Effect of 3 Single Doses of Trazodone on QTc Interval in Healthy Subjects

Valeria Tellone, PhD1, Maria Teresa Rosignoli, MSc1, Rossella Picollo, MSc1, Patrizia Dragone, MChem1, Alessandra Del Vecchio, MSc1, Alessandro Comandini, MD1, Milko Radicioni, MD2, Chiara Leuratti, PhD2 and Fabrizio Calisti, MD1

Abstract
This study evaluated the effect of 3 doses of a trazodone hydrochloride 6% oral drops solution on the QT interval of healthy volunteers. Subjects were randomly assigned to receive a single dose of trazodone 20 mg, 60 mg, and 140 mg, moxifloxacin 400 mg, and trazodone-matched placebo in 5 periods separated by 7-day washouts, according to a double-blind, crossover study design. Subjects were monitored continuously, and triplicate ECGs were extracted from baseline (predose) until 24 hours postdose. Blood samples for trazodone and moxifloxacin analyses were collected at the same time points. The concentration-QTc relationship assessed on placebo-adjusted change from baseline for Fridericia-corrected QT (\(\Delta QTc_F\)) was the primary end point. \(\Delta QTc_F\) values of 4.5, 12.3, and 19.8 ms for the 20-, 60-, and 140-mg doses were observed at the corresponding trazodone peak plasma concentrations. The upper bound of the 90% CI exceeded 10 ms for the 60- and the 140-mg doses. Time-matched analysis results were in line with these findings. No significant trazodone effect on heart rate or PR or QRS intervals and no clinically significant new morphological changes were present. In this moxifloxacin-validated ECG trial, trazodone had a modest, dose-dependent effect on cardiac repolarization, with no QTc prolongation observed with the 20-mg dose and an effect exceeding the values set in E14 guideline with the 60- and 140-mg doses. The effect on cardiac repolarization is unlikely to represent a clinical risk for ventricular proarrhythmia, but caution should be used with concomitant use of other medications that prolong QT or increase trazodone exposure.

Keywords
Trazodone, QT prolongation, QTcF, pharmacokinetics/pharmacodynamics

Trazodone hydrochloride is a triazolopyridine derivative antidepressant, classified as serotonin type 2 receptor (5-HT2) antagonist and 5-HT reuptake inhibitor.1-3 After oral administration, trazodone is completely absorbed by the gastrointestinal tract, and the rate of absorption may be affected by the presence of food.4 Trazodone exhibits linear pharmacokinetics (PK) after single and repeated administration of pharmaceutical forms with different release rates, in a wide dose range.1,5,6 Trazodone is indicated for the treatment of major depressive disorder with or without anxiety in adults,7 and since the early 1970s it has been available in many countries worldwide.8-11 Due to its multifunctional mechanism of action,3 trazodone demonstrates unique therapeutic flexibility, which has given rise to its effectiveness in a broad range of comorbidities of major depressive disorder and to its use in off-label indications, including insomnia, anxiety, dementia, Alzheimer disease, substance abuse, schizophrenia, bulimia, and fibromyalgia.1 In particular, literature data suggest its effectiveness in the treatment of insomnia when used at doses (ie, 25-100 mg) lower than the 300 mg/d indicated for the treatment of major depressive disorder.3,12-14 Trazodone has a positive effect on sleep architecture and has been demonstrated to be able to improve the quality of sleep in depressed patients.12-14 It has been observed that sleep-related disturbances, such as difficulty in initiating or maintaining sleep, are often not resolved or even worsened by antidepressant treatments. An antidepressant able to reduce sleep disturbance in depression may improve the quality of life of patients, targeting a symptom that can strongly affect depression relapse and recurrence.15 Trazodone sedative properties have also been observed in patients with insomnia.16-18

The present study was designed to evaluate the effect of 2 low doses of trazodone (20 and 60 mg) in

1 Angelini SpA, Piazzale della Stazione, Pomezia, Italy
2 Cross Research SA, Arzo, Switzerland

This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

Submitted for publication 3 February 2020; accepted 16 April 2020.

Corresponding Author:
Valeria Tellone, PhD, Angelini S.p.A., Piazzale della Stazione, snc-00071, Pomezia, Italy
Email: valeria.tellone@angelinipharma.com
comparison to a higher trazodone dose (140 mg) on the QT/QTc interval of healthy volunteers.

The most recent R3 Q&A document updating the ICH E14 Guidance specifies that concentration-response analysis can serve as an alternative to the by-time-point analysis or intersection-union test as the primary basis for decisions to classify the risk of a drug. In this regard this study was designed to detect the lowest dose of trazodone that provokes a significant QT prolongation. According to the E14 guideline on the evaluation of QT/QTc interval prolongation and proarrhythmic potential of antiarrhythmic drugs, a negative control (placebo) and a positive control (moxifloxacin) were also assessed.

Methods

Study and Ethics

The study (Protocol No. 039PO16364; Clinicaltrial.gov N. NCT03516630) was approved by the Ethics Committee of Canton Ticino (Switzerland) and the Swiss Federal Health Authorities and was performed in accordance with the Declaration of Helsinki and the International Council for Harmonisation Guidelines for Good Clinical Practice. All subjects were given a detailed description of the study, and all of them gave written informed consent before enrollment. The study was conducted at the Clinical Phase I Unit, Cross Research SA (Arzo, Ticino, Switzerland), between March and May 2017 and was designed as a single-dose, randomized, double-blind, 5-period, 5-way crossover, placebo- and active-controlled investigation in healthy female and male subjects.

The study design took into account the ICH E14 guideline for QT/QTc prolongation studies and the E14 guideline Q&A (R3) document.

Investigational Product and Study Procedures

The investigational product was trazodone hydrochloride 6% oral drops solution (Angelini SpA, Rome, Italy). Eligible subjects were randomly assigned, according to a randomization list generated using Microsoft Access, to a treatment sequence in the 5 study periods, separated by a washout interval of at least 7 days, in which the subjects received single doses of trazodone 20, 60, and 140 mg, moxifloxacin (positive control) 400 mg, and trazodone-matched placebo (negative control) under fasting conditions. The 3 trazodone doses and placebo were administered in a double-blind manner; moxifloxacin, as a 400-mg tablet, was administered open label.

During each study period, the subjects were confined at the clinical center from the evening before the investigational product administration up to 35 hours postdose. During their confinement, study subjects received standardized meals. Water was allowed as desired, except for 1 hour before and 1 hour after administration of the investigational product.

Study Subjects

Healthy male and female volunteers, aged 20-50 years, with a body mass index of 18.5-28.0 kg/m², were enrolled in the study. All volunteers were in good physical health, as assessed through full physical examination, ECG recording, vital signs measurement, and clinical laboratory assays, according to the study inclusion criteria. No subjects were on abnormal diets or had a history of drug, alcohol, caffeine, or tobacco abuse. Main exclusion criteria were abnormal ECG at screening (eg, heart rate [HR] <50 or >90 bpm, PR <120 or >200 ms, QRS >110 ms, Fridericia corrected QT interval [QTcF] >430 ms for men and >450 ms for women); any qualitative/morphological abnormality (except for sinus arrhythmia, isolated premature atrial complexes/premature ventricular complexes); T-wave/U-wave characteristics making determination of end of T wave difficult; history of risk factors for torsade de pointes (ie, heart failure, hypokalemia, family history of long-QT syndrome); or a history of hypersensitivity or allergic reactions to the active principle and/or formulations’ ingredients. Medications, including over-the-counter medications and herbal products, and in particular drugs that prolong the QT/QTc interval, potentially hepatotoxic drugs or hepatic/gastric enzyme inducers (ie, phenobarbital, phenytoin, carbamazepine, chlorzoxazone, and rifampicin) were not allowed for 2 weeks before the study. Hormonal contraceptives for women were allowed. Subjects were not enrolled if they had participated in other clinical trials or donated blood in the past 3 months.

