Sunday - 200

Pharmacokinetics and Safety of Omadacycline in Patients with Uncomplicated Urinary Tract Infections

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ABSTRACT

Background: Omadacycline (OMC) is an aminomethylcycline antibiotic currently in phase 3 development as a once-daily intravenous (IV) and oral (PO) monotherapy for community-acquired bacterial pneumonia and acute bacterial skin and skin structure infections. Early clinical studies indicate partial renal excretion of OMC. This phase 1 study evaluated OMC in female patients with uncomplicated urinary tract infections (uUTI).

Methods: This randomized, open-label study enrolled adult women with acute uUTI defined as cystitis symptoms and a positive urine leukocyte esterase test, excluding those with any evidence of complicated UTI. Patients received 1 of 3 OMC regimens for 5 days (Group 1: 200 mg IV on Day 1 then 300 mg PO Q24h; Group 2: 300 mg PO Q12h on Day 1 then 300 mg PO Q24h; Group 3: 450 mg PO Q12h on Day 1 then 450 mg PO Q24h). Blood and urine samples were collected on Days 1 and 5. Investigator-assessed clinical response was determined at end of treatment (EOT, Day 6) and at a posttherapy evaluation (PTE, 5-9 days after the last dosing). Urine cultures were performed at baseline, daily through EOT, and at PTE.

Results: 31 female patients were enrolled and treated; median age, 38 years (range, 19–75 yr); median weight, 72 kg (range, 47–121 kg); median body mass index, 27 kg/m^2 (range, 20–43 kg/m^2). At steady state (on Day 5), the mean amount of OMC excreted in urine over 24 hours was 21.7, 31.5, and 43.6 mg, in Groups 1, 2, and 3, respectively. Investigator-determined clinical success was observed in 94% and 84% of all patients at EOT and PTE, respectively, with similar results across the 3 treatment groups. A baseline urine pathogen (≥10^5 CFU/mL) was isolated in 18/31 (58%) patients, with *E. coli* being the most common (N=10). A favorable microbiological response at PTE (negative urine culture) was observed in 14/18 (78%) patients. The most common treatment-emergent adverse events (TEAEs) in all groups were gastrointestinal (GI), including nausea (60%–73% per group) and vomiting (20%–40% per group). In general, the GI TEAEs were mild, did not result in treatment discontinuation, and were usually self-limiting. There were no serious TEAEs and no treatment discontinuations due to TEAEs.

Conclusion: OMC is partially excreted in the urine of female patients with cystitis and a high percentage of patients achieved clinical success and favorable microbiological response. OMC appeared safe and well tolerated with the most common TEAEs being GI. OMC may be a useful alternative for uUTIs and warrants evaluation in larger controlled studies for this indication.

INTRODUCTION

- Omadacycline (OMC) is the first antibiotic in a new class of compounds, the aminomethylcyclines, which are semi-synthetic antibiotics related to the tetracyclines[1,2]
- Modifications in the chemical structure of OMC allow it to overcome the two main mechanisms of tetracycline resistance: efflux pumps and ribosomal protection[2,3]
- OMC demonstrates potent, broad-spectrum *in vitro* activity against common Gram-positive aerobes (including methicillin- and penicillin-resistant strains), Gram-negative aerobes, anaerobes, and atypical bacterial pathogens[4,5]
- OMC is in late stage clinical development as an intravenous (IV) and once-daily oral monotherapy for acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP)
- Uncomplicated UTIs are most commonly caused by *E. coli* and *Staphylococcus saprophyticus* in 80% and 5% to 15% of cases, respectively[6]
- OMC MIC$_{90}$s are 1 µg/mL for *S. saprophyticus*, 2 µg/mL for ESBL-negative *E. coli*, and 4 µg/mL for ESBL-producing *E. coli*[7]
- A prior Ph1 absorption, distribution, metabolism, and excretion (ADME) study in healthy human subjects indicated partial renal excretion of OMC. No metabolites of OMC were detected in human plasma, urine, or feces[8]
- The primary objective of this study was to evaluate the urine and plasma concentrations of OMC in female adults with cystitis
- Additional objectives of this study were to evaluate the safety of OMC in female adults with cystitis and to explore the potential clinical efficacy of OMC for the treatment of cystitis in female adults

