Omadacycline in female adults with acute pyelonephritis: Results from a randomized, double-blind, adaptive phase 2 study

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Background

Acute pyelonephritis is a common infection of the kidney and renal pelvis.[1] It occurs most often in young adult women (ages 15–29 years), and accounts for ~200,000 hospitalizations per year in the US.[1]

Escherichia coli is the most common cause of infection, and current guidelines recommend outpatient treatment with oral fluoroquinolones[1].

Omadacycline has *in vitro* activity against most common uncomplicated urinary tract infection uropathogens, most notably *E. coli* and *Staphylococcus saprophyticus*.[2,3]

Omadacycline is the first member of the aminomethylcycline class, and is currently approved in the US for community-acquired bacterial pneumonia and acute bacterial skin and skin structure infections in adults.[4,5]

Methods

In this randomized, double-blind, double-dummy, adaptive-designed phase 2 study, females aged ≥18 years with acute uncomplicated pyelonephritis were initially randomized to one of four once-daily regimens of omadacycline (OMC) versus a once-daily standard regimen of IV-to-oral levofloxacin (LVX).

The primary objective of this study was to evaluate the efficacy of intravenous (IV) and IV-to-oral dosing regimens of OMC and LVX in the treatment of adults with acute pyelonephritis.

The planned total duration of study therapy was 7–10 days (IV only, or IV + oral); subjects with bacteremia confirmed from local blood culture drawn at screening were allowed to receive up to 14 days of treatment.

The randomization algorithm was subsequently adapted by the data monitoring committee following interim analyses of efficacy in the microbiological-intent-to-treat (micro-ITT) population (**Table 1**).[6]

Table 1. Study design and dosing groups[a]

Group	Test article	Dose Day 1	Dose Days 2–10
1	Omadacycline	200 mg IV	200 mg IV
2	Omadacycline	200 mg IV	100 mg IV
3	Omadacycline	200 mg IV	300 mg PO or 100 mg IV
4	Omadacycline	200 mg IV	450 mg PO or 100 mg IV
5	Levofloxacin	750 mg IV	750 mg PO or IV

IV, intravenous; PO, oral.

[a] Initially, participants were randomized to 1 of 5 treatment groups. Interim analyses were conducted by the data monitoring committee (blinded to investigators) in the microbiological-intent-to-treat (micro-ITT) population (all randomized participants who had ≥1 uropathogen in baseline urine culture present at ≥10^5 colony-forming units/mL, and ≤2 bacterial isolates at any colony count).

Primary and secondary efficacy were assessed for noninferiority according to:

- Investigator's assessment of clinical response (IACR) at post-therapy evaluation (PTE; Day 21) and at end of therapy (EOT).
- Microbiological response at PTE and EOT.

Clinical success was defined as sufficient resolution of signs and symptoms such that no additional systemic antimicrobial therapy was required for the current infection; treatment-emergent adverse events (TEAEs) were also assessed.

Statistical analysis

Noninferiority of OMC to LVX was demonstrated if the lower limit of the 2-sided exact 95% confidence interval (CI) for the difference in IACR at PTE was within -10%.

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Omadacycline demonstrated high clinical success rates despite not meeting noninferiority criteria versus levofloxacin in women with acute pyelonephritis

Objective

Phase 2 study to evaluate the efficacy of intravenous (IV) and IV-to-oral dosing regimens of omadacycline (OMC) versus levofloxacin (LVX) in the treatment of adults with acute pyelonephritis (NCT03757234).

Conclusions

Clinical success rates were high in both groups, although no OMC group met criteria for noninferiority to LVX.

A trend within the OMC groups toward no difference for clinical success when higher doses were given may suggest that a higher dose would be required in future studies.

OMC was well tolerated, with a safety profile consistent with its current labeling.

Further evaluation of available pharmacokinetic data and known pharmacodynamic drivers of efficacy for AP is warranted to determine an optimal dose–response relationship.

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Results

201 patients were randomized (OMC, n=127; LVX, n=74).

- Based on interim analysis of the mITT population by the data monitoring committee (DMC), randomization into OMC Groups 2–4 was stopped because of lower response rates.

Baseline characteristics were generally similar across groups, and *E. coli* was the most prevalently identified pathogen species (**Table 2**).