ECG Assessments and End Points

ECGs were obtained digitally, using a continuous Mortara H12+ 12-lead recording device (Mortara Instrument Co, Milwaukee, Wisconsin) with the capacity for digital signal processing, adequately serviced and calibrated. The continuous recording was started approximately 1 hour before the dosing time, in order to obtain the baseline ECGs, and continued to approximately 24 hours and 15 minutes postdosing. Subjects rested quietly in a fully supine position for at least 10 minutes before each scheduled time point for ECG evaluation and sample collection for PK analyses.

The ECGs were extracted in triplicate at −0.75, −0.5, and −0.25 hours (baseline assessments) and at 5, 10, 20, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours postdose at the ECG central laboratory (eResearch Technology Inc, Philadelphia, Pennsylvania) by a central cardiologist who was blind to study treatment.
On-screen measurements of the RR, PR, QRS, and QT interval durations were performed, and the estimate of each parameter was obtained as the average of the 3 extractions. QTcF and HR were calculated using the following formulas: QTcF \(=\) QT/(RR)\(^{1/3}\) and HR = \(60[\text{RR1} + \text{RR2} + \text{RR3}]/3\).

The primary end point was the evaluation of the relationship between the plasma concentration of trazodone (free base) and the change from baseline in QTcF.

Secondary end points included time-matched change from baseline in QTcF, placebo-adjusted \(\Delta\Delta\text{QTcF}\), HR, PR, QRS, and ECG morphology. The relationship between the plasma concentration of moxifloxacin and the change from baseline in QTcF was also evaluated for assay sensitivity demonstration.

**PK Assessments**

**Blood Sampling.** In each period, venous blood samples for trazodone or moxifloxacin determination were collected from a forearm vein, using an indwelling catheter with switch valve, at predose (–0.25 hour) and 5, 10, 20, 30, and 45 minutes and 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours postdose. After each sampling, the cannula was rinsed with about 1 mL of sterile saline solution. At each collection time 1 mL of blood was discarded to avoid contamination of the sample. The remaining 4.5 mL was collected from the catheter and transferred with a syringe into tubes containing K\(_2\)EDTA as anticoagulant. The samples were stored on ice for a maximum of 20 minutes and then were centrifuged at 4°C for 10 minutes at 1500 g to obtain plasma. Each plasma sample was immediately divided into 2 aliquots in prelabeled polypropylene tubes. Before freezing, plasma aliquots for the determination of moxifloxacin were acidified with a 25% orthophosphoric acid solution in a 1:40 ratio of acid/plasma in order to stabilize the acylglucuronide metabolite. Plasma aliquots for trazodone analysis were directly frozen. All plasma aliquots were stored at a temperature between –40°C and –20°C within 20 minutes from the end of centrifugation.

**Bioanalytical Assay.** Concentrations of trazodone free base and moxifloxacin in plasma were determined at Pharma Medica Research Inc (Mississauga, Ontario, Canada) using liquid chromatography tandem mass spectrometry methods developed and fully validated according to the requirements of the European Medicines Agency and Food and Drug Administration guidelines on bioanalytical method validation.\(^{22,23}\) The standard calibration range was from 3.00 to 5000 ng/mL using a plasma volume of 0.05 mL for trazodone and from 5.00 to 5000 ng/mL using a plasma volume of 0.100 mL for moxifloxacin. The methods adhered to the regulatory requirements for selectivity, sensitivity, precision, accuracy, recovery, carryover, matrix effect, and stability. The methods are further described in Supplementary Material 1. A summary of validation results is presented in Supplementary Table S1.

Plasma sample analyses were performed in compliance with GCP regulations.\(^{24}\) Calibration standards, between-day precision and accuracy, as well as quality-control samples within/between-day precision and accuracy data are presented in Supplementary Material 1 for both trazodone and moxifloxacin analyses.

Throughout the experimental phase, the personnel of the bioanalytical laboratory were blinded with respect to the treatment with trazodone and placebo and open with respect to the treatment with moxifloxacin.

**PK Parameters.** The following PK parameters were measured or calculated for trazodone (free base) and moxifloxacin with a noncompartmental analysis, using the validated software Phoenix WinNonlin 6.3 (Certara, Inc, Princeton, New Jersey): peak plasma concentration (C\(_{\text{max}}\)), time to C\(_{\text{max}}\) (t\(_{\text{max}}\)), and area under the concentration-time curve up to 24 hours postdose (AUC\(_{0-24\text{h}}\)), calculated using the linear trapezoidal rule.

**Sample Size**
The sample size for this trial was based on the assessment of noninferiority of trazodone relative to placebo in the primary analysis. Trazodone would be declared to have no influence on QTc if the null hypothesis, that the upper bound of the 2-sided 90%CI of the predicted mean placebo-adjusted change from baseline for QTcF was greater than 10 ms at the observed mean C\(_{\text{max}}\) for trazodone dose, was rejected. The sample size was also justified based on the cohort sizes in the “Results from the IQ-CSRC prospective study support replacement of the thorough QT study by QT assessment in the early clinical phase” trial.\(^{25}\)

The present trial randomized 20 subjects, which more than doubled the number of subjects exposed to the test product in the aforementioned IQ-CSRC trial.

**Statistical Analyses**

Statistical analysis on ECG data and the relevant correlation with treatment plasma concentrations were performed at eResearch Technology (Philadelphia, Pennsylvania) using SAS for Windows software (SAS Institute, Cary, North Carolina) version 9.4.

**Primary Analyses**

**PK-Pharmacodynamic Response Analyses.** All study subjects with matched PK samples and ECG data were included in the analyses. A plasma concentration of 0 was imputed for placebo subject observations unless valid plasma concentration analyses were available.
The PK-pharmacodynamic (PD) relationship between the change from baseline in QTcF and other ECG parameters (HR, PR, and QRS) and plasma concentrations of trazodone was examined using linear mixed-effects modeling and the model proposed in 2017 by Garnett et al26 according to equation 1:

\[ Y_{lkt} = \mu_l + p_t + \theta C_{lkt} + W_k + D_k C_{lkt} + B_{lk} + \varepsilon_{lkt} \]  

where \( \Delta QTc \) (ie, \( Y_{lkt} \) in equation 1) is the dependent variable for the l-th treatment, k-th subject, and t-th time point, and where \( \mu_l \) is the treatment-specific intercept, \( \theta \) is the slope, \( C \) is the concentration ( \( C_{lkt} \) is the concentration at the l-th treatment for the k-th subject at the t-th time point, and \( C_{lkt} \) is the concentration for the k-th subject at the t-th time point), \( W_k \) is the random subject effect on the intercept, \( D_k \) is the random subject effect on the slope, \( p_t \) is the time effect on the intercept, \( B_{lk} \) is the baseline adjustment for the l-th treatment for the k-th subject, and \( \varepsilon_{lkt} \) is the residual error. If the above model (equation 1) did not converge, the same model was refit without the random subject effect on plasma concentration.

This model included plasma concentration, time (categorical), treatment (active versus placebo), and a baseline correction (each baseline value minus the matched mean placebo baseline value), with random subject effects on plasma concentration and the intercept included in the model. The primary end point for this analysis was the change from baseline in QTcF. A negative result (ie, no evidence of a QTc prolongation) would be a model-based upper bound for the 2-sided 90%CI of the predicted mean \( \Delta QTcF \) less than 10 ms at the observed mean \( C_{max} \) for the highest dose of trazodone. This model was used to estimate the placebo-adjusted change from baseline in QTcF intervals (\( \Delta QTcF \), \( \Delta HR \), \( \Delta PR \), and \( \Delta QRS \)), at the mean trazodone \( C_{max} \). The placebo-adjusted change from baseline was calculated by subtracting the predicted QTc for each treatment dose (at its mean \( C_{max} \)) from the predicted QTc for placebo at a concentration of 0 within each replicate (ie, iteration) of the bootstrap methodology (see below). If this model did not converge, then plasma concentration was included as a fixed effect only with subject random effects on the intercept as the random-effect term. A rescaling of concentration was attempted before the removal of plasma concentration from random effect. The placebo-adjusted change from baseline at the mean \( C_{max} \) and its upper 1-sided 95%CI were calculated using the following equation (equation 2):

\[
\text{Mean maximum effect } : \Delta \Delta QTc_{\text{max}} = (\mu_l + \theta C_{\text{max}}) - (u_{\text{placebo}} + \theta C_0)
\]  

The estimate and upper 1-sided 95%CI were obtained from the upper 1-sided 95%CI obtained from the SAS procedure PROC MIXED (using a REML method) at the mean \( C_{max} \). By calculating the placebo-adjusted predicted QTc within each iteration, the correct confidence intervals were calculated using the bootstrap methodology.

Demonstration of assay sensitivity was performed using moxifloxacin plasma concentrations and the same concentration-QTc effect modeling applied to trazodone QTcF analysis. To establish assay sensitivity, the slope of the relationship between the placebo-adjusted change from baseline for QTcF and moxifloxacin concentration should be positive, and the lower limit of the 1-sided 95%CI (ie, 2-sided 90%CI) at the observed mean moxifloxacin \( C_{max} \) should be \( >5 \) ms.

**Secondary Analyses**

**Time-Matched Analyses.** The analysis set for the time-matched analysis was comprised of all subjects who had at least 1 predose baseline ECG with 1 on-treatment postdose ECG (ie, had at least 1 valid change from baseline). The 90%CIs were calculated for descriptive purposes.

**Outlier Analyses.** Outlier analyses for QTcF, HR, PR, and QRS intervals were based on the most extreme values (minimal and maximal) across all times for each subject. The QTcF outlier values included those which were new measurements \( >500 \) ms, \( >480 \) ms, and \( >450 \) ms when the subject’s baseline mean QTcF interval was \( \leq 500, \leq 480, \) and \( \leq 450 \) ms, respectively, and changes from baseline \( >30-60 \) ms or \( >60 \) ms.

A bradycardic outlier was defined as a \( HR < 50 \) bpm and a \( \geq 25\% \) decrease from baseline mean HR. A tachycardic outlier was defined as a \( HR > 100 \) bpm and a \( \geq 25\% \) increase from baseline mean HR. A PR interval outlier was defined as \( >200 \) ms and a \( \geq 25\% \) increase from the baseline mean PR interval. A QRS interval outlier was defined as \( >100 \) ms and a \( \geq 25\% \) increase from the baseline mean QRS interval.

**Morphological Analyses.** Morphological analyses were performed with regard to the ECG waveform interpretation as defined by the central ECG laboratory’s cardiologist. Changes from baseline to on treatment were evaluated. New-onset findings are presented as the percentage of subjects meeting the “new” criteria within each treatment period (“new” means not present on any baseline ECG and becoming present on at least 1...
### Table 1. Plasma Trazodone PK Parameters After Single-Dose Administration of 20 mg, 60 mg, and 140 mg Trazodone 6% Drops and Moxifloxacin 400-mg Tablets

| PK Parameter       | Trazodone 20 mg | Trazodone 60 mg | Trazodone 140 mg | Moxifloxacin 400 mg |
|--------------------|-----------------|-----------------|------------------|---------------------|
| N                  | N = 18          | N = 18          | N = 20           | N = 18              |
| C$_{\text{max}}$ (ng/mL) | 413.4 ± 79.1    | 1269.0 ± 598.2  | 2083.5 ± 600.2   | 2758.3 ± 559.2      |
| t$_{\text{max}}$ (h)  | 0.5 (0.3-1.0)   | 0.5 (0.3-2.0)   | 0.3 (0.2-3.0)    | 1.0 (0.5-4.0)       |
| AUC$_{0-24h}$ (ng · hr/mL) | 2148.2 ± 908.8  | 6236.2 ± 2030.4 | 12827.6 ± 4907.8 | 24665.2 ± 5238.7    |

AUC$_{0-24h}$ indicates area under the curve from time 0 to 24 hours postdose; C$_{\text{max}}$, peak concentration; max, maximum; min, minimum; PK, pharmacokinetics; t$_{\text{max}}$, time to peak concentration. C$_{\text{max}}$ and AUC$_{0-24h}$ values are reported as mean ± SD; t$_{\text{max}}$ as median (min-max).

on-treatment ECG) for the following variables: second-degree heart block, third-degree heart block, atrial fibrillation, atrial flutter, complete right bundle branch block, complete left bundle branch block, ST-segment elevation, ST-segment depression, T-wave abnormalities (negative T waves only), myocardial infarction pattern, and any new abnormal U waves.

### Safety Assessments

The safety profile of the investigational products was assessed in all subjects who received at least 1 dose of study product, by evaluating treatment-emergent adverse events (TEAEs), manual ECG, full physical examinations, laboratory tests, and vital signs (blood pressure and HR) measurement results.

AEs were assessed throughout the study and were coded using MedDRA version 20.0. Any on-therapy ECG with a QTcF $>500$ ms (automatically measured) determined at any time point during safety ECG at the clinical site was to be confirmed by a second ECG taken within 1 hour. If the second repeat safety ECG was confirmed to have a QTcF $>500$ ms, the subject was monitored closely, and repeat safety ECGs were collected until the QTcF had declined below 500 ms. A QTcF value $>500$ ms did not automatically lead to the exclusion of the concerned subject. However, if a QTcF value $>500$ ms and in particular a QTcF change from baseline $>60$ ms was observed, the investigator could decide to withdraw the subject from the study for safety reasons.

### Results

#### Study Population

Twenty subjects (11 women and 9 men), aged 20-49 years and with a body mass index of 22.8 ± 2.1 kg/m$^2$, were randomized in the study, received at least 1 dose of the investigational product, and were included in the safety analyses. Seventeen subjects completed the study per protocol, whereas 3 subjects discontinued the study prematurely, 1 for the occurrence of 2 AEs with trazodone 140 mg (ie, treatment-related QT prolongation and presyncope, see below) and 2 for protocol deviations (intake of prohibited medication for 1 subject and positivity to recreational drug test for the other subject). The number of subjects included in the PK-PD and ECG analyses for each treatment was:

- Trazodone 20 mg, trazodone 60 mg, and moxifloxacin 400 mg: 18 subjects each
- Trazodone 140 mg: 20 subjects
- Placebo: 18 subjects

#### PK-PD Analyses

The PK data of trazodone and moxifloxacin are shown in Table 1. The trazodone PK profile is also visually represented in Figure 1.

Both the rate and extent of trazodone exposure proportionally increased with the dose, as indicated by the mean C$_{\text{max}}$ values (413.4, 1269.0, and 2083.5 ng/mL for 20-mg, 60-mg, and 140-mg trazodone doses, respectively), and the mean AUC$_{0-24h}$ values (2148.2, 6236.2, and 12 827.6 ng·h/mL for the 3 trazodone doses). Median t$_{\text{max}}$ was similar for the 3 doses (0.3-0.5 hours) with ranges of 0.3-1, 0.3-2, and 0.2-3 hours for 20, 60, and 140 mg, respectively.

