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# Absence of QTc Prolongation with Domperidone: A Randomized, Double-Blind, Placebo- and Positive-Controlled Thorough QT/QTc Study in Healthy Volunteers

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## Abstract

Domperidone effects on QTc duration were assessed in a single-center, double-blind, four-way crossover study of 44 healthy participants randomized to one of four treatment sequences consisting of four treatment periods separated by 4–9 days washout. On Day 1 of each 4-day period, participants began oral domperidone 10 or 20 mg q.i.d., matching placebo q.i.d., or single-dose moxifloxacin 400 mg (positive control)/placebo q.i.d. In each period, triplicate 12-lead electrocardiograms were recorded at baseline (30, 20, and 10 minutes predose), 8 timepoints after dosing on Days 1 and 4, and predose on Day 4. In mixed effects models, the largest difference for domperidone in least squares means for change from baseline QTcP versus placebo was 3.4 milliseconds (20 mg q.i.d., Day 4), 90% CI: 1.0–5.9, and $<$10 milliseconds at all timepoints for both domperidone dosages. Moxifloxacin response confirmed assay sensitivity. Participants achieved expected domperidone plasma exposures. No significant exposure-response relationship was found for QTc increase per ng/mL domperidone (90% CI of the slope estimate included zero at mean $C_{max}$ on Day 1 or Day 4). In summary, domperidone at doses up to 80 mg/day did not cause clinically relevant QTc interval prolongation.

## Keywords

domperidone, QTc, cardiac safety

Domperidone, a peripheral dopamine receptor antagonist with gastrokinetic and anti-emetic properties,[1] has been marketed for over 35 years in more than 100 countries for the relief of nausea and vomiting symptoms, epigastric sense of fullness, upper abdominal discomfort, and regurgitation of gastric contents in adults, and for the relief of nausea and vomiting symptoms in children. The highest dose approved globally for prescription use in adults is 20 mg up to four times daily (q.i.d.), that is, up to 80 mg/day.[2]

Non-clinical data, clinical studies, and post-marketing safety case reports have suggested that domperidone at very high concentrations (e.g., following high doses administered intravenously [IV] via bolus injection or rapid infusion) has a propensity to prolong the QT interval and result in cardiac conduction adverse events.[3] Nonetheless, a large cardiovascular safety margin of domperidone was confirmed in a comprehensive range of non-clinical studies and an "Integrated Risk Assessment" per the International Conference on Harmonisation (ICH) S7B guidelines.[4]

Clinical study and extensive post-marketing experience show that heart rate and rhythm disorders and

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sudden death are very rare events after oral administration of domperidone. Some epidemiology studies have shown a significant association between domperidone and serious ventricular arrhythmia (SVA)/sudden cardiac death (SCD); however, these studies do not address the question of whether this association is causal or due to potential confounders such as smoking, obesity, or alcohol use, which are not well captured in the health services databases used to conduct these studies. In addition, only one study[5] offered information on the relationship of age to the risk of SCD, and only one study[6] offered information on the relationship of domperidone dose to the risk of SCD.

The Pharmacovigilance Working Party (PVWP) of the European Medicines Agency (EMA) evaluated available preclinical and clinical data related to the cardiac safety of domperidone and concluded in October 2011 that the benefit-risk remained positive.[7] To further inform this position, European agencies requested that an ICH-E14 QT/QT corrected for heart rate (QTc) study[8] be conducted for labeled doses of domperidone. We report herein the results of this thorough QT/QTc study of domperidone, which advances our understanding of the cardiac safety of domperidone.

The primary objective of the study was to assess the effects of single and multiple doses of domperidone on QTc duration in healthy adult volunteers at domperidone doses of 10 and 20 mg q.i.d. Secondary objectives of the study were to: assess the relationship between the dose of domperidone and QTc changes for single and multiple doses; evaluate the single- and multi-dose pharmacokinetics (PK) of domperidone; assess the relationship between plasma concentrations of domperidone and QTc changes, both for single and multiple doses of domperidone; and, evaluate the safety and tolerability of domperidone, including effects on electrocardiogram (ECG) morphology and ECG interval durations other than QTc.

