SYNOPSIS

(Page 1 of 5)

Company: ALZA Corporation **Investigational Product:** Dapoxetine HCl **Active ingredient:** dapoxetine		

Title: A Placebo-Controlled, Double-Blind, Randomized, Parallel Study of the Efficacy and Safety of Dapoxetine HCl in the Treatment of Rapid Ejaculation (CR006088)	
Investigator(s)/Study Center: Multicenter (62 study sites in the US screened participants)	
Publication (reference): none	
Study period: **First participant treated:** 24 June 2003 **Last participant completed:** 1 June 2004	**Phase of Development:** 3

Objective:

- To determine the efficacy and safety of two dosage strengths of dapoxetine HCl (dapoxetine) (30 mg and 60 mg) in males with premature ejaculation (PE)
- To characterize the population pharmacokinetics of dapoxetine in males with PE

Methodology: This was a multicenter, double-blind, parallel, placebo-controlled, randomized study in adult males with PE. After a 2-week Screening/Baseline period, the participants were stratified into 2 groups by baseline average intravaginal ejaculatory latency time (IELT), ≤1 minute or >1 minute, and randomized equally into either placebo, dapoxetine 30 mg, or dapoxetine 60 mg treatment groups within each stratum and investigational center. Study drug was taken as needed (prn) for 12 weeks. Follow-up visits were conducted at End of Baseline (2 weeks), and after 4, 8, and 12 weeks of treatment.

Number of participants (planned and analyzed): Planned: up to 1200 enrolled with 900 completing the study; Screened: 1822; Randomized and Treated: 1294 (440 placebo, 429 dapoxetine 30 mg, 425 dapoxetine 60 mg); Completed: 941 (339 placebo, 316 dapoxetine 30 mg, 286 dapoxetine 60 mg).

Diagnosis and main criteria for inclusion: Heterosexual males, aged 18 years and older who had been in a stable, monogamous, sexual relationship with a female partner for at least 6 months and had an intravaginal ejaculatory latency time (IELT) ≤2 minutes in a minimum of 75% of evaluable events recorded in the baseline event log.

Test product, dose and mode of administration, batch number:
Dapoxetine 60 mg and 30 mg tablets for oral administration 1 to 3 hours prior to intercourse. Lot numbers for the dapoxetine tablets used in this study were 02E07/F006 for the 60 mg tablets and 02E06/F005 for the 30 mg tablets.

Duration of trial: Approximately 11 months

Duration of individual participation: Approximately 14 weeks (2-week Baseline period followed by 12 weeks of treatment with study drug)

Reference therapy: Placebo tablets that matched the 60 mg and 30 mg dapoxetine tablets. Lot numbers for the placebo tablets used in this study were 02E03/F008 and 02E06/F008 for the 60 mg tablets and 02E02/F007 for the 30 mg tablets.

SYNOPSIS

(Page 2 of 5)

Company: ALZA Corporation **Investigational Product:** Dapoxetine HCl **Active ingredient:** dapoxetine		

Criteria for Evaluation:

Efficacy

Primary Variable: IELT, the primary endpoint, was defined as the average duration of intercourse attempts since the last clinic visit for which ejaculation was recorded as occurring intravaginally or prior to penetration and was assessed at each clinic visit after screening. Duration of intercourse was measured with a calibrated stopwatch and documented on event logs throughout the baseline and treatment periods.

Secondary Variables: Based on responses to questions administered at baseline and follow-up visits the following variables were assessed: change from baseline in participant's control over ejaculation, satisfaction with sexual intercourse, and symptom severity impression; change from baseline in partner's satisfaction with sexual intercourse. Participant's global impression of change was assessed at follow-up visits.

Other Variables: Based on responses to questions administered at follow-up visits the following measures were assessed: medication helpfulness assessed by participants and partners; change from baseline in partner's perception of the participant's severity of condition and control over ejaculation; partner's global impression of change; participant's assessment of the frequency with which erections were firm enough for intercourse. In addition, the average duration of all intercourse attempts (including events recorded as "after withdrawal" and "did not ejaculate") was computed.

Safety:

Vital signs (systolic and diastolic blood pressure and heart rate) were measured at each clinic visit and ECG and physical examinations were performed at screening and study termination. Clinical laboratory assessments (complete blood count, chemistry, and urinalysis) were performed at screening, Visit 3, and study termination. Adverse events experienced by the participants were assessed throughout study participation. Each randomized participant underwent metabolic genotyping for specific cytochrome P450 (CYP) isozymes. Each partner was tested for pregnancy at screening.

