SYNOPSIS

Name of Sponsor/Company	Janssen Research & Development*
Name of Finished Product	PRILIGY®
Name of Active Ingredient(s)	R096769 (dapoxetine hydrochloride)

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Status: Approved

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Prepared by: Janssen Research & Development, LLC

Protocol No.: R096769-PRE-1005

Title of Study: A Randomized, Double-Blind, Placebo-Controlled, Crossover Study Assessing the Pharmacodynamic Effects of Dapoxetine Concomitantly Administered in Subjects Taking Terazosin

NCT No.: NCT01366664

Clinical Registry No.: CR018607

Coordinating Investigator(s): Kenneth Kim, MD, WCCT, 5630 Cerritos Avenue, Cypress, CA 90630, US

Study Center(s): The study was conducted at 4 sites in the US.

Publication (Reference): None

Study Period: 19 July 2011 to 22 April 2012

Phase of Development: Phase 1

Objectives: The primary objective of this study was to assess the pharmacodynamic effect of dapoxetine 60 mg when concomitantly administered in subjects taking terazosin.

The secondary objectives of this study were to assess the pharmacokinetics, safety, and tolerability of dapoxetine 60 mg when concomitantly administered in subjects taking terazosin.

Methodology: This was a multiple-center, randomized, multiple-dose (MD), double-blind, placebo-controlled, 2-period crossover study in adult male subjects who had been on a stable regimen of terazosin (2 to 10 mg daily [q.d.]) or doxazosin (2 to 8 mg q.d.) for at least 6 weeks; subjects on a stable regimen of doxazosin were converted to a stable dosage of terazosin for at least 7 days before Day -1. The study consisted of a screening phase (within 21 days before admission into the study center on Day -1), followed by a double-blind, placebo-controlled treatment phase consisting of 2 treatment periods, each 7 days in duration (Day -1 to Day 6), and an end-of-study/early withdrawal phase that occurred after the completion of the final pharmacokinetic sample collection. For subjects who were taking doxazosin before study entry and were converted from terazosin back to doxazosin after the double-blind treatment phase, an end of-study visit (or telephone contact) occurred approximately 7 to 14 days after treatment with doxazosin restarted.

Number of Subjects (planned and analyzed): Twenty-four men were to be enrolled into the study to ensure that at least 20 men completed both treatment periods. The number of subjects enrolled into the study on a stable regimen of terazosin 2 to 4 mg was restricted to 50% of the total enrolled population while at least 50% of subjects were required to be treated with a regimen of 5 to 10 mg of terazosin. Overall, 24 subjects were enrolled in the study, of which 22 subjects were confirmed to have been taking either terazosin or doxazosin before study entry. The remaining 2 subjects (100401 and 100402) were enrolled into Amendment INT-2 before a provision was added requiring documentation of previous alpha-blocker treatment.

Diagnosis and Main Criteria for Inclusion: The study was comprised of men who had been on a stable regimen of terazosin (2 to 10 mg q.d.) or doxazosin (2 to 8 mg q.d.) for at least 6 weeks for the treatment of documented hypertension and/or benign prostatic hyperplasia (BPH). Subjects were to be ≥18 years of age with a body mass index (BMI) between 18 and 35 kg/m2, inclusive, a body weight of not less than 50 kg, supine blood pressure (BP) measurements between 90 and 150 mmHg, inclusive, and diastolic blood pressure (DBP) measurements ≤95 mmHg. Subjects with symptomatic orthostatic hypotension (a decrease of ≥20 mmHg systolic blood pressure (SBP) measured after 2 minutes but before 3 minutes after changing from a supine to a standing position) were to be excluded from the study. Subjects also had to use a medically acceptable method of contraception throughout the study.

Test Product, Dose and Mode of Administration, Batch No.: Each dose of dapoxetine consisted of one film-coated tablet, containing 60 mg of dapoxetine. The batch number for the 60-mg dose of dapoxetine was 09H25/F006.

