Omadacycline in female adults with cystitis: Results from a randomized, double-blinded, adaptive phase 2 study

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Background

Urinary tract infections (UTIs) are the most common outpatient infections, affecting around 150 million people globally every year, with an estimated incidence of 0.5 to 0.7 per person-year in young women.[1,2]

The majority of uncomplicated UTIs, such as cystitis, are caused by *Escherichia coli*, and large increases in resistance rates to antimicrobials (e.g. ciprofloxacin and trimethoprim-sulfamethoxazole) have been observed in urinary *E. coli* isolates in the US.[3,4]

Omadacycline (OMC) is approved in the US as a once-daily intravenous (IV) and oral antibiotic monotherapy for treatment of adults with acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia.[5]

In an exploratory analysis of a phase 1b study of 31 women with cystitis, IV-to-oral and oral-only OMC regimens resulted in high clinical response rates (94% at end of treatment (EOT) and 84% at post-treatment evaluation (PTE)).[6]

Methods

Females aged ≥18 years with a diagnosis of uncomplicated symptomatic cystitis were randomized to receive one of four oral dose regimens of OMC, or nitrofurantoin (NIT), for 7 days (**Table 1**), in this Bayesian adaptive phase 2 study.

Table 1. Treatment groups

Group	Test article	Study Day 1	Study Days 2–7[a]	Participants enrolled, n
1	Omadacycline	300 mg PO q12h, fed	300 mg PO q24h	55
2	Omadacycline	450 mg PO q12h, fed	300 mg PO q24h	54
3	Omadacycline	450 mg PO q12h, fed	450 mg PO q24h	54
4[b]	Omadacycline	450 mg PO q12h, fed	450 mg PO q12h	8
5	Nitrofurantoin	100 mg PO q12h, fed	100 mg PO q12h	54

fed = patient was not fasted; PO, oral; q#h, once every # hours.
[a] First doses on Study Days 2–7 were taken in a fasted state. Second doses on Study Days 2–7, where applicable, were administered ~2 hours following a light meal.
[b] Group 4 was added per Amendment 2 after the study had already enrolled >80% of planned subjects based on the Bayesian adaptive study design.

Efficacy was assessed as noninferiority of investigator's assessment of clinical response (IACR) at PTE (Day 14) in the intent-to-treat (ITT) population, i.e. all randomized patients (primary endpoint), and for the secondary endpoints:

- IACR at EOT (day of last dose).
- Microbiological response at EOT and PTE in the microbiological-ITT (micro-ITT) population, i.e. all randomized patients who had a study-qualifying pre-treatment baseline urine culture.
- Composite clinical and microbiological responses at EOT and PTE.

Clinical success was defined as sufficient resolution of signs and symptoms such that no additional systemic antimicrobial therapy was required for the current infection. Microbiological response was defined as eradication or presumed eradication of the causative pathogen.

Safety was assessed as treatment-emergent adverse events (TEAEs), laboratory evaluations, and vital signs.

Statistical analysis

Noninferiority of OMC to NIT 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%.

Funding and disclosures JSO: Advisor – Paratek Pharmaceuticals, Inc. ET: Employee at time of the study – Paratek Pharmaceuticals, Inc. AM, AS, AWS, KW: Employee – Paratek Pharmaceuticals, Inc. TKW, SC, PBE: Consultant – Paratek Pharmaceuticals, Inc. This study was funded by Paratek Pharmaceuticals, Inc. Medical editorial assistance, funded by Paratek Pharmaceuticals, Inc., was provided by Innovative Strategic Communications.

Omadacycline demonstrated lower microbiological success despite high clinical success versus nitrofurantoin in women with cystitis

Objective

Phase 2 study to assess the safety and efficacy of multiple dosing regimens of omadacycline (OMC) versus nitrofurantoin (NIT) for treatment of cystitis (NCT03425396).