METHODS

Study Design	Randomized, open-label, parallel-group study evaluating 3 dosing regimens of OMC in the treatment of female adults with cystitis
Population	Female adults with cystitis (age ≥ 18 y) • ≤ 72h onset of ≥ 2 cystitis symptoms (dysuria, urgency, frequency, suprapubic pain) • Positive urine leukocyte esterase test • Excluded Pregnant or breastfeeding • Excluded known or suspected complicated UTI • Excluded prior treatment with a systemic antibiotic within ≤ 48h
Treatments	Group 1: OMC 200 mg IV, then 300 mg PO Q24h Group 2: OMC 300 mg PO Q12h x 2 doses, then 300 mg PO Q24h Group 3: OMC 450 mg PO Q12h x 2 doses, then 450 mg PO Q24h
Formulations	OMC IV solution and 150-mg tablets
Treatment Duration	5 days
Planned Number of Subjects	24
End Points	• Plasma PK, urinary concentrations on Days 1 and 5 • Safety • Clinical response and microbiologic outcome at End of Treatment (EOT, day 6) and at Post-Therapy Evaluation (PTE, 5-9 days after last dose)
Analysis Populations	• Safety Population – All randomized subjects who received any amount of OMC • Pharmacokinetic (PK) Population – All subjects who received OMC and had evaluable PK parameter data

RESULTS

Table 1. Demographics—Safety Population

	Omadacycline Dose			
	IV 200 mg → PO 300 mg (n = 11)	PO 300 mg (n = 10)	PO 450 mg (n = 10)	All Subjects (N = 31)
Female, n (%)	11 (100)	10 (100)	10 (100)	31 (100)
Age, years				
Median (range)	51 (20-60)	31 (25-54)	41 (19-75)	38 (19-75)
Weight, kg				
Median (range)	72 (47-95)	75 (54-121)	69 (51-111)	72 (47-121)
BMI, kg/m^2				
Median (range)	27 (20-39)	28 (20-43)	27 (21-41)	27 (20-43)

Table 2: Baseline Pathogens[a]—Safety Population

		Omadacycline Dose			
		IV 200 mg → PO 300 mg (n = 11)	PO 300 mg (n = 10)	PO 450 mg (n = 10)	All Subjects (N = 31)
Subjects with pathogen growth at Baseline[b]	**N1 (%)**	**6 (54.5)**	**5 (50.0)**	**7 (70.0)**	**18 (58.1)**
Subjects with Gram-negative pathogens[c]	**n (%)**	6 (100.0)	4 (80.0)	6 (85.7)	16 (88.9)
Escherichia coli		3 (50.0)	3 (60.0)	4 (57.1)	10 (55.6)
Klebsiella pneumoniae		0 (0.0)	1 (20.0)	2 (28.6)	3 (16.7)
Proteus mirabilis		3 (50.0)	1 (20.0)	0 (0.0)	4 (22.2)
Subjects with Gram-positive pathogens[b]	**n (%)**	1 (16.7)	1 (20.0)	2 (28.6)	4 (22.2)
Aerococcus urinae		0 (0.0)	0 (0.0)	1 (14.3)	1 (5.6)
Enterococcus faecalis		1 (16.7)	0 (0.0)	0 (0.0)	1 (5.6)
Staphylococcus saprophyticus		0 (0.0)	0 (0.0)	1 (14.3)	1 (5.6)
***Streptococcus agalactiae* (Group B)**		0 (0.0)	1 (20.0)	0 (0.0)	1 (5.6)

[a]Pathogens were defined as bacteria identified in urine at 1 × 10^5 CFU/mL or greater
[b]Percentages were calculated as 100 × (N1/N).
[c]Percentages were calculated as 100 × (n/N1).

Figure 1: Mean (± SD) Plasma Concentrations of Omadacycline—PK Population.

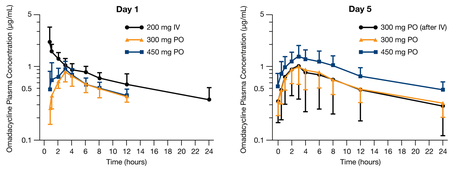


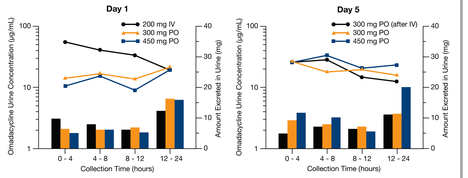
Table 3: Mean Omadacycline Plasma Pharmacokinetic Parameters—PK Population

Day 1				Day 5			
Parameter (Unit)	IV 200 mg → PO 300 mg (n = 11)	PO 300 mg (n = 10)	PO 450 mg (n = 10)	Parameter (Unit)	IV 200 mg → PO 300 mg (n = 11)	PO 300 mg (n = 10)	PO 450 mg (n = 10)
C_{max} (µg/mL)	2.16 (59.0)	0.88 (25.6)	0.99 (30.6)	C_{max} (µg/mL)	1.12 (58.8)	1.12 (37.2)	1.49 (36.2)
t_{max} (h)	0.75 (0.72, 1.60)	3.0 (2.0, 4.0)	3.0 (0.97, 4.0)	t_{max} (h)*	3.0 (0.0, 4.0)	3.0 (2.0, 8.0)	3.0 (0.50, 4.0)
AUC_{0-24} (µg•h/mL)	16.02 (28.7)	ND	ND	AUC_{0-24} (µg•h/mL)	13.16 (59.7)	13.50 (33.7)	19.83 (30.8)
AUC_{0-12} (µg•h/mL)	ND	6.26 (18.9)	6.85 (23.2)	C_{12H} (µg/mL)	0.29 (60.4)	0.32 (35.4)	0.48 (27.6)
$T_{1/2}$ (h)	11.38 (1.543)	ND	ND				
Clearance (L/h)	10.27 (1.553)	ND	ND				
V_z (L)	167.57 (29.438)	ND	ND				

