SYNOPSIS CR003451

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: dapoxetine NAME OF ACTIVE INGREDIENT(S): [(+)-(S)-N,N-dimethyl-(a)-[2-(1-naphthalenyloxy)ethyl]-benzenemethanamine	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Protocol No.: CR003451

Title of Study: A Placebo-Controlled, Double-Blind, Randomized, Parallel Study of the Withdrawal Effects of Chronic Daily and As Needed Dosing With Dapoxetine in the Treatment of Premature Ejaculation

Coordinating Investigator: Joel Kaufmann, M.D. - Urology Research Options, Aurora, CO; USA

Publication (Reference): None

Study Initiation/Completion Dates: 08 Nov 2004/30 Aug 2005	**Phase of development: 3**

Objectives: The primary objective was to assess the possible withdrawal effects as measured by Discontinuation-Emergent Signs and Symptoms (DESS) after abrupt cessation of chronic (62 days of once daily [q.d.] therapy followed by 7 days of placebo) administration of dapoxetine (60 mg), as compared to continuous (69 days) dosing of dapoxetine (60 mg q.d.) in men with premature ejaculation (PE).

Secondary objectives were to assess the possible withdrawal effects as measured by DESS after cessation of 62 days of "as needed" (p.r.n.) therapy with dapoxetine (60 mg) followed by 7 days of placebo as compared to p.r.n. (69 days) dosing of dapoxetine (60 mg); 2) to further evaluate the tolerability and safety of dapoxetine, such as effects on vital signs, effects on mood, anxiety, and the potential for sexual side effects, and 3) to further assess the efficacy (patient-reported outcomes) of dapoxetine (60 mg) both q.d. and p.r.n., versus placebo.

Methodology: This was a placebo-controlled, double-blind, randomized, parallel-group study in men with PE conducted in multiple centers in the United States and Canada. The study consisted of a prerandomization phase (a screening visit and 7-day baseline period), a 69-day double-blind treatment phase (62 days of double-blind treatment followed by a second randomization on Day 63 to the same treatment or placebo for 7 days) with an end of treatment visit on Day 70 or at the time of early termination, a follow-up visit 7 days after discontinuation of study drug, and a post-study telephone contact (approximately 14 days after discontinuation of study drug to assess new and existing adverse events). The total duration of the study was approximately 91 days (13 weeks).

Number of Subjects (planned and analyzed): The planned sample size was 1,010 men with PE (202 subjects per treatment sequence). 1238 subjects were randomized to 3 parallel groups (placebo, dapoxetine 60 mg p.r.n., and dapoxetine 60 mg q.d.) and comprised the intent-to-treat (ITT) analysis set, which was used for all analyses of safety. A total of 811 of the 1238 ITT subjects completed the treatment period, were randomized at Day 63 to receive either their previous treatment or placebo, and comprised the intent-to-treat-extended (ITTE) analysis set, which was used for all analyses of safety during the withdrawal assessment (WA) period. Of the 1238 randomized subjects, 1236 comprised the cardiovascular assessment (CV) analysis set, which was used for analyses of cardiovascular safety on the first dose day, 1099 comprised the modified intent-to-treat (MITT) analysis set, which was used for analyses of efficacy data, and 749 comprised the modified-intent-to-treat-extended (MITTE) analysis set, which was used for analyses of the primary endpoint (withdrawal effects).

Diagnosis and Main Criteria for Inclusion: Heterosexual men at least 18 years of age, and in a stable, monogamous sexual relationship with the same woman (also at least 18 years of age) for at least 6 months and were planning to maintain this relationship for the duration of the study. Subjects were to meet the diagnostic criteria for PE as specified in the DSM-IV-TR for at least 6 months before enrolling in the study. During the 7-day baseline period, subjects were expected to attempt sexual intercourse and to record the assessments on the Baseline Event Log a minimum of 1 time.

Test Product, Dose and Mode of Administration, Batch No.: Dapoxetine 60 mg tablets (Batch # 03118/F006 and 04127/F006) taken q.d. in the evening before bedtime or taken p.r.n. 1-3 hours prior to sexual activity. Subjects randomized to receive p.r.n. dosing received treatment with matching placebo q.d.; subjects randomized to receive q.d. dosing received treatment with matching placebo p.r.n.. No more than 1 q.d. tablet and 1p.r.n. tablet of study medication were to be taken in a 24 hour period.

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Reference Therapy, Dose and Mode of Administration, Batch No.: Matching placebo tablets (Batch # 02103/F008, 03117/F008, and 05B07/F008).

Duration of Treatment: Sixty-two days of double-blind treatment with dapoxetine 60 mg p.r.n., dapoxetine 60 mg q.d., or placebo followed by an additional 7 days of treatment with the same treatment or placebo.

