Randomized, Double-Blind, Placebo- and Positive-Controlled Crossover Study of the Effects of Omadacycline on QT/QTc Intervals in Healthy Subjects

Borje Darpo, Hongqi Xue, S. Ken Tanaka, Evan Tzanis

**ABSTRACT** Omadacycline, an aminomethylcycline, is an antibiotic that is approved in the United States for once-daily intravenous (i.v.) and oral use for treatment of adults with acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia. In this thorough QT study, the effects of a therapeutic (100 mg i.v.) dose and a supratherapeutic (300 mg i.v.) dose of omadacycline on the electrocardiogram were studied, with placebo and moxifloxacin as negative and positive controls. Omadacycline at these doses had no effect on the QTc interval. The largest mean placebo-corrected change-from-baseline QTcS (ΔQTcS) were 1.7 ms (90% confidence interval [CI], 0.06 to 3.30) and 2.6 ms (90% CI, 0.55 to 4.67), observed at 20 min and 2 h after the start of the infusion of 100 mg and 300 mg, respectively. Assay sensitivity was demonstrated with moxifloxacin, which caused clear prolongation of QTcS, with the largest mean placebo-corrected ΔQTcS of 9.8 ms at 1.5 and 2 h. With a linear exposure-response model, the estimated slope of the concentration-change-from-baseline QTcF (ΔQTcF) relationship was very shallow: 0.0007 ms per ng/ml (90% CI, 0.0000 to 0.0014). The possibility of an effect on placebo-corrected ΔQTcS exceeding 10 ms can be excluded at omadacycline concentrations in plasma of up to 8 μg/ml. Omadacycline had no effect on cardiac conduction (PR and QRS intervals) but caused an increase in heart rate of 16.8 beats per min at 35 min after the 100-mg dose and 21.6 beats per min at 50 min after the 300-mg dose.

**KEYWORDS** QTc study, acute bacterial skin and skin structure infections, community-acquired pneumonia, omadacycline

Omadacycline, the first aminomethylcycline antibiotic approved in the United States for once-daily intravenous (i.v.) and oral use in adults with acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP), exhibits in vitro microbiological activity against Gram-positive and many Gram-negative aerobes and anaerobes and against atypical bacteria (1–3). Omadacycline is active against bacterial pathogens expressing the two forms of tetracycline resistance, i.e., efflux and ribosomal protection (4). In healthy volunteers who received either i.v. or oral doses, omadacycline exhibited a terminal elimination half-life of ~17 to ~18 h; peak drug concentrations in plasma were 1.8 μg/ml after a 100-mg i.v. dose, which is the dose being evaluated for treatment of community-acquired bacterial infections (5, 6). Omadacycline administered as a once-daily 100-mg i.v. or 300-mg oral dose demonstrated efficacy for the treatment of ABSSSI and CABP in phase 3 studies (7, 8) and is undergoing clinical development for urinary tract infections.

Cardiotoxic effects, primarily prolonged QTc interval, while rare, have been reported with fluoroquinolones, ketolide, and macrolide antibiotics (9–11). Because of the risk of...
drug-induced proarrhythmias, a thorough QTc study is typically required for drugs with systemic exposure, including antibiotics, as part of the clinical development program to fully characterize potential effects of the drug on electrocardiogram (ECG) parameters (12). In accordance with these requirements, this study evaluated the effect of therapeutic and supratherapeutic i.v. doses of omadacycline on QT/QTc intervals and the relationship between these intervals and plasma levels of omadacycline in healthy subjects.

RESULTS

Eligible subjects were randomized to one of four treatment sequences. In the randomized sequences, each subject was to receive each of the following treatments: omadacycline 100 mg i.v. over 30 min, omadacycline 300 mg i.v. over 60 min, moxifloxacin 400 mg orally, or placebo. Placebo infusions to match omadacycline and placebo capsules to match moxifloxacin were used to maintain the study in a blind manner. Sixty-four eligible subjects were randomized, but two discontinued prior to receiving all four study treatments. An additional subject was not dosed with omadacycline 300 mg i.v. Thus, 61 subjects received all four study treatments. Data were analyzed per treatment for all the subjects receiving that treatment, regardless of whether they completed all four study treatments. The mean age of the randomized subjects was 27.6 years, 63% were male, 83% were Caucasian, mean body weight was 167 lb, and mean body mass index was 25.5 kg/m².

Pharmacokinetic analyses. Mean area under the concentration-time curve from 0 to 24 h (AUC₀–₂₄) and maximum concentration in plasma (C_max) were dose proportional for omadacycline 100- and 300-mg i.v. doses (Table 1). C_max was observed at the end of the infusion for both doses (Fig. 1), reflecting the difference in infusion times (30 versus 60 min).

