Poster 1321

# Omadacycline, an Aminomethylcycline Antibiotic, Has No Effect on QT/QTc Intervals in Healthy Subjects

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## ABSTRACT

**Background:** Omadacycline (OMC), a first-in-class aminomethylcycline, is a once daily oral and intravenous (IV) broad spectrum antibiotic that is undergoing clinical development for treatment of serious bacterial infections. The objective of this study was to evaluate the effect of single therapeutic and supratherapeutic IV doses of omadacycline on ventricular repolarization and the relationship between plasma concentrations of omadacycline and QTc intervals.

**Methods:** This was a single dose, double-dummy, randomized, crossover study. Healthy adult volunteers were randomized to one of four treatment sequences: OMC 100 mg IV, OMC 300 mg IV, moxifloxacin 400 mg oral or placebo. Baseline ECGs were obtained one day prior to the first treatment at timepoints to match those obtained post-dose. After dosing, 12-lead Holter monitoring was recorded over 24 hours, and omadacycline plasma concentrations were measured at set timepoints over 96 hours. The primary ECG parameter of interest was the placebo- and baseline-adjusted QTcF value (ddQTcF) at each defined post-dose timepoint.

**Results:** 64 subjects were enrolled (mean age 28 years, 63% male). Mean $AUC_{0-24}$ and $C_{max}$ were dose proportional for omadacycline 100 mg and 300 mg and were consistent with previous studies. OMC did not increase QTcF as demonstrated by one-sided 95% upper confidence bounds on ddQTcF <10 msec at all post-dose timepoints – the largest value was 1.53 msec for OMC 100 mg (6 hours post-dose) and 0.83 msec for OMC 300 mg (2 hours post-dose). Assay sensitivity was confirmed by increases in ddQTcF >5 msec at multiple timepoints for moxifloxacin. There was no relationship between OMC plasma concentrations and ddQTcF. The most common adverse event (AE) was infusion site pain (all mild intensity): 6% for OMC 100 mg and 11% for OMC 300 mg. There were no serious AEs. Within one hour after dosing, mean peak increases in heart rate were observed for OMC (17 bpm for 100 mg and 24 bpm for 300 mg) vs. 3 bpm for placebo and 5 bpm for moxifloxacin; the changes were asymptomatic and became comparable across all groups by 12-24 hours after dosing.

**Conclusion:** Omadacycline at doses of 100 mg and 300 mg IV did not increase QTcF.

## INTRODUCTION

- The first-in-class aminomethylcycline antibiotic, omadacycline, exhibits *in vitro* microbiological activity against Gram-positive and Gram-negative aerobes and anaerobes, and atypical bacteria (Flamm et al, 2012; Macone et al, 2014). In healthy volunteers, omadacycline exhibited a terminal elimination half-life of approximately 17 hours and peak plasma concentrations of 1.8 mg/L after a 100 mg IV dose (Sun et al, 2012; Ting et al, 2010; Sun et al, 2011). Omadacycline administered as a once daily oral or IV dose is being developed for the treatment of acute bacterial skin and skin structure infections (ABSSSI), community acquired bacterial pneumonia (CABP), and urinary tract infections (UTI).
- Cardiotoxic effects, primarily prolonged QTc interval, while rare, have been reported with fluoroquinolone, ketolide, and macrolide antibiotics (Iananni, 2002; Owens and Nolin, 2006; Mehrzad and Barza, 2015). Following initial FDA approval, reports of prolonged QT intervals and cardiac toxicity resulted in warnings in the product label about the risk of cardiac effects for telithromycin and azithromycin (Ray et al, 2012; Owens and Nolin, 2006). Because of these risks, a QTc study typically is required for systemic drugs including antibiotics as part of the clinical development program required for registration, in order to fully characterize the effects on ventricular repolarization (FDA Guidance 2005).
- In the current development program for omadacycline, the anticipated therapeutic dose for the IV formulation is 100 mg administered once daily. This study evaluated the effect of 100 mg and 300 mg IV doses of omadacycline on QT/QTc intervals and the relationship between these intervals and plasma levels of omadacycline in healthy subjects.

## METHODS

### Study Design

- This was a single dose, double-dummy, randomized, crossover study.
- Eligible subjects were randomized to one of four treatment sequences, each including the following four treatments:
  - Omadacycline 100 mg IV infusion over 30 minutes
  - Omadacycline 300 mg IV infusion over 60 minutes
  - Moxifloxacin 400 mg oral dose
  - Placebo (to match both omadacycline IV infusion and moxifloxacin capsules)
- Men or women age 18 to 45 years were eligible.
- Subjects were excluded for a history of cardiovascular disease, family history of QT prolongation or any other medical condition or electrocardiogram (ECG) abnormality.