Reference Therapy, Dose and Mode of Administration, Batch No.: Each dose of placebo consisted of one film-coated tablet. The batch number for placebo was 09H24/F008. Terazosin was supplied as 2-, 5-, or 10-mg capsules. Doses and batch numbers for terazosin were as follows: 2 mg (1060280), 5 mg (1060235), or 10 mg (1060276).

Duration of Treatment: Dapoxetine or placebo was taken for 5 days during each of two 7-day treatment periods that were separated by a 6- to 14-day washout period starting after the last administration of dapoxetine or placebo on the morning of Day 5 of Treatment Period 1. A stable dose of terazosin was taken for the duration of the study, including the washout period.

Criteria for Evaluation:

Pharmacokinetics: Blood and plasma samples were collected at the time points indicated in the Time and Events Schedule located in the study protocol to determine concentrations of dapoxetine, desmethyldapoxetine (DED), and terazosin. After single-dose (SD) administration, the following pharmacokinetic parameters were determined from plasma concentration data for each subject for dapoxetine and the DED metabolite: maximum plasma concentration during a dosing interval (C_{max}), time to reach the maximum plasma concentration (t_{max}), elimination half-life associated with the terminal slope (λ_z) of the semilogarithmic drug concentration-time curve, calculated as $0.693/\lambda_z$ ($t_{1/2,\lambda}$), first-order rate constant associated with the terminal portion of the curve, determined as the negative slope of the terminal log-linear phase of the drug concentration-time curve (λ_z), and area under the plasma concentration-time curve during a dosing interval (τ) after a single dose, where τ equals 24 hours (h) ($AUC_{\tau,SD}$). After MD administration, pharmacokinetic parameters were determined from plasma concentration data for each subject for dapoxetine and the DED metabolites (maximum plasma concentration during a dosing interval at steady state [$C_{max,SS}$], minimum plasma concentration during a dosing interval at steady state [$C_{min,SS}$], trough plasma concentration before dosing or at the end of the dosing interval of any dose other than the first dose [C_{trough}], time to reach the maximum plasma concentration at steady state [$t_{max,SS}$], and area under the plasma concentration-time curve during a dosing interval [τ] at steady state, where τ equals 24 h [$AUC_{\tau,SS}$]).

For terazosin, plasma $C_{max,SS}$, C_{trough}, and $t_{max,SS}$ were determined on Days 1 and 5.

Pharmacodynamics: During each treatment period, serial supine and standing BP measurements were collected at the time points indicated in the Time and Events Schedule located in the study protocol with a completely automated device consisting of an inflatable cuff and an oscillatory detection system. All values were to be registered on a built-in recorder so that the measurements were observer-independent. The pharmacodynamic assessments were to occur just before the collection of the pharmacokinetic blood sample. A manual measurement of BP could be taken in the event that the automated BP device malfunctioned and a recording was not obtainable.

The supine and standing BP measurements were to be collected as orthostatic BP measurements, which were assessed by measuring both systolic and diastolic BP in a resting supine position and again shortly after maintaining a standing position. For this study, orthostatic BP measurements consisted of supine systolic and diastolic BP obtained after the subject remained in that position for 5 minutes and a standing systolic and diastolic BP obtained after the subject remained in that position for at least 2 but before 3 minutes.

The primary pharmacodynamic evaluation consisted of the calculation of the orthostatic BP (systolic and diastolic) for each subject and treatment, calculated as the difference between standing and supine BP values at each time point of measurement (orthostatic BP = standing BP - supine BP) and the estimation of the maximum effect (E_{max}) of dapoxetine on orthostatic BP (systolic and diastolic) in comparison to placebo, which was estimated by the largest negative mean difference between dapoxetine and placebo (minimum mean reduction) over time in each pharmacodynamic serial measurement day (Days 1-2 or Days 5-6). The secondary pharmacodynamic evaluation consisted of the estimation of the E_{max} of dapoxetine on BP (supine systolic, supine diastolic, standing systolic, and standing diastolic) in comparison to placebo, estimated by the largest negative mean difference between dapoxetine and placebo (maximum mean reduction) over time in each pharmacodynamic serial measurement day (Days 1-2 or Days 5-6), and the calculation of change from predose baseline (e.g., Day -1 for each treatment period) in orthostatic BP, SBP, and DBP in supine and standing positions, calculated for serial pharmacodynamic measures taken during the serial pharmacodynamic sampling days.

