SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development*
Name of Finished Product	MOTILIUM®
Name of Active Ingredient(s)	JNJ-17296812-AAA (Domperidone)

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Status: Approved

Date: 1 March 2013

Prepared by: Janssen Research & Development, LLC

Protocol No.: DOM-DYP-1001

Title of Study: A Randomized, Double-Blind, Placebo- and Positive-Controlled, Single- and Multiple-Dose, 4-Way Crossover Study to Evaluate the Effects of Domperidone on Cardiac Repolarization in Healthy Subjects

EudraCT Number: 2012-001567-70

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Principal Investigator: Katrien Lemmens, MD

Study Center(s): Clinical Pharmacology Unit, Janssen Pharmaceutica NV, Lange Bremstraat 70, 2170 Merksem, Belgium

Publication (Reference): None

Study Period: 31 July 2012 to 05 November 2012

Phase of Development: 1

Objectives: The primary objective of this study was to assess the effects of single and multiple doses of domperidone on the QT interval corrected for heart rate (QTc) duration in healthy adult subjects at domperidone doses of 10 mg four times daily (qid) and 20 mg qid.

The secondary objectives were to assess the relationship between the dose of domperidone and QTc changes, both for single and multiple doses of domperidone, to assess the relationship between the systemic plasma concentrations of domperidone and QTc changes, both for single and multiple doses of domperidone, to evaluate the single- and multiple-dose pharmacokinetics (PK) of domperidone, and to evaluate safety and tolerability of domperidone, including effects on electrocardiogram (ECG) morphology and ECG interval durations other than QTc.

Methodology: This was a randomized, double-blind, 4-way crossover, placebo- and positive-controlled, single-center, single- and multiple-dose Phase 1 study. A placebo control was used to evaluate the effect

of domperidone on QTc intervals in comparison with placebo. Moxifloxacin, which is known to prolong QTc intervals, was used as positive control to establish assay sensitivity.

The study consisted of 3 phases: a screening phase (Day -21 to Day -2); a double-blind treatment phase (4 treatment periods each consisting of a baseline assessment, and stabilization day [Day -1], a treatment assessment period [Day 1 to Day 4], and each treatment period was separated by a minimum 4-day washout (maximum 9 days) between the last dosing in the previous treatment period and the first dosing in the next treatment period); and a posttreatment phase (end-of-study procedures 4 to 10 days after the last dose of study drug or at the time of early withdrawal). Baseline ECG recordings were obtained before dosing on Day 1 of each treatment period.

Subjects were confined to the clinical testing facility for approximately 5 days in each treatment period. Subjects who met the selection criteria were randomly assigned to 1 of 4 treatment sequence groups (ADBC, BACD, CBDA, or DCAB) based on a computer-generated randomization schedule. Subjects received the following 4 treatments 1 in each period in the order specified by the randomization:

Treatments

Treatment	Description of Treatment
A (domperidone 10 mg)	Domperidone 10 mg qid + domperidone-placebo qid on Day 1 to Day 3 and a single dose on Day 4; moxifloxacin-placebo single dose on the morning of Day 1.
B (domperidone 20 mg)	Domperidone 2 x 10 mg qid on Day 1 to Day 3 and a single dose on Day 4; moxifloxacin-placebo single dose on the morning of Day 1.
C (placebo)	2 x domperidone-placebo qid on Day 1 to Day 3 and a single dose on Day 4; moxifloxacin-placebo single dose on the morning of Day 1.
D (moxifloxacin)	2 x domperidone-placebo qid on Day 1 to Day 3 and a single dose on Day 4; moxifloxacin 400 mg single dose on the morning of Day 1.

Key: qid = four times daily

The first dose of study drug on Day 1 of each treatment period was administered between 7:00 and 10:00 in the morning. The second, third, and fourth (last) doses on Day 1 were administered at 5 hours and 10 minutes (following the last triplicate 12 lead ECG recording), 10 hours, and 15 hours after the first dose of study drug. Doses on Day 2 and Day 3 were administered at approximately the same clock time as on Day 1. The dose of study drug on Day 4 of each treatment was administered at the same clock time as on Day 1. Study drug was administered with 240 mL of non-carbonated water 20 minutes before food intake, with the exception of the first intake on Day 1 and Day 4 (dosing was 2 hours after a light snack, which was followed by a continuation of the fasting period up to 5 hours and 30 minutes after dosing) and the fourth dose on Day 1 to Day 3 (dosing was 2 hours after an optional light snack).