Criteria for Evaluation:

Evaluation of Withdrawal Effects (Primary endpoint): Withdrawal effects were assessed as measured by DESS. Assessment of possible discontinuation-emergent events was solicited from subjects at Days 63 and 70 using the weekly (7-day recall) DESS checklist. For each subject, a discontinuation syndrome was defined as an increase in weekly DESS score by at least 4 points from the day of second randomization to the end of the withdrawal assessment period.

Efficacy: Patient-reported efficacy outcomes that were collected to evaluate the subject's perceptions of sexual function and response to treatment prior to, during, and following treatment include: Control Over Ejaculation, Satisfaction With Sexual Intercourse, Symptom Severity Impression, Clinical Global Impression of Change, Medication Helpfulness, Personal Distress, and Interpersonal Difficulty.

Safety: Safety was evaluated by examining incidence, severity and type of adverse events, changes in clinical laboratory results, physical examination results, 12-lead electrocardiogram (ECG), vital sign measurements, including orthostatic BP and HR measurements, Holter monitoring, as well as monitoring for syncopal episodes and concomitant therapy. Mood, anxiety, incidence of akathisia, and sexual side effects were assessed using the following scales: (Mini International Neuropsychiatric Interview [M.I.N.I. at screening only], Beck Depression Inventory (BDI-II, self-reported), Montgomery-Asberg Depression Rating Scale (MADRS, observer rated), Hamilton Anxiety Scale (HAM-A, observer rated), Barnes Akathisia Scale (BARS), and International Index of Erectile Function Questionnaire [IIEF]). If any major DSM-IV-TR psychiatric disorders were noted at screening or baseline, the subject was excluded from the study. If during the study a subject developed clinically concerning signs of anxiety, depression, or suicidal ideation, the study drug was discontinued, and the subject was followed until the adverse event resolved and was referred for further evaluation and treatment. The medical monitor was notified.

Statistical Methods: Withdrawal Effects: The incidence of discontinuation syndrome was analyzed by means of logistic regression. The model included terms for treatment arm and pooled center. A 95% confidence interval for the following between-group difference was estimated:

- (69-day dapoxetine q.d.) vs. (62-day dapoxetine q.d., 7-day placebo)
- (69-day dapoxetine p.r.n.) vs. (62-day dapoxetine p.r.n., 7-day placebo).

DESS was analyzed using 2 approaches: scores from all subjects who completed DESS sheets at Days 63 and 70 (primary analysis), and modified DESS scores from subjects who have completed or partially completed DESS sheets at Days 63 and 70 (worst –case scenario). Mean and mean changes from baseline in DESS scores including pairwise comparisons between the dapoxetine treatments and placebo were also evaluated.

Efficacy: Mean and mean changes from baseline in scores for the Control Over Ejaculation, Satisfaction With Sexual Intercourse, Symptom Severity Impression, Personal Distress, and Interpersonal Difficulty PROs and changes over time for the Clinical Global Impression of Change and Medication Helpfulness PROs using an Analysis of Variance (ANOVA) model with factors for treatment group and pooled center were analyzed. Pairwise comparisons between the dapoxetine treatments and placebo were evaluated for all PROs. Spearman Rank Correlation analyses among PROs and correlation analyses of Global Impression of change at the end of the treatment period with the Control Over Ejaculation, Satisfaction With Sexual Intercourse, Symptom Severity Impression, Personal Distress, and Interpersonal Difficulty PROs, as well as a comparison of the number of satisfactory sexual experiences based on the Event Log with scores on the Satisfaction With Sexual intercourse PRO were performed.

Safety: The number and percentage of subjects with treatment-emergent adverse events was summarized by

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treatment group/sequence. Descriptive statistics, change from baseline, and the number and percentage of subjects exceeding predefined limits for clinical laboratory test, vital sign, and ECG data were summarized. Descriptive statistics were provided for physical examination data. Evaluations of cardiovascular safety on the first dose day included orthostatic vital signs changes and the occurrence of abnormalities on Holter monitoring. Descriptive statistics for individual item and total scores for the BDI-II, MADRS, HAM-A, and BARS as well as cross tabulations by baseline and postbaseline score were provided. Frequency tables and descriptive statistics were provided for module scores for the IIEF.