Pharmacogenomics: One pharmacogenomic blood sample (10 mL) was collected from all subjects who had given separate written informed consent, to allow for pharmacogenomic analysis. Samples were genotyped for variation in the cytochrome P450 (CYP) 2C19 and CYP2D6 genes.

Safety: Safety and tolerability were evaluated throughout the study by examining the incidence, severity, and type of adverse events, serious adverse events, adverse events of special interest, clinical laboratory results, 12-lead electrocardiogram (ECG, at screening only), vital sign measurements, and physical examination results.

The investigator was required to capture additional information on adverse events of special interest (i.e., syncope) in a specialized adverse event report form, which was designed to maximize the information collected on these events. Syncope was identified as an adverse event of special interest and was defined as a sudden loss of consciousness associated with the inability to maintain postural tone, followed by spontaneous recovery. Other adverse events of special interest were to be communicated to the investigator in a separate guidance if the sponsor identified any during the course of the study.

Statistical Methods:

Planned Analyses

Pharmacokinetic Analysis

Data were listed for all subjects with available plasma concentrations per treatment. All concentrations below the limit of quantification (LOQ) or missing data were labeled as such in the concentration data findings. Concentrations below the LOQ were treated as zero in the summary statistics and for the calculations of pharmacokinetic parameters. Additionally, for terazosin, because subjects received different terazosin doses (2 to 10 mg), plasma concentrations and derived pharmacokinetic parameters ($C_{max,SS}$, C_{trough}) were normalized by the terazosin dose that each subject received.

Factors that could influence the plasma concentrations (e.g., comedication, fever, high predose concentration) were checked before performing the pharmacokinetic analysis. If an influencing factor was present, a decision was made by the responsible clinical pharmacologist whether to include or exclude the specific sample or subjects. Reasons for exclusion of a subject or a sample from the analysis could have included, but was not limited to: 1) predose dapoxetine or DED plasma concentrations on Day 1 >5% of C_{max}; 2) too few data (greater than 10% missing values per each subject); and 3) noncompliance with the study procedures affecting pharmacokinetics (e.g., comedication).

Descriptive statistics, including arithmetic mean, standard deviation (SD), coefficient of variation (CV%), geometric mean, median, minimum, and maximum, were calculated for all pharmacokinetic parameters of dapoxetine, DED, and terazosin. The attainment of steady-state for dapoxetine and terazosin was evaluated graphically. Graphical representations of the results included, but were not limited to, the following graphs for dapoxetine, DED, and terazosin: 1) log-linear and linear-linear plasma concentration-time profiles for each individual subject; 2) log-linear and linear-linear plasma concentration-time profiles for the mean values per treatment; and 3) log-linear and linear-linear overlay plots of the individual plasma concentration-time profiles for each treatment.

Pharmacodynamic Analysis

The statistical analysis included only the data from subjects who completed the study. Unless otherwise specified, the pharmacodynamic analysis set was used for the analysis of all pharmacodynamic analyses.

All pharmacodynamic variables (orthostatic SBP/DBP, supine SBP/DBP, standing SBP/DBP) as well as changes from baseline were summarized by treatment using descriptive statistics. The estimated E_{max} values of all pharmacodynamic variables for dapoxetine in comparison with placebo were presented along with 95% confidence intervals (CIs).

Mean BP (supine SBP/DBP, standing SBP/DBP, orthostatic SBP/DBP) over time as well as mean change from baseline in BP over time was plotted for both treatments on the same graph.

The primary pharmacodynamic variable of interest was the orthostatic BP (SBP/DBP). The primary objective was the comparison of orthostatic BP between the 2 treatments (dapoxetine 60 mg + terazosin and terazosin + placebo).