### Study Assessments

- Time-matched baseline ECGs were obtained pre-treatment using a graded exercise protocol to provide ECGs over a range of heart rates (modified Bruce protocol Parts 1 and 2 with the goal of elevating heart rate >90 beats/min).
- During each treatment period, the subject wore a 12-lead Holter monitor that recorded ECG data over 24 hours.
- ECG recordings were captured in triplicate at 14 timepoints over the 24-hour period.
- Blood samples were obtained pre-dose and at intervals up to 96 hours to measure omadacycline concentrations.
- Safety was assessed from laboratory tests, ECG, vital signs, and adverse events (AEs).

### Study Analysis

- The primary ECG parameter of interest was the QT interval corrected using the Fridericia formula (QTcF).
- Baseline-adjusted QTcF (dQTcF) was analyzed by a repeated measures, mixed effects, linear model analysis of variance (ANOVA) that included terms for treatment sequence, subjects within sequence, study drug, study period, ECG timepoint, and study drug-by-ECG timepoint interaction.
- The primary endpoint analyses evaluated the placebo-adjusted dQTcF (ddQTcF) at each timepoint after dosing (i.e., relative to the start of the infusion for omadacycline groups and the time of oral dosing for the moxifloxacin group).
- ANOVA was used to determine at each timepoint the one-sided upper 95% confidence bounds (95% CB) for the mean difference between omadacycline and placebo across all subjects.
- A favorable outcome for omadacycline would be demonstrated if all one-sided upper 95% CB were <10 msec.
- Assay sensitivity was evaluated with moxifloxacin by observing if the one-sided lower 95% CB was >5 msec for at least one timepoint in the first 6 hours after dosing.
- Analyses using alternate QTc correction formulas and analyses for outlying values were performed.
- A dose response analysis of change in QTc vs. plasma omadacycline concentration was performed using a linear mixed effects model.

## RESULTS

- 64 subjects were randomized, and 61 received both doses of omadacycline.
- Mean age of randomized subjects was 27.6 years, 63% were male, and 83% were Caucasian (**Table 1**).

### Table 1. Baseline Characteristics of Randomized Subjects

| | Subjects (n=64) |
|---|---|
| Age, years[a] | 27.6 (8.1) |
| Range | 18–45 |
| Body mass index, kg/m²[a] | 25.5 (2.7) |
| Range | 19–30 |
| Height, in[a] | 67.9 (3.8) |
| Range | 60–77 |
| Weight, lb[a] | 167.2 (24.0) |
| Range | 118–219 |
| Male, n (%) | 40 (62.5) |
| Race, n (%) | |
| Caucasian | 53 (82.9) |
| Black or African American | 7 (10.9) |
| Asian | 2 (3.1) |
| American Indian or Alaska Native | 2 (3.1) |

[a]Mean (standard deviation).

### Pharmacokinetic Analysis

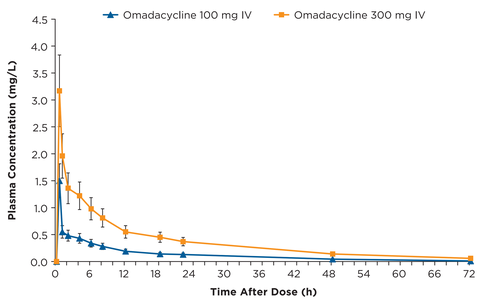
- Mean $AUC_{0-24}$ and $C_{max}$ were dose proportional for omadacycline 100 mg and 300 mg IV doses (**Table 2**).
- The plasma concentration vs. time curve showed a more rapid decline in plasma concentrations with the 100 mg dose than the 300 mg dose that corresponded to a 30 minute vs. 60 minute infusion time (**Figure 1**).
- The longer $T_{max}$ with the 300 mg dose also was related to the longer IV infusion time.
- After 1 hour, plasma concentrations were approximately 3-fold higher with the 300 mg dose.

### Table 2. PK Parameters After Single 100 and 300 mg IV Doses of Omadacycline

| | Omadacycline 100 mg (N=61) | Omadacycline 300 mg (N=61) |
|---|---|---|
| $AUC_{0-24}$ (mg*h/L)[a] | 6.18 (1.07) | 17.85 (2.92) |
| Range | 4.44–9.15 | 9.48–25.32 |
| CV (%) | 17.32 | 16.34 |
| $C_{max}$ (mg/L)[a] | 1.40 (0.25) | 3.32 (0.92) |
| Range | 0.91–1.94 | 2.04–7.16 |
| CV (%) | 17.83 | 27.71 |
| $T_{max}$ (h)[a] | 0.34 (0.04) | 0.80 (0.11) |
| Range | 0.33–0.58 | 0.33–1.08 |

[a]Mean (standard deviation).