At 2 hours after placebo administration, 1 subject had a measurable trazodone plasma concentration. For this reason, C$_{\text{max}}$ was calculated also for the placebo group (as mean ± SD of all individual C$_{\text{max}}$ values, where values below the lower limit of quantification were considered as 0) and corresponded to 42.9 ± 182.0 ng/mL.

Assay sensitivity was met because the slope of the relationship between the placebo-adjusted change from baseline for QTcF and moxifloxacin plasma concentration was positive (4.24 ms/[μg/mL]) and the predicted effect of moxifloxacin on placebo-adjusted and baseline-corrected QTcF at the mean C$_{\text{max}}$ was 15.2 ms (2-sided 90%CI 13.6-16.9 ms) (Table 2), with the lower limit of the 2-sided 90%CI at the observed mean C$_{\text{max}}$ above 5 ms. The relationship between the change from baseline in QTcF and trazodone plasma concentration is shown in Figure 2. The slope (SE) of the plasma-concentration effect on placebo-adjusted and baseline-corrected QTcF for trazodone was 9.65 ms/[μg/mL] (SE 1.1094; P-value .000). The overall predicted
Figure 1. Mean trazodone concentration-vs-time profiles after single-dose administration of trazodone HCl 20 mg (T1), 60 mg (T2), and 140 mg (T3) 6% oral drops solution. Linear scale.

Table 2. Placebo-Corrected Change From Baseline Versus Trazodone and Moxifloxacin Plasma Concentration, Predicted From Mean C\textsubscript{max} and QTc Fridericia Interval

| Treatment Dose | Mean C\textsubscript{max} (ng/mL) | Predicted Mean Effect at Mean C\textsubscript{max} (ms) | 95%CI Lower (ms) | 95%CI Upper (ms) |
|----------------|-----------------------------------|------------------------------------------------------|-----------------|------------------|
| Trazodone 20 mg| 413.4                             | 4.5                                                  | 3.7             | 5.3              |
| Trazodone 60 mg| 1269.0                            | 12.3                                                 | 11.0            | 13.6             |
| Trazodone 140 mg| 2083.5                           | 19.8                                                 | 17.6            | 22.1             |
| Moxifloxacin 400 mg| 2758.3                          | 15.2                                                 | 13.6            | 16.9             |

CI indicates 1-sided 95% limit based on bootstrap methods using percentile confidence intervals of 1000 replicates; C\textsubscript{max}, peak concentration.

---

placebo-adjusted and baseline QTcF corrected value at mean C\textsubscript{max} was approximately 4.5 ms (2-sided 90%CI upper limit 5.3 ms) for the 20-mg dose, 12.3 ms (2-sided 90%CI upper limit 13.6 ms) for the 60-mg dose, and 19.8 ms (2-sided 90%CI upper limit 22.1 ms) for the 140-mg dose (Table 2).

Figure 2. QTcF change from baseline vs trazodone plasma concentrations. Prediction lines are based on model estimates using concentration, treatment (active/placebo), times, and a baseline adjustment. QTcF indicates Fridericia-corrected QT interval.

The PK-PD analysis results also showed that trazodone did not have a clinically significant effect on HR, PR interval, or QRS duration. In detail, the slope for the relationship between HR change from baseline and trazodone plasma concentrations corresponded to 2.199 (SE 0.8013), and the overall predicted
placebo-adjusted and baseline HR corrected value at mean $C_{\text{max}}$ was 1.45 bpm (1-sided 95%CI 0.9-2.1) for the 20-mg dose, 2.12 bpm (1-sided 95%CI 1.3-3.0) for the 60-mg dose, and 2.76 bpm (1-sided 95%CI 1.2-4.4) for the 140-mg dose.

The PK-PD analysis demonstrated that the slope of the relationship between PR change from baseline and trazodone was negative (slope = -3.6040), and the overall predicted placebo-adjusted and baseline-corrected value for the 140-mg dose at predicted $C_{\text{max}}$ was -7.4 ms (1-sided 95%CI -9.3 to 5.4). The slope for the relationship between QRS change from baseline and trazodone plasma concentrations was flat (slope = 0.0445), and the overall predicted placebo-adjusted and baseline-corrected value for the 140-mg dose at predicted $C_{\text{max}}$ was 0.115 ms (1-sided 95%CI 0.115-0.70).

**Time-Matched Analyses: QTcF**

The time-matched analyses for the QTcF end point revealed that the moxifloxacin treatment met the assay sensitivity criteria with 3 of the 4 predefined time points having a lower confidence bound $\geq$ 5 ms, with the typical moxifloxacin profile.

Figure 3 details the placebo-adjusted change from baseline in QTcF values (means $\pm$ 90% CIs) for each time point. Multiple trazodone time points from 0.33 to 12.0 hours postdose demonstrated an upper bound that exceeded 10 ms. The highest QTcF placebo-adjusted change from baseline was 7.0 ms (upper CI limit 12.8 ms) at 0.75 hour postdose for the 20-mg dose, 16.9 ms (upper CI limit 21.3 ms) at 0.75 hour postdose for the 60-mg dose, and 24.5 ms (upper CI limit 28.7 ms) at 1 hour postdose for the 140-mg dose (Table 3).

Placebo-adjusted changes from baseline data (means $\pm$ 90% CIs) for HR, showing that trazodone did not have a clinically significant effect on this parameter, are presented in Figure 4.

**Outlier Analyses**

No subjects met the specific outlier criteria (Table 4). Two subjects in the 140-mg dose group had a QTcF value $>480$ ms, not present at baseline. One subject in the trazodone 60-mg dose group, 6 subjects in the trazodone 140-mg dose group, and 2 subjects in the moxifloxacin dose group met the nonspecific outlier criterion, ie, a QTcF $>30$-60 ms change from baseline.

Results also showed that trazodone does not have a clinically significant effect on HR, PR, or QRS interval. One subject in the trazodone 140-mg dose group met the bradycardic outlier criteria, whereas 4 subjects in the 60-mg dose group, 2 in the trazodone 140-mg dose group, and 1 in the moxifloxacin dose group met the tachycardic outlier criteria. In addition, 1 subject each in the trazodone 20-mg and 140-mg dose groups met the PR outlier criteria. These findings were regarded by the study cardiologist as having no clinical significance. No subjects met the QRS outlier criteria.
Table 3. Time-Matched Analysis Results for Placebo-Adjusted Change From Baseline QTcF

