CLINICAL STUDY REPORT SYNOPSIS

Document No.: EDMS-PSDB-4083647:2.0

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	

Protocol No.: R096769-PRE-3001 (CR004231)

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

Principal Investigator: Jacques Buvat, M.D. - CETPARP/Le grand Hunier, Lille, France

Publication (Reference): None

Study Period: 6 December 2004—31 October 2006 | **Phase of Development:** 3

Objectives: The primary objective was to demonstrate that dapoxetine (30 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 24-week treatment phase.

Key secondary objectives were to assess the effects of dapoxetine 30 or 60 mg for 24 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 the comparison of patient-reported outcomes (PRO measures) between dapoxetine- and placebo-treated subjects. This study also assessed the safety and tolerability of treatment, including cardiovascular safety, mood and anxiety assessment, incidence of akathisia, and sexual side effects. A 1-week withdrawal assessment period following the double-blind treatment phase assessed the effects of abrupt discontinuation of study drug as measured by the Discontinuation Emergent Signs and Symptoms (DESS) checklist.

Methodology: This was a multicenter, multinational, placebo-controlled, double-blind, randomized, parallel group study in men with PE conducted in 22 countries that included Europe and South America, Israel, South Africa, Canada, and Mexico. The study consisted of a prerandomization phase (a screening visit and a 4-week baseline period), a 24-week double-blind treatment phase with an end of treatment or early termination visit, a 1-week double-blind withdrawal assessment (WA) phase with the same treatment or placebo during the assessment (WA) period, a follow-up visit approximately 1 week later (Week 25), and a poststudy telephone contact (approximately 2 weeks after completion of the WA period or upon early termination from the study. The total duration of the study was approximately 31 weeks.

Number of Subjects (planned and analyzed): The planned sample size was 1300 subjects and a total of 1162 subjects (385, 388, and 389 per placebo, dapoxetine 30 and 60 mg p.r.n., respectively) were randomized. These 1162 subjects comprised the intent-to-treat (ITT) analysis set. A total of 618 of the 1162 ITT subjects completed the treatment period, and 550 of the 618 subjects entered the WA period, which was completed by 549 subjects.

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, the protocol stipulated that approximately 1300 men with PE were to be randomized. The study was conducted in 22 countries that included countries in Europe and South America, Israel, South Africa, Canada, and Mexico at 130 centers.

Test Product, Dose and Mode of Administration, Batch No.: Dapoxetine was supplied as 30-mg and 60-mg tablets for oral administration and the batch numbers were: 04H25/F005, 04I24/F005, 04H27/F006, 04I27/F006, and 04I28/F006.

Reference Therapy, Dose and Mode of Administration, Batch No.: Matching placebo tablets were supplied for oral administration and their batch numbers were: 03I15/F007, 04J04/F007, 05B08/F007, 04A15/F008, 03I17/F008, 04I29/F008, 05B16/F008.

Duration of Treatment: Subjects received 30 mg dapoxetine, 60 mg dapoxetine, or placebo on a p.r.n. basis for 24 weeks. Subjects in the dapoxetine 30-mg and 60-mg groups were randomly assigned at the Week-24 visit to receive either the same treatment assigned on Day 1 or placebo during the 7-day WA period (placebo was randomized to placebo or placebo).

Criteria for Evaluation:

Efficacy: The criterion for the primary efficacy variable was a statistically significant increase in the least square mean estimate of the average IELT in the dapoxetine groups compared with the placebo group. Three key secondary subject PRO measures included: Control Over Ejaculation, Personal Distress, and Satisfaction with Sexual Intercourse, which were defined as the proportion of subjects who had the following responses in PRO scores: (1) at least a 2 category increase in Control Over Ejaculation and an at least 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, and (3) at least a 1 Category increase in Satisfaction With Sexual Intercourse.

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), mood (MADRS and BDI-II), anxiety (HAM-A), akathisia (BARS), and sexual function (IIEF) scales, and frequency of intercourse events. 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. The goal of the pharmacogenomic analysis was to evaluate whether any differences in efficacy and safety results observed between subjects treated with dapoxetine can be explained by differences in predicted CYP2D6 and CYP2C19 phenotype. There were 2 parts of the pharmacogenomic testing that included the analyses by predicted phenotype (CYP2D6 and CYP2C19) (Part 1), and the optional consent for possible future genetic testing of genes related to dapoxetine (Part 2).

Statistical Methods:

Efficacy: The comparison of average IELT between the dapoxetine and placebo groups used an analysis of covariance (ANCOVA) that included factors for the effect of treatment, pooled country, and calculated baseline average IELT (≤1 minute vs >1 minute) stratum. The baseline average IELT was also included as a covariate. Cochran-Mantel-Haenszel (CMH) tests of the subject response rates for the composite of Control Over Ejaculation and Personal Distress, and for Personal Distress, Satisfaction with Sexual Intercourse (key secondary variables), and Clinical Global Impression of Change at both Week 12 and Week 24 (LPOCF) were performed by treatment group, with adjustment for baseline average IELT stratum and pooled country. The differences in the response rates between each of the active doses (30 or 60 mg) and placebo, and their 95% confidence intervals were estimated. For each of the subject and partner PRO measures, an analysis of variance (ANOVA) was performed to compare treatment groups for the changes from baseline to Week 24 (LPOCF). The analysis of variance (ANOVA) model included factors for treatment group, pooled country, and baseline average IELT stratum.