Arithmetic mean (CV%) is shown for C_{max}, AUC_{0-24}, and AUC_{0-12}; t_{max} is shown as median and range (minimum, maximum); $T_{1/2}$, Clearance and V_z are shown as mean (SD).
ND, not determined

RESULTS

Figure 2: Median Omadacycline Concentrations and Amount Excreted in Urine—PK Population.



Lines refer to omadacycline urine concentration (left y-axis).
Bars refer to amount excreted in urine (right y-axis).

Table 4: Mean and Range of Omadacycline Concentrations in Urine Over Various Time Intervals—PK Population

	Omadacycline concentration Mean (min, max) (ng/mL)					
	Day 1			Day 5		
	IV 200 mg → PO 300 mg	PO 300 mg	PO 450 mg	IV 200 mg → PO 300 mg	PO 300 mg	PO 450 mg
0-4 h	65360.0 (9840, 160000)	14003.0 (2740, 27300)	23008.0 (1030, 96500)	42710.0 (4260, 138000)	30900.0 (11100, 76100)	35988.9 (10300, 76900)
4-8 h	43548.2 (7530, 99200)	19088.9 (6030, 33200)	20537.8 (3750, 64900)	26090.0 (6760, 59000)	29111.1 (10800, 67000)	48117.0 (9470, 149000)
8-12 h	32407.3 (7480, 72100)	19981.0 (4880, 67900)	11699.0 (2710, 25300)	33237.0 (5120, 90100)	25350.0 (12300, 68600)	30466.0 (9000, 83500)
12-24 h	22410.0 (7770, 71800)	20772.0 (3320, 39600)	25713.0 (6430, 50100)	21480.0 (2390, 70400)	17940.0 (5040, 46900)	30280.0 (4200, 61200)

Table 5: Omadacycline Urine Pharmacokinetic Parameters—PK Population

	Day 1			Day 5		
Parameter (Unit)	IV 200 mg → PO 300 mg (n = 11)	PO 300 mg (n = 10)	PO 450 mg (n = 10)	IV 200 mg → PO 300 mg (n = 11)	PO 300 mg (n = 10)	PO 450 mg (n = 10)
Ae_{0-24} (mg)	40.70 (44)	39.24 (34)	35.95 (33)	32.27 (79)	38.21 (52)	54.87 (67)
Total dose within 24 hours, (mg)	200 IV	600 PO	900 PO	300 PO	300 PO	450 PO
fe_{0-24} (%) [dose administered]	20.4	6.5	4.0	10.8	12.7	12.2

Ae, amount excreted in urine; fe, fraction of dose excreted in urine; Mean (%CV).

- The mean fraction of dose excreted in urine based on the dose assumed to be absorbed ranged between 11.4% and 20.4% on Day 1, and between 30.7% and 36.4% on Day 5 of therapy with the 3 dosage regimens

Table 6: Investigator Assessment of Clinical Response—Safety Population

	Omadacycline Dose		
	IV 200 mg → PO 300 mg (n = 11)	PO 300 mg (n = 10)	PO 450 mg (n = 10)
EOT			
Clinical success, n (%)	10 (90.9)	10 (100)	9 (90.0)
Clinical failure	0	0	1 (10.0)
Indeterminate	1 (9.1)	0	0
PTE			
Clinical success, n (%)	11 (100)	7 (70.0)	8 (80.0)
Clinical failure	0	2 (20.0)	2 (20.0)
Indeterminate	0	0[a]	0

Clinical success indicates resolution of signs & symptoms and no use of additional systemic antimicrobial therapy for the UTI.
Indeterminate indicates the visit was not completed.
[a]1 subject in the PO 300 mg group failed to return for the PTE visit and should be considered indeterminate.