ECG evaluations. A similar diurnal pattern of change-from-baseline heart rate (ΔHR) was seen in the placebo and moxifloxacin periods, whereas omadacycline caused a clear effect on heart rate. The largest mean placebo-corrected ΔHR values seen with omadacycline were 16.8 beats per min (bpm) at 35 min postdose after the 100-mg dose and 21.6 bpm at 50 min after the 300-mg dose. The effect thereafter declined but remained above 5 bpm during 6 h after the 100-mg dose and for the full observation period up to 22 h in the highest dose group (Fig. 2).

Since the heart rate effect was pronounced, alternative ways of correcting the QT interval were explored. The mean correction factors for QTcP, QTcS, QTcI, and optimized QTcI (see Materials and Methods for definitions) were 0.34, 0.37, 0.37, and 0.33, which can be compared with Fridericia’s correction coefficient, 0.33. For QTcI, which included time points of graded exercise, the range of RR intervals (i.e., the time elapsed between two successive heartbeats) varied across subjects—between 160 and

### Table 1: Pharmacokinetic parameters after single 100-mg and 300-mg i.v. doses of omadacycline

| Parameter          | Value(s) for indicated omadacycline dose | 100 mg (n = 61) | 300 mg (n = 61) |
|--------------------|-----------------------------------------|----------------|----------------|
| AUC₀–₂₄ (µg * h/ml) |                                         | 6.2 (1.1)      | 17.8 (2.9)     |
| Range              |                                         | 4.4–9.2        | 9.5–25.3       |
| CV (%)             |                                         | 17.3           | 16.3           |
| C_max (µg/ml)      |                                         | 1.4 (0.25)     | 3.3 (0.92)     |
| Range              |                                         | 0.9–1.9        | 2.0–7.2        |
| CV (%)             |                                         | 17.8           | 27.7           |
| T_max (h)          |                                         | 0.34 (0.04)    | 0.80 (0.11)    |
| Range (h)          |                                         | 0.33–0.58      | 0.33–1.08      |

| Parameter          | Value(s) for indicated omadacycline dose | 100 mg (n = 61) | 300 mg (n = 61) |
|--------------------|-----------------------------------------|----------------|----------------|
| AUC₀–₂₄, area under the concentration-time curve from 0 to 24 h; CV, coefficient of variation; C_max, maximum concentration of drug in plasma; T_max, time to maximum concentration of drug in plasma. |
| Mean (standard deviation). | |

---

Darpo et al. Antimicrobial Agents and Chemotherapy

October 2019 Volume 63 Issue 10 e00922-19

aac.asm.org 2
720 ms—with a mean range of 375 ms. The observed range of RR intervals used to calculate the QTcI covered on-treatment RR ranges in 14 (22.2%) and 15 (24.6%) subjects in the omadacycline 100- and 300-mg i.v. groups, respectively. When day −1 baseline QT/RR data were used for derivation of optimized QTcI, the RR range by subject was substantially wider—between 800 and 2,995 ms—with a mean range of 1,175 ms. This RR range covered the on-treatment RR ranges in all subjects for both doses.

The abilities to remove heart rate dependence were compared among correction methods (Table 2). QTcS and QTcI resulted in the lowest mean sum of squared slopes (SSS), which was 0.0012 under drug-free conditions (placebo). Since QTcS resulted in lower mean SSS values on active doses, this correction method was selected as the primary endpoint.

Single doses of 100 and 300 mg omadacycline did not have an effect on the QTc interval. The pattern of mean change-from-baseline QTcS (ΔQTcS) closely followed that...
The largest mean placebo-corrected ΔQTcS values were only 1.7 ms (90% confidence interval [CI], 0.06 to 3.30) and 2.6 ms (90% CI, 0.55 to 4.67), observed at 20 min and 2 h after the start of the infusion of 100 and 300 mg, respectively (Table 3). After dosing with moxifloxacin, clear prolongation of QTcS was seen, with a largest mean placebo-corrected ΔQTcS of 9.8 ms at 1.5 and 2 h. All lower bounds of the 90% CI of placebo-corrected ΔQTcS values determined at 1.5, 2, and 4 h postdosing were above 5 ms, thereby demonstrating assay sensitivity. The results seen with other correction factors were similar to those determined for QTcS, with all mean placebo-corrected ΔQTc values below 2 ms and all upper bounds of the 90% CI below 5 ms. All mean placebo-corrected change-from-baseline QTcF (ΔQTcF) values were negative, and the upper bound of the 90% CI did not exceed 1.85 ms; for QTcI, the largest (positive) mean placebo-corrected ΔQTcI reached 1.6 ms (90% CI, −0.66 to 3.94) at 2 h, and for QTcP and optimized QTcI, the corresponding mean values were 0.0 ms (90% CI, −2.12 to 2.10) and −0.2 ms (90% CI, −2.37 to 1.97). There were no outliers in terms of QTcS above 480 ms or ΔQTcS above 60 ms.