| Time (h) | Trazodone 20 mg (N = 16) | Trazodone 60 mg (N = 16) | Trazodone 140 mg (N = 18) | Moxifloxacin 400 mg (N = 17) |
|----------|-------------------------|-------------------------|--------------------------|-----------------------------|
| 0.0833   | –3.3 (–7.8 to 1.1)      | –2.3 (–6.7 to 2.1)      | 0.8 (–2.7 to 4.4)        | 2.5 (–1.9 to 7.0)           |
| 0.1666   | –1.2 (–6.2 to 3.8)      | 0.3 (–4.1 to 4.6)       | 0.5 (–3.0 to 4.0)        | 1.6 (–1.9 to 5.0)           |
| 0.3333   | –0.2 (–5.4 to 5.0)      | 4.8 (–0.4 to 10.0)      | 11.6 (7.8–15.5)          | 1.0 (–3.5 to 5.5)           |
| 0.5      | 2.1 (–0.3 to 4.6)       | 11.9 (8.6–15.3)         | 20.2 (16.4–23.9)         | 6.7 (2.6–10.8)              |
| 0.75     | 7.0 (1.2–12.8)          | 16.9 (–12.6 to 21.3)    | 21.4 (16.3–26.5)         | 13.0 (8.8–17.2)             |
| 1        | 6.6 (1.5–11.7)          | 11.4 (–6.3 to 16.5)     | 24.5 (20.3–28.7)         | 11.9 (8.3–15.6)             |
| 1.5      | 5.0 (0.6–9.5)           | 14.4 (–10.0 to 18.8)    | 19.6 (15.3–24.0)         | 12.2 (7.5–16.9)             |
| 2        | 3.5 (0.5–6.5)           | 8.8 (4.2–13.4)          | 17.1 (13.4–20.8)         | 14.5 (9.7–19.4)             |
| 3        | 1.7 (–2.7 to 6.1)       | 6.1 (1.9–10.2)          | 14.5 (7.6–21.5)          | 13.9 (8.9–19.0)             |
| 4        | 3.2 (–2.3 to 8.6)       | 7.9 (4.3–11.5)          | 12.8 (8.5–17.1)          | 15.0 (10.3–19.7)            |
| 6        | 0.2 (–4.8 to 4.3)       | 2.2 (–1.8 to 6.2)       | 6.7 (2.3–11.2)           | 9.1 (5.0–13.2)              |
| 8        | 1.2 (–2.3 to 4.6)       | –0.4 (–3.4 to 2.7)      | 5.8 (0.9–10.7)           | 10.1 (6.6–13.7)             |
| 12       | 0.6 (–4.7 to 5.8)       | 6.4 (1.7–11.0)          | 7.9 (4.3–11.6)           | 10.0 (5.4–14.7)             |
| 16       | –3.3 (–6.9 to 0.3)      | –1.4 (–5.6 to 2.7)      | –0.7 (–5.2 to 3.8)       | 8.6 (4.6–12.6)              |
| 24       | 1.8 (–3.5 to 7.1)       | 2.0 (–3.0 to 6.9)       | 1.7 (–1.4 to 4.8)        | 7.1 (3.6–10.6)              |

QTcF indicates Fridericia-corrected QT interval. CIs are not model-based estimates. CIs are 2-sided 90% (ie, 1-sided 95%).

Figure 4. Placebo-adjusted mean change in heart rate from baseline values (means ± 90%CIs).

Morphological Changes
One subject in each of the trazodone 60-mg, moxifloxacin, and placebo dose groups developed new ST-segment depression change. One subject each in the trazodone 20-mg, moxifloxacin, and placebo dose groups developed new T-wave inversion. These ST and T-wave changes were nonspecific, and none of the ECGs with ST depression or T-wave inversion was suggestive of myocardial ischemia. No other morphological changes were observed (Table 4).

Safety
Overall, 58 TEAEs were experienced by 95% of the subjects. Fifty-seven of the reported AEs were deemed related to the study treatment.

Somnolence was experienced at an increased frequency with increased trazodone dose (44.4, 50.0, and 85.0% of subjects, respectively, with 20-, 60-, and 140-mg trazodone). Dizziness events also increased with trazodone dose (0, 5.6%, and 15% of subjects with the 3 ascending doses), whereas nausea, presyncope,
Table 4. Outlier and Morphological Analyses

| Parameter | Trazodone 20 mg (n = 18) | Trazodone 60 mg (n = 18) | Trazodone 140 mg (n = 20) | Moxifloxacin 400 mg (n = 18) | Placebo (n = 18) |
|-----------|-------------------------|-------------------------|--------------------------|-----------------------------|-----------------|
| QTcF      |                         |                         |                          |                             |                 |
| New >500 ms, n (%) | 0                      | 0                       | 0                        | 0                           | 0               |
| New >480 ms, n (%) | 0                      | 0                       | 2 (10)                   | 0                           | 0               |
| >30-60 ms inc, n (%) | 0                      | 1 (6)                   | 6 (30)                   | 2 (11)                      | 0               |
| >60 ms inc, n (%) | 0                      | 0                       | 0                        | 0                           | 0               |
| Heart rate |                         |                         |                          |                             |                 |
| Tachycardic outliers, n (%) | 0                      | 1 (6)                   | 2 (10)                   | 1 (6)                      | 0               |
| Bradycardic outliers, n (%) | 0                      | 0                       | 1 (5)                    | 0                           | 0               |
| PR interval |                         |                         |                          |                             |                 |
| Outliers, n (%) | 1 (6)                   | 0                       | 1 (5)                    | 0                           | 0               |
| QR5 interval |                         |                         |                          |                             |                 |
| Outliers, n (%) | 0                      | 0                       | 0                        | 0                           | 0               |
| Morphological changes |                         |                         |                          |                             |                 |
| New atrial fibrillation, n (%) | 0                      | 0                       | 0                        | 0                           | 0               |
| New atrial flutter, n (%) | 0                      | 0                       | 0                        | 0                           | 0               |
| New abnormal U waves, n (%) | 0                      | 0                       | 0                        | 0                           | 0               |
| New ST-segment depression changes, n (%) | 0                      | 1 (6)                   | 0                        | 1 (6)                      | 1 (6)           |
| New ST-segment elevation changes, n (%) | 0                      | 0                       | 0                        | 0                           | 0               |
| New T-wave inversion, n (%) | 1 (6)                   | 0                       | 0                        | 1 (6)                      | 1 (6)           |
| New second-degree heart block, n (%) | 0                      | 0                       | 0                        | 0                           | 0               |
| New third-degree heart block, n (%) | 0                      | 0                       | 0                        | 0                           | 0               |
| New complete RBBB, n (%) | 0                      | 0                       | 0                        | 0                           | 0               |
| New complete LBBB, n (%) | 0                      | 0                       | 0                        | 0                           | 0               |
| New MI, n (%) | 0                      | 0                       | 0                        | 0                           | 0               |

inc indicates inclusive; LBBB, left bundle branch block; MI, myocardial infarction; “new,” not present at baseline and only seen after baseline; QTcF, Fridericia correction to QT; RBBB, right bundle branch block.

headache, and vomiting were only experienced with trazodone 140 mg at a frequency of 20%, 15%, and 10%, respectively. With the highest trazodone dose, treatment-related abdominal discomfort, hypertension, hypotension, palpitations, and ECG QT prolongation were reported for 1 subject (5%) each.

One subject (5.6%) suffered from somnolence after receiving moxifloxacin 400 mg. Another subject experienced 2 TEAEs related to trazodone 140 mg (ie, ECG QT prolongation and presyncope) and was discontinued from the study. The same subject also suffered from somnolence and hypotension. No other clinically significant change in ECG parameters, vital signs, or laboratory tests results was observed.

Discussion

The PK-PD model analyses based on the most recent Garnett et al publication showed a positive relationship between QTc and trazodone plasma concentrations, indicating a modest effect of trazodone on cardiac repolarization: no effect was present at the 20-mg dose, but a QT prolongation exceeding the limits set in the E14 guidelines was observed starting at 60 mg (QTcF 12.3 ms) and increased at the 140-mg dose (QTcF 19.8 ms).

The PK-PD analyses results were consistent with the observed results in the time-matched analysis, which showed a mild/moderate increase in the QTcF interval >10 ms between 30 minutes and 1.5 hours postdose for the 60-mg dose and between 15 minutes and 4 hours postdose for the 140-mg dose. For comparison, a similar increase was observed for moxifloxacin between 45 minutes and 4 hours postdose.

It should be noted that there is general consensus in classifying an effect between 10 and 20 ms as uncertain.