## Materials and Methods

### Participants

Eligibility criteria required that study participants were healthy, non-smoking male and female volunteers aged 18–55 years old, with body mass index (BMI) of 18–30 $kg/m^2$, body weight $\geq$50 kg, systolic blood pressure 90–140 mmHg, diastolic blood pressure $\leq$90 mmHg, and heart rate 45–100 beats per minute (bpm)/normal sinus rhythm. With regard to ECG at screening and baseline, participants were required to have a QT interval corrected for heart rate using Fridericia formula (QTcF) of 350–450 milliseconds, QRS interval of $<$110 milliseconds, PR interval $<$200 milliseconds, and morphology consistent with healthy cardiac conduction and function.

Eligibility criteria also required that participants did not have a current, clinically significant medical illness, including cardiac arrhythmias or other cardiac disease, at the time of study screening, family history of Short QT Syndrome or Long QT Syndrome, and hypo- or hyperkalemia, -magnesemia, or -calcemia. In addition, they were not to be treated with any prescription or over-the-counter medications within 14 days of Day 1 of the first treatment period, with the exception of paracetamol, continued use of a hormonal intrauterine device and, if female, was not pregnant or lactating.

### Study Design

This randomized, double-blind, four-way crossover, placebo- and positive-controlled, single- and multiple-dose phase 1 study was conducted between 31 July and 05 November 2012 at a single study center in Belgium. The design followed the general design principles outlined in the ICH-E14 guidance for the clinical evaluation of the QT/QTc interval with non-antiarrhythmic drugs.[8]

The study consisted of three phases: a screening phase, a double-blind treatment phase, and a post-treatment phase. Volunteers were screened for eligibility between Day $-$21 and Day $-$2. The treatment phase included four treatment periods each consisting of a baseline assessment and stabilization day (Day $-$1) and a 4-day treatment period (Day 1–Day 4), with each treatment period separated by a 4- to 9-day washout. End-of-study procedures were conducted 4–10 days after the last dose of study drug in the final treatment period or at the time of early withdrawal.

At the beginning of the double-blind treatment phase, eligible volunteers (criteria summarized above) were assigned to one of four treatment sequences based on a computer-generated randomization schedule. Randomization was balanced using randomly permuted blocks. On Day 1 of each treatment period, participants began domperidone 10 or 20 mg q.i.d. (dosing at 0, 5 hours and 10 minutes, 10 hours, and 15 hours), matching placebo q.i.d., or single-dose moxifloxacin 400 mg (positive control)/placebo q.i.d., taking the remaining study drugs in order based on the treatment sequence. Study drugs were over-encapsulated to maintain the double-blind.

An independent Ethics Committee (Comité voor Medische Ethiek, University Hospital Antwerp, Edeghem, Antwerp, Belgium) reviewed and approved the study protocol. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, consistent with Good Clinical Practices and applicable regulatory requirements. All participants provided written informed consent before their study participation commenced. The study is registered at www.clinicaltrials.gov, NCT 01643889.

## Assessments

*ECG/QTc.* In each treatment period, serial 12-lead ECGs were recorded in triplicate during the first dosing interval at 30, 20, and 10 minutes before dosing on Day 1 (the average of which was defined as baseline), at 10 minutes before dosing (predose) on Day 4, and at 8 (0.5, 1, 1.5, 2, 2.5, 3, 4, 5 hours) post-dose timepoints on Days 1 and 4, always before PK sampling. During the collection of ECGs, participants were in a quiet setting without distractions, rested in a supine position for at least 10 minutes before ECG collection, and refrained from talking or moving arms or legs. To minimize the effect of food on ECG assessments, participants' meal intake and content during residence at the study center were strictly controlled, with them having limited access to only water from 2 hours before to 3 hours after the morning drug administration and fluids other than water, but no food, between 3 and 5.5 hours after dosing on Day 1 and Day 4. In addition, for safety monitoring, ECG was monitored by telemetry from 6 hours after the morning dose on Day 1 until 2 hours before dosing on Day 4 in each treatment period.