To minimize the effect of food on ECG assessments, meal intakes and contents during residence at the study center were strictly controlled and recorded. Subjects had limited access to fluids (water only) from 2 hours before to 3 hours after the morning drug administration on Day 1 and Day 4. Between 3 hours and 5 hours and 30 minutes after dosing, subjects continued to fast, but were allowed to drink other fluids than water. Subjects were instructed to remain in supine position from 1 hour predose up to 3 hours after the morning drug administration on Day 1 and Day 4.

Number of Subjects (planned and analyzed): Planned: Forty-four healthy subjects (men and women) were to be enrolled to ensure that at least 36 subjects completed the study. At least 12 subjects per sex were to be enrolled. Analyzed: A total of 44 subjects (11 subjects in each treatment sequence group) were enrolled in the study. All 44 subjects received at least 1 dose of the study drug and were included in the safety and tolerability analysis. Forty-four subjects were included in the PK and pharmacodynamic (PD) analysis.

Diagnosis and Main Criteria for Inclusion: Healthy, non-smoker men and women between 18 and 55 years of age (inclusive), who had a body mass index (BMI) between 18 kg/m² and 30 kg/m² (inclusive), body weight of not less than 50 kg, systolic blood pressure between 90 mmHg and 140 mmHg (inclusive), and diastolic blood pressure no higher than 90 mmHg, normal sinus rhythm with heart rate between 45 and 100 beats per minute (bpm) (inclusive); QT interval corrected for heart rate, using Fridericia formula (QTcF) between 350 msec to 450 msec (inclusive); QRS interval of <110 msec; PR interval <200 msec; ECG morphology consistent with healthy cardiac conduction and function were eligible for enrollment into the study. Subjects should not have had history of or current clinically significant medical illness including cardiac arrhythmias or other cardiac disease, the presence of a family history of Short QT Syndrome, Long QT Syndrome and should have had no hypo- or hyperkalemia, -magnesemia, or -calcemia.

Test Product, Dose and Mode of Administration, Batch No.: Domperidone treatment was given orally, 10 mg or 20 mg, in a double-blind double-dummy fashion and consisted of film coated tablets containing 10 mg domperidone base and were over-encapsulated with red DBAA capsules filled with microcrystalline cellulose (MCC) spheres as much as suffices (qs) (Batch/Lot No.: 12F04/F074, and Formulation No: F074. Expiration date: December 2013).

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo and moxifloxacin treatments were given orally in a double-blind double-dummy fashion.

Domperidone-placebo capsules consisted of Red DBAA capsules (identical to those of over-encapsulated domperidone) filled with MCC spheres qs. (Batch/Lot No.: 12F04/G001, and Formulation No.: G001. Expiration date: December 2013).

Moxifloxacin was supplied as 400 mg film-coated tablets over-encapsulated with Red DBAA elongated capsules filled with MCC spheres qs. (Batch/Lot No.: 12E31/G055 and Formulation No.: G055. Expiration date: June 2014).

Moxifloxacin-placebo capsules contained Red DBAA elongated capsules (identical to those of over-encapsulated moxifloxacin) filled with MCC spheres qs. (Batch/Lot No.: 12E31/G053, and Formulation No.: G053. Expiration date: June 2014).

Duration of Treatment: The total duration of the study was approximately 54 days (a minimum of 33 days), plus a 20-day screening phase (Day -21 to Day -2).

Criteria for Evaluation:

Pharmacokinetics:

Venous blood samples of 4 mL were taken at 10 minute before dosing and at 8 predefined timepoints (0.5-, 1-, 1.5-, 2-, 2.5-, 3-, 4-, and 5-hour after dosing) following dose administration on Day 1 and Day 4 of each period for the determination of plasma concentrations of domperidone and/or moxifloxacin. Blood samples for PK evaluation were collected within 5 minutes after completing the recording of the triplicate ECG (PD evaluation).

The following PK parameters were calculated for domperidone using non-compartmental analysis: C_{max}, t_{max}, AUC_{tau} (single dose administration: Day 1) and $C_{min,ss}$, $C_{max,ss}$, t_{max}, and AUC_{tau} (multiple dose administration: Day 4).