In a previous study published in 1982, QT prolongation was consistently above 20 ms starting from 30 minutes after trazodone 90-mg oral administration. The study, however, was not controlled, and the effect was evaluated on (not placebo-adjusted) QTcB. The design of the present study followed the current established guidelines for the clinical evaluation of QT/QTc interval and included a positive control, a placebo control, appropriate blinding, and randomization. The sensitivity of the assay to detect small increases in QT was established, with the data demonstrating the expected small change in the QTc interval following moxifloxacin administration, consistent with the results of the observed QTcF measurements in the trial as well as with already published data.
The primary analysis of the study was based on QTcF, the correction of the QT interval for HR using the Fridericia formula, according to the recommendations of the ICH E14 Q&A (R3). QT-interval prolongation, which according to European Society of Cardiology guidelines is defined as a QT interval >470 ms in women and >450 ms in men, is associated with a higher risk of polymorphic ventricular tachycardia or torsade de pointes (TdP), which may ultimately lead to sudden cardiac death. As also reported by Thind et al, the degree of QT prolongation of a single drug should be considered in the larger picture of other proarrhythmic factors. Several risk factors are associated with an increased risk for QT-interval prolongation, eg, hypokalemia, renal impairment, use of diuretics, other QTc-prolonging drugs including several classes of antidepressants, and unmodifiable risk factors such as age >65 years and female gender. In particular, combining QTc-prolonging drugs (drug-drug interaction) may increase the risk of QT prolongation or TdP. A recent systematic review, which analyzed the cardiac safety of drugs known to affect the QT interval in 14,756 patients, showed that the frequency of ventricular arrhythmias, TdP, and sudden cardiac deaths was 2.6%, 0.33%, and 0.03%, respectively, and the risk of developing arrhythmias was higher with the concomitant use of multiple QT-prolonging drugs.

It is estimated that depression affects approximately 21.5% of heart failure patients, is associated with increased hospitalization and mortality rates, and may decrease patient adherence to treatment plan. In addition, depressed patients are at increased risk of cardiovascular diseases and death. Specific preferred treatment for depression in patients with cardiac disease has been established, and conflicting information has been reported in the literature. Among the AEs that were observed, orthostatic hypotension was more common with tricyclic antidepressants (TCAs), trazodone, and monoamine oxidase inhibitors (MAOIs) and hypertension more common with serotonin norepinephrine reuptake inhibitors (SNRIs) and MAOIs. The potential for QT prolongation was reported with TCAs, specific serotonin reuptake inhibitors, SNRIs, and mirtazapine. Due to the increased mortality associated with comorbid cardiovascular disease and depression, the authors recommend that the choice of antidepressant should take into account the potential impact of the various agents, balancing safety and efficacy.

Although trazodone is considered to have a favorable cardiovascular safety profile, at clinically relevant plasma concentrations in vitro it demonstrates potent dose-dependent inhibition of human ether-a-go-go–related gene potassium channels, which correlates with prolongation of QT. QTC prolongation on ECG is a risk marker for the potentially fatal arrhythmia TdP and can be caused by a wide range of medications, including psychotropic agents. In addition to polypharmacy, older adults are at increased risk of QTc prolongation owing to advanced age and medical comorbidities such as cardiovascular disease and electrolyte disturbances.

It is to be noted that development of TdP with trazodone has been reported mainly in the presence of additional risk factors or overdose in older adults. In the study by Armstrong et al, the association between trazodone and QTc was studied in a large geriatric health care center (Baycrest, University of Toronto, Toronto, Ontario, Canada) on nursing home and rehabilitation patients taking additional psychotropic medication (58%) and nonpsychotropic QT-prolonging medication (63%), by reviewing electronic health records (Meditech, search medical orders for trazodone and ECG terms) over a 7-year period (April 2008 to July 2015). This retrospective review did not find an association between trazodone and QTc interval or increased risk of sudden cardiac death. Regression analyses showed no significant association between trazodone and QTc interval (adjusted $\beta = 0.03$, $P$-value = .64). Male gender was significantly associated with QTc in univariable ($\beta = 16.31$, $P$-value = .03) but not multivariable analyses, whereas no other covariates were statistically significant. The current findings of a lack of association between trazodone and QTc are in line with a previous negative finding in a population-based study of antidepressant use, although the sample included only 3 trazodone users over the age of 55 years.

Trazodone may be associated with prolongation of the corrected QT interval (QTc) and TdP at toxic plasma concentrations (pharmacovigilance data report cases of overdose and De Meester et al). Trazodone has minimal anticholinergic activity, but the risk of orthostatic hypotension has been reported, especially in elderly patients or in patients with pre-existing heart disease. At therapeutic doses, sporadic cases of life-threatening cardiac arrhythmias, including a case of ventricular tachycardia, a case of complete AV block, and 2 cases of prolonged PQ interval, have been reported. The results of this ECG study, however, did not show any clear signal of an effect of trazodone on HR, AV conduction as measured by the PR interval, or cardiac depolarization as measured by the QRS duration. There were no new clinically relevant morphological changes demonstrating a signal of concern.

Concerning the risk of higher QTc prolongation that could be expected in patients with impaired clearance of the drug and therefore higher mean $C_{max}$ levels, no
data are available so far indicating a proper adjustment of the dose and therefore careful dosing and regular monitoring must be adopted in patients with hepatic or renal impairment.

Trazodone is primarily metabolized by CYP3A4. For this reason potent CYP3A4 inhibitors may lead to increases in trazodone plasma levels with potential for increased adverse events related to increased exposure. If trazodone is used with a potent CYP3A4 inhibitor, a lower trazodone dose should be considered. Also, concomitant use of trazodone at therapeutic doses with drugs known to prolong the QT interval may increase the risk of ventricular arrhythmias. The use of trazodone should thus be avoided in patients with known QT prolongation or in combination with other drugs that are inhibitors of CYP3A4 (eg, itraconazole, clarithromycin, and voriconazole), or known to prolong QT interval, including Class 1A antiarrhythmics (eg, quinidine and procainamide) or Class 3 antiarrhythmics (eg, amiodarone and sotalol), certain antipsychotic medications (eg, ziprasidone, chlorpromazine, and thioridazine) and certain antibiotics (eg, gemifloxacin).

In a single-dose, blinded, 4-way crossover study, 10 healthy volunteers received 50 mg of trazodone HCl or matching placebo concurrent with a low dose of the potent CYP3A4 inhibitor ritonavir (4 doses of 200 mg each) or placebo. Compared with the control conditions, ritonavir significantly reduced apparent oral clearance of trazodone (155 ± 23 versus 75 ± 12 mL/min, \( P < .001 \)), prolonged elimination half-life (6.7 ± 0.7 versus 14.9 ± 3.9 hours, \( P < .05 \)), and increased peak plasma concentrations (842 ± 64 versus 1125 ± 111 ng/mL, \( P < .05 \) (mean ± SE)). In addition to a warning about drug-drug interactions between trazodone and CYP3A4 inhibitors or QT-prolonging drugs, caution is also needed in patients with hepatic impairment.

Trazodone (75 mg/day) PK was evaluated in patients with mixed neuroses and normal or impaired renal function. Although higher blood concentrations of trazodone were observed in patients with renal impairment, compared with those with normal renal function, these differences were not statistically significant.

Specific studies in patients suffering from hepatic or renal impairment to allow determination of appropriate adjustment of dose regimens have not been performed so far. Given the overall available data on trazodone PK and safety profile, trazodone product labeling advises careful dosing and regular monitoring in patients with hepatic and renal impairment, particularly in severe cases, although no dose adjustment is necessary for mild to moderate renal impairment.