A blinded reader at a central laboratory (Quintiles Limited, Cardiac Safety Services, Mumbai, India) measured ECG interval durations using a high-resolution, semi-automatic (computer-assisted) on-screen annotation (caliper) method. A blinded cardiologist at the central laboratory evaluated all triplicate ECGs for abnormalities (rhythm, axis, conduction, hypertrophy, myocardial infarction, and ST-, T-, and U-wave morphology), with focus on T- and U-wave morphology, according to predefined criteria. The reader and cardiologist at the central laboratory were blinded to treatment (domperidone vs. placebo vs. moxifloxacin), treatment period, dosing day within period (baseline vs. on-drug), timepoint within the day, and the participant identifiers.

Clinically significant findings on ECGs observed by the investigator were reported as adverse events, whereas those observed post-hoc by the cardiologist at the central laboratory were included in the statistical analysis but not reported as adverse events.

*Pharmacokinetics.* Venous blood samples of 4 mL were taken at 10 minutes before dosing and at 8 predefined timepoints after dosing (within 5 minutes after the last of the triplicate 12-lead ECG recording) on Day 1 and Day 4 of each period for the determination of plasma concentrations of domperidone. The whole blood samples for PK evaluation were centrifuged at room temperature for 10 minutes, beginning within 2 hours of collection; the resulting $\sim$1.7 mL plasma samples were frozen within 2 hours of whole blood sample collection and stored at approximately $-20^{\circ}$C until transferred to the bioanalytical facility (PRA Early Development Services, Assen, The Netherlands) for analysis.

Concentrations of domperidone in EDTA plasma were determined using a validated,[9,10] sensitive liquid chromatography–tandem mass spectrometry (LC–MS/MS) method. The method consisted of a solid-phase extraction in a micro-elution plate with Oasis MCX, followed by reversed phase chromatography using a Waters XBridge C18 column (Waters, Milford, MA) using a HTC PAL autosampler (CTC Analytics, Zwingen, Switzerland) with LC-10Advp pump (Shimadzu, Columbia, MD) coupled with a Applied Biosystems/MDS SCIEX API3000 triple quadrupole mass spectrometer. The quantification range was 1–500 ng/mL.

PK parameters were calculated for domperidone using standard non-compartmental analysis methods.

*Non-ECG Safety Assessments.* Adverse events were monitored, clinical laboratory tests were performed, physical examinations were conducted, and vital signs were measured at prespecified timepoints throughout the conduct of this study.

## Data Analysis

*Sample Size Determination.* Based on a SD of 10 milliseconds for change from baseline in QTc ($\Delta$QTc) as observed in previously conducted thorough QT studies using a crossover design, a sample size of 36 subjects would be sufficient for the estimate of the difference in change from baseline QTc between each treatment and placebo ($\Delta\Delta$QTc; point estimate) to be within 4 milliseconds of its true value with 90% confidence at each timepoint of measurement.

Assay sensitivity was assessed by evaluating the difference in mean $\Delta\Delta$QTc between moxifloxacin and placebo when averaged over the four timepoints between 2 and 4 hours after dosing.[11] With an intrasubject SD of 10 milliseconds and a sample size of 36 subjects, the probability that the lower limit of the two-sided 90% confidence interval (CI) exceeded 5 milliseconds was estimated to be 80% when the true difference in means was $\geq$11 milliseconds.

*Pharmacodynamic (ECG/QTc) Analyses.* Heart rate, QT interval, and change from baseline in heart rate and QT for each treatment and timepoint of measurement were summarized using descriptive statistics, as was the difference in the change from baseline in heart rate and QT between each domperidone dose and placebo.