A linear exposure-response model provided an acceptable fit to the observed concentration and QT data. The relationship between the individual observed omadacycline concentrations and placebo-corrected ΔQTcS is visualized in the top panel in Fig. 4. The goodness-of-fit plot (Fig. 4, bottom panel) shows the mean placebo-corrected ΔQTcS (90% CI) within each omadacycline concentration decile and the model-predicted mean placebo-corrected ΔQTcS with 90% CI. From the plot, it can be seen that the predicted placebo-corrected ΔQTcS values are relatively close to the observed values, indicating that the proposed linear model provides an acceptable representa-

**TABLE 2** Comparison of the abilities of the correction methods to remove heart rate dependence

| Treatment                  | Slope estimate | QTcF | QTcI | Opt QTcI | QTcP | QTcS |
|----------------------------|----------------|------|------|----------|------|------|
| 100 mg i.v. omadacycline   | 0.0015         | 0.0018| 0.0018| 0.0014   | 0.0012|      |
| 300 mg i.v. omadacycline   | 0.0017         | 0.0028| 0.0021| 0.0016   | 0.0020|      |
| Moxifloxacin               | 0.0019         | 0.0020| 0.0019| 0.0018   | 0.0015|      |
| Placebo                    | 0.0017         | 0.0012| 0.0016| 0.0016   | 0.0012|      |

*Slope estimate data represent means of squared individual slopes. i.v., intravenous; Opt, optimized.*
tion of the relationship between placebo-corrected ΔQTcS and omadacycline concentrations without accounting for hysteresis. The estimated slope of the concentration-ΔQTcS relationship was very shallow at 0.0007 ms per ng/ml (90% CI, 0.0000 to 0.0014), with a treatment effect-specific intercept of −0.6 ms (90% CI, −1.2 to 0.11). It can also be seen from the plot that the possibility of an effect on placebo-corrected ΔQTcS exceeding 10 ms can be excluded at omadacycline plasma levels up to ~8 μg/ml.

### TABLE 3 Placebo-corrected change-from-baseline QTcS

| Time point (postdose) and parameter | Value(s) (ms) for indicated treatment | Omadacycline dose | Moxifloxacin |
|------------------------------------|--------------------------------------|-----------------|--------------|
|                                    |                                      | 100 mg i.v.     | 300 mg i.v.  |
| **20 min**                         |                                      | 1.7             | 2.0          | 1.1          |
| LS mean                            |                                      | 0.98            | 0.99         | 0.98         |
| SE                                 |                                      | (0.06 to 3.30)  | (0.39 to 3.67) | (−0.49 to 2.76) |
| **35 min**                         |                                      | 0.8             | 1.5          | 4.5          |
| LS mean                            |                                      | 1.15            | 1.17         | 1.15         |
| SE                                 |                                      | (−1.13 to 2.67) | (−0.44 to 3.41) | (2.56 to 6.37) |
| **50 min**                         |                                      | −0.1            | 0.9          | 6.3          |
| LS mean                            |                                      | 1.11            | 1.12         | 1.11         |
| SE                                 |                                      | (−1.91 to 1.74) | (−0.97 to 2.73) | (4.45 to 8.12) |
| **65 min**                         |                                      | −1.9            | −0.3         | 7.0          |
| LS mean                            |                                      | 1.20            | 1.22         | 1.20         |
| SE                                 |                                      | (−3.86 to 0.10) | (−2.27 to 1.74) | (5.06 to 9.04) |
| **1.5 h**                          |                                      | 0.0             | 1.9          | 9.8          |
| LS mean                            |                                      | 1.15            | 1.17         | 1.16         |
| SE                                 |                                      | (−1.90 to 1.92) | (−0.05 to 3.81) | (7.87 to 11.70) |
| **2 h**                            |                                      | 0.1             | 2.6          | 9.8          |
| LS mean                            |                                      | 1.23            | 1.25         | 1.24         |
| SE                                 |                                      | (−1.98 to 2.09) | (0.55 to 4.67) | (7.73 to 11.82) |
| **4 h**                            |                                      | 0.7             | 0.0          | 9.4          |
| LS mean                            |                                      | 1.13            | 1.15         | 1.14         |
| SE                                 |                                      | (−1.13 to 2.61) | (−1.87 to 1.93) | (7.56 to 11.33) |
| **6 h**                            |                                      | 1.0             | 1.0          | 7.6          |
| LS mean                            |                                      | 1.23            | 1.24         | 1.23         |
| SE                                 |                                      | (−1.05 to 3.01) | (−1.07 to 3.03) | (5.59 to 9.65) |
| **12 h**                           |                                      | −0.2            | −1.5         | 4.1          |
| LS mean                            |                                      | 1.25            | 1.26         | 1.25         |
| SE                                 |                                      | (−2.28 to 1.85) | (−3.59 to 0.59) | (2.05 to 6.19) |
| **18 h**                           |                                      | −1.1            | −3.7         | 3.9          |
| LS mean                            |                                      | 1.30            | 1.31         | 1.30         |
| SE                                 |                                      | (−3.26 to 1.03) | (−5.86 to −1.51) | (1.72 to 6.02) |
| **22 h**                           |                                      | 0.7             | −1.4         | 5.0          |
| LS mean                            |                                      | 1.32            | 1.34         | 1.32         |
| SE                                 |                                      | (−1.49 to 2.88) | (−3.57 to 0.84) | (2.84 to 7.22) |