For each serial pharmacodynamic sampling day (Days 1-2, Days 5-6), mixed-effects models were fitted to the orthostatic BP data with sequence group, period, treatment, time point of measurement, and treatment by time point of measurement interaction as fixed effects and subject as a random effect. Using the estimated least-square means and intrasubject SD from the model, the difference in means between the treatments as well as 95% CIs for the difference in means were constructed at each time point of measurement.

To compare pulse rate change (standing-supine) between the 2 treatments (dapoxetine 60 mg + terazosin and terazosin + placebo) at each time point of measurement for each of the serial pharmacodynamic sampling days (Days 1-2 or Days 5-6), similar analysis of variance (ANOVA) modeling was performed using the pulse rate change as a dependent variable, sequence group, period treatment, time point of measurement, and treatment by time point of measurement interaction as fixed effects, and subject as a random effect.

Additionally, the number of orthostatic events was tabulated for each treatment and visit day. The number of events with a SBP of <90 mmHg, and a DBP of <50 mmHg at any time, as well as the number of events in subjects with symptoms of lightheadedness, dizziness, or fainting after standing was tabulated for each treatment and serial pharmacodynamic sampling days.

Pharmacogenomics Analysis

Allele and genotype frequencies for analyzed genes were tabulated. The effect of the Predicted CYP2C19 and CYP2D6 Phenotypes on dapoxetine $AUC_{\tau,SD}$ and $AUC_{\tau,SS}$ on Days 1 and 5, respectively, was explored graphically.

Subject Demographics Analysis

Demographic and baseline characteristics were summarized by treatment sequence and overall.

Safety Analysis

All subjects who were randomized and received at least one dose of study drug were included in the safety and tolerability analysis. Safety was evaluated by examining the incidence and types of adverse events, changes in clinical laboratory test values (blood chemistry, hematology, and urinalysis) from Day -1, physical examination results from Day -1, and vital signs, (including serial pharmacodynamic supine and standing BP) from Day -1 through study completion, including the washout period.

The original terms used in the electronic case report forms (eCRFs) by investigators to identify adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA). The percentage of subjects with specific treatment-emergent adverse events (TEAEs) was summarized for each treatment. A data listing for subjects who discontinued treatment due to an adverse event was generated and data listings for adverse events were generated by subject.

Laboratory data were summarized by the type of laboratory test and descriptive statistics were calculated for each laboratory analyte at baseline and at each scheduled time point. Changes from baseline results were presented descriptively as well as in pre- versus posttreatment cross tabulations (with classes for below, within, and above normal ranges). A listing of subjects with any laboratory results outside the reference range was provided.

Standing and supine pulse, respiratory rates, and systolic and diastolic BP were summarized and descriptive statistics were provided to evaluate the changes at each scheduled time point. Results of the physical examination were listed.

Changes in Planned Analyses

Exploratory Analyses

Exploratory pharmacodynamic analyses were performed to assess the effect of the 2 cases of hypotension on the pharmacodynamic analysis results. The reanalysis excluded Subjects 100404 and 100421 and followed the same methods for analyzing orthostatic BP and pulse rate change data as was done for the full pharmacodynamic analysis set. In addition, the mean supine and standing pulse rate over time was

plotted for both treatments on the same graph for each of the pharmacodynamic sampling days (Days 1-2 or Days 5-6).

Pharmacokinetic Analysis

Four subjects were excluded from the analysis for various reasons (Subjects 100701 and 100702 were excluded from all dapoxetine and terazosin analyses and Subjects 100421 and 100426 were excluded from all terazosin analyses on Day 5 for terazosin + placebo treatment). Although the protocol stated that plasma concentration data from subjects who discontinued were not to be included in the descriptive statistics of pharmacokinetic parameters, the dapoxetine and terazosin plasma concentration and pharmacokinetic parameter data on Day 1 of Treatment Period 1 (dapoxetine + terazosin treatment) from Subject 100402, who discontinued on Day 3 of Treatment Period 1, were included in the descriptive statistics of plasma concentration data and pharmacokinetic parameters. Likewise, the terazosin plasma concentration and pharmacokinetic parameter data for Treatment Period 1 (terazosin + placebo treatment) for Subject 100428, who discontinued before receiving his first dose of dapoxetine in Treatment Period 2, were also included in the descriptive statistics of plasma concentration data and pharmacokinetic parameters.