SUMMARY - CONCLUSIONS

EVALUATION OF WITHDRAWAL EFFECTS: The incidence of discontinuation syndrome, as measured by DESS, was rare, regardless of treatment sequence. Overall, 8 subjects had discontinuation syndrome during the WA period: 2 (1.3%), 1 (0.6%), 1 (0.7%), 2 (1.4%), and 2 (1.3%), in the dapoxetine 60 mg q.d./placebo, dapoxetine 60 mg q.d./q.d., dapoxetine 60 mg p.r.n./placebo, dapoxetine 60 mg p.r.n./p.r.n., and placebo/placebo treatment sequences, respectively. Mean and mean changes from baseline in DESS scores were similar in all treatment sequences. Changes from baseline in DESS scores were similar in magnitude in subjects who received either dapoxetine treatment (q.d. or p.r.n.) continuously for 69 days and in subjects who were switched to placebo after receiving dapoxetine (q.d. or p.r.n.). Thus, there is no evidence of withdrawal effects (based on DESS) when dapoxetine treatment (q.d. or p.r.n.) is abruptly discontinued. Consistent with results using weekly DESS, evaluation of daily DESS showed no clear evidence of SSRI-induced discontinuation syndrome.

EFFICACY RESULTS: Seven key PROs were measured during the study. Five PROs (Control Over Ejaculation, Satisfaction with Sexual Intercourse, Personal Distress, Interpersonal Difficulty, and Symptom Severity Impression) were measured at baseline and during the treatment period, and 2 PROs (Clinical Global Impression of Change and Medication Helpfulness) were measured during the treatment period. Responses were measured on a scale of 0 to 4 (except for the question on Symptom Severity Impression which was evaluated on a scale from 0 to 3 and Clinical Global Impression of Change and Medication Helpfulness, which were evaluated on a scale of -3 to 3). For all PROs, both dosing regimens (p.r.n. and q.d.) of dapoxetine were significantly better than placebo. In all 3 treatment groups there was a time dependent increase in Satisfaction with Sexual Intercourse and Control Over Ejaculation and a time dependent decrease in Personal Distress, Interpersonal Difficulty, and Symptom Severity. Improvement in sexual functioning as measured by PROs was greater in both the dapoxetine q.d. and p.r.n. groups, compared to the placebo group. In general, average PRO response was slightly higher in the dapoxetine 60-mg p.r.n. group than in the dapoxetine 60-mg q.d. group.

SAFETY RESULTS: The results of this study showed that dapoxetine 60 mg, administered q.d. or p.r.n. was generally safe and well tolerated by subjects with PE. There were no deaths during the study and a low incidence of serious adverse events (placebo: 1 subject; dapoxetine 60 mg p.r.n., 2 subjects; dapoxetine 60 mg q.d., 7 subjects). A total of 9.6% of subjects in each of the dapoxetine groups and 2.0% of placebo-treated subjects discontinued from the study due to an AE that began during the treatment period. Nausea and dizziness were the most frequently reported AEs resulting in early discontinuation from the study in the dapoxetine 60 mg pr.n. and q.d. groups. Adverse events were reported by 44.1%, 61.3%, and 62.5% of subjects in the placebo, dapoxetine 60 mg p.r.n., and dapoxetine 60 mg q.d. groups during the treatment period and by 16.8%, 13.1%, 18.8%, 23.6%, and 26.5% of subjects in the placebo/placebo, dapoxetine 60 mg p.r.n/placebo, dapoxetine 60 mg p.r.n/pr.n., dapoxetine 60 mg q.d/placebo, and dapoxetine 60 mg q.d./q.d. treatment sequence during the WA period. During the treatment period, the most commonly reported AEs (those occurring in ≥5% of subjects in any treatment group) were nausea, dizziness, headache, diarrhea, fatigue and insomnia. Most adverse events were mild or moderate in severity. All were reported more frequently in the dapoxetine groups than in the placebo group. Adverse events reported in at least 2% of subject during the WA period included diarrhea, headache, insomnia, nausea, irritability, and dizziness. The type and frequency of treatment-emergent AEs and early study discontinuation AEs observed for dapoxetine during this study are similar to those reported for dapoxetine in previous Phase 3 clinical studies. There was no difference in the frequency of AEs reported between the dapoxetine q.d. and dapoxetine p.r.n. groups, indicating that dapoxetine when dosed either q.d. or p.r.n. has a similar safety profile.

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Adverse event data showed no clear pattern of treatment-emergent suicidality with dapoxetine. During the study, 1 subject in the dapoxetine dapoxetine 60 mg p.r.n./placebo group reported an adverse event of suicidal ideation (verbatim term: 1 suicidal thought) that was accompanied by a moderate stress reaction to a psychosocial event that began on Day 31 and resolved on Day 76. One subject in the dapoxetine 60 mg q.d. group reported an adverse event of abnormal dreams (verbatim term: suicidal dreams) on Day 39. The subject decided to stop taking study medication, discontinued from the study on Day 40 and did not enter the WA period. He reported no further suicidal dreams after discontinuing treatment with study medication. Consistent with the adverse event data, scores on the suicidality item of the BDI-II and MADRS questionnaires also showed no evidence of clinical worsening suggestive of treatment-emergent suicidal ideation associated with dapoxetine treatment.