*CI, confidence interval; i.v., intravenous; LS, least squares.
Safety/tolerability. Adverse events were generally mild: more subjects had events of infusion-site pain following treatment with omadacycline 300 mg (11%) than with omadacycline 100 mg (6%), with rates for placebo and moxifloxacin of 0% and 2%, respectively. Infusion-site rash was reported in 5% of subjects following omadacycline 300 mg; no such events followed the other treatments. Headache was reported with an incidence of 3% to 7% following each treatment. There were no serious adverse events. One subject discontinued the study due to hives after receiving omadacycline 300 mg. This event was considered of moderate intensity and treated with oral diphenhydramine; it resolved ~1 h after onset. No abnormal laboratory findings were reported.
DISCUSSION

Prolongation of the QT interval is a well-documented effect of certain antibiotics, including fluoroquinolones, ketolides, and macrolides (10, 13, 14). For some of these drugs (e.g., telithromycin and azithromycin), postapproval warnings about potential cardiac toxicity were added to the product labeling (15). In addition, based on results of a thorough QTc study (16), telavancin carries a warning about QT interval prolongation in its product labeling. Thus, it is important to assess new antibiotics for their effects on ventricular repolarization.

Omadacycline is approved in the United States for treatment of adults with ABSSSI and CABP. For these indications, following an initial “loading” dose of 200 mg i.v. over 60 min or 100 mg i.v. over 30 min twice daily on day 1, omadacycline is administered once daily (either i.v. or orally), and the therapeutic i.v. dose is 100 mg (7, 8, 10). In healthy volunteers given a single 100-mg i.v. dose of omadacycline, mean $C_{\text{max}}$ was 1.8 to 1.9 $\mu$g/ml (standard deviation, 0.4 to 0.7) (6, 17).

In this thorough QTc study, a therapeutic (100 mg i.v.) dose and a supratherapeutic (300 mg i.v.) dose of omadacycline had no effect on the QT interval. Since the possibility of an effect on placebo-corrected $\Delta QTC_{S}$ above 10 ms could be excluded at all postdosing time points with both doses, the findings clearly represent negative QT study results as defined in the International Conference on Harmonisation E14 guidance (12). Using exposure-response analysis, as suggested in the recently revised E14 guidelines, the slope of the relationship between omadacycline concentrations in plasma and placebo-corrected $\Delta QTC_{S}$ was very shallow—only 0.0007 ms per ng/ml. Consequently, estimating the effect throughout the full range of observed plasma levels, the possibility of an effect on placebo-corrected $\Delta QTC_{F}$ exceeding 10 ms can be excluded up to omadacycline concentrations in plasma of $\sim$8 $\mu$g/ml, which is $\sim$4.4-fold above the mean $C_{\text{max}}$ ($\sim$1.8 $\mu$g/ml) in patients given the therapeutic dose of 100 mg i.v. over 30 min. In patients receiving the 200-mg i.v. dose, mean $C_{\text{max}}$ levels would be somewhat higher ($\sim$2.2 $\mu$g/ml), but the safety margin is still severalfold greater than that seen with concentrations that may lead to clinically relevant QT prolongation. It therefore seems highly unlikely that omadacycline will cause clinically concerning QT prolongation.