Pharmacodynamics:

After the subject had rested in supine position for at least 10 minutes, triplicate 12-lead ECG recordings were obtained within 5 minutes at 30, 20, and 10 minutes before dosing (predose) on Day 1, at 10 minutes

before dosing (predose) on Day 4 and at 8 predefined timepoints after dosing on Day 1 and Day 4 of each period always before PK sampling. The measured QT intervals were corrected for heart rate using 3 correction methods (Fridericia [QTcF], Bazett [QTcB] and study-specific power [QTcP] correction). The average of the 3 sets of triplicate values obtained 30, 20, and 10 minutes before dosing on Day 1 was taken as baseline measurement for that period. The change from baseline (predose on Day 1) in QTc intervals (ΔQTc) was calculated at each timepoint after dosing. The difference in mean change from baseline, ΔΔQTc, between each dose of domperidone and placebo (Day 1 and Day 4) and between moxifloxacin and placebo (Day 1 only) was calculated at each timepoint. Similar analyses were performed for heart rate and QT interval. Moxifloxacin effect on QTc intervals served to determine assay sensitivity only.

Pharmacogenomics:

Participation in the pharmacogenomics research was optional. Blood sample for pharmacogenomic evaluation was collected from subjects who consented to the pharmacogenomic component of the study to allow the detection of genetic variants in genes such as *KCNE1*, *KCNE2, KCNH2, KCNQ1, SCN5A, NOS1AP*, and *PLN* that had been associated with irregular QT/QTc intervals. These variants were to be analyzed upon unexplained observation of very long (QTc >500 msec or ΔQTc >60 msec) or of highly irregular QT/QTc intervals during the study. The deoxyribonucleic acid samples could also be analyzed for additional genes related to cardiovascular safety, or to the PK, PD, or safety/tolerability of domperidone during the study, if necessary. Where appropriate consent was obtained, deoxyribonucleic acid samples were to be stored in non-identifiable format for future pharmacogenomic research.

Safety:

Safety and tolerability was evaluated throughout the study based on adverse event (AE) monitoring, clinical laboratory tests (hematology, serum chemistry, and urinalysis), 12-lead ECG monitoring, vital signs (blood pressure, pulse, and temperature) measurements, and physical examination findings. To monitor ongoing safety, ECG was monitored by telemetry from 6 hours after the first study drug administration on Day 1 onwards until 2 hours before dosing on Day 4.

Statistical Methods:

Sample Size Determination:

The study enrolled 44 healthy subjects. The intrasubject standard deviation (SD) for ΔQTc was estimated to be less than 10 msec in previously conducted thorough QT studies using a crossover design. Thus, the intrasubject SD for ΔQTc was assumed to be 10 msec for this sample size calculation. Using an SD of 10 msec for ΔQTc, a sample size of 36 subjects would be sufficient for the estimate of the mean ΔΔQTc (point estimate) to be within 4 msec of its true value with 90% confidence at each timepoint of measurement.

The assay sensitivity was assessed by evaluating the difference in mean ΔQTc between moxifloxacin and placebo (ΔΔQTc) when averaged over all timepoints between 2 and 4 hours after dosing (ie, 2, 2.5, 3, and 4 hours) (global test). With an intrasubject (SD) of 10 msec and a sample size of 36 subjects, the probability that the lower limit of the 2-sided 90% confidence interval (CI) for the difference in mean ΔQTc between moxifloxacin and placebo (ΔΔQTc) averaged over the 2- to 4-hour time interval was greater than 5 msec was estimated to be 80% when the true difference in means was greater or equal to 11 msec.

Subjects who withdrew from the study were not to be replaced unless more than 8 subjects withdrew from the study before the last triplicate 12-lead ECG assessment. If more than 8 subjects withdrew, additional

subjects were to be enrolled and were to be assigned to the same treatment sequence group as the subject being replaced (the last subject who dropped out), until 36 subjects completed the study.

For all subjects who received at least 1 dose of study drug, descriptive statistics (mean, SD, median, minimum, and maximum) were calculated for age, BMI, weight, and height. Sex and race were listed and tabulated.

Pharmacokinetics:

Domperidone plasma concentration-time profiles for each subject and mean plasma concentration-time profiles were plotted per dosing day (Day 1 to Day 4) and treatment. Domperidone plasma concentration data and its derived PK parameters were listed and were summarized for a single dose (Day 1) and after multiple dosing (Day 4) for both domperidone treatments (10 mg and 20 mg) separately. Descriptive statistics included mean, geometric mean, median, minimum, maximum, SD, and coefficient of variation. If deemed necessary, additional analyses were performed.