Although the protocol stated that dapoxetine terminal half-life ($t_{1/2}$) would be reported after single-dose administration, pharmacokinetic samples were collected only for 24 h postdose due to a second dapoxetine dose being administered on the morning of Day 2. As such, the dapoxetine plasma concentration-time data after single-dose administration were not sufficient to calculate the terminal elimination $t_{1/2}$ and therefore, this parameter is not reported.

These changes in the planned analyses were not considered to have an impact on the pharmacokinetic results of the study.

RESULTS:

STUDY POPULATION:

Of the 24 randomized subjects, 22 (92%) subjects completed the study and 2 (8%) subjects were withdrawn early from treatment. The percentage of subjects withdrawn early from treatment was the same between both treatment sequences. One subject (100402) withdrew after dosing on Day 3 of Treatment Period 1 (terazosin + dapoxetine 60 mg) due to the physician's decision and the other subject (100428) withdrew after completing Treatment Period 1 (terazosin + placebo) but before taking dapoxetine on Day 1 of Treatment Period 2 due to a reason of other (i.e., positive urine drug screen).

In general, there were no apparent differences in demographic or baseline characteristics between the treatment sequence groups. The mean age was 61.5 (range 41 to 76) years and the majority (75%) of subjects were White.

One protocol deviation was reported in each of the treatment sequence groups. Both deviations involved Inclusion Criterion 2, which required that subjects be on a stable dose of terazosin for at least 6 months before study entry. In each case, the deviation was noted after the subject had completed the study. In the first case, pharmacy prescription records obtained after the subject completed the study indicated that the subject had been taking 4 mg q.d. rather than 5 mg q.d. as reported by the subject during the screening visit. In the second case, the subject had been on a stable dose of terazosin for one day less than the required 6 weeks. These deviations were related to inclusion criteria and are therefore classified as major protocol deviations. However, because neither deviation was considered likely to impact the integrity of the study, data from both of these subjects were included in the analysis.

The following deviations associated with isolated pharmacokinetic samples resulted in the exclusion of data for 4 subjects from the pharmacokinetic analysis sets. Subjects 100701 and 100702 were excluded

from the dapoxetine, DED, and terazosin pharmacokinetic analysis sets because the pharmacokinetic samples were mislabeled for both Treatment Periods 1 and 2. Terazosin pharmacokinetic parameters were excluded for Subjects 100421 and 100426 on Day 5 of Treatment Period 2 (terazosin + placebo for both subjects) because pharmacokinetic plasma sampling times at 96.5 h and 97 h on Day 5 of Treatment Period 2 were incorrectly recorded for both subjects. These deviations were not considered to have impacted the pharmacokinetic findings for dapoxetine and DED as the number of subjects with evaluable pharmacokinetic data (N=20-21) met the number of protocol-specified completers (N=20). For terazosin, the number of subjects with evaluable pharmacokinetic data (N=19) fell below the protocol-specified number of completers (N=20) only on Day 5 for the terazosin + placebo treatment; this slight deviation was not considered to have meaningfully impacted the terazosin pharmacokinetic outcomes.

Subjects were randomized to 1 of 2 treatment sequence groups (AB or BA) and received the treatments in the order as determined by their randomization. Twenty-two of the 24 subjects completed all assigned treatments.

PHARMACOKINETIC AND PHARMACODYNAMIC RESULTS

Pharmacokinetic Results

Plasma concentrations of dapoxetine increased rapidly after oral administration of dapoxetine 60 mg q.d. and terazosin on Days 1 and 5. Dapoxetine had a median t_{max} of 2.00 to 2.50 h and rapidly achieved peak plasma concentration (C_{max}) following oral administration with mean C_{max} of 473 ng/mL on Day 1 after a single dose and 585 ng/mL at steady state on Day 5. Graphical assessment of mean dapoxetine plasma concentrations suggested that dapoxetine steady state was reached by Day 3 of the coadministered treatment with terazosin. Mean dapoxetine $AUC_{\tau,SS}$ on Day 5 was approximately 52% greater than the mean $AUC_{\tau,SD}$ on Day 1. Dapoxetine mean plasma trough concentration 24 h after the last coadministered dapoxetine and terazosin treatment was approximately 15% of mean Day 5 dapoxetine $C_{max,SS}$.