A clear and quite marked effect on heart rate was observed with mean peak effects of 16.8 and 21.6 bpm after the i.v. infusion of 100 mg and 300 mg, respectively. In such cases, it is important to evaluate which method for correction represents the best way to remove the heart rate dependence of the QTc interval. Tested in the manner proposed by a team from the U.S. Food and Drug Administration (18), the differences as shown by the SSS across the five methods applied to the data ($QTC_{F}$, $QTC_{S}$, $QTC_{I}$, optimized $QTC_{I}$ and $QTC_{P}$) were small. As a consequence, the result of the QT evaluation was negative (i.e., upper bound of 90% CI of placebo-corrected $\Delta QTC$ of $<$10 ms) with all correction methods. Interestingly, $QTC_{S}$ and $QTC_{I}$ removed the heart rate dependence of the QT interval somewhat better than other methods using placebo data, but not consistently on omadacycline treatment. At the highest dose, 300 mg i.v., population-based methods ($QTC_{F}$ and $QTC_{P}$), optimized $QTC_{I}$ and $QTC_{S}$ all worked better than $QTC_{I}$. In our view, this observation argues for the importance of testing the ability of heart rate correction methods to remove the heart rate dependence of the QTc interval (19) and goes against the view that an individualized QTc method is by default always the best way to evaluate QT effect with drugs that have a pronounced heart rate effect (20).

When a heart rate effect of this magnitude is observed in healthy subjects, it becomes important to evaluate the effect in patients, to place the finding into a clinical context. It is not obvious that patients with infections who are febrile and experiencing stress would react the same way as healthy subjects when exposed to a drug that provides effective treatment for the infection. In a phase 3 study in adult patients with ABSSSI (7), no clinically significant heart rate changes were observed with omadacycline. In patients with CABP, the population was older and preexisting cardiovascular.
disease more frequent than were seen with the population in the infected-skin studies (21). Baseline heart rate was higher, and it seems reasonable to assume that the patients who were older with CABP—and who were, at times, hypoxic—were in greater distress than those with infected skin and skin structure. ECGs were recorded before and 30 to 90 min after the start of the 30-min infusion of the first and third doses. A small ΔHR (4.3 bpm) was observed after the first dose of omadacycline. With continued effective antibacterial therapy, no such effect was seen before or after the third dose, but the reduction of mean ΔHR was somewhat smaller than in the moxifloxacin group (1.8 and −1.1 versus −5.4 and −6.8 bpm, respectively). Importantly, throughout the omadacycline development program, very few outliers in terms of pronounced heart rate effects (patients with heart rate of >120 bpm and ΔHR of >15 bpm) have been observed, with no notable differences compared to active comparators. The observed increase in heart rate was small and transient and would not be expected to lead to adverse cardiac events. Such events, e.g., myocardial ischemia and episodes of decompensated heart failure, were few (0% to 0.3% and 0% to 0.8%, respectively) and occurred at rates similar to the observed incidence for comparators (0.3% to 0.5% for linezolid and moxifloxacin) (7, 8).

Nonclinical studies performed with omadacycline have demonstrated that the drug inhibits the M₂ subtype of the muscarinic acetylcholine receptor, resulting in a non-adrenergic, vagolytic effect (22). In isolated rabbit sinus node preparations, omadacycline did not affect the intrinsic rate of the sinus node and, interestingly, reversed the bradycardia caused by cholinergic stimulation with carbamylcholine. These nonclinical results are consistent with the clinical observation that the heart rate effect of omadacycline is more pronounced in subjects with greater vagal tone and relatively low resting heart rate (i.e., in healthy subjects than in patients suffering from disease). A possible explanation for the difference observed to date between heart rate effects in healthy subjects and in patients with infections might be that in patients with active infections, the cholinergic impact on heart rate is attenuated through the effects of fever, dehydration, and systemic hypermetabolic manifestations of inflammation and distress with increased sympathetic tone.

In summary, these results demonstrate that omadacycline, at doses of 100 and 300 mg i.v., does not prolong the QTc interval. The observed heart rate effect in healthy subjects seems much less pronounced in patients with infections and is therefore not clinically concerning. The ability to place omadacycline in a category of low cardiac risk will be an important component to the overall benefit-risk assessment for this new antibiotic.

MATERIALS AND METHODS

Study design. This was a single-dose, double-blind, randomized, four-way crossover study with an enrollment period extending from September 2008 to January 2009. The study was conducted in accordance with the ethical principles relating to biomedical research involving human subjects as adopted by the 18th World Medical Association General Assembly, Helsinki (1964) and subsequently amended. It was also conducted in accordance with local laws and regulations for the use of investigational therapeutic agents. The study protocol and all amendments were reviewed by the Institutional Review Board for the study center (PRACS Institute, Ltd.). The study investigator reviewed the study, and written information was provided to eligible subjects. Informed consent was obtained from each subject in writing before randomization.

Because the omadacycline i.v. solution had a yellow tint and the infusions were of different duration (30 or 60 min), all infusion bags were covered for anonymization and infusions were administered by personnel who did not participate in any other study procedures or assessments.

Subject selection. Healthy men and women aged 18 to 45 years were eligible, using standard criteria for clinical pharmacology studies. Women of childbearing potential had to use an effective birth control method from the time of screening until 30 days after the study; they also had to have had a negative pregnancy test at screening and on the day before dosing. Subjects were excluded for the following reasons: a history of allergy to any tetracycline or quinolone antibiotic; body weight of <45 or >100 kg; body mass index value of <18 or >30 kg/m²; systolic or diastolic blood pressure of >140 or >90 mm Hg, respectively; use of any investigational drug within 1 month prior to enrollment; clinically significant electrolyte abnormality; a history of cardiovascular disease, family history of QT prolongation, or any other medical condition or ECG abnormality that could interfere with the conducting of the study.
Treatment groups. Subjects were randomized to 1 of 4 treatment sequences, with the same treatments delivered in different orders. Subjects received an omadacycline therapeutic dose (100 mg i.v., infused over 30 min), an omadacycline supratherapeutic dose (300 mg i.v., infused over 60 min), a placebo infusion (negative control), and moxifloxacin (400 mg orally; active control). Moxifloxacin 400 mg or placebo capsules were given orally at the start of a 60-min placebo infusion. The omadacycline therapeutic dose corresponded to the proposed therapeutic dose for the phase 3 clinical trial of omadacycline in ABSSSI; the supratherapeutic dose was chosen because of good tolerability at this dose in phase 1 studies of omadacycline in healthy, young males.

Study procedures. The study was performed on an inpatient basis, and in each treatment period, subjects were admitted to the clinical site on day −2, 2 days before the day of dosing (day 1), and were discharged after completion of safety procedures on the day after dosing (day 2). The washout between consecutive study periods was ≥7 days. Study treatment was administered with subjects in the fasting state in the morning of day 1.

In treatment period 1, continuous 12-lead ECG data were recorded for 24 h on day −1, and subjects underwent a graded exercise test using a modified Bruce protocol with a target heart rate of > 90 bpm 24 h and 25 min before dosing. On day 1 in all treatment periods, a continuous 12-lead ECG recording procedure was performed from 1.5 h before dosing to 24 h after dosing. The 12-lead ECGs were extracted in triplicate at three time points (1.5, 1.0, and 0.5 h) before dosing and at 20, 35, 50, and 65 min and 1.5, 2, 4, 6, 12, 18, and 22 h after dosing. ECG intervals were measured by a central ECG laboratory with a semiautomated technique.

Blood samples were obtained before dosing, at time points similar to those used for the postdose ECG extractions, and at 48, 72, and 96 h after the dose to measure omadacycline plasma levels and determine pharmacokinetic parameters, including $C_{\text{max}}$, time to maximum concentration, and $AUC_{24h}$. Blood samples were obtained 5 min after each timepoint indicated for ECG measurement.

Statistical analysis. Sample size was calculated based on the following assumptions: (i) the intra-subject standard deviation for change-from-baseline QTcF (ΔQTcF) would be 7 ms; (ii) the underlying QT effect for omadacycline would be 4 ms; (iii) ΔQTcF would be determined at 11 ECG time points per dose and at two doses. Based on these assumptions, a sample size of 50 subjects would provide more than 90% overall power to demonstrate that the upper bound of each one-sided 95% CI falls below 10 ms for up to 11 time points. Allowing for potential dropouts, a total of 64 subjects were to be randomized.

Baseline for each period was defined as the average of the measured QTc intervals from the three ECG time points (−1.5, −1.0, and −0.5 h) recorded before dosing in that period on day 1. The primary endpoint was the placebo-corrected change-from-baseline QTc (ΔQTc) determined using Fridericia’s correction (ΔQTcF) with QTcF = QT/RR$^{1/3}$, unless a substantial peak heart rate (i.e., a mean placebo-corrected change-from-baseline HR [ΔHR] of > 10 bpm in the “by time point” analysis) was observed in either of the two omadacycline treatment groups. In such cases, the following correction methods for QTc were to be explored and tested for their ability to remove the heart rate dependence.

Method I. Method I employed an individualized HR-corrected QT interval (QTcI) calculated from QT/RR data obtained at supine resting time points on day −1 in the first treatment period. Based on QT/RR pairs from all subjects, the QTcI correction coefficient was derived from a linear mixed-effects model as follows: $\log(\text{QTcI}) = \log(a) + b \times \log(\text{RR})$ (with gender included as a fixed effect and subject included as a random effect for both intercept and slope). The coefficient of log( RR) for each subject, $b_s$, was then used to calculate QTcI for each subject as follows: $\text{QTcI} = \text{QTcI}_{\text{base}} + b_s \times \log(\text{RR})$.

