figure 1 gives the mean (SE) percent reduction in maximal lesion dimension from baseline to the 24-72 hours following the start of therapy and at the end of treatment for both treatment arms. At both time points, OMC was associated with a greater mean reduction compared to linezolid. Following 24-72 hours of therapy, patients receiving OMC had a 31.8% mean reduction in maximal lesion dimension compared to a 6.7% mean reduction for linezolid. At the end of treatment, patients who had received 24-72 hours of IV OMC had a mean reduction in maximal lesion dimension of 81.1% compared to 63.2% for those who had received 24-72 hours of linezolid.

Figure 1. Mean (SE) Percent Reduction in Maximal Lesion Dimension for ITT Patients Following 24-72 Hours of Therapy

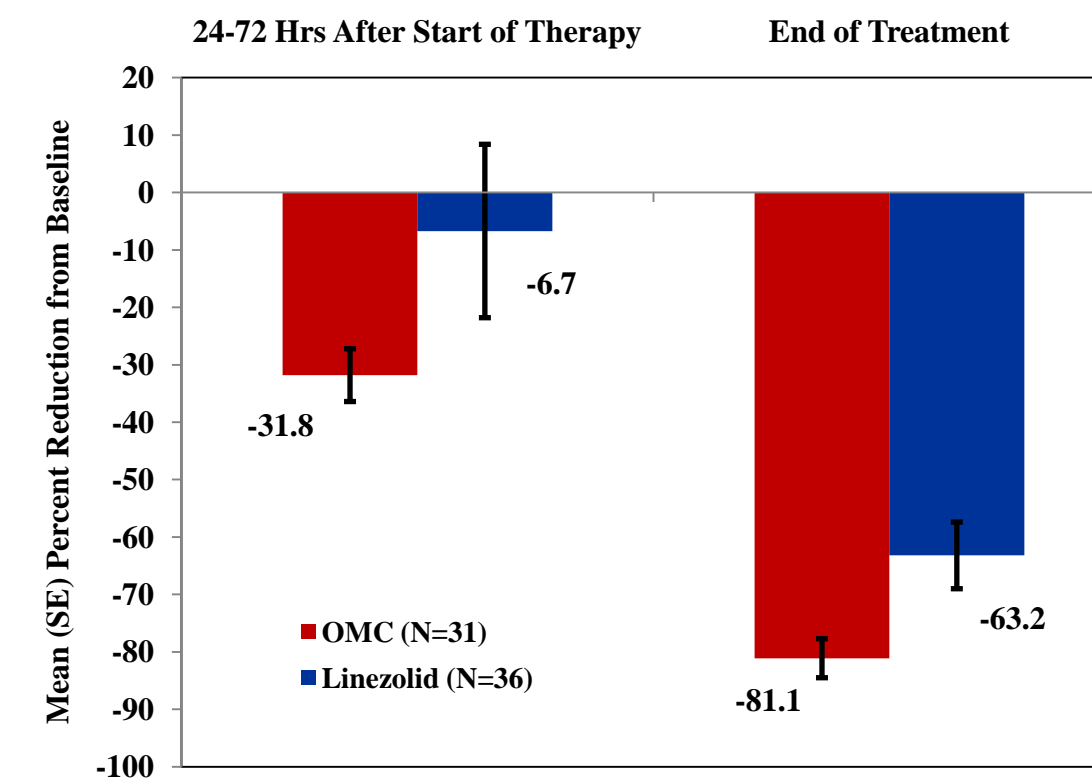


Figure 2 provides a similar presentation of reduction in maximal lesion dimension in patients for whom no systemic antibiotic use was reported during the 72 hours prior to their enrollment in the study. Results mirror those seen for all patients, suggesting that prior antibiotic use as reported in this study had little effect on the magnitude of wound healing observed for either treatment group. Note that the net mean increase seen in the linezolid group was associated with a large standard error, attributable to one patient with a small lesion dimension (0.5 cm) that increased to 2.5 cm at the completion of IV, a 500% recorded increase.

Figure 3 summarizes mean reductions in maximal lesion dimension among patients who had a baseline lesion dimension of at least 10 cm. As demonstrated in the other analyses, greater mean reductions were observed in patients receiving OMC compared to those on linezolid.

RESULTS (continued)

Figure 2. Mean (SE) Percent Reduction in Maximal Lesion Dimension for ITT Patients Following 24-72 Hours of Therapy Who Had No Systemic Antibiotic Use Within 72 Hours of Study Enrollment