Pharmacodynamics:

The analysis was done separately for single dose and multiple dose days (Day 1 and Day 4). The primary correction method for QT intervals was selected based on an evaluation of baseline (QTc, RR) data for the 3 correction methods (Fridericia; Bazett; study-specific power). A regression modeling of logarithm of QTc vsersus logarithm of RR was used for this evalution; the correction method with the lowest value for the upper 95% CI limit for estimated slope was selected as the primary correction. Calculated QTc values for the other 2 corrections were reported for completeness only. The primary variable of interest was the change from baseline (predose) in QTc intervals (ΔQTc). All ECG variables (heart rate, ΔHR, QT, ΔQT, QTc, ΔQTc, QRS, and PR) were summarized for each treatment and timepoint. The difference in ΔQTc between each dose of domperidone or moxifloxacin and placebo (ΔΔQTc) was summarized by treatment and timepoint. The difference in the change from baseline in heart rate and QT between each treatment and placebo (ΔΔHR and ΔΔQT) was also summarized for each treatment. Mixed effects models with sequence, treatment, period, timepoint of measurement, and treatment by timepoint interaction as fixed effects and subject as a random effect was fit to ΔQTc data. Using the estimated least-square means and intrasubject variance from the model, 90% CI for the difference in means between each treatment and placebo was constructed at each timepoint of measurement. The 90% CI for the difference in means between the 2 doses of domperidone was also constructed at each timepoint of measurement. The difference in mean ΔQTc between moxifloxacin and placebo (ΔΔQTc) along with 90% CI over all timepoints of measurements was evaluated to assess the response profile of moxifloxacin. Assay sensitivity was established if the lower limit of the 2-sided 90% CI for the difference in mean ΔQTc between moxifloxacin and placebo, averaged over the 2-, 2.5-, 3- and 4-hour timepoints, exceeded 5 msec.

Pharmacokinetics/Pharmacodynamics:

Pharmacokinetic/pharmacodynamic analysis was done for single-dose (Day 1) and multiple-dose (Day 4) domperidone separately. Only the primary correction method for QT intervals was used for PK/PD analysis. To describe the relationship between domperidone plasma concentration and change in QTc interval, the following plots were presented: (1) ΔQTc at each timepoint of measurement against the corresponding plasma concentration of domperidone, with placebo data included with zero concentration; (2) ΔΔQTc between domperidone and placebo at each timepoint of measurement against the corresponding plasma concentration of domperidone. Linear mixed effects models were fit to the ΔΔQTc data from both doses of domperidone with concentration as a predictor and subject as a random effect. If the intercept effect was not significant, the model was re-fit with a zero intercept term. The predicted value of ΔΔQTc (along with 90% CI) was estimated at the mean C_{max} values for each dose of domperidone investigated.

Pharmacogenomics:

Pharmacogenomic analyses were not performed during the course of the study.

Safety:

All subjects who were randomized to a treatment sequence and received at least 1 dose of the study drug were included in the safety and tolerability analysis. Baseline for all laboratory evaluations and vital signs meseaurements were defined as the last evaluation done before the first study drug administration of each treatment separately. Adverse events, and physical examination were listed or summarized; descriptive statistics were calculated for laboratory evaluations and vital signs.

RESULTS:

STUDY POPULATION: A total of 44 subjects (32 men and 12 women) were enrolled and assigned to 1 of the 4 treatment arms (Sequences ADBC, BACD, CBDA, or DCAB). Out of 44 subjects, 42 were white, 1 was Asian and 1 was other. The majority of subjects in the 4 treatment sequence groups were not Hispanic or Latino. Forty subjects completed the study. The reasons for withdrawal are listed below:

- Subject 04605 (Sequence CBDA) was withdrawn due to treatment-emergent adverse event (TEAE) of dermatitis allergic during Period 3 (moxifloxacin 400 mg).
- Subject 01564 (Sequence CBDA) was withdrawn due to a protocol violation on Day -1 of Period 2 due to confirmed positive drug screen.
- Subject 00566 and Subject 04048 (Sequence DCAB and Sequence BACD, respectively) were withdrawn from the study due to other reason (family reason and not available for Period 3 and Period 4 due to work, respectively).

Subjects were healthy men and women aged 28 to 55 years, inclusive. The mean age, weight, BMI and height between the 4 treatment sequence groups were comparable. The median age of the subjects was 45.0 years (range: 28 to 55 years), mean weight was 74.63 kg (SD: 10.296 kg), and mean BMI was 24.72 kg/m^2 (SD: 2.794 kg/m^2).

PHARMACOKINETIC AND PHARMACODYNAMIC RESULTS:

PHARMACOKINETIC: Pharmacokinetic parameters were close to proportional with dose between 10 and 20 mg, and an approximately 2- to 3-fold accumulation is found at Day 4 of domperidone treatment.