Safety: Treatment-emergent adverse events, and those events of special interest were summarized by treatment group. For the BDI-II, HAM-A, MADRS, BARS, and IIEF scales, descriptive statistics for individual item and total (except for the IIEF) scores over time were provided. Possible suicide-related adverse events were identified using search and screening strategies based on the approach developed by the FDA Division of Psychiatry Products and those events relevant to suicidality were summarized in narratives that were classified by an independent external consultant as to their relation to suicidality. Descriptive statistics for laboratory analytes and for changes from baseline at each postbaseline visit and the incidence of markedly abnormal laboratory values were provided by treatment group.

Withdrawal Effects: The incidence of discontinuation syndrome was analyzed by means of logistic regression. The logistic model included terms for treatment arm and pooled country. A 95% confidence interval for the mean difference in the change in Discontinuation Emergent Signs and Symptoms (DESS) scores during the WA period between treatment sequences was estimated with second treatment assignment, country of the investigator site, and baseline Discontinuation Emergent Signs and Symptoms (DESS) scores as covariates.

SUMMARY - CONCLUSIONS

EFFICACY RESULTS: Average IELT increased from approximately 0.9 minutes at baseline to 3.1 and 3.5 minutes in dapoxetine 30-mg and 60-mg groups, respectively, at the Week 24 endpoint, which was nearly identical to the results at Week 12. In contrast, the average IELT increased to only 1.9 minutes in the placebo group at both Week 24 and Week 12 ($P<0.001$ for both dapoxetine groups vs. placebo). A significant improvement (increase) in the average IELT in each of dapoxetine dose groups versus placebo was observed at all timepoints beginning at first dose and Week 4 and was maintained at all subsequent timepoints (all $p\leq0.001$), with most of the increase by Week 12. Similar results were obtained for subjects in each IELT stratum.

Results of the key secondary endpoints were consistent with those of the primary efficacy analyses. At the Week-24 endpoint, there were significantly more 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) in the dapoxetine 30-mg (25.3%) and 60-mg groups (37.1%) than in the placebo group (13.0%) ($p<0.001$). A significantly larger proportion of subjects in both dapoxetine groups experienced improvement in Personal Distress scores (at least a 1-category decrease) compared with placebo ($p<0.001$ for both comparisons) at the Week-12 and Week 24 endpoints. In addition, significantly more subjects experienced improvement in Satisfaction score after treatment with 30 or 60 mg dapoxetine than with placebo ($p<0.001$ for both comparisons). The effect of dapoxetine compared with placebo on other secondary efficacy endpoints support its efficacy 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.

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 38.4%, 56.2%, and 68.1% of subjects in the placebo, dapoxetine 30-mg, and dapoxetine 60-mg groups. The most common adverse events reported in this study were nausea, headache, dizziness, and diarrhea, and are consistent with the gastrointestinal and CNS adverse effects of the SSRI class of drugs. The percentage of subjects who discontinued treatment due to an adverse event was 1.3%, 3.9%, and 8.2% in the placebo, dapoxetine 30-mg, and dapoxetine 60-mg groups, respectively. There was a low incidence of serious adverse events (~1%) across treatment groups, and most of these events were not related to study drug and resolved without sequelae. There were no reports of syncope in the 30-mg dapoxetine group and 2 cases including loss of consciousness in the 60-mg dose group. There was no evidence of deleterious effects on sexual functioning as measured by the IIEF and the incidence of urogenital system and sexual function adverse events was low and similar across treatment groups, with 3.1%, 3.1%, and 4.9% of subjects reporting an event in the placebo, dapoxetine 30-mg, and dapoxetine 60-mg groups, respectively. Adverse event data as well as the MADRS and BDI-II questionnaires showed no evidence of treatment-emergent suicidality with dapoxetine. Similarly, there was no evidence of effects of anxiety or akathisia, as measured by the HAM-A and BARS, respectively. The percentage of subjects who reported an accidental injury was 1.8%, 2.8%, and 2.3% in the placebo, dapoxetine 30-mg, and dapoxetine 60-mg groups, respectively. Most of the events were mild or moderate in severity and did not result in study discontinuation, and most were considered not related to therapy. There was no evidence of treatment-emergent suicidality with dapoxetine and no clinically relevant effects of dapoxetine on clinical laboratory tests. During the withdrawal phase of the study, discontinuation of dapoxetine treatment did not cause SSRI withdrawal syndrome.

PHARMACOGENOMICS:

There was a low number of subjects in each treatment group whose predicted CYP2D6 and CYP2C19 phenotype classified them as poor metabolizers, making it difficult to compare the adverse events reported by these subjects and those classified as extensive metabolizers.

CONCLUSIONS:

- Dapoxetine at doses of 30 mg and 60 mg was more effective than placebo in increasing average IELT, improving control over ejaculation, increasing satisfaction with sexual intercourse, and decreasing personal distress related to PE.
- Improvements in sexual functioning as measured by subject and partner self-reported categorical measures were significantly greater in each dapoxetine group when compared with placebo at the Week-12 and Week-24 endpoints and confirm the results of the primary efficacy analyses.
- Dapoxetine was well tolerated with no new safety issues identified. The most common AEs reported by subjects in the dapoxetine group were nausea, headache, and dizziness. Syncope appears to be related to dapoxetine treatment, although infrequent in occurrence. No syncope occurred in subjects administered 30 mg dapoxetine.
- Abrupt discontinuation of dapoxetine treatment did not result in withdrawal syndrome.

Issue Date of the Clinical Study Report: 11 JULY 2007

Disclaimer

Information in this posting shall not be considered to be a claim for any marketed product. Some information in this posting may differ from, or not be included in, the approved labeling for the product. Please refer to the full prescribing information for indications and proper use of the product.