Pharmacokinetics/Pharmacodynamics

Sixteen study sites conducted pharmacokinetic (PK) and pharmacodynamic (PD) assessments. Blood samples for pharmacokinetic (PK) measurements were collected 1 to 2 hours, 4 to 8 hours, and 24 to 32 hours postdose on the day of first dosing. Participants at these sites also underwent ECG analyses predose, 1 to 2 hours and 4 to 8 hours postdose on the first day of dosing.

Statistical methods:

Analysis Populations: Efficacy data were analyzed for all available parameters for all randomized participants (ie, all participants who were dispensed study medication at Visit 2) who were on their randomized treatment and for their partners. (Data from 4 participants who were inadvertently cross treated were excluded when the participant was not on his randomized treatment.) Available data from all participants were summarized. All participants were analyzed for safety. The PK and PD measurements were obtained from participants who were enrolled at a subset of study sites.

SYNOPSIS

(Page 3 of 5)

Company: ALZA Corporation **Investigational Product:** Dapoxetine HCl **Active ingredient:** dapoxetine		

Statistical methods continued:

Efficacy Analysis: The primary time point for analysis was study endpoint, defined as the last available post-baseline assessment. IELT, the primary endpoint, was analyzed using an analysis of covariance (ANCOVA) model adjusted for baseline IELT. Additionally, the actual changes from baseline in IELT were compared across treatment groups using an analysis of variance (ANOVA) model with treatment center, stratum main effects, and treatment-by-stratum interaction effects. These tests were performed at the α=0.05 significance level. If a significant overall effect between the treatment groups was observed, pairwise comparisons between the 2 dapoxetine doses and placebo were performed, also at the α=0.05 significance level. The same approach was used to analyze the secondary and other efficacy variables. A hierarchical order of testing was employed to control for multiple tests between endpoints.

Pharmacokinetics/Pharmacodynamic Analysis: In the PK/PD substudy, individual and mean plasma concentrations of dapoxetine and dapoxetine metabolites were tabulated and compared with demographic characteristics (eg, age, predicted metabolic phenotype) as covariates. ECG data from participants in the PK/PD substudy were tabulated.

Safety Analysis: The incidence of adverse events (AEs) that occurred during the treatment phase were summarized for each treatment group and sorted by primary system organ class and/or preferred term, severity, seriousness, and relationship to study drug. The incidence of AEs that occurred between screening and randomization were summarized separately. Laboratory test results were summarized using tables displaying laboratory results over time and shift tables. The incidence of clinically relevant abnormalities in vital signs and ECGs was analyzed.

Summary of Results:

Demographics and baseline characteristics: The 1294 men randomized into this study averaged 40.7 years of age (range, 18-76 years) and were predominately Caucasian (1126/1294, 87.0%). The mean (SD) baseline IELT for randomized participants was 0.92 (0.49) minutes and was similar across the 3 treatment groups.

Efficacy Results Summary: Both the 30 mg and 60 mg dapoxetine treatments showed significant improvement in PE compared with placebo, and the 60 mg dose gave consistently better results than the 30 mg dose. Dapoxetine treatment significantly increased IELT at both doses studied compared with placebo for all randomized participants ($p<0.0001$ for the comparison of each active treatment with placebo at study endpoint). Statistically significant increases were seen for both dapoxetine doses from the first dose through all evaluations to study endpoint. In addition, results suggest that the effects of dapoxetine can be seen within 30 minutes of dosing.

In the subgroup analysis, results showed that IELT was significantly increased for both doses of dapoxetine compared with placebo for participants assigned to the stratum of average IELT $\leq$1 minute at baseline and for those assigned to the stratum of average IELT >1 minute at baseline.

SYNOPSIS

(Page 4 of 5)

Company: ALZA Corporation **Investigational Product:** Dapoxetine HCl **Active ingredient:** dapoxetine		

Efficacy Results Summary continued: Results of secondary endpoints were also significantly better for both doses of dapoxetine versus placebo ($p<0.0001$ for all):

- Participant perception of control over ejaculation was statistically significantly better with dapoxetine than with placebo treatment.
- Participant perception of satisfaction with sexual intercourse was statistically significantly better with dapoxetine than with placebo treatment.
- Participant perception of severity of PE was statistically significantly less with dapoxetine than with placebo treatment.
- Participant global impression of change was statistically significantly better with dