

# A Thorough QTc Study Demonstrates That Olmesartan Medoxomil Does Not Prolong the QTc Interval

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## Abstract

Two studies (ROADMAP and ORIENT) evaluating the renoprotective effects of olmesartan medoxomil (OM) in patients with type 2 diabetes suggested OM is associated with increased cardiovascular mortality. We conducted a thorough QTc study to evaluate the effects of OM on cardiac repolarization. A randomized, double-blind, phase I study was conducted per E14 Guidance to assess the effects of single doses of OM therapeutic dose (40 mg), OM suprathreshold dose (160 mg), placebo, or moxifloxacin (MOXI; 400 mg) on QTc in 56 healthy subjects. The primary endpoint was the baseline-adjusted, placebo-corrected QTc interval using Fridericia's formula ( $\Delta\Delta\text{QTcF}$ ) for OM and MOXI. Assay sensitivity was concluded if lower limit of 1-sided 95%CI  $> 5$  milliseconds of  $\Delta\Delta\text{QTcF}$  for MOXI. No threshold pharmacologic effect for OM was concluded if upper limit of 1-sided 95%CI  $< 10$  milliseconds for  $\Delta\Delta\text{QTcF}$  at any timepoint. Pharmacokinetics, ECGs, and safety were assessed. Assay sensitivity was demonstrated. The largest upper limit of the 1-sided 95%CI for  $\Delta\Delta\text{QTcF}$  was  $< 5$  milliseconds for OM. No clinically significant changes were observed in ECGs. Pharmacokinetics and safety profile were consistent with previous data. Therapeutic and suprathreshold OM doses had no clinically significant effect on cardiac repolarization and were well tolerated.

## Keywords

olmesartan, angiotensin receptor blocker, cardiac safety, QTc interval

Olmesartan medoxomil (Benicar<sup>®</sup>; Daiichi Sankyo, Inc, Parsippany, New Jersey) is a selective angiotensin II receptor antagonist indicated for the treatment of hypertension. Olmesartan medoxomil (OM) was initially approved in the United States in 2002. The usual US Food and Drug Administration (FDA) recommended starting dose of OM is 20 mg once daily when used as monotherapy in patients who are not volume contracted.<sup>1</sup> For patients requiring further reduction in blood pressure after 2 weeks of therapy, the dose of OM may be increased to 40 mg. OM is a prodrug that is hydrolyzed in the gastrointestinal tract by carboxymethylenebutenolidase to olmesartan and rapidly absorbed with maximum plasma concentrations of olmesartan observed within 1 to 3 hours postdose.<sup>2</sup> Olmesartan has an absolute bioavailability of approximately 26% when orally administered as OM and is highly bound to plasma proteins (99%).<sup>1</sup> Once absorbed systemically, olmesartan is not further metabolized. Approximately 35% to 50% of the absorbed dose is recovered in urine, whereas the remainder is eliminated by biliary excretion. Hepatic uptake and biliary excretion of olmesartan are mediated by organic anion-transporting polypeptides and multidrug resistance protein 2, respectively.<sup>3</sup> The terminal elimination half-life of olmesartan is approximately 13 hours.<sup>1</sup>

In the Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP; ClinicalTrials.gov

identifier: NCT00185159) study and the Olmesartan Reducing Incidence of End-Stage Renal Disease in Diabetic Nephropathy Trial (ORIENT; ClinicalTrials.gov identifier: NCT00141453), patients with type 2 diabetes mellitus received either OM or placebo on a background of other antihypertensive agents to determine if treatment with OM would either prevent or delay onset of microalbuminuria and thus provide protection against renal disease (ROADMAP) or reduce the incidence of end-stage renal disease (ORIENT).<sup>4,5</sup> An unexpected finding observed in both studies was a greater number of deaths from a cardiovascular cause (heart attack, sudden

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death, or stroke) in the OM-treated patients compared to placebo-treated patients.

More specifically, 15 patients treated with OM 40 mg once daily and 3 patients treated with placebo experienced a fatal cardiovascular event (0.7% vs 0.1%,  $P = .01$ ) in the ROADMAP study, whereas in ORIENT, 10 patients treated with OM 10–40 mg once daily and 3 patients treated with placebo experienced cardiovascular death (3.5% vs 1.1%, adjusted hazard ratio 2.81 [95% confidence interval (CI) 0.76–10.38]).<sup>4,5</sup> In ROADMAP, significantly more patients with preexisting cardiovascular disease treated with OM died from a cardiovascular event compared with placebo-treated patients (11 of 564 patients [2.0%] vs 1 of 540 [0.2%],  $P = .02$ ), possibly contributing to the observed increased deaths.<sup>4</sup> In ORIENT, more patients randomized to OM had preexisting cardiovascular disease at baseline compared with those randomized to placebo (21.3% vs 11.6%).<sup>5</sup>

In response to the cardiovascular event imbalances reported in ROADMAP and ORIENT, the FDA requested Daiichi Sankyo, Inc. to conduct additional analyses to provide more complete information regarding cardiovascular risks or benefits in various clinical settings. Similar to other angiotensin receptor blockers (ARBs) that received FDA approval during the same time period as OM, a thorough corrected QT interval (QTc) study to assess the potential effects of OM on the electrical activity of the heart had not been conducted as part of clinical development for registration. Therefore, in accordance with the FDA's comprehensive initiative to evaluate potential cardiovascular concerns, the purpose of this study was to conduct a thorough QTc study to assess the effects of therapeutic and suprathreshold OM doses on cardiac conduction/repolarization in healthy subjects using the standard methodologies outlined in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E14 Guidance.

## Methods

The study protocol and subsequent amendment were approved by an institutional review board. The study was conducted at Celerion (Tempe, Arizona) in accordance with Title 21 of the US Code of Federal Regulations, Good Clinical Practice Guidelines, and the Declaration of Helsinki Principles. All subjects provided written informed consent before screening.

### Study Subjects

All subjects were healthy men and women aged 18 to 45 years, with a body mass index (BMI) between 19 and 31 kg/m<sup>2</sup>. Subjects who received any prescribed or over-the-counter medications within 14 days of the first study dose were excluded from participation.

### Study Design

This study was a postmarketing, phase 1, single-center, randomized, single-dose, double-blind, double-dummy, placebo- and active-controlled, 4-period crossover study conducted to evaluate the effect of OM active treatment on QTc prolongation in healthy male and female subjects. The study design followed the ICH guidelines for a thorough QTc study.<sup>6</sup>

Prior to study enrollment, subjects were screened for eligibility criteria by physical examination, medical history, clinical laboratory data, and electrocardiogram (ECG). On day 1 of each 7-day treatment period, subjects received 5 blinded film-coated tablets; a single oral dose of 1 of the following medications (40 mg OM, 160 mg OM, 400 mg moxifloxacin, or placebo) along with placebo tablets to match moxifloxacin or OM. The sequence of medications across all 4 treatment periods was determined by a randomization schedule. Treatments were administered to patients in a fasting state and were separated by at least 7 days of washout between doses. The 40-mg dose of OM is based on the highest approved therapeutic dose, whereas 160 mg of OM represents a suprathreshold dose.<sup>1</sup>

The cardiodynamic analysis set included all subjects who received at least 1 dose of study medications (OM, moxifloxacin, or placebo) and had valid baseline and postdose QT/QTc data from at least 1 study period. The safety analysis set included all subjects who received  $\geq 1$  dose of study medications (OM, moxifloxacin, or placebo) and had  $\geq 1$  postdose safety assessment. The safety analysis set was used for the statistical analysis of safety endpoints but not for the primary QTc analysis. Standard clinical safety measurements were assessed throughout the study, including resting vital signs (blood pressure, heart rate [pulse], oral temperature, and respiratory rate), which were monitored at check-in, predose, and at 1, 2, 3, 4, 8, 12, 24, 48, and 72 hours postdose. Local serial ECGs (heart rate, PR, QRS, QT) for safety were evaluated at screening, check-in, predose, up to 6 hours postdose, and at the end of study or early termination. For the cardiodynamic evaluation of QTc interval, serial 12-lead ECGs were extracted from a dual-lead, 12-lead continuous ECG recorder (Model H12+, Mortara Instrument, Inc., Milwaukee, Wisconsin) from approximately 24 hours predose to 24 hours postdose. Blood samples were collected for the determination of olmesartan concentrations for up to 72 hours postdose.

To ensure continued eligibility throughout the study, subjects received an abbreviated medical history, concomitant medication history (since screening), and physical exam as well as a urine screen for drugs of abuse and alcohol, serum pregnancy test (for female subjects only), laboratory safety tests, vital signs, standard resting triplicate 12-lead ECG, and fecal occult blood assessment at the check-in for each of all 4 treatment

periods. Subjects were discharged from the study after completion of the fourth treatment period.

### ECG Recordings

Continuous ECG recording was obtained through 12 lead Holter monitors. ECGs were reviewed by a technician, and a fully annotated record was compiled indicating any 10-second periods with significant artifact, technical failure, or any nonsinus beats. The 10-second digital 12-lead ECGs were extracted from 12 lead Holter monitors in triplicate by the central ECG laboratory at Celerion (Tempe, Arizona) during the periods of verified stable heart rate at the specified clock times and read locally at the clinical site to ensure safety. On-treatment ECGs were extracted from day 1 recordings at 0 (predose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, and 24 hours postdose. The baseline measurements allowed for time-matched corrections. The baseline value for the QT/QTc interval is defined as the average of the 9 ECG measurements (average, rounded to 1 decimal greater than the original measurement precision, of the nonmissing measures taken at hours  $-0.75$ ,  $-0.5$ , and  $-0.25$ ) recorded prior to day 1 dosing for each treatment. ECGs were read in a blinded manner by the core reading laboratory. The ECG recordings were measured and classified by software from AMPS, LLC. The ECG recordings not meeting specific quality criteria thresholds and all waveforms identified for review by the automated algorithm were assigned to a board certified cardiologist for review. The cardiologist was blinded to subject, time, and treatment. QT interval data were extracted from the Holter monitor recordings. QTc was derived from a superimposed median beat.

The following 2 QT interval-correction methods were implemented in this study, and the corrected QT interval using Fridericia's formula (QTcF) was used for the primary endpoint analysis:

Fridericia's correction :  $QTcF = QT/(RR)^{1/3}$

Bazett's correction (QTcB) :  $QTcB = QT/(RR)^{1/2}$

where RR interval is measured in seconds. All derived QTcF and QTcB values were rounded to the nearest tenth. The average of the 3 ECG interval durations for each nominal time point was calculated and treated as a single observation for the descriptive summaries and statistical analysis.

In addition to QT interval, heart rate, and the PR, QRS, and ECG waveform morphology (ie, arrhythmia, rhythm, conduct, ST segment, T-waves, and U-waves) were evaluated and summarized for each treatment group at all study time points.

### Pharmacokinetic Analyses

Blood samples were collected for the determination of plasma olmesartan concentrations at 0 (predose), 0.5, 1,

1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, 36, 48, and 72 hours postdose of OM administration. Plasma olmesartan concentrations were analyzed by Celerion (Lincoln, Nebraska) using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method developed by Celerion. An aliquot of human plasma (ethylenediaminetetraacetic acid [EDTA]) containing the analyte and internal standard was extracted using a liquid-liquid extraction procedure. The extracted samples were analyzed by high-performance liquid chromatography (HPLC) equipped with an AB SCIEX API 4000<sup>TM</sup> triple quadrupole mass spectrometer using an electrospray ionization (ESI) source. Positive ions were monitored in the multiple reaction monitoring (MRM) mode.

Quantification was determined using a weighted linear regression analysis ( $1/\text{concentration}^2$ ) of peak area ratios of the analyte and internal standard. The following sets of calibration standards (10 concentrations ranging from 2.5 to 1500 ng/mL) and quality control samples (at 7.5, 37.5, 375, 1150, and 5000 ng/mL) were used for the analysis of clinical samples.

Pharmacokinetic (PK) parameters were calculated using noncompartmental approaches. The PK parameters calculated, as appropriate, from the individual plasma concentrations of olmesartan were area under the curve (AUC) up to the last measurable point ( $AUC_{\text{last}}$ ), AUC up to infinity ( $AUC_{0-\infty}$ ), maximum concentration ( $C_{\text{max}}$ ), time to maximum concentration ( $T_{\text{max}}$ ), half-life ( $t_{1/2}$ ), apparent total body clearance (CL/F), and apparent volume of distribution ( $V_z/F$ ). OM dose was adjusted by molecular weight (molecular weights of OM and olmesartan are 558.59 and 446.51 g/mol, respectively) in the calculation of PK parameters. Therefore, a dose of 40 mg of OM corresponded to a dose of 31.974 mg of olmesartan, and a dose of 160 mg of OM corresponded to a dose of 127.90 mg of olmesartan. Concentrations below the lower limit of quantification were set to 0 in the calculation of PK parameters. PK variables were computed using WinNonlin Professional Version 5.2 professional software (Pharsight Corporation, Mountain View, California). Plasma concentrations for olmesartan and PK parameters were summarized with descriptive statistics.

## Statistical Analysis Methods

### Sample Size

A total of 56 healthy male and female subjects were enrolled and subsequently randomized to 1 of 4 sequences, with the expectation that at least 44 subjects would complete the study. This sample size was based on the hypothesis test for a noninferiority hypothesis, with the upper bound of noninferiority margin being 10 milliseconds. The within-subject standard deviation (SD) was assumed to be 7 milliseconds, the expected difference in QTc interval between olmesartan and placebo was

$\leq 5$  milliseconds (and this maximum effect would only be reached at  $\leq 3$  time points), and the power of the hypothesis test was set to 85%.

### ECG Data

The primary endpoint for each OM dose was the time-matched difference in QTcF interval of each OM dose and placebo after baseline adjustment, the so-called double delta method ( $\Delta\Delta\text{QTcF}$ ). The analysis of the central tendency for  $\Delta\Delta\text{QTcF}$  was performed using a mixed-model repeated-measures analysis of covariance (ANCOVA). The model included treatment, sequence, period, hour, treatment-by-hour interaction, and period-by-hour interaction as fixed factor, subject nested in sequence as a random effect, and the time-matched baseline values for each subject at each treatment period as covariate. Observations within each subject's period (period  $\times$  subject[seq]) were treated as repeated measurements, and the (co) variance structure of the residual term of the model was chosen from CS, heterogeneous compound symmetry (CSH), SP(POW), and ANTE(1) on the basis of Akaike's information criterion. Following the recommendations in ICH E14 Guidance,<sup>6</sup> if the upper bound of the 1-sided 95%CI of the  $\Delta\Delta\text{QTcF}$  effect was  $< 10$  milliseconds at all of the time points after dosing, then it could be concluded that the drug had no threshold effect on ventricular repolarization. In addition, sensitivity of the study could be demonstrated if the lower bound of the 1-sided 95%CI for  $\Delta\Delta\text{QTcF}$  at 1 hour, 2 hours, or 3 hours after dosing with moxifloxacin was  $> 5$  milliseconds.

Categorical summaries of QT/QTc outliers were also provided. The maximum individual change from baseline ( $\Delta\text{QTc}$ ) was determined at each postdose time. The number and percentage of subjects having maximum changes in the categories of  $< 0$ ,  $\geq 0$  to  $\leq 30$ ,  $> 30$  to  $\leq 60$ , and  $> 60$  milliseconds were presented by treatment for each QT parameter. Similar summaries were provided for maximum individual postdose absolute values for  $\leq 450$ ,  $> 450$  to  $\leq 480$ ,  $> 480$  to  $\leq 500$ , and  $> 500$  milliseconds.

To correlate the results from the statistical analysis of central tendency of QTc with drug exposure, the following scatter plots were provided for the active treatments (each OM dose) with regression lines and the  $R^2$  for the slope: (a) the largest individual  $\Delta\Delta\text{QTc}$  vs the corresponding plasma concentration, (b) the individual peak plasma concentration of olmesartan vs the corresponding  $\Delta\Delta\text{QTc}$ , and (c) all individual  $\Delta\Delta\text{QTc}$  vs the corresponding plasma concentration.

## Results

### Subject Demographics and Disposition

A total of 56 subjects (28 men, 28 women) were enrolled with 51 subjects completing the study. The majority of

**Table 1.** Demographics and Baseline Characteristics

Characteristics	Overall (N = 56)
Sex, N (%)	
Female	28 (50.0%)
Male	28 (50.0%)
Race, N (%)	
American Indian or Alaskan Native	1 (1.8%)
Black or African American	4 (7.1%)
White	51 (91.1%)
Ethnicity, N (%)	
Hispanic/Latino	48 (85.7%)
Not Hispanic/Latino	8 (14.3%)
Age (years), N (%)	
18-29	27 (48.2%)
30-39	18 (32.1%)
40-49	11 (19.6%)

study subjects were white (91%) and Hispanic/Latino (86%), with equal proportions of females and males. Mean age of the subjects was 31.9 years (range 19-45 years) with a mean BMI of 26.2 kg/m<sup>2</sup> (range 19.1-30.6 kg/m<sup>2</sup>) (Table 1). Five subjects were discontinued: 2 subjects withdrew consent, 2 subjects were discontinued due to low blood pressure (at predose), and 1 subject was discontinued for the protocol violation of ingestion of a prohibited concomitant medication.

### Cardiodynamic Analysis Set

Inferential statistical analyses (ie, statistical tests, confidence intervals) were performed for the QT/QTc data from the Cardiodynamic Analysis Set, which included 55 subjects. Data from 1 subject who had vomited were excluded (cohort defined as the exploratory analysis set), and the period 4 data of another subject who had received incorrect treatment in period 4 were excluded.

### Effect of Moxifloxacin on QTc

The lower confidence limit (LCL) of the 1-sided 95%CI of the difference in least squares means of  $\Delta\text{QTcF}$  between moxifloxacin and placebo was  $> 5$  milliseconds for the 3 preselected postdose time points (1, 2, and 3 hours), as shown in Table 2. The minimum mean effect in  $\Delta\Delta\text{QTcF}$  was 9.9 milliseconds at 1 hour (1-sided 95% LCL 8.38 milliseconds). The positive control (moxifloxacin) met the criteria for QTc prolongation of  $> 5$  milliseconds at the specified time points, and, therefore, the thorough QTc study was adequately sensitive to detect the potential effect of olmesartan on QTcF intervals.

### Effect of Olmesartan on QTc

The mean change from baseline in QTcF is shown in Figure 1. In the cardiodynamic analysis set, the largest

**Table 2.** Statistical Comparisons of Cardiodynamic  $\Delta\text{QTcF}$  Between Moxifloxacin and Placebo

Time Point (Hours)	LSM $\Delta\text{QTcF}$ (Milliseconds)		$\Delta\Delta\text{QTcF}$ (Milliseconds)	P Value	2-Sided 90%CI
	Moxifloxacin 400 mg	Placebo			
1	9.9515	0.0653	9.8862	<.0001	(8.3750, 11.3973)
2	13.4183	1.4659	11.9523	<.0001	(10.4412, 13.4635)
3	14.7548	0.4168	14.3380	<.0001	(12.8269, 15.8491)

CI, confidence interval; LSM, least-squares means;  $\Delta\text{QTcF}$ , baseline-adjusted corrected QT interval using Fridericia's formula;  $\Delta\Delta\text{QTcF}$ , difference in baseline-adjusted corrected QT interval using Fridericia's formula.

$\Delta\Delta\text{QTcF}$  was 1.51 milliseconds (hour 3) for the 40-mg dose of OM and 2.47 milliseconds (hour 2.5) for the 160-mg dose as shown in Figure 2. The largest 1-sided 95% upper confidence limit (UCL) for  $\Delta\Delta\text{QTcF}$  was 3.16 milliseconds (hour 3) for the 40-mg dose and 3.99 milliseconds (hour 3) for the 160-mg dose. Because the upper limit of the 1-sided 95%CI of  $\Delta\Delta\text{QTcF}$  did not exceed 10 milliseconds at all postdose times, the drug was concluded to have no threshold pharmacologic effect.

The largest  $\Delta\Delta\text{QTcB}$  was 2.66 milliseconds (hour 2.5) for the 40-mg dose of OM and 4.66 milliseconds (hour 1) for the 160-mg dose. The largest 1-sided 95% UCL for  $\Delta\Delta\text{QTcB}$  was 5.01 milliseconds (hour 6) for

the 40-mg dose and 6.90 milliseconds (hour 3) for the 160-mg dose.

In the exploratory analysis set, the largest  $\Delta\Delta\text{QTcF}$  was 1.52 milliseconds (hour 3) for the 40-mg dose of OM and 2.67 milliseconds (hour 3) for the 160-mg dose. The largest 1-sided 95% UCL for  $\Delta\Delta\text{QTcF}$  was 3.21 milliseconds (hour 3) for the 40-mg dose and 4.36 milliseconds (hour 3) for the 160-mg dose.

#### Categorical Analysis

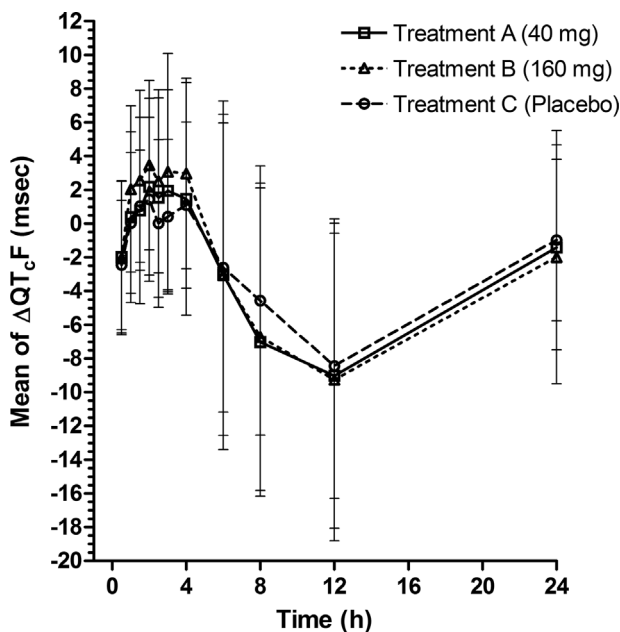
A total of 52 subjects (98.1%) who received the 40-mg dose of OM had QTcF values  $\leq 450$  milliseconds at all time points, and 1 subject (1.9%) had QTcF values  $> 450$  milliseconds to  $\leq 480$  milliseconds (Table 3). All 54 subjects (100%) who received the 160-mg dose of OM had QTcF values  $\leq 450$  milliseconds at all time points. Similarly, none of the 52 subjects who received placebo or moxifloxacin had QTcF values  $> 450$  milliseconds.

#### Pharmacokinetics of Olmesartan

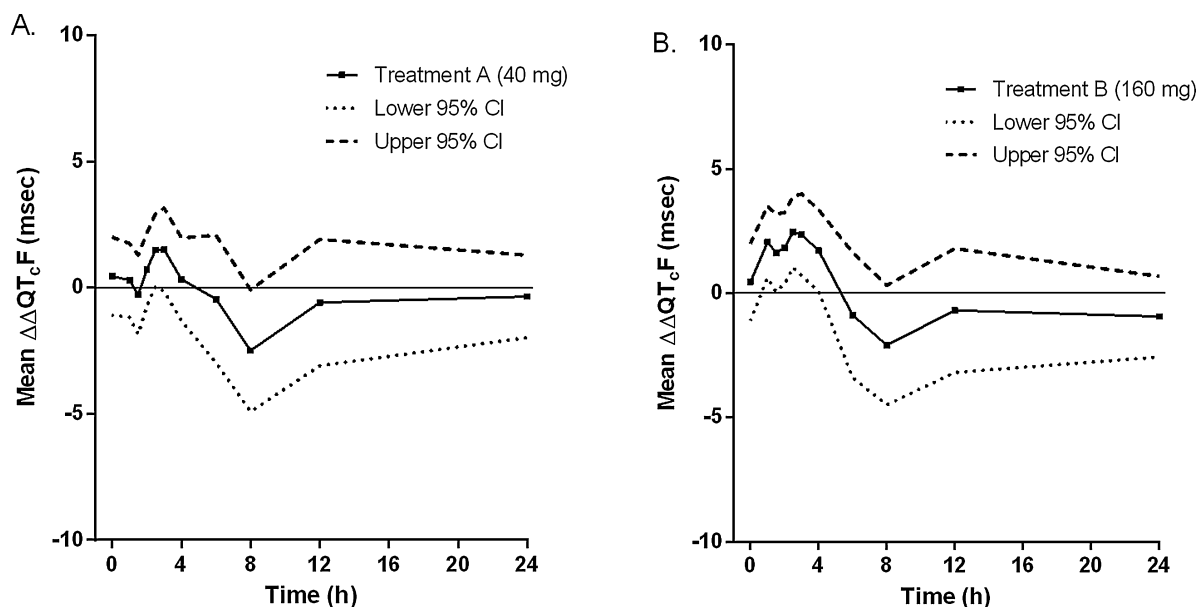
Mean plasma concentrations of olmesartan versus time are shown in Figure 3 and presented in linear and semilog scales. Mean ( $\pm$ SD) values for  $\text{AUC}_{0-\infty}$  for the OM 40-mg dose and OM 160-mg dose were  $5544 \pm 1379$  ng·h/mL and  $18,243 \pm 5165$  ng·h/mL, respectively. Mean ( $\pm$ SD) values for  $C_{\text{max}}$  for the OM 40-mg dose and OM 160-mg dose were  $863.3 \pm 268.7$  ng/mL and  $2440 \pm 678$  ng/mL, respectively. A 4-fold increase in OM oral dose (ie, 40 mg to 160 mg) resulted in a 3.3-fold increase in mean AUCs, whereas mean  $C_{\text{max}}$  increased by 2.8-fold from lower to higher dose. Median  $t_{\text{max}}$  values ranged from 1.05 hours to 4.05 hours for both doses. Mean ( $\pm$ SD) terminal elimination  $t_{1/2}$  for the OM 40-mg dose and OM 160-mg dose were  $10.2 \pm 4.79$  hours and  $12.0 \pm 5.84$  hours, respectively.

#### Exposure-Response Relationship Between Olmesartan Concentrations and $\Delta\text{QTc}$ Intervals

Scatter plots assessing the individual QTcF change from baseline in all subjects vs the corresponding plasma concentration, the peak plasma concentration of olmesartan vs the corresponding QTcF change from baseline, and the largest individual QTcF change from baseline vs the corresponding plasma concentration are presented in



**Figure 1.** Statistical comparison of cardiodynamic  $\Delta\text{QTcF}$  between olmesartan medoxomil (OM; treatments A and B) and placebo (treatment C): means of  $\Delta\text{QTcF}$  vs time for OM treatments and placebo. Treatment A: single oral 40-mg dose (1  $\times$  40-mg tablet) of OM, 3 placebo-matching OM tablets, and 1 placebo-matching moxifloxacin tablet. Treatment B: single oral 160-mg dose (4  $\times$  40-mg tablets) of OM and 1 placebo-matching moxifloxacin tablet. Treatment C: single oral dose of 4 placebo-matching OM and 1 placebo-matching moxifloxacin tablet.



**Figure 2.** Mean of  $\Delta\Delta\text{QTcF}$  vs time for olmesartan medoxomil (OM) treatments with lower-upper 1-sided 95% CIs: (A) treatment A = 40-mg dose, (B) treatment B = 160-mg dose. CI, confidence interval.

Figures S1, S2, and S3, respectively. No consistent trend was observed across the plots of  $\Delta\text{QTcF}$  and plasma olmesartan concentrations, and slopes were minimally positive, negative, or equal to 0. These results indicate no consistent relationship between plasma concentrations of olmesartan and  $\Delta\text{QTcF}$  values.

#### Adverse Events

Abnormal ECG results were noted on occasion, randomly distributed by treatment and not considered to be clinically significant. No serious adverse events (SAEs) occurred in this study, and no subjects were withdrawn from the study due to an AE.

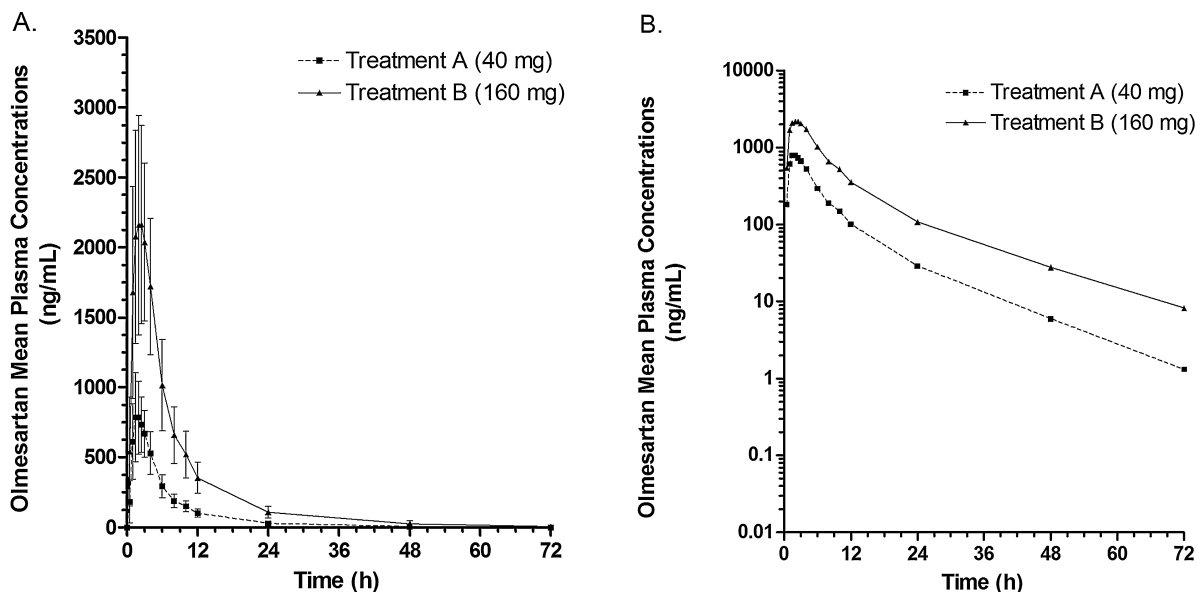
The majority of treatment-emergent AEs (TEAEs) reported during this study were nervous system disorders and gastrointestinal disorders. The most common nervous system disorder was headache, with a total of 15 mild

TEAEs reported by 11 subjects overall (19.6%). Five subjects (9.3%) each reported 1 headache following dosing with 40 mg of OM, 4 subjects (7.1%) following 160 mg of OM, 3 subjects (5.7%) following placebo, and 3 subjects (5.7%) following 400 mg of moxifloxacin. Most of the gastrointestinal disorders in the study were reported following the 400-mg dose of moxifloxacin (13.2% vs 5.4% and 5.6% for OM [160-mg and 40-mg doses, respectively], and 3.8% for placebo). The most common gastrointestinal disorder was nausea with a total of 7 mild TEAEs reported by 7 subjects overall (12.5%). Two subjects (3.7%) experienced nausea following a 40-mg dose of OM, 1 subject (1.8%) following a 160-mg dose of OM, no subjects after placebo, and 4 subjects (7.5%) after 400-mg doses of moxifloxacin. Most TEAEs resolved without concomitant medication. All other TEAEs were reported by  $\leq 5$  subjects overall (8.9%).

**Table 3.** Categorical Summary: Maximum Postdose QTcF Interval and Maximum Change From Baseline ( $\Delta\text{QTcF}$ )

Parameter	Interval Category (Milliseconds)	OM 40 mg N = 53 n (%)	OM 160 mg N = 54 n (%)	Placebo N = 52 n (%)	Moxifloxacin 400 mg N = 52 n (%)
QTcF	$\leq 450$	52 (98.1%)	54 (100%)	52 (100%)	52 (100%)
	$> 450$ to $\leq 480$	1 (1.9%)	0 (0%)	0 (0%)	0 (0%)
	$> 480$ to $\leq 500$	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	$> 500$	0 (0%)	0 (0%)	0 (0%)	0 (0%)
$\Delta\text{QTcF}$	$< 0$	3 (5.7%)	4 (7.4%)	2 (3.8%)	0 (0%)
	$\geq 0$ to $\leq 30$	50 (94.3%)	50 (92.6%)	50 (96.2%)	51 (98.1%)
	$> 30$ to $\leq 60$	0 (0%)	0 (0%)	0 (0%)	1 (1.9%)
	$> 60$	0 (0%)	0 (0%)	0 (0%)	0 (0%)

OM, olmesartan medoxomil; QTcF, corrected QT interval using Fridericia's formula;  $\Delta\text{QTcF}$ , baseline-adjusted corrected QT interval using Fridericia's formula.



**Figure 3.** Mean ( $\pm$ SD) plasma olmesartan concentrations vs time for (A) olmesartan medoxomil (OM) 40-mg dose (linear) and (B) OM 160-mg dose (log-linear). Treatment A = single oral 40-mg dose of OM. Treatment B = single oral 160-mg dose of OM.

## Discussion

An unexpected finding from the ROADMAP and ORIENT studies that were conducted in patients with type 2 diabetes was the observation of a greater number of deaths from a cardiovascular cause (heart attack, sudden death, or stroke) in the OM-treated patients compared to placebo.<sup>4,5</sup> Paradoxically, safety data reported from previous hypertension studies demonstrated that OM had a good overall tolerability and a safety profile similar to that of placebo. Consequently, the FDA requested that additional studies and analyses be performed to provide more complete information regarding the numerical imbalances reported in ROADMAP and ORIENT. Because OM was approved prior to the implementation of the E14 Guidance, which requires ECG assessments on all new chemical entities, thorough preclinical and clinical QTc studies had not been conducted. A previously conducted preclinical, *in vitro* study evaluated the electrophysiological effect of olmesartan on the potassium currents in human ether-a-go-go-related gene (hERG) in transfected CHO-K1 cells. The study had shown that there was no significant inhibitory effect of olmesartan on the potassium currents of transfected CHO-K1 cells at 100 to 300 times the expected therapeutic olmesartan concentration.<sup>1</sup>

In the present QTc study, olmesartan has minimal potential for QTc prolongation as evidenced by the study results. The upper limit of the 1-sided 95%CI for the difference between olmesartan and placebo in the baseline-adjusted QTcF ( $\Delta\Delta$ QTcF) for all time points up to 24 hours postdose was <5 milliseconds for both the

maximum recommended daily dose of OM (40 mg) and for the suprathreshold dose (160 mg), well below the threshold for regulatory concern (ie, 10 milliseconds). Moreover, as the lower limit of the 1-sided 95%CI for the difference in baseline-adjusted QTcF ( $\Delta\Delta$ QTcF) for moxifloxacin was >5 milliseconds, the study was adequately sensitive to detect a prolongation of QTc interval with olmesartan. By categorical analysis, the majority (>98.1%) of OM-treated subjects had QTcF values  $\leq$ 450 milliseconds at all postdose time points, and the majority (>92.6%) had a  $\Delta$ QTcF of  $\leq$ 30 milliseconds. The cardiodynamic findings of this thorough QTc study therefore confirm the findings from the previous preclinical human hERG study (data on file). Based on the evidence reported from both studies, olmesartan does not appear to affect cardiac repolarization, and, therefore, it is unlikely that this mechanism was associated with the increased cardiovascular events reported in the ROADMAP and ORIENT studies.

The safety of OM for the treatment of hypertension, both as monotherapy and as part of combination therapy, has been demonstrated across multiple patient subgroups in numerous hypertension studies.<sup>7-17</sup> Importantly, the findings of increased rates of cardiovascular death in OM-treated patients in ROADMAP and ORIENT are not supported by more recent large-scale retrospective cohort analyses, which observed no difference in risk between patients initiating OM and those initiating other ARBs or angiotensin-converting enzyme inhibitors.<sup>18-21</sup> Some concern for increased risk was raised with the use of high-dose olmesartan for  $\geq$ 6 months' duration in elderly patients with type 2 diabetes.<sup>19</sup> Similarly, results from a

retrospective cohort study conducted by Padwal et al found that there was “no robust signal for harm with olmesartan use”; however, their finding that patients with chronic kidney disease might be at higher risk of all-cause mortality or hospitalization led them to suggest that it might be prudent to use this agent with caution in this patient population until additional studies can be performed.<sup>18</sup>

In the present thorough QTc study, OM did not demonstrate a threshold pharmacologic effect on cardiac repolarization, and no new safety concerns were observed. The most common AEs in healthy subjects were nausea and headache. No abnormal ECG findings of clinical significance were noted in either the safety or postdose cardiodynamic evaluations.

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