The primary correction method for QT intervals was selected based on an evaluation of baseline (QTc, RR) data for three correction methods (Fredericia [QTcF], Bazett [QTcB], study-specific power [QTcP]). Regression modeling of the logarithm of QTc versus logarithm of RR was used for this evaluation to allow objective selection of the method; the correction method with the lowest value for the upper 95% CI limit for estimated slope was selected as the primary correction.

Mixed effects models with sequence, treatment, period, timepoint of measurement, and treatment-by-timepoint interaction as fixed effects and participant as a random effect was fit to ΔQTc data. Using the estimated least squares (LS) means and intrasubject variance from the model, 90% CIs for the difference in means between each treatment and placebo (ΔΔQTc) and for the difference between the two doses of domperidone were constructed at each timepoint of measurement.

In concordance with the ICH-E14 guidance, a threshold level of QTc change was defined as >5 milliseconds, as evidenced by an upper limit of two-sided 90% CI for the difference in means exceeding 10 milliseconds.[8]

*Pharmacokinetic Analyses.* Domperidone plasma concentration data and its derived PK parameters were summarized for a single dose (Day 1) and after multiple dosing (Day 4) for both domperidone dosages (10 and 20 mg) using descriptive statistics.

*Pharmacokinetic/Pharmacodynamic Analyses* The ΔΔQTcP between each dose of domperidone and placebo at each timepoint of measurement was plotted against the corresponding plasma concentration of domperidone.

Linear mixed effects models were fit to the ΔΔQTcP data for treatment Day 1 and Day 4, separately, with concentration as a predictor and subject as a random effect; if the intercept term was not significant, the model was re-fitted with a zero intercept term. The model-estimated value of ΔΔQTcP and two-sided 90% CIs were calculated at the mean observed maximum plasma concentration ($C_{max}$) values at Day 1 and Day 4 for each domperidone dose.

## Results

The study population was comprised of 44 volunteers, with the majority being white (n = 42, 95%) and male (n = 32, 73%). The mean (SD) age was 43.5 (8.0) years and BMI, 24.7 (2.8) $kg/m^2$.

Of the 44 volunteers enrolled, 40 completed the study and 4 discontinued prematurely: 1 due to an adverse event (allergic dermatitis during moxifloxacin treatment in period 3 after completing domperidone placebo and domperidone 20 mg), 1 due to a protocol violation (confirmed positive drug screen after domperidone placebo in treatment period 1), 1 due to family reasons (after 2 days of moxifloxacin in treatment period 1), and 1 due to conflicting work schedule and was not available for period 3 and period 4 (after completing domperidone 20 mg in period 1 and domperidone 10 mg in period 2).

All 44 participants were included in QTc and safety analyses, 42 had at least 1 post-dose PK concentration measurement and were included in PK analyses, and 41 of 42 were included in PK/PD analyses.

### Pharmacodynamics

On Day 1, mean heart rate values for domperidone 10 mg, domperidone 20 mg, moxifloxacin 400 mg, and placebo ranged, respectively, from 57.8 to 62.4, 57.3 to 62.4, 57.7 to 62.4, and 57.4 to 63.2 bpm. On Day 4, mean heart rate values for the respective treatment groups ranged from 60.1 to 64.7, 57.8 to 64.5, 59.4 to 64.4, and 59.3 to 64.4 bpm. For both doses of domperidone, the difference in mean change from baseline in heart rate between domperidone and placebo ranged from −1.3 to 2.1 bpm. The 95% CI for the difference in mean change from baseline in heart rate between domperidone and placebo included 0 bpm at all except two timepoints (1 and 2 hours post-dose on Day 1 for domperidone 20 mg vs. placebo).

On Day 1, mean QT interval values for domperidone 10 mg, domperidone 20 mg, moxifloxacin, and placebo ranged from 401.9 to 415.1, 401.2 to 413.9, 402.2 to 425.1, and 400.5 to 414.0 milliseconds, respectively. On Day 4, mean QT interval values for the respective treatment groups ranged from 393.5 to 406.2, 393.2 to 410.4, 393.6 to 407.0, and 392.3 to 407.6 milliseconds. For both doses of domperidone, the difference in mean change from baseline in QT intervals between domperidone and placebo ranged from −3.6 to 3.6 milliseconds. The 95% CI for the difference in mean change from baseline in QT intervals between domperidone and placebo included 0 millisecond on both days and at all timepoints.

QTcP was selected as the primary correction method (correction factor = 0.2434). Results for QTcF and QTcB were consistent with that of QTcP. The difference in LS means for change from baseline QTcP for the positive control, moxifloxacin, versus placebo, averaged over timepoints between 2 and 4 hours, was 10.3 milliseconds (90% CI: 9.4–11.2), and the moxifloxacin response confirmed assay sensitivity (Figure 1). For domperidone, the largest difference in LS means for change from baseline QTcP for domperidone versus placebo was 3.4 milliseconds (90% CI: 1.0–5.9), which occurred at 1 hour post-dose on Day 4 during 20 mg q.i.d. dosing (Table 1 and Figure 1). When a typically used domperidone dose of 10 mg q.i.d. was given, the largest difference in LS means for change from baseline QTcP for domperidone versus placebo was 2.0 milliseconds (90% CI: 0.2–3.8). The upper limit of the 90% CI was <10 milliseconds at all timepoints on Day 1 (after single dose) and Day 4 (after multiple doses) for both domperidone doses. The largest difference in LS means for change from baseline QTcP between the 20 and 10 mg doses of domperidone was 1.2 milliseconds (90% CI: −0.6 to 3.0) at Day 1 and 2.7 milliseconds (90% CI: −0.3 to 5.1) at Day 4. Results for QTcF and QTcB (data not shown) were consistent with that of QTcP.

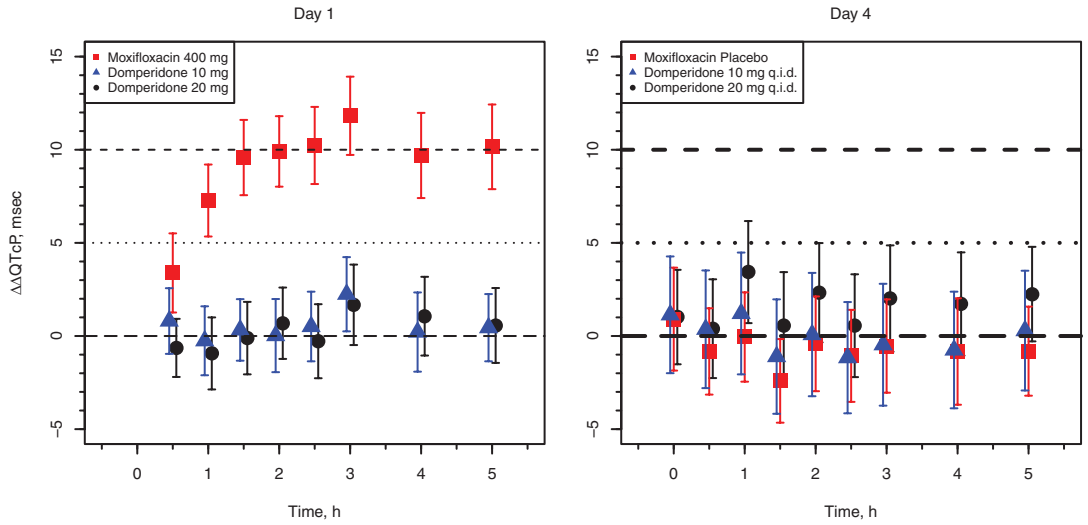


**Figure 1.** Difference between each treatment and placebo based on mixed effects modeling on QTcP changes from baseline (LS mean and 90% CI).

**Table 1.** Maximum Difference in LS Mean QTcP—Active Drug versus Placebo

| Comparison | Visit | Maximum differences in LS means at any timepoint (QTcP) | 90% CI |
|---|---|---|---|
| Domperidone 10 mg vs. placebo | Day 1 | 2.0 | (0.2, 3.8) |
| Domperidone 10 mg vs. placebo | Day 4 | 1.1 | (−1.3, 3.6) |
| Domperidone 20 mg vs. placebo | Day 1 | 1.7 | (−0.1, 3.5) |
| Domperidone 20 mg vs. placebo | Day 4 | 3.4 | (1.0, 5.9) |
| Moxifloxacin vs. placebo | Day 1 | 10.3[a] | (9.4, 11.2) |

CI, confidence interval; QTcP, QT interval corrected for heart rate, using a study-specific power model.
[a]Averaged over all timepoints between 2 and 4 hours after dosing.

## *Pharmacokinetics*

Participants achieved expected domperidone exposures ($C_{max}$ and area under the plasma concentration–time curve [AUC]) (Table 2). PK parameters were close to proportional for domperidone 10 and 20 mg doses; an approximately two- to three-fold accumulation was found on Day 4 of domperidone treatment. The between-subject variability (% coefficient of variation) for $C_{max}$ and AUC was less than 51% following a single dose and less than 40% following multiple doses.

## *Pharmacokinetics/Pharmacodynamics*

No significant or clinically relevant exposure-QTc response effects were observed at Day 1 or Day 4 of

**Table 2.** Summary of Pharmacokinetic Parameters

| | Mean (% CV) | | | |
|---|---|---|---|---|
| | Domperidone 10 mg | | Domperidone 20 mg | |
| | Day 1 (N = 40) | Day 4 (N = 40) | Day 1 (N = 41) | Day 4 (N = 41) |
| $C_{min}$ (ng/mL) | NA | 5.26 (31.1%) | NA | 10.1 (29.7%) |
| $C_{max}$ (ng/mL) | 11.6 (50.8%) | 17.3 (35.4%) | 20.1 (48.2%) | 35.7 (39.9%) |
| $t_{max}$ (h)[a] | 1.02 (0.52–5.02) | 1.02 (0.5–4.03) | 1.03 (0.52–4.03) | 1.02 (0.50–2.52) |
| $AUC_{0-5\,h}$ (ng · h/mL) | 20.4 (34.4%) | 47.8 (30.5%) | 38.2 (38.0%) | 96.4 (28.9%) |

$AUC_{0-5\,h}$, area under the plasma concentration–time curve over the first dosing interval (from 0 to 5 hours); $C_{min}$, minimum plasma concentration; $C_{max}$, maximum plasma concentration; CV, coefficient of variance; q.i.d., four times daily; NA, not applicable; $t_{max}$, median time to reach $C_{max}$.
[a]Median (range).

domperidone treatment (Figure 2). On Day 1, the model-estimated increase in ΔΔQTcP at the mean $C_{max}$ was 0.029 milliseconds for the 10 mg dose and 0.0503 milliseconds for the 20 mg dose, and on Day 4 the estimated increase was 1.07 milliseconds for the 10 mg dose and 2.21 milliseconds for the 20 mg dose, with the 90% CI including zero at mean $C_{max}$ for both days. As a result of distance in time from the baseline QTc measurement, the variability in ΔΔQTcP on Day 4 was larger than that on Day 1, resulting in a wider CI for the slope.

### *ECG Intervals and Morphology*

No participant had a QTcP interval >450 milliseconds during treatment with domperidone 20 mg, moxifloxacin, or placebo. One participant (baseline value 443.1 milliseconds) had two QTcP intervals >450 milliseconds measured during domperidone 10 mg treatment—456.1 at 3 hours post-dose on Day 1 and 452.5 milliseconds at 5 hours post-dose on Day 4. No participant had a >30 milliseconds change from baseline in QTcP interval during treatment with domperidone 10 mg, domperidone 20 mg, or placebo. After a moxifloxacin dose, one participant had a >30 milliseconds increase from baseline QTcP value at 5 hours post-dose on Day 1 (412.6–443.5 milliseconds).