Mean Plasma Domperidone Pharmacokinetic Parameters After Four-daily Oral Doses of 10, or 20 mg MOTILIUM® in the Fasted State, 2 hour After a Light Snack

	Domperidone 10 mg qid		Domperidone 20 mg qid	
	Day 1	Day 4	Day 1	Day 4
PK Parameters	(N=40)	(N=40)	(N=41)	(N=41)
C_{min} (ng/mL)	NA	5.26 (± 1.64)	NA	10.1 (± 2.99)
C_{max} (ng/mL)	11.6 (± 5.87)	17.3 (± 6.14)	20.1 (± 9.67)	35.7 (± 14.2)
t_{max} (h)[a]	1.02 (0.52 - 5.02)	1.02 (0.50 - 4.03)	1.03 (0.52 - 4.03)	1.02 (0.50 - 2.52)
AUC_{0-5h} (ng.h/mL)	20.4 (± 7.04)	47.8 (± 14.6)	38.2 (± 14.5)	96.4 (± 27.8)

[a] t_{max} reported as median (minimum-maximum)

Key: h = hour(s); qid = four times daily; N = number of subjects; NA = not applicable; PK = pharmacokinetic.

PHARMACODYNAMIC: 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 2 timepoints (Day 1, 1 hour and 2 hour for domperidone 20 mg vs placebo), suggesting no

clinically meaningful difference in mean change from baseline in heart rate between domperidone and placebo. 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 msec. The 95% CI for the difference in mean change from baseline in QT intervals between domperidone and placebo included 0 msec on both days and at all timepoints, indicating no difference in mean change from baseline between domperidone and placebo.

The study-specific correction (QTcP) was selected as the primary correction method based on regression modleing of logarithm of QTc versus logarithm of RR for all 3 correction methods. No clinically relevant increase was observed in QTcP at the commonly used 10 mg single dose and at 10 mg qid multiple dosing, and at the maximum labelled doses of 20 mg qid multiple dosing. As there was no clinically relevant increase in QTcP at any dosing regimen, no relevant dose-response is discernible. There were only small (1.2 to 2.7 msec) differences in QTcP between 20 mg and 10 mg doses, statistically significant only at 3 hour and 4 hour after the morning dose on Day 4 due to a negative change for 10 mg qid at this timepoints.

PHARMACOKINETIC/PHARMACODYNAMIC: Exposure-response analysis indicated a small increase in ΔΔQTcP with domperidone plasma concentration on Day 4. The upper limit of this increase in ΔΔQTcP was well below 10 msec at the observed mean C_{max} of both doses of Domperidone, indicating that in healthy volunteers doses of 10 and 20 mg domperidone do not result in clinically relevant QTc prolongation. Statistical analysis of models describing the exposure-response relationship including and excluding an intercept and/or a slope, indicated that both parameters were not significantly different from zero.

PHARMACOGENOMIC RESULTS: No genotyping was performed for this study, as there were no unexplained observation of very long (QTc >500 msec or ΔQTc >60 msec) or highly irregular QT/QTc intervals.

SAFETY RESULTS: All randomized subjects were included in the safety analysis. The overall incidence of subjects with TEAEs was slightly lower in the domperidone 10 mg (19.5%; 8/41) than in the placebo (33.3%; 14/42) and the domperidone 20 mg and moxifloxacin 400 mg (28.6%; 12/42 each) treatment groups. Overall, the majority of the TEAEs by system organ class were reported in skin and subcutaneous tissue disorders (29.5%), gastrointestinal disorder (25.0%), nervous system disorder (15.9%), musculoskeletal and connective tissue disorder (13.6%) and infections and infestations (9.1%). The most common TEAEs were skin irritation reported in 5 (11.9%) of 42 subjects in the placebo treatment group and headache in 3 (7.1%) of 42 subjects in moxifloxacin 400 mg treatment group. The majority of the TEAEs in all treatment groups were reported by the investigator as doubtfully- or possibly-related to the study drug except for 1 case each of vomiting, nausea, allergic dermatitis and alopecia, which were reported to be probably related to study drug in 2 subjects while receiving moxifloxacin. The investigator assessed all TEAEs as either mild or moderate in severity.

There were no deaths, other serious AEs and, persistent AEs reported in this study. Subject 04605 (Sequence CBDA) on moxifloxacin treatment discontinued due to a TEAE of dermatitis allergic.

For all treatment sequence groups, there were no treatment-related changes from baseline (Period 1, Day -1) in any of the clinical laboratory tests that were considered to be clinically significant. In addition, there were no consistent treatment-related changes from baseline in mean vital sign measurements, physical examinations, or ECG parameters.

STUDY LIMITATIONS: No notable study limitations were identified by the Sponsor.

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