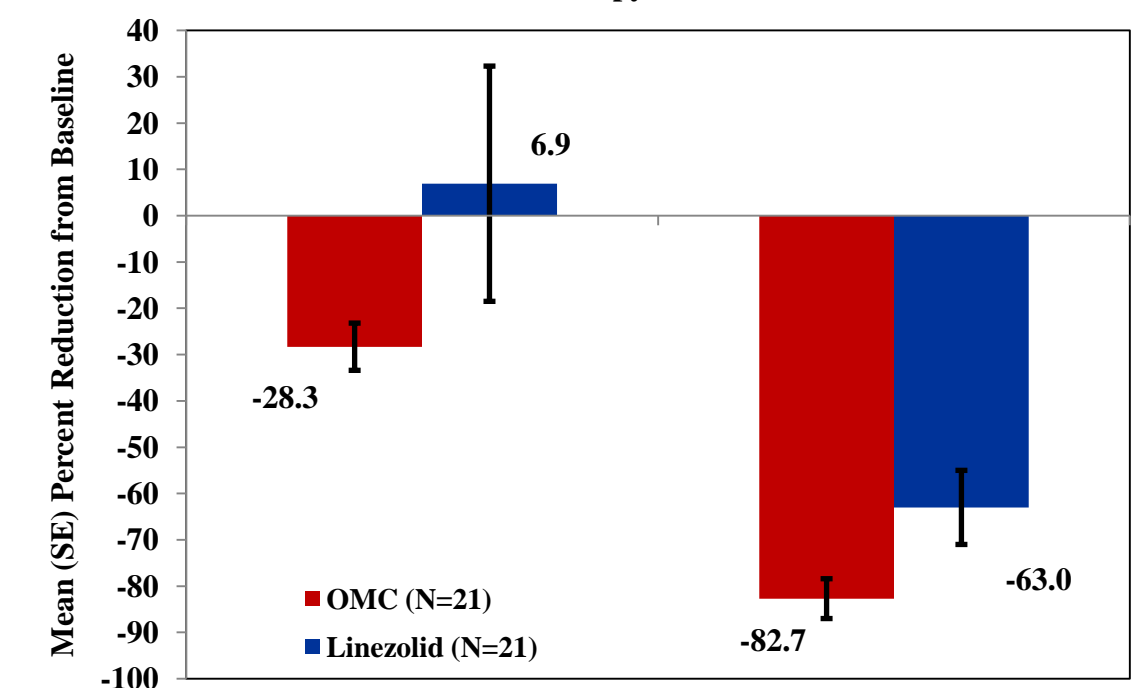
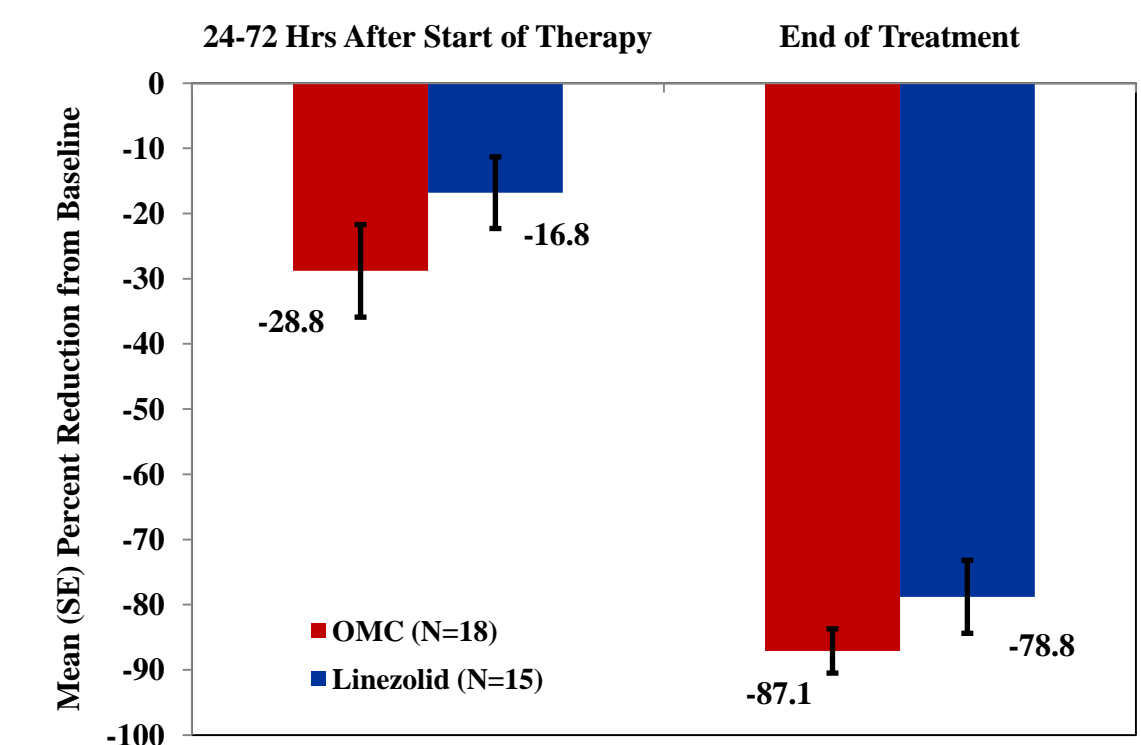


Figure 3. Mean (SE) Percent Reduction in Maximal Lesion Dimension for ITT Patients Following 24-72 Hours of Therapy With Baseline Maximal Lesion Dimension of > 10 cm



CONCLUSION

Treatment outcomes of cSSTI patients randomized to OMC compared favorably to those measured in linezolid-treated patients. In post-hoc analyses conducted to address recently raised issues about measurement of lesion size and resolution of fever during antibiotic therapy, similar favorable outcomes were evident in OMC-treated subjects.

Results of this phase 2 trial comparing OMC to linezolid support the continued development of omadacycline as a treatment for patients with serious infections involving the skin and adjacent structures.

REFERENCES

- DAIOP "Ceftaroline Fosamil for the Treatment of CABP and cSSSI" <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM224656.pdf>
- CDER "Guidance for Industry: ABSSI: Developing Drugs for Treatment" <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071185.pdf>