ECG morphology abnormalities occurred infrequently, were balanced in frequency across the treatment groups, and were all determined to be clinically insignificant in blinded review. Non-specific, flat T-wave abnormalities were observed in one participant each in the placebo and domperidone 20 mg groups and two participants each in the domperidone 10 mg and moxifloxacin groups. There were no abnormalities in U-wave morphology. There were no other treatment-emergent ECG abnormalities or ECG morphology findings.

### *Other Safety Findings*

The overall incidence of treatment-emergent adverse events was numerically lower in the domperidone 10 mg group (19.5%; 8/41) than in the placebo group (33.3%; 14/42) and the domperidone 20 mg and moxifloxacin 400 mg groups (each 28.6%; 12/42). The most common events (i.e., reported in ≥5% patients in any treatment group) were skin irritation at the site of ECG electrodes application, which was reported in 5 (11.9%) of 42 participants in the placebo treatment group, and headache in 3 (7.1%) of 42 participants in moxifloxacin 400 mg treatment group. The investigator assessed all events as either mild or moderate in severity. One participant discontinued study drug prematurely due to an adverse event of allergic dermatitis during treatment with moxifloxacin. No clinically significant changes in laboratory tests were observed during the study.

## Discussion

In this current study, the results showed the largest difference in LS means for change from baseline QTcP for both domperidone 10 and 20 mg q.i.d. doses versus placebo was below 5 milliseconds, and the upper limit of the 90% CI was well below 10 milliseconds at all timepoints on Day 1 (after single dose) and on Day 4 (after multiple doses), indicating that this is a negative thorough QT/QTc study.[8] There were no abnormalities in U-wave morphology or other treatment-emergent ECG abnormalities or ECG morphology findings associated with the

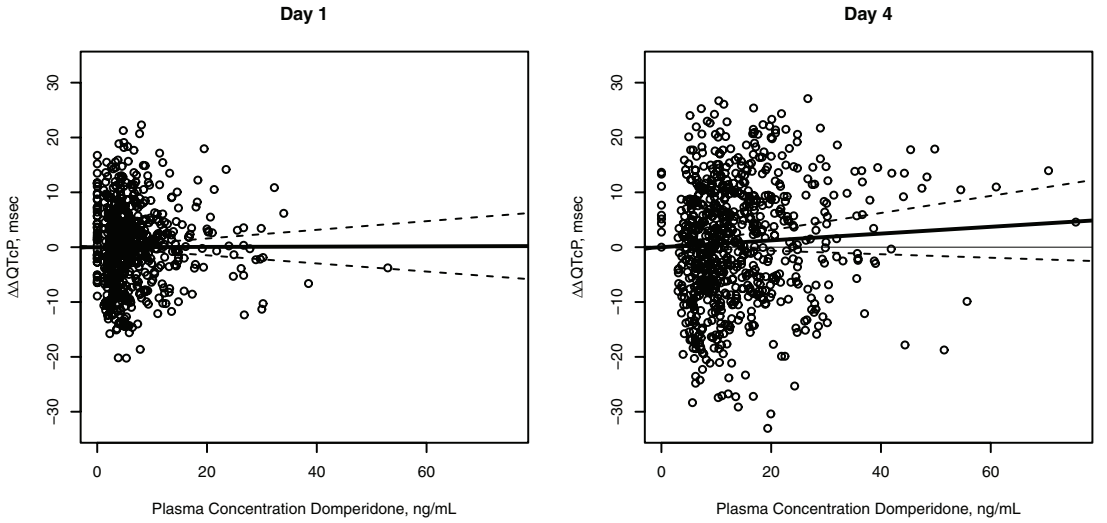


**Figure 2.** Individual domperidone plasma concentration versus ΔΔ QTcP and estimated linear mixed effects model. Solid line

administration of domperidone. Doses exceeding the highest dose approved globally for prescription use of domperidone were not tested in this study because preclinical electrophysiological in vitro and in vivo studies have already shown that domperidone, at very high concentrations, may prolong the QTc interval, without arrhythmogenic or torsadogenic effects at these concentrations.[2]