Method II. Method II employed an individualized HR-corrected QTcS (QTcS) derived from QT/RR pairs, the QTcS correction coefficient was derived from a linear mixed-effects model as follows: $\log(\text{QTcS}) = \log(a) + b \times \log(\text{RR})$. The coefficient of log( RR) for each subject, $b_s$, was then used to calculate QTcS for the subject as follows: $\text{QTcS} = \text{QTcS}_{\text{base}} + b_s \times \log(\text{RR})$.

Method III. Method III employed a population HR-corrected QT interval (QTcP) derived from the same data as QTcS from all subjects. Based on QT/RR pairs from all subjects, QTcP was derived from a linear regression model as follows: $\log(\text{QTcP}) = \log(a) + b \times \log(\text{RR})$. The coefficient of log( RR) (b), was then used to calculate QTcP for each subject as follows: $\text{QTcP} = \text{QTcP}_{\text{base}} + b \times \log(\text{RR})$.

For each method, the relationship between QTc and RR interval was then investigated using on-treatment data (omadacycline, moxifloxacin, and placebo) and a linear regression model as follows: $\text{QTc} = c + d \times \text{RR}$. Mean QTc and RR values from all nominal time points (including predose) were used. The RR coefficient for each subject, $d_s$, was then used to calculate the average SSS for each of the different QT-RR correction methods. The QTc method for which the average on-treatment slope value was closest to zero (i.e., the lowest average SSS value) for omadacycline and placebo was then selected as the primary endpoint (18).

The by-time-point analysis for QTc was based on a linear mixed-effects model with change-from-baseline QTc for the selected primary endpoint as the dependent variable; period, sequence, time (categorical), treatment (omadacycline, moxifloxacin, and placebo), and time-by-treatment interaction as
ACKNOWLEDGMENTS

We are grateful for medical review by Paul McGovern and Stephen Villano and for the assistance of Richard S. Perry and Innovative Strategic Communications, LLC, in the preparation of this article.

This work was funded by Paratek Pharmaceuticals, Inc.

All of us contributed to the design, analysis, and interpretation of the study and approved the final draft for publication.

B.D. is Chief Scientific Officer of ERT and owns stock and is eligible for stock options in the company. H.X. is a senior statistician employed by ERT. S.K.T. was an employee of Paratek Pharmaceuticals, Inc., at the time of the reported research and is now a consultant. E.T. was an employee of Paratek Pharmaceuticals, Inc., at the time of the reported research and is now employed by Neuraptive Therapeutics.