The shape of the mean plasma concentration-time profile of DED after oral administration of dapoxetine 60 mg q.d. and terazosin was similar on Days 1 and 5. Median t_{max} was similar on Days 1 and 5 (3.0 and 3.5 h, respectively), and mean DED $AUC_{\tau,SS}$ on Day 5 was approximately 80% greater than $AUC_{\tau,SD}$ on Day 1.

The mean dose-normalized plasma concentration-time profile of terazosin after oral administration with dapoxetine 60 mg q.d. and placebo was similar on both Day 1 and Day 5. Median terazosin t_{max} and mean C_{max} were similar for the terazosin + dapoxetine and terazosin + placebo treatments on both Days 1 and 5. Mean terazosin C_{trough} was approximately 32% higher for the terazosin + dapoxetine versus the terazosin + placebo treatment on Day 1 but similar between the 2 treatments on Day 5.

Pharmacodynamic Results

As presented in the table below, on pharmacodynamic sampling Days 1-2, a numerical trend was observed of lower orthostatic DBP measures for dapoxetine compared with placebo. However, the upper limits of the 95% CIs for the difference in mean orthostatic DBP between terazosin + dapoxetine and terazosin + placebo were positive at all time points of measure, except at the 1.5-h (mean: -4.77 mmHg; 95% CI: -7.97, -1.57) and 3-h (mean: -4.09; 95% CI: -7.29, -0.89) time points. On pharmacodynamic sampling Days 5-6, the upper limits of the 95% CIs for the difference in mean orthostatic DBP between terazosin + dapoxetine and terazosin + placebo were positive at all time points of measure, except at the 120-h (mean: -4.23mmHg; 95% CI: -7.56, -0.90) time point.

As presented in the table below, on pharmacodynamic Days 1-2, a numerical trend was observed of lower orthostatic SBP measures for dapoxetine compared with placebo. However, the upper limits of the

95% CIs for the difference in mean orthostatic SBP between terazosin + dapoxetine and terazosin + placebo were positive at all time points of measure, except at the 1.5-h (mean: -7.14mmHg; 95% CI: -12.4, -1.88) time point. On pharmacodynamic sampling Days 5-6, the upper limits of the 95% CIs for the difference in mean orthostatic SBP between terazosin + dapoxetine and terazosin + placebo were positive at all time points of measure, except at the 98-h (mean: -5.32 mmHg; 95% CI: -10.6, -0.04) time point.

Pairwise Comparisons (Dapoxetine vs Placebo) for Serial PD Sampling Days 1-2 and Days 5-6 on Orthostatic BP (Systolic and Diastolic) Based on Mixed Effects Model

(Study R096769-PRE-1005: Pharmacodynamic Analysis Set)

