CLINICAL STUDY REPORT SYNOPSIS

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Name of Sponsor/Company	Johnson & Johnson Pharmaceutical Research & Development	
Name of Finished Product	Dapoxetine	
Name of Active Ingredient(s)	Dapoxetine	

Protocol No.: CR004228

Title of Study: A Placebo-Controlled, Double-Blind, Randomized, Parallel-Group Study of the Efficacy and Safety of Dapoxetine in the Treatment of Men With Premature Ejaculation

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Publication (Reference): None

Study Period: 12 April 2005 to 22 June 2006 | **Phase of Development:** 3

Objectives: The primary objective was to demonstrate that dapoxetine (30 mg or 60 mg p.r.n.) could prolong IELT as measured by partner-operated stopwatch when compared to placebo in men with PE during the 12-week treatment phase.

Key secondary objectives were to assess the effects of dapoxetine 30 or 60 mg for 12 weeks compared with placebo on the proportion of subjects who met the following criteria:

1. At least a 2-category increase in Control Over Ejaculation and at least a 1-category decrease in Personal Distress (a subject who met these criteria was considered a responder)
2. At least a 1-category decrease in Personal Distress
3. At least a 1-category increase in Satisfaction With Sexual Intercourse.

Other secondary objectives were to assess the effect of treatment with dapoxetine 30 or 60 mg for 12 weeks compared with placebo on changes in the following efficacy evaluations captured at each scheduled visit: Clinical Global Impression of Change, Control Over Ejaculation, Satisfaction With Sexual Intercourse, Symptom Severity Impression, Personal Distress, Interpersonal Difficulty, Medication Helpfulness, Satisfaction With Sexual Intercourse (recorded on the event log), change in average IELT, the number of all intercourse attempts recorded in the event log, and average duration of all intercourse attempts.

Methodology: This was a multicenter, placebo-controlled, double-blind, randomized, parallel-group study in men with PE. The study consisted of a prerandomization phase (a screening visit and a 4-week baseline period), a 12-week double-blind treatment phase with an end of treatment or early termination visit, and a poststudy telephone contact (approximately 2 weeks after discontinuation of study drug to assess new and existing adverse events). The total duration of the study was approximately 18 weeks.

Number of Subjects (planned and analyzed): Approximately 1,110 men with PE were to be randomized into the study.

Diagnosis and Main Criteria for Inclusion: The study was comprised of men with PE (onset of orgasm and ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the subject wishes it in the majority of intercourse experiences in the past 6 months). Subjects were ≥18 years of age and in a stable, monogamous sexual relationship with the same woman for at least 6 months and planned to maintain this relationship for the duration of the study. Eligible subjects met all of the inclusion and none of the exclusion criteria.

In order to collect safety data required for registration in specific countries/regions, the protocol stipulated that at least 300 subjects of Chinese ethnicity, at least 100 subjects of Taiwan-Chinese ethnicity and at least 200 subjects of Korean ethnicity were to be randomized. The remaining 510 subjects were recruited either in these 3 countries/regions or other Asian-Pacific countries/regions, including Australia.

Test Product, Dose and Mode of Administration, Batch No.: Doses of dapoxetine were taken on an as needed (p.r.n.) basis. Each dose, containing either 30 mg or 60 mg, consisted of 2 tablets. Doses and batch numbers were as follows: 30 mg (04H25/F005 and 04I24/F005) or 60 mg (04I27/F006 and 04I28/F006)

Reference Therapy, Dose and Mode of Administration, Batch No.: Placebo tablets were taken on prn basis. Each dose consisted of 2 tablets. Doses and batch numbers were as follows: 30 mg (04J04/F007 and 05B08/F008) or 60 mg (04J01/F008, 05B16/F008, and 05B23/F008).

Duration of Treatment: Dapoxetine or placebo was taken p.r.n. for 12 weeks.