RESULTS

- 4 subjects (2 in PO 300 mg group and 2 in PO 450 mg group) presented with clinical failure at PTE
  - 2 of these subjects presented with no baseline pathogen
  - 1 of these subjects had a favorable microbiological response
  - 1 of these subjects had an unfavorable microbiological response. *E. coli* was identified as the persistent pathogen. The OMC MIC values were ≤4.0 µg/mL, indicating that the clinical failure was not due to bacterial resistance

Table 7: Per-Subject Microbiological Response at the PTE Visit, Subjects with a Baseline Pathogen—Safety Population

		Omadacycline Dose		
		IV 200 mg → PO 300 mg (n = 11)	PO 300 mg (n = 10)	PO 450 mg (n = 10)
Subjects with pathogen growth at Baseline[a]	**N1 (%)**	**6 (54.5)**	**5 (50.0)**	**7 (70.0)**
Favorable[b]	n (%)	6 (100.0)	4 (80.0)	4 (57.1)
Unfavorable		0 (0.0)	1 (20.0)	3 (42.9)
Indeterminate		0 (0.0)	0 (0.0)	0 (0.0)

Favorable indicates each baseline pathogen was reduced to less than 10^5 CFU/mL.
Unfavorable indicates any baseline pathogen was not reduced to less than 10^5 CFU/mL.
Indeterminate indicates that follow-up cultures were not obtained.
[a]Percentages were calculated as 100 × (N1/N).
[b]Percentages were calculated as 100 × (n/N1).

- There were no positive blood cultures at any timepoint in the study
- 4 subjects (1 in PO 300 mg group and 3 in PO 450 mg group) presented with an unfavorable microbiological response. These subjects had persistent pathogens (3 subjects with *E. coli* and 1 subject with *K. pneumoniae*). The OMC MIC values for these pathogens were ≤4 µg/mL, indicating that the persistence was not due to bacterial resistance

Table 8: TEAEs Occurring in ≥1 Subject—Safety Population

	Omadacycline Dose			
	IV 200 mg → PO 300 mg (n = 11)	PO 300 mg (n = 10)	PO 450 mg (n = 10)	All Subjects (N = 31)
Subjects with any TEAE, n (%)	**9 (81.8)**	**9 (90.0)**	**8 (80.0)**	**26 (83.9)**
Nausea	8 (72.7)	6 (60.0)	6 (60.0)	20 (64.5)
Vomiting	4 (36.4)	4 (40.0)	2 (20.0)	10 (32.3)
Headache	3 (27.3)	2 (20.0)	1 (10.0)	6 (19.4)
Amylase increased	0	3 (30.0)	1 (10.0)	4 (12.9)
Vulvovaginal mycotic infection	1 (9.1)	1 (10.0)	2 (20.0)	4 (12.9)
Diarrhea	0	2 (20.0)	1 (10.0)	3 (9.7)
Gastroesophageal reflux disease	1 (9.1)	0	1 (10.0)	2 (6.5)
Pruritus	2 (18.2)	0	0	2 (6.5)

- All TEAEs were of mild or moderate intensity
- No subjects experienced severe or life-threatening TEAEs, TEAEs leading to premature discontinuation of study drug, SAEs resulting in death, or other SAEs
- Laboratory analyses found no clinically meaningful changes or differences between groups for all parameters measured, except alanine aminotransferase (ALT)
  - The median increase from baseline for ALT values were 5.0, 6.0 and 18.0 U/L in the IV 200 mg to PO 300 mg, PO 300 mg, and PO 450 mg groups, respectively
  - Overall, only 1 subject had an ALT elevation to Grade 2. This subject was in the PO 450 mg group and their ALT reached a maximum value of 92 U/L or 2.8 fold above ULN
- Urinalysis was notable only for leukocyte esterase testing, which for most subjects shifted from positive at baseline (from trace to 3+) to a less severe category or negative at EOT
- Transient elevations in pulse rates were observed in all groups. The largest median increase in pulse rate (20 bpm) was observed in Group 1 after the 200-mg IV dose. For Groups 2 and 3 the largest median increase in pulse rate was approximately 15 bpm after PO doses of 300 mg or 450 mg
- There were no clinically significant findings in blood pressure, 12-lead ECG results, or physical examination findings

CONCLUSIONS

- The *in vitro* activity against common urinary pathogens and the sustained urine concentrations for 24 hours suggest that omadacycline has the potential to be a useful antibacterial agent for the treatment of lower urinary tract bacterial infections caused by susceptible pathogens
- The PK of omadacycline in women with cystitis is similar to the previously reported PK in healthy subjects[8]
- With the omadacycline treatment regimens studied, the observed urine concentrations of omadacycline compared favorably with the minimum inhibitory concentration (MIC) values for common UTI pathogens, and a high percentage of subjects achieved clinical success and favorable microbiological responses
- Overall safety and tolerability of omadacycline in this study was consistent with prior studies
- The most frequent TEAEs in all groups were gastrointestinal (GI) including nausea and vomiting. In general the GI TEAEs were mild, did not result in treatment discontinuation and were usually self limiting

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