	Dapoxetine 60 mg vs Placebo (Days 1-2)				Dapoxetine 60 mg vs Placebo (Days 5-6)		
Time	LS Mean	SE	95% CI	**Time**	LS Mean	SE	95% CI
Parameter: Orthostatic Diastolic BP (mmHg)							
Predose	0.41	1.63	(-2.79; 3.61)	**96 H**	1.59	1.70	(-1.74; 4.92)
0.5 H	0.14	1.63	(-3.07; 3.34)	**96.5 H**	-0.36	1.70	(-3.70; 2.97)
1 H	-0.95	1.63	(-4.16; 2.25)	**97 H**	-0.95	1.70	(-4.29; 2.38)
1.5 H	-4.77	1.63	(-7.97; -1.57)	**97.5 H**	-0.73	1.70	(-4.06; 2.60)
2 H	-2.68	1.63	(-5.88; 0.52)	**98 H**	2.50	1.70	(-0.83; 5.83)
2.5 H	-0.27	1.63	(-3.47; 2.93)	**98.5 H**	0.18	1.70	(-3.15; 3.51)
3 H	-4.09	1.63	(-7.29; -0.89)	**99 H**	0.14	1.70	(-3.20; 3.47)
4 H	-1.45	1.63	(-4.66; 1.75)	**100 H**	1.77	1.70	(-1.56; 5.10)
6 H	-0.05	1.63	(-3.25; 3.16)	**102 H**	0.50	1.70	(-2.83; 3.83)
8 H	-0.82	1.63	(-4.02; 2.38)	**104 H**	0.09	1.70	(-3.24; 3.42)
12 H	3.95	1.63	(0.75; 7.16)	**108 H**	2.77	1.70	(-0.56; 6.10)
24 H	2.18	1.63	(-1.02; 5.38)	**120 H**	-4.23	1.70	(-7.56; -0.90)
Parameter: Orthostatic Systolic BP (mmHg)							
Predose	4.32	2.67	(-0.94; 9.57)	**96 H**	-1.36	2.69	(-6.65; 3.92)
0.5 H	-4.55	2.67	(-9.80; 0.71)	**96.5 H**	2.14	2.69	(-3.15; 7.42)
1 H	-0.18	2.67	(-5.44; 5.07)	**97 H**	0.50	2.69	(-4.78; 5.78)
1.5 H	-7.14	2.67	(-12.4; -1.88)	**97.5 H**	-0.41	2.69	(-5.69; 4.87)
2 H	1.23	2.67	(-4.03; 6.48)	**98 H**	-5.32	2.69	(-10.6; -0.04)
2.5 H	-3.18	2.67	(-8.44; 2.07)	**98.5 H**	1.77	2.69	(-3.51; 7.06)
3 H	-4.82	2.67	(-10.1; 0.44)	**99 H**	2.05	2.69	(-3.24; 7.33)
4 H	-4.59	2.67	(-9.85; 0.66)	**100 H**	-0.59	2.69	(-5.87; 4.69)
6 H	-3.73	2.67	(-8.98; 1.53)	**102 H**	0.59	2.69	(-4.69; 5.87)
8 H	-2.00	2.67	(-7.25; 3.25)	**104 H**	-2.14	2.69	(-7.42; 3.15)
12 H	3.14	2.67	(-2.12; 8.39)	**108 H**	-1.00	2.69	(-6.28; 4.28)
24 H	0.00	2.67	(-5.25; 5.25)	**120 H**	-1.23	2.69	(-6.51; 4.06)

BP=blood pressure; CI=confidence interval; H=hours; LS Mean=least squares mean;
PD=pharmacodynamic; SE=standard error
Orthostatic BP= Standing BP-Supine BP
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On pharmacodynamic sampling Days 1-2, mean E_{max} (maximum reduction) in orthostatic DBP and SBP was -4.77 and -7.14 mmHg, respectively. On pharmacodynamic sampling Days 5-6, mean E_{max} (maximum reduction) in orthostatic DBP and SBP was -4.23 and -5.32 mmHg, respectively.

In orthostatic BP outlier analyses, a minimal trend was observed towards more dapoxetine-treated subjects than those who received placebo having met specified criteria across a range of systolic and diastolic changes and absolute thresholds, which suggests a possible orthostatic effect with the combination of dapoxetine and terazosin, as shown in the table below.