REFERENCES

1. Pfaffer MA, Huband MD, Rhomberg PR, Flamm RK. 2017. Surveillance of omadacycline activity against clinical isolates from a global collection (North America, Europe, Latin America, Asia-Western Pacific), 2010–2011. Antimicrob Agents Chemother 61:e00018-17. https://doi.org/10.1128/AAC.00018-17
2. Macone AB, Caruso BK, Leahy RG, Donatelli J, Weir S, Draper MP, Tanaka SK, Levy SB. 2014. In vitro and in vivo antibacterial activities of omadacycline, a novel aminomethylcycline. Antimicrob Agents Chemother 58:1127–1135. https://doi.org/10.1128/AAC.01242-13
3. Tanaka SK, Steenbergen JJ, Villano S. 2016. Discovery, pharmacology, and clinical profile of omadacycline, a novel aminomethylcycline antibiotic. Bioorg Med Chem 24:6409–6419. https://doi.org/10.1016/j.bmc.2016.07.029
4. Draper MP, Weir S, Macone A, Donatelli J, Trieber CA, Tanaka SK, Levy SB. 2014. Mechanism of action of the novel aminomethylcyclin antibacterial omadacycline. Antimicrob Agents Chemother 58:1279–1283. https://doi.org/10.1128/AAC.01066-13
5. Flarakos J, Du Y, Gu H, Wang L, Einolf HJ, Chun DY, Zhu B, Alexander N, Nattrillo A, Hanna I, Ting L, Zhou W, Dole K, Sun H, Kovacs SJ, Stein DS, Tanaka SK, Villano S, Mangold JB. 2017. Clinical disposition, metabolism and in vitro-drug interaction properties of omadacycline. Xenobiotica 47:682–696. https://doi.org/10.1080/00912700.2016.1213465
6. Sun H, Ting L, Machinini S, Praegastgaard J, Kuemmel A, Stein DS, Sunkara G, Kovacs SJ, Villano S, Tanaka SK. 2016. Randomized, open-label study of the pharmacokinetics and safety of oral and intravenous administration of omadacycline to healthy subjects. Antimicrob Agents Chemother 60:7431–7435. https://doi.org/10.1128/AAC.01207-16
7. O’Riordan W, Green S, Overcash JS, Puljiz I, Metallidis S, Gardovskis J, Garry-Ryan L, Das AF, Tzanis E, Eckburg PB, Manley A, Villano SA, Steenbergen JN, Loh E. 2019. Omadacycline for acute bacterial skin and skin-structure infections. N Engl J Med 380:528–538. https://doi.org/10.1056/NEJMoa1800170.
8. Stets R, Popescu M, Gonong JR, Mitha I, Nseir W, Madej A, Kirsch C, Das AF, Garry-Ryan L, Steenbergen JN, Manley A, Eckburg PB, Tzanis E, McGovern PC, Loh E. 2019. Omadacycline for community-acquired bacterial pneumonia. N Engl J Med 380:517–527. https://doi.org/10.1056/NEJMoa1800201.
9. Mehrzad R, Barza M. 2015. Weighing the adverse cardiac effects of fluoroquinolones: a risk perspective. J Clin Pharmacol 55:1198–1206. https://doi.org/10.1002/jcph.553
10. Goldstein EJ, Owens RC, Jr, Nolin TD. 2006. Antimicrobial-associated QT interval prolongation: points of interest. Clin Infect Dis 43:1603–1611. https://doi.org/10.1086/508873
11. Iannini PB. 2002. Cardiotoxicity of macrolides, ketolides and fluoroquinolones that prolong the QTc interval. Expert Opin Drug Saf 1:121–128. https://doi.org/10.1517/14740338.1.2.121.
12. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. 2005. ICH harmonized tripartite guideline E14: the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/ Guidelines/Efficacy/E14_Guideline.pdf. Accessed 12 May 2019.
13. Frothingham R. 2001. Rates of torsades de pointes associated with ciprofloxacin, ofloxacin, levofloxacin, gatifloxacin, and moxifloxacin. Pharmacotherapy 21:1468–1472. https://doi.org/10.1592/phco.21.10.1468.34482.
14. Guo D, Cai Y, Chai D, Liang B, Bai N, Wang R. 2010. The cardiotoxicity of macrolides: a systematic review. Pharmazie 65:631–640.
15. Ray WA, Murray KT, Hall K, Arboag PS, Stein CM. 2012. Azithromycin and the risk of cardiovascular death. N Engl J Med 366:1881–1890. https://doi.org/10.1056/NEJMoa1003833.
16. Barriere S, Genter F, Spencer E, Kitt M, Hoelscher D, Manganroth J. 2004. Effects of a new antibacterial, telavancin, on cardiac repolarization (QTc interval duration) in healthy subjects. J Clin Pharmacol 44:569–695. https://doi.org/10.1121(00170024266620.
17. Berg JK, Tzanis E, Garry-Ryan L, Bai S, Chitra S, Manley A, Villano S. 2017. Pharmacokinetics and safety of omadacycline in subjects with impaired renal function. Antimicrob Agents Chemother 62:e02057-17. https://doi.org/10.1128/AAC.02057-17.
18. Tornoe CW, Garnett CE, Wang Y, Florian J, Li M, Gobburu JV. 2011. Creation of a knowledge management system for QT analyses. J Clin Pharmacol 51:1035–1042. https://doi.org/10.1177/0002847710378408.
19. Ferber G. 2018. Correcting QT for heart rate when both are affected by a drug. Drug Saf. https://doi.org/10.1007/s40264-018-0749-9.
20. Malik M, Garnett C, Hnatkova K, Vicente J, Johannesen L, Stockbridge N.
2018. Implications of individual QT/RR profiles—part 1: inaccuracies and problems of population-specific QT/heart rate corrections. Drug Saf. https://doi.org/10.1007/s40264-018-0736-1.

21. Darpo B, Tzanis E, Garrity-Ryan L, Manley A, McGovern P, Loh E. 2017. Cardiac safety of omadacycline in the IV/oral phase 3 Acute Bacterial Skin and Skin Structure Infection (ABSSSI) and in the IV/oral phase 3 Community-acquired Bacterial Pneumonia (CABP) studies. Open Forum Infect Dis 4:S544–S545. https://doi.org/10.1093/ofid/ofx163.1416.

22. Tanaka SK, Villano S. 2016. In vitro and in vivo assessments of cardiovascular effects with omadacycline. Antimicrob Agents Chemother 60:5247–5253. https://doi.org/10.1128/AAC.00320-16.

23. Hochberg Y. 1988. A sharper Bonferroni procedure for multiple tests of significance. Biometrika 75:800–802. https://doi.org/10.2307/2336325.