The PK profile of trazodone is well established following administration of different single and multiple doses in healthy volunteers, obtained from products endowed with different release rates and higher strengths than those tested in the current study. Trazodone exhibits a linear PK whatever the dose regimen and release rate from the finished product. Therefore, plasma concentrations of trazodone are easily predictable from single-dose data.

The results of the current study confirmed the proportional increase of trazodone \( C_{\text{max}} \) with the dose, as indicated by the mean values of 413.4, 1269.0, and 2083.5 ng/mL for the 20-mg, 60-mg, and 140-mg trazodone doses, respectively. It is worth mentioning that the study was conducted in fasting conditions to increase the \( C_{\text{max}} \), thus assessing the effect on QTc prolongation in the worst case scenario.

With all the above considerations taken into account, mean \( C_{\text{max}} \) levels that can be expected with the recommended daily doses of 100 mg to 600 mg and the relevant predicted QTc effect at these levels could potentially be extrapolated using the plasma concentration–QTc analysis from this study. However, this extrapolation was not performed in the present study, which was aimed at investigating the effect of trazodone on QTc prolongation at very low doses, currently applied off-label for indications such as insomnia, in order to establish a no-effect dose-related plasma concentration.

Trazodone at the study doses was well tolerated, and the reported safety data were consistent with the known trazodone safety profile.

No serious or severe AEs occurred during the study. Overall, the AEs observed were consistent with those observed during trazodone therapy, with the most common being somnolence (drowsiness), which occurred at a greater frequency with the highest studied trazodone dose. It is known that the incidence of side effects present at the start of the therapy for major depressive disorder, with doses of 100-600 mg/day depending on the therapy setting, normally decreases on continued treatment. There were no safety concerns with respect to the laboratory or vital-signs assessments.

**Conclusions**

In conclusion, this well-conducted and valid (assay sensitivity confirmed) dedicated ECG trial demonstrated that trazodone had no effects on HR, PR, and QRS interval duration or other ECG morphologic parameters. There was a modest, dose-dependent effect on cardiac repolarization as evidenced by the concentration-dependent effect on QTc in the PK-PD analysis, with no QTc prolongation observed at the lowest 20-mg trazodone dose and an effect exceeding
the values set in the E14 guideline with the 60- and 140-mg doses. This effect may even be smaller in clinical practice because summary of product characteristics instructions recommend that trazodone drops are administered in fed conditions in order to have lower peak plasma concentrations. The effect on cardiac repolarization (QTc) is unlikely to represent a clinical risk for ventricular proarrhythmia, but caution should be used in patients with concomitant use of other medications that are known to prolong QT or to increase trazodone exposure.

Acknowledgments
We would like to gratefully acknowledge CROSS Research SA (Mendrisio, Switzerland) for study coordination, PK, demography, and safety analyses; Pharma Medica Research Inc (Mississauga, Ontario, Canada) for bioanalyses; and eResearch Technology, Inc (Philadelphia, Pennsylvania) for ECG analyses.

Conflicts of Interest
V.T., R.P., M.T.R., P.D., A.D.V., A.C., and F.C. are employees of Angelini SpA, Pomezia, Italy; C.L. and M.R. are employees of Cross Research SA, Arzo, Switzerland. Cross Research SA was contracted by Angelini SpA as Clinical Research Organization for the conduct of this study and received financial support for its services. The authors declare that they have no other relationships or activities that could appear to have influenced the submitted work.

Funding
This study was funded by Angelini SpA, Pomezia, Italy.

Data Accessibility
The study has been registered in clinicaltrials.gov (NCT03516630). For data access please contact Valeria Tellone at valeria.tellone@angelinipharma.com.

References
1. Fagioliini A, Comandini A, Catena Dell’Osso M, et al. Rediscovering trazodone for the treatment of major depressive disorder. CNS Drugs. 2012;26(12):1033-1049.
2. Roth BL, Shapiro DA. Insights into the structure and function of 5-HT(2) family serotonin receptors reveal novel strategies for therapeutic target development. Expert Opin Ther Targets. 2001;5(6):685-695.
3. Stahl SM. Mechanism of action of trazodone: a multifunctional drug. CNS Spectr. 2009;14(10):536-546.
4. Haria M, Fitton A, Mc Tavish D. Trazodone. A review of its pharmacology, therapeutic use in depression and therapeutic potential in other disorders. Drugs Aging. 1994;4(4):331-335.
5. Karhu D, Groomewond G, Potgieter MA, Mould DR. Dose proportionality of once-daily trazodone extended-release caplets under fasting conditions. J Clin Pharmacol. 2010;50(12):1438-1449.
6. Nilsen OG, Dale O, Husebo B. Pharmacokinetics of trazodone during multiple dosing to psychiatric patients. Pharmacol Toxicol. 1993;72(4-5):286-289.
7. Feighner JP, Boyer WF. Overview of USA controlled trials of trazodone in clinical depression. Psychopharmacology. 1988;95:550-553.
8. Trazodone 75 and 150 mg Tablets. Summary of the product characteristics. https://www.medicines.org.uk/emc/product/4202/smpc. Accessed on July 2, 2019.
9. Trittico: Scheda Tecnica e Prescrivibilità. https://www.torrinomedica.it/schede-farmaci/trittico. Accessed on July 2, 2019.
10. [No authors listed.] Oleptro (trazodone hydrochloride) extended-release tablets. P T. 2011;36(2):2-18.
11. Trazodone Hydrochloride 50mg/5ml Oral Solution. Summary of product characteristics. https://www.medicines.org.uk/emc/product/4202/smpc. Accessed on July 2, 2019.
12. Thase ME. Evaluating antidepressant therapies: remission as the optimal outcome. J Clin Psychiatry. 2003;64(Suppl 13):18-25.
13. Kasper S, Olivieri L, di Loreto G, Dionisio P. Comparison between trazodone and paroxetine for the treatment of major depressive disorder. Curr Med Res Opin. 2005;21(8):1139-1146.
14. Munizza C, Olivieri L, Di Loreto G, Dionisio P. A comparative, randomised, double-blind study of trazodone prolonged-release and sertraline in the treatment of major depressive disorders. Curr Med Res Opin. 2006;22(6):1703-1713.
15. Nutt D, Wilson S, Paterson L. Sleep disorders as core symptoms of depression. Dialogues Clin Neurosci. 2008;10(3):329-336.
16. Walsh KW, Erman M, Erwin CW, et al. Subjective hypnotic efficacy of trazodone and zolpidem in DSMIII-R primary insomnia. Hum Psychopharmacol Clin Exp. 1998;13:191-198.
17. Roth AJ, McCall WV, Liguori A. Cognitive, psychomotor, and polysomnographic effects of trazodone in primary insomnias. J Sleep Res. 2011;20(4):552-558.
18. Camargos EF, Louzada LL, Quintas JL, Naves JO, Louzada FM, Nóbrega OT. Trazodone improves sleep parameters in Alzheimer disease patients: a randomized, doubleblind, and placebo-controlled study. Am J Geriatr Psychiatry. 2014;22(12):1565-1574.
19. ICH Guideline E14 (R3): Clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs—questions and answers. EMA/CHMP/IHC/310133. January 25, 2016.
20. ICH Topic E14. The clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. CHMP/I/204. November 2005.
21. FDA Guidance for Industry. E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. October 2005.
22. Guideline on bioanalytical method validation. EMEA/CHMP/ EWP/192217/2009 Rev.1 Corr.* 21JUL2011. https://www.ema. europa.eu/documents/scientific-guideline/guideline-bioanalytical method-validation_en.pdf. Accessed January 23, 2019.
23. Guidance for Industry: Bioanalytical method validation. US Department of Health and Human Services Food and Drug Administration. May 2001. https://www.fda.gov/downloads/drugs/guidancecompliance-regulatoryinformation/bioanalyticalmethods/bioanalyticalmethods心中的.pdf. Accessed January 23, 2019.
24. Reflection Paper for Laboratories that perform the analysis or evaluation of clinical trial samples. European Medicines Agency EMA/INS/GCP/532137/2010(28 February 2012.
25. Darpo B, Benson C, Dota C, et al. Results from the IQ-CSR prospective study support replacement of the thorough QT study by QT assessment in the early clinical phase. Clin Pharmacol Ther. 2015;97(4):326-335.
26. Garnett C, Bonate PL, Dang Q, et al. Scientific white paper on concentration-QTc modeling. *J Pharmacokinet Pharmacodyn.* 2018;45(3):383-397.