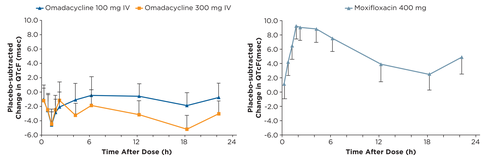
### Figure 1. Plasma Concentration vs. Time Curve for Omadacycline 100 and 300 mg IV Doses




### ECG Analysis

- The largest one-sided upper 95% CB on ddQTcF occurred at 2 hours post-dose for the omadacycline 300 mg group (0.83 msec) and at 6 hours for the omadacycline 100 mg group (1.53 msec) (**Figure 2**).
- Since all upper 95% CB were <10 msec, it can be concluded that omadacycline does not increase QTcF.
- Assay sensitivity was confirmed in the positive control group. The lower 95% CB for ddQTcF for moxifloxacin exceeded 5 msec at 1.5, 2, 4, and 6 hours (**Figure 2**).
- Results were similar for unadjusted ddQTcF values: the maximum upper 95% CB on unadjusted ddQTcF occurred at 2 hours post-dose for the omadacycline 300 mg group (0.74 msec), at 22 hours for the omadacycline 100 mg group (1.54 msec).

### Figure 2. ddQTcF for Omadacycline (Left, With Upper 95% One-Sided CB) and Moxifloxacin (Right, With Lower 95% One-Sided CB)



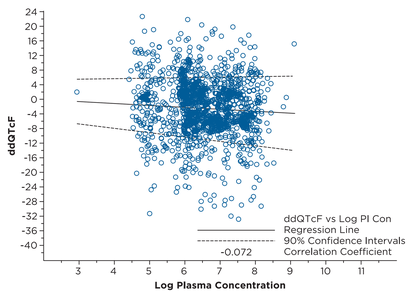

### Other Analyses

- Results were similar for analyses of QT using individual subject correction (QTci).
- Because of an observed effect of omadacycline on heart rate (see Safety results), the Bazett correction of QT (QTcB), which overcorrects at elevated heart rates, is unreliable for this analysis.
- No subject had an increase from baseline in QTcF >30 msec at any timepoint.

### Correlation of Plasma Concentrations With ddQTcF

- The variation in omadacycline concentrations was large, resulting in wide confidence bounds.
- Nevertheless, no relationship was observed between omadacycline plasma concentrations and ddQTcF (correlation coefficient -0.072; **Figure 3**).

### Figure 3. Scatter Plot of Change in QTcF vs. Log Omadacycline Plasma Concentrations




### Safety and Tolerability

- The incidence of treatment-emergent AE's is shown in **Table 3**.
- A higher incidence of infusion site pain (all mild intensity) accounted for the difference in AE incidence between omadacycline and placebo.
- One subject discontinued for hives (moderate intensity) after receiving omadacycline 300 mg; this event was treated with oral diphenhydramine and resolved approximately 1 hour after onset.
- No serious AEs occurred, and no abnormal laboratory findings were reported.

### Table 3. Incidence of Treatment-Emergent Adverse Events

| | Number (%) of Subjects With Events | | | |
|---|---|---|---|---|
| | Omadacycline | | | |
| | 100 mg (N=63) | 300 mg (N=62) | Placebo (N=63) | Moxifloxacin (N=62) |
| ≥1 treatment-emergent AE | 11 (18) | 20 (32) | 8 (13) | 9 (15) |
| Infusion site pain | 4 (6) | 7 (11) | 0 | 1 (2) |
| Headache | 3 (5) | 4 (7) | 3 (5) | 2 (3) |
| Infusion site rash | 0 | 3 (5) | 0 | 0 |
| Infusion site hematoma | 1 (2) | 2 (3) | 0 | 0 |
| Dizziness | 0 | 0 | 2 (3) | 0 |
| Rhinorrhea | 0 | 0 | 2 (3) | 0 |

NOTE: shown are events occurring in >1 subject in any treatment group.

- ECG data provided frequent heart rate assessments during the study.
- Within 1 hour after dosing, maximum mean increases in heart rate were observed for IV omadacycline (17 bpm for 100 mg and 24 bpm for 300 mg), versus 3 bpm for placebo and 5 bpm for oral moxifloxacin.
- Subsequently, differences between all groups narrowed but heart rate increases relative to placebo remained notable through approximately 6 hours post-dose; within this time period maximum mean increases from baseline for IV omadacycline were 18 bpm for 100 mg and 25 bpm for 300 mg, versus 11 bpm for placebo and 12 bpm for oral moxifloxacin.
- Heart rate changes were asymptomatic and became comparable across all groups by 12-24 hours after dosing.
- No notable change in blood pressure occurred, and no vital sign abnormalities were reported as AEs.

## SUMMARY AND CONCLUSIONS

- Omadacycline at doses of 100 mg and 300 mg IV did not prolong QTc intervals.
- Omadacycline was associated with asymptomatic increases in heart rate for several hours after dosing, but both doses were well tolerated.
- These results support the findings from preclinical studies, which indicated that omadacycline has a low potential for cardiac arrhythmia or clinically significant cardiovascular toxicity.
- The ability to place omadacycline in a category of low cardiac risk will be an important component to the overall benefit-to-risk assessment for this new antibiotic.

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