SYNOPSIS (CONTINUED)

Criteria for Evaluation:

Efficacy: The primary endpoint of assessing the efficacy of dapoxetine versus placebo was the average IELT at the end of the double-blind treatment phase, as measured by stopwatch. Measurement of IELT via the stopwatch provided an objective assessment of the pharmacologic effects of dapoxetine. Secondary endpoints consisted of the following reported outcomes (recorded by subject): Control Over Ejaculation, Satisfaction With Sexual Intercourse, Symptom Severity Impression, Clinical Global Impression of Change, Personal Distress, Interpersonal Difficulty, Medication Helpfulness Question, and Satisfaction With Sexual Intercourse (recorded on the event log). Of these, three key patient reported outcomes (PROs) were used to assess key concepts in the evaluation of PE. The PROs of Control Over Ejaculation, Personal Distress, and Satisfaction With Sexual Intercourse were included in the key secondary efficacy evaluations.

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, at screening only), vital sign measurements, including orthostatic BP and HR measurements, Holter monitoring at first dose (using 12 leads), sexual function scales, International Index of Erectile Function [IIEF] Questionnaire), and frequency of intercourses. If during the study, a subject developed clinically concerning signs of anxiety, depression, suicidal ideation, or akathisia, the study drug was discontinued at the discretion of the investigator, and the subject was followed until the adverse event resolved.

Pharmacogenomics: Whole blood was taken for genetic analysis from subjects who gave informed consent for this part of the study. Pharmacogenomic samples were applicable only for those countries/regions where the health authorities have approved of this testing. The goal of the pharmacogenomic analysis is to evaluate whether any differences in dapoxetine efficacy or safety, observed between Caucasian (from earlier studies) and Asian populations can be explained by differences in predicted CYP2D6 metabolizer status. Pharmacodynamic effects such as drug-related adverse effects may also potentially be influenced by genetic variability in drug targets. Hence, pharmacogenomic variations in putative drug targets may help to explain the mode of drug action in relation to drug safety and efficacy. However, due to local regulations only a limited number of samples have been collected and analyzed for *CYP2D6* and *CYP2C19*. Data will be combined with data from other suitable studies for a separate pharmacogenomics analysis.

Statistical Methods: Analysis of covariance (ANCOVA) was performed for the average IELT at Week 12. The model included factors accounting for the effect of treatment, region/country, and the stratification where subjects were classified according to the length of their baseline average IELT (≤1 minute versus >1 minute). The baseline average IELT was also included as a covariate. For discontinued subjects, their last postbaseline assessments were carried forward to Week 12.

The key secondary efficacy variables were the following response rates (1.At least a 2-category increase in Control Over Ejaculation and at least a 1-category decrease in Personal Distress (a subject who met these criteria was to be considered a responder); 2. At least a 1-category decrease in Personal Distress; and 3. At least a 1-category increase in Satisfaction With Sexual Intercourse) for selected subject PRO measures at Week 12 using the LPOCF approach. Cochran-Mantel-Haenszel tests of these response rates were performed by treatment group, with adjustment for baseline average IELT stratum and region/country. The differences in proportion of responders between active doses (30 or 60 mg) and placebo, and their 95% confidence intervals were estimated. In addition, the response rates were assessed at Weeks 4, 8, and 12. Subgroup analyses were also provided for the key secondary measures as performed for the primary efficacy measure.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS: Average IELT increased from approximately 1.1 minutes at baseline to 3.85 and 4.22 minutes in dapoxetine 30 mg and 60 mg groups, at the Week 12 endpoint ($P<0.001$ for both dapoxetine groups vs. placebo). In contrast, the average IELT increased to 2.41 minutes in the placebo group. A significant improvement (increase) in the average IELT in each of dapoxetine dose groups versus placebo was observed at all timepoints beginning at Week 4 and was maintained at all subsequent timepoints (all $p < 0.001$). The increases in IELT were numerically greater in the dapoxetine 60 mg group than the dapoxetine 30 mg group; however, the difference between these treatments was not statistically significant.