Historically, in less well controlled studies, when domperidone was given together with the strong CYP3A4 inhibitors ketoconazole or erythromycin, drugs that prolong QT by themselves, the upper limit of the 90% two-sided CI for the largest mean difference in change of QTc from baseline versus placebo was shown to exceed 10 milliseconds.[2] Domperidone is metabolized by CYP3A4 enzymes,[12] and the $C_{max}$ of domperidone has been shown to increase less than three-fold under maximal CYP3A4 inhibition. In those interaction studies, the mean increase in QTc for domperidone 10 mg q.i.d. at steady-state was 1.6–2.5 milliseconds, and for ketoconazole (200 mg b.i.d.) and erythromycin (500 mg t.i.d.), 3.8 and 4.9 milliseconds, respectively. For the combined treatment of domperidone with ketoconazole or erythromycin, the mean increase in QTc was 9.8–9.9 milliseconds.[2] Thus, domperidone is not recommended to be administered concomitantly with strong CYP3A4 inhibitors that also prolong QT.

Several animal models have been used to investigate the electrocardiographic effects of domperidone. In anesthetized and conscious dogs, safety margins for QT prolongation were greater than 25- and nine-fold plasma concentrations at maximum recommended therapeutic doses, respectively, and in a rabbit proarrhythmia model, no proarrhythmia was observed at concentrations 367-fold plasma concentrations at maximum recommended therapeutic doses. In an isolated Langendorff-perfused rabbit heart model (Hondeghem Screenit™ system), no effects were found on proarrhythmic parameters at 100 nM (17-fold margin). TdP was observed in one of six hearts at 300 nM (52-fold margin) and in three of six hearts at 1,000–3,000 nM (173- to 519-fold margin). A subsequent publication of an extensive validation of this isolated heart test system found comparable results and margins for domperidone.[13] However, publications of more recent experiments using the Screenit™ system, revised to enhance sensitivity, have shown effects of domperidone at lower concentrations by using a lower concentration range (30, 60, and 100 nM), a higher incubation temperature of 37˚C, and a longer exposure time of 150 minutes.[14,15] These changes to the experimental protocol, as well as the absence of concurrent vehicle controls and the lack of blinded validation of the revised model with a series of other drugs with and without known arrhythmogenic liabilities in humans, as was done previously,[13] limit the relevance of the testing model for predicting safety and informing the assessment of risk in humans. Furthermore, the relevance of nonclinical studies with domperidone is progressively being outweighed by accruing post-marketing safety information and clinical trial evidence as reported herein.

In summary, domperidone at doses up to 80 mg/day—the highest oral dose approved globally for prescription use—did not cause clinically relevant prolongation of the QTc interval in this thorough QT study. No new safety signal was observed in this study based on assessments of ECG morphology, adverse events, or changes in laboratory parameters.

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P.S., S.D., J.B., J.N., and G.L. designed the research study. S.D., J.B., C.K., B.S., and G.L. collected and analyzed the data. P.S. and C.K. contributed to writing the introduction and discussion. All authors contributed to reviewing and contributing intellectually to drafts of the article. All authors approved the final version of the article, including the authorship list.

## Declaration of Conflicting Interests

All authors are employees of Janssen Research and Development, in either Raritan/Titusville, New Jersey, USA (Dr. Keung, Dr. Leitz, Ms. Solanki, and Dr. Natarajan) or Beerse/Merksem, Belgium (Dr. Biewenga, Dr. Deleu, and Dr. Soons).

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