Table 2. Baseline demographics and disease characteristics

	Omadacycline[a]				Levofloxacin
	200 mg IV n=75	100 mg IV n=18	300 mg PO or 100 mg IV n=17	450 mg PO or 100 mg IV n=17	750 mg PO or 750 mg IV n=74
Age, years, mean (SD)	38.2 (15.0)	33.9 (14.5)	37.1 (16.0)	38.2 (17.7)	38.8 (14.7)
Weight, kg, mean (SD)	68.1 (15.2)	65.5 (15.5)	68.5 (14.9)	69.5 (14.9)	66.4 (13.7)
Renal function, n (%)[b]					
Normal renal function [>89 mL/min]	59 (78.7)	16 (88.9)	13 (76.5)	13 (76.5)	48 (64.9)
Mild renal impairment [>60–89 mL/min]	12 (16.0)	1 (5.6)	3 (17.6)	4 (23.5)	20 (27.0)
Moderate renal impairment [30–60 mL/min]	4 (5.3)	1 (5.6)	1 (5.9)	0	12 (6.0)
Baseline pathogens, n (%) (micro-ITT)[c]					
Escherichia coli	36 (78.3)	11 (100)	12 (85.7)	9 (69.2)	45 (86.5)
Klebsiella pneumoniae	6 (13.0)	0	0	0	3 (5.8)
Proteus mirabilis	1 (2.2)	0	1 (7.1)	1 (7.7)	1 (1.9)
Pseudomonas aeruginosa	0	0	0	1 (7.7)	2 (3.8)
Enterococcus faecalis	3 (6.5)	0	0	0	1 (1.9)

[a] OMC treatment arms are described by dosing regimen for Days 2–10. All OMC treatment arms used 200 mg IV dosing on Day 1.
[b] Renal function based on creatinine clearance at baseline, calculated from the Cockcroft-Gault equation for females and non-missing age, weight, and creatinine values.
[c] Micro-ITT: All randomized subjects who had a study-qualifying pre-treatment baseline urine culture.

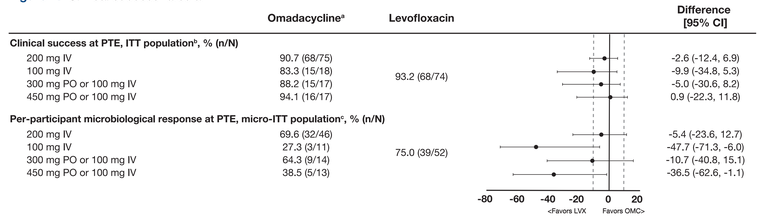
Clinical success rates for the intent-to-treat (ITT) population at PTE were high for all groups (OMC 83–94%, LVX 93%; **Figure 1**). However, the lower limit of the 95% CI for the treatment difference (OMC vs LVX) ranged from -12.4% to -34.8% across the OMC treatment groups. None of the OMC groups met the criterion for noninferiority to LVX.

Responses at EOT were generally consistent with those at PTE (clinical success at EOT: OMC 88–96%, LVX 95%).

Microbiological responses in each OMC group were lower than LVX (OMC 27–70%, LVX 75%).

OMC was well tolerated, and consistent with current labeling. One TEAE occurred in 36.2% and 32.4% of OMC- and LVX-treated patients, respectively. The most frequently reported TEAEs (≥5%) in the OMC and LVX groups, respectively, were: headache (10.2% vs 6.8%), asymptomatic bacteriuria (6.3% vs 1.4%), diarrhea (2.4% vs 6.8%), and nausea (5.5% vs 6.8%).

Figure 1. Clinical success rates at PTE



CI, confidence interval; ITT, intent-to-treat; IV, intravenous; LVX, levofloxacin; micro-ITT, microbiological-intent-to-treat; OMC, omadacycline; PO, oral; PTE, post-therapy evaluation; QD, once daily.
[a] OMC treatment arms are described by dosing regimen for Days 2–10. All OMC treatment arms used 200 mg IV dosing on Day 1.
[b] ITT population: All randomized participants.
[c] Micro-ITT population: All randomized participants who had ≥1 uropathogen in baseline urine culture present at ≥10^5 colony-forming units/mL, and ≤2 bacterial isolates at any colony count.

References

1. Colgan R, et al. *Am Fam Physician*. 2011;84:519–26.
2. Pagano P, et al. *J Antimicrob Chemother*. 2020;75:2160–63.
3. Karlowsky JA, et al. *Clin Infect Dis*. 2019;69(suppl 1):S6–15.
4. Stets R, et al. *N Engl J Med*. 2019;380:517.
5. O'Riordan W, et al. *Lancet Infect Dis*. 2019;19:1080–90.
6. Curran M, et al. ASM/ESCMID Conference on Drug Development to Meet the Challenge of Antimicrobial Resistance 2019;P36

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