SYNOPSIS (CONTINUED)

Pairwise Comparison of Average IELT at Endpoint
(Study R096769-PRE-3003: Intent-to-Treat Analysis Set)

	Parameter: Average IELT (min)		
Overall Population	PLACEBO (N=357)	DPX 30 MG PRN (N=354)	DPX 60 MG PRN (N=356)
n	342	333	331
Mean (SD)	2.419 (2.0536)	3.850 (3.9463)	4.226 (3.9687)
Overall P-value	<0.001		
P-value (minus Placebo)		<0.001	<0.001
Diff. of LS Means (SE)		1.367 (0.2552)	1.774 (0.2555)
95% CI		(0.8662;1.8676)	(1.2724;2.2751)

Results of the key secondary endpoints were consistent with those for average IELT. At the end of the 12-week treatment period, there were 74 (21.7%), 114 (34.7%), and 125 (37.2%) responders (i.e., subjects who had at least a 2-category increase in Control Over Ejaculation and at least a 1-category decrease in Personal Distress) from baseline to Week 12 endpoint (LPOCF), in the placebo, dapoxetine 30 mg, and dapoxetine 60 mg groups, respectively ($p<0.001$ for both dapoxetine doses vs. placebo). A significantly higher percentage of subjects in both dapoxetine groups experienced improvement in Distress scores (at least a 1-category decrease) compared with placebo (60 mg dapoxetine $p<0.001$; 30 mg dapoxetine $p=0.007$) at endpoint. In addition, a higher percentage of subjects experienced improvement in Satisfaction score (at least a 1 category increase) after treatment (dapoxetine 60 mg, $p<0.001$ vs. placebo and dapoxetine 30 mg, $p=0.002$ vs. placebo).

The effect of dapoxetine compared with placebo on other secondary efficacy endpoints are consistent with the effect seen with the primary and key secondary efficacy analyses. Significant improvements compared with placebo were seen for all PROs and other secondary efficacy variables for both dosing regimens of dapoxetine. The positive efficacy results demonstrated in this study confirm the positive efficacy results demonstrated in previous Phase 3 studies of dapoxetine.

SAFETY RESULTS: Overall, AE data from this study demonstrate that both dosing regimens of dapoxetine (30 and 60 mg) were well tolerated. No new safety issues were identified in this study. Adverse events were reported by 17.9%, 33.3%, and 49.7% of subjects in the placebo, dapoxetine 30 mg, and dapoxetine 60 mg groups. Adverse events reported most commonly (≥ 2%) were nausea, dizziness, somnolence, headache, vomiting, diarrhea, and nasopharyngitis, all of which were reported in a greater proportion of subjects in the dapoxetine groups than in the placebo group. Dose-related increases (placebo vs. dapoxetine 30 mg vs. 60 mg) in nausea (2.0% vs. 10.5% vs. 26.4%), dizziness (3.9% vs. 10.5% vs. 18.8%), and somnolence (0.6% vs. 3.4% vs. 6.2%) were noted. There were no reports of syncope or suidicality or suicidal ideation during the study. For the by region/country analyses of AEs, the safety trends were consistent with the overall population in the TEAEs reported at anytime during the study and with an onset of Day 1.

Serious adverse events were uncommon (3 subjects each in the placebo and dapoxetine 30 mg groups), and all were judged not related to treatment with study medication. There was one death in this study in the 30 mg dapoxetine group. The investigator did not consider this event to be related to study drug. The incidence of study medication discontinuation due to AEs was higher in the dapoxetine 60 mg group (18 subjects, 5.1%) than the dapoxetine 30 mg (6 subjects, 1.7%) and placebo (1 subject, 0.3%) groups. Nausea and dizziness were the most frequently reported TEAEs resulting in early discontinuation from the study in the dapoxetine 60 mg group (9 and 6 subjects, respectively).

CONCLUSION:

- Dapoxetine 30 and 60 mg significantly prolonged IELT compared with placebo in men with PE.
- A significantly higher percentage of men treated with dapoxetine 30 and 60 mg were responders as defined by at least a 2-category increase in Control Over Ejaculation and at least a 1-category decrease in Personal Distress, indicating a meaningful treatment benefit to the subject.
- Significant improvements compared to placebo were seen for all PROs for both dosing regimens of dapoxetine. These secondary efficacy results support the results of the primary and key secondary efficacy analyses.
- Dapoxetine was well tolerated with no new safety issues identified. No noteworthy cardiovascular safety issues or sexual side effects were demonstrated. The most common AEs reported by subjects on dapoxetine were nausea and dizziness.
- Analyses of the efficacy and safety in this study demonstrate that this population of Asian men showed improvements in PE and have an adverse event profile consistent with previously established efficacy and safety data from the dapoxetine clinical program.

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