Number and Percentage of Subjects with Orthostatic Blood Pressure Changes After Standing: All Subjects
(STUDY R096769-PRE-1005: Pharmacodynamic Analysis Set)

Days Orthostatic Event	Terazosin+Placebo (N=22)	Terazosin+Dapoxetine 60 mg (N=22)
1-2	22 (100)	22 (100)
>20 mmHg systolic BP decrease from supine	2 (9)	5 (23)
>30 mmHg systolic BP decrease from supine	0	3 (14)
>10 mmHg diastolic BP decrease from supine	3 (14)	1 (5)
>20 mmHg diastolic BP decrease from supine	0	1 (5)
Any 4 criteria above	5 (23)	5 (23)
JNC-7 criteria met	7 (32)	5 (23)
Supine systolic BP <90 mmHg	0	0
Standing systolic BP <90 mmHg	2 (9)	2 (9)
Supine diastolic BP <50 mmHg	3 (14)	4 (18)
Standing diastolic BP <50 mmHg	0	1 (5)
5-6	22 (100)	22 (100)
>20 mmHg systolic BP decrease from supine	3 (14)	5 (23)
>30 mmHg systolic BP decrease from supine	0	1 (5)
>10 mmHg diastolic BP decrease from supine	2 (9)	1 (5)
>20 mmHg diastolic BP decrease from supine	0	0
Any 4 criteria above	4 (18)	6 (27)
JNC-7 criteria met	7 (32)	7 (32)
Supine systolic BP <90 mmHg	0	0
Standing systolic BP <90 mmHg	0	0
Supine diastolic BP <50 mmHg	1 (5)	3 (14)
Standing diastolic BP <50 mmHg	1 (5)	1 (5)

BP=blood pressure; JNC-7=Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; N=number
Note: Percentages were calculated with the number of subjects in each group as the denominator.
Note: JNC-7: ≥20 mmHg systolic BP drop from supine or ≥10 mmHg diastolic BP drop from supine.
Note: Subjects who had orthostatic BP decreases at the baseline (predose) visit were not counted.
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A trend of slight reduction in pulse rate change was observed, with a maximum mean difference of -5.00 and -3.73 at the 2.5-h and 98.5-h time points, respectively. Similarly, a trend suggestive of pulse rate change decreases was observed at other time points on Days 1-2 and 5-6.

Pharmacogenomics Results

Individuals classified as CYP2D6 Intermediate or Poor Metabolizers demonstrated a trend towards greater exposure to dapoxetine than those classified as CYP2D6 Extensive Metabolizers. No clear relationship was observed between exposure to dapoxetine and Predicted CYP2C19 Phenotypes.

SAFETY RESULTS:

Overall, TEAEs were reported by 8 (33%) subjects in the study. The overall incidence of TEAEs was similar after single (17%) and multiple (13%) doses of terazosin + dapoxetine 60 mg. There was no difference in the overall incidence of TEAEs between terazosin + dapoxetine 60 mg and terazosin + placebo after multiple doses. No subject experienced a TEAE during treatment with terazosin + placebo (SD).

Overall, the most common TEAEs were headache and hypotension (8%). All of the TEAEs were mild or moderate in intensity. Overall, although the majority of TEAEs were considered possibly related to the study drug, most were considered specifically not related to terazosin.

There were no deaths, serious adverse events, or TEAEs leading to discontinuation from the study. Two TEAEs (dry mouth and urine flow decreased) were persisting at the end of the study after multiple doses

of terazosin + placebo and terazosin + dapoxetine 60 mg, respectively. Both TEAEs were mild in intensity and not considered related to the study drug.

Two cases of hypotension were reported after a single dose of terazosin + dapoxetine 60 mg. Both events were moderate in intensity and occurred within 1 to 1.5 h after the first dose was taken on Day 1 of Treatment Period 1. Both events resolved within an hour and were considered by the investigator to be related to the study drug.

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

CONCLUSION(S):

Dapoxetine was well tolerated and no new safety concerns were identified in this study. The administration of dapoxetine 60 mg may reduce orthostatic tolerance when it is coadministered with other drugs with potent vasodilatory properties, such as terazosin, possibly secondary to a neurocardiogenic mechanism. The effect on orthostatic tolerance observed in this study appears greatest within the first few hours of initial dosing. Dapoxetine plasma concentrations associated with the 60-mg dose administered in this study was generally greater than expected, although consistent with previous findings when variability is considered. Although a pharmacokinetic interaction between dapoxetine and terazosin cannot be ruled out, the greater dapoxetine C_{max} and area under the plasma concentration-time curve (AUC) may have been related to population or study design characteristics.

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