Overall, 5 subjects reported adverse events that coded to the MedDRA preferred term syncope or syncope vasovagal during the study. Among these 5 subjects, 3 experienced a loss of consciousness varying from 15 seconds to 1 minute, meeting the protocol-specified definition of syncope. The other 2 subjects did not lose consciousness. All cases of syncope resolved spontaneously with no further reports of syncope in subjects who continued in the study following the syncopal event (2 of the 5 subjects). Overall, the clinical circumstances surrounding these events – the observed decrease in blood pressure and/or heart rate, the occurrence of typical vasovagal symptoms with the syncopal events, the occurrence of the majority of cases during a study site visit, and the absence of an alternative mechanism – suggests a vasovagal etiology for all episodes.

Holter monitoring performed on the first dose day to assess cardiovascular safety showed a higher percentage of abnormalities in the dapoxetine group (60.3%) than in the placebo group (54.7%). The most frequently occurring abnormalities were supraventricular arrhythmias and ventricular arrhythmias. Three cases of ventricular tachycardia were detected during Holter monitoring, all in subjects who received dapoxetine. All cases were asymptomatic, nonsustained (less than 30 seconds in duration), and had not been reported as adverse events by the investigator. The morphology of the QRS complexes during these episodes of ventricular tachycardia suggests an automatic mechanism, and that these episodes of ventricular tachycardia are thus likely not related to treatment with dapoxetine.

Consistent with the lack of withdrawal effects based on DESS, adverse event data from this study generally showed little indication of withdrawal symptoms with dapoxetine treatment. However, the slightly higher incidence of mild or moderate insomnia and dizziness (6.1% and 4.8%) in subjects who were switched to placebo after receiving dapoxetine 60 mg q.d. for 62 days compared with subjects who received dapoxetine 60 mg q.d. continuously for 69 days (2.4% and 1.2%) suggests that the occurrence of generally mild withdrawal symptoms following daily dosing dapoxetine cannot be excluded.

Taken together, adverse event data and scores on the HAM-A and BARS questionnaires showed no evidence of treatment-emergent anxiety or akathisia with dapoxetine. There was no evidence of a treatment-emergent effect on sexual functioning based on IIEF questionnaire scores or on erectile dysfunction based on adverse event data.

There were no clinically relevant effects of dapoxetine on clinical laboratory test, ECG, vital signs, or physical examination data.

CONCLUSIONS: The results of this 9-week double-blind study indicate that dapoxetine 60 mg when administered q.d. for the treatment of PE produced no evidence of a withdrawal effect when abruptly discontinued, based on weekly DESS (the primary variable). Consistent with this finding, dapoxetine 60 mg produced no evidence of a withdrawal effect when administered p.r.n. for treatment of PE and abruptly discontinued, based on weekly DESS. The positive results on the primary endpoint measurement are supported by secondary analyses of daily DESS results.

Dapoxetine treatment caused significant improvement in ejaculatory control in this population of PE subjects with severe (poor or very poor) impairment of ejaculatory control at baseline. Significant improvement in all PROs (Control Over Ejaculation, Satisfaction With Sexual Intercourse, Personal Distress, Interpersonal Difficulty, Symptom Severity Impression, Clinical Global Impression of Change, and Medication Helpfulness) was seen with dapoxetine when administered at a 60 mg dose p.r.n or q.d. for the treatment of PE. In general, average PRO response was slightly higher in the dapoxetine p.r.n. group than in the dapoxetine q.d. group.

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Consistent with the lack of withdrawal effects based on DESS, adverse event data generally showed little indication of withdrawal symptoms of dapoxetine. However, the slightly higher incidence of mild or moderate insomnia and dizziness in subjects who were switched to placebo after receiving dapoxetine 60 mg q.d. for 62 days compared with subjects who received dapoxetine 60 mg q.d. continuously for 69 days suggests that the occurrence of generally mild withdrawal symptoms following daily dosing dapoxetine cannot be excluded.

Dapoxetine when dosed either q.d. or p.r.n. has a similar safety profile. Adverse event data together with scores on the suicidality item of the BDI-II and MADRS questionnaires showed no clear pattern of treatment-emergent suicidality or other psychiatric symptoms with dapoxetine. Adverse event data and scores on the HAM-A and BARS questionnaires showed no evidence of treatment-emergent anxiety or akathisia with dapoxetine. IIEF questionnaire scores showed no evidence of treatment-emergent effect on sexual functioning; adverse event data showed no evidence of a treatment-emergent erectile dysfunction.

Of the 5 subjects who reported syncope during the study, 3 experienced a loss of consciousness. These adverse events of syncope occurred after administration of the first dose of dapoxetine at the study site on Day 1 and appeared to have a vasovagal etiology.

There were no clinically relevant effects of dapoxetine on clinical laboratory test, ECG, vital signs, or physical examination data.

Date of the report: 16 August 2006

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