Conclusions

Clinical success rates were high in the OMC and NIT groups, although no OMC group met criteria of noninferiority to NIT.

Microbiological responses with all doses of OMC were lower than the NIT group.

Results were potentially influenced by the higher baseline MICs observed in this study compared with the previous phase 1b study.

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

Further analyses are needed to fully understand study outcomes.

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Results

Of the 225 enrolled patients, 93.8% completed the study.

Baseline characteristics were similar across groups, except Group 4, which only included eight patients. Most patients had normal renal function (76.4% to 87.5% across groups) and moderate UTI symptoms (50.0% to 64.8% across groups). The most common baseline pathogen was *E. coli* (73.9% to 88.2% across groups). Baseline minimum inhibitory concentration (MIC) values against *E. coli* ranged from 0.5 to 8 µg/mL for OMC and from <2 to 64 µg/mL for NIT.

Clinical success rates for the ITT population at PTE were high for both treatments (OMC 77.8% to 87.5%; NIT 90.7%; **Figure 1A**).

Microbiologic (**Figure 1B**) and composite response rates were higher with NIT (76.7% and 73.3%, respectively) versus OMC Groups 1–3 (56.0% to 65.2% and 50.0% to 60.9%, respectively) at PTE. With regards to OMC, the highest clinical and microbiological success was seen in Group 4, which was the highest daily dose of OMC administered (80.0% for both measures).

The lower limit of the 95% CI for the treatment difference (OMC – NIT) ranged from -16.8% to -44.1% across the OMC treatment groups; therefore, none of the OMC groups met the criterion for noninferiority to NIT.

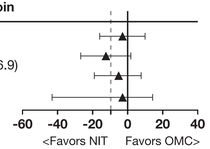
Similar findings to those seen at PTE were observed at EOT (clinical success rates: OMC, 87.0% to 90.7%; NIT, 90.7%).

The most frequently reported TEAEs across all treatment groups were gastrointestinal disorders (OMC 22.2%; NIT 14.8%).

Figure 1: Clinical success rates at post-treatment evaluation (PTE) in the intent-to-treat (ITT) population and microbiological response rates at PTE in the micro-ITT population

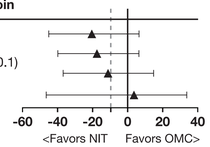
A. Clinical success rates

ITT	Clinical success, % (95% CI)	Difference vs nitrofurantoin	Nitrofurantoin
Omadacycline 300/300 q24h	87.3 (75.5, 84.7)	-3.5 (-16.8, 9.6)	90.7 (79.7, 96.9)
Omadacycline 450/300 q24h	77.8 (64.4, 88.0)	-13.0 (-27.4, 1.2)	
Omadacycline 450/450 q24h	85.2 (72.9, 93.4)	-5.6 (-19.6, 7.4)	
Omadacycline 450/450 q12h	87.5 (47.3, 99.7)	-3.2 (-44.1, 14.0)	



B. Microbiological response rates

Micro-ITT	Success, % (95% CI)	Difference vs nitrofurantoin	Nitrofurantoin
Omadacycline 300/300 q24h	56.0 (34.9, 75.6)	-20.7 (-45.1, 6.0)	76.7 (57.7, 90.1)
Omadacycline 450/300 q24h	58.8 (40.7, 75.4)	-17.8 (-40.2, 5.9)	
Omadacycline 450/450 q24h	65.2 (42.7, 83.6)	-11.4 (-36.8, 14.7)	
Omadacycline 450/450 q12h	80.0 (28.4, 99.5)	3.3 (-47.0, 33.2)	



Micro-ITT, microbiological intent-to-treat; q#h, every # hours.
Analysis sets were defined as follows: ITT = all randomized patients; micro-ITT = all randomized patients who had a study-qualifying pre-treatment baseline urine culture.
Vertical line at -10 indicates the NI margin.

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Acknowledgments

The authors thank all the patients, study sites, and data monitoring committee that took part in this phase 2 study.

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