27. Morganroth J. Cardiac repolarization and the safety of new drugs defined by electrocardiography. *Clin Pharmacol Ther.* 2007;81(1):108-113.

28. Burgess CD, Hames TK, George CF. The electrocardiographic and anticholinergic effects of trazodone and imipramine in man. *Eur J Clin Pharmacol.* 1982;22(5):417-421.

29. Florian JA, Tornoe CW, Brundage R, Parekh A, Garnett CE. Population pharmacokinetic and concentration-QTc models for moxifloxacin: pooled analysis of 20 thorough QT studies. *J Clin Pharmacol.* 2011;51:1152-1162.

30. Morganroth J, Wang Y, Thorn M, et al. Moxifloxacin-induced QTc interval prolongations in healthy male Japanese and Caucasian volunteers: a direct comparison in a thorough QT study. *Br J Clin Pharmacol.* 2015;80(3):446-445.

31. Priori SG, Blomström-Lundqvist C, Mazzanti A, et al. 2015 ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: the Task Force for the Management of Patients With Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). *Eur Heart J.* 2015;36(41):2793-2867.

32. Strauss SM, Strukenboom MC, Bleumink GS, et al. Non-cardiac QTc-prolonging drugs and the risk of sudden cardiac death. *Eur Heart J.* 2005;26(19):2007-2012.

33. Thind M, Rodriguez I, Kosari S, Turner JR. How to prescribe drugs with an identified proarrhythmic liability. *J Clin Pharmacol.* 2020;60(3):284-294.

34. Duan J, Tao J, Zhai M, et al. Anticancer drugs-related QTc prolongation, torsade de pointes and sudden death: current evidence and future research perspectives. *OncoTarget.* 2018;9(39):25738-25749.

35. Arunachalam K, Lakshmanan S, Maan A, Kumar N, Dominic P. Impact of drug induced long QT syndrome: a systematic review. *J Clin Med Res.* 2018;10(5):384-390.

36. Marashdeh RAM, Parsons R, Sim TF. Antidepressant prescribing patterns in heart failure patients at residential aged care facilities in Australia: a cross-sectional study. *J Res Pharm Pract.* 2019;8(2):69-74.

37. Teply RM, Parke SW, White ND, Hilleman DE, Dinicolantonio JJ. Treatment of depression in patients with concomitant cardiac disease. *Prog Cardiac Dis.* 2016;58:514-528.

38. Armstrong SM, Brown HK, Shorey C, et al. No association between trazodone and corrected-QT prolongation in older adults. *J Clin Psychopharmacol.* 2019;39(5):528-530.

39. Lee S, Lee HA, Kim SJ, Kim KS. Cellular mechanisms for trazodone-induced cardiotoxicity. *Hum Exp Toxicol.* 2016;35:501-510.

40. Rodríguez-Menchaca AA, Ferrer T, Navarro-Polanco RA, Sanchez-Chapula JA, Moreno-Galindo EG. Impact of the whole-cell patch-clamp configuration on the pharmacological assessment of the hERG channel: trazodone as a case example. *J Pharmacol Toxicol Methods.* 2014;69:237-244.

41. Ziton E, Kiesecker C, Scholz E, et al. Inhibition of cardiac HERG potassium channels by the atypical antidepressant trazodone. *Nanwyn Schmiedebergs Arch Pharmacol.* 2004;370:146-156.

42. Beach SR, Kostis WJ, Celano CM, et al. Meta-analysis of selective serotonin reuptake inhibitor-associated QTc prolongation. *J Clin Psychiatry.* 2014;75:e441-e449.

43. Vandael E, Vandenberk B, Vandenbergh J, Willems R, Foulon V. Risk factors for QTc-prolongation: systematic review of the evidence. *Int J Clin Pharm.* 2017;39:16-25.

44. van Noord C, Straus SM, Strukenboom MC, et al. Psychotropic drugs associated with corrected QT interval prolongation. *J Clin Psychopharmacol.* 2009;29:9-15.

45. De Meester A, Carbutti G, Gabriel L, Jacques JM. Fatal overdose with trazodone: case report and literature review. *Acta Clin Belg.* 2001;56(4):258-261.

46. American Psychiatric Association. *Clinical Practice Guidelines for the Treatment of Patients With Major Depressive Disorder, Third Edition.* https://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/mdd.pdf. Published 2010. Accessed May 20, 2020.

47. Aronson MD, Hafez H. A case of trazodone-induced tachycardia. *J Clin Psychiatry.* 1986;47(7):388-389.

48. Rausch JL, Pavlinac DM, Newman PE. Complete heart block following a single dose of trazodone. *Am J Psychiatry.* 1984;141(11):1472-1473.

49. Winkler D, Ortmann T, Pjrek E, Aschauer H, Kasper S. Trazodone-induced cardiac arrhythmias: a report of two cases. *Hum Psychopharmacol.* 2006;21(1):61-62.

50. Rotzinger S, Fang J, Baker GB. Trazodone is metabolized to m-chlorophenylpiperazine by CYP3A4 from human sources. *Drug Metab Dispos.* 1998;26:572-575.

51. Zalma A, von Moltke LL, Grandia BW, Harmatz JS, Shader RI, Greenblatt DJ. In vitro metabolism of trazodone by CYP3A: inhibition by ketoconazole and human immunodeficiency viral protease inhibitors. *Biol Psychiatry.* 2000;47:655-661.

52. Greenblatt DJ, Harmatz JS. Ritonavir is the best alternative to ketoconazole as an index inhibitor of cytochrome P450-3A in drug-drug interaction studies. *Br J Clin Pharmacol.* 2015;80(3):342-350.

53. Greenblatt DJ, von Moltke LL, Harmatz JS, et al. Short-term exposure to low-dose ritonavir impairs clearance and enhances adverse effects of trazodone. *J Clin Pharmacol.* 2003;43(4):414-422.

54. Catanese B, Dionisio A, Barillari G, De Martino C. A comparative study of trazodone serum concentrations in patients with normal or impaired renal function. *Boll Chim Farm.* 1978;117(7):424-427.

55. Cuomo A, Ballerini A, Brunì AC, et al. Clinical guidance for the use of trazodone in major depressive disorder and concomitant conditions: pharmacology and clinical practice. *Riv Psichiatr.* 2019;54(4):137-149.

56. Karhu D, Groenewoud G, Potgieter MA, Mould DR. Dose proportionality of once-daily trazodone extended-release caplets under fasting conditions. *J Clin Pharmacol.* 2010;50(12):1438-1449.

57. Otani K, Mihara K, Yasui N, et al. Plasma concentrations of trazodone. *Biochem Pharmacol.* 1984;33:1449-1452.

Supplemental Information

Additional supplemental information can be found by clicking the Supplements link in the PDF toolbar or the Supplemental Information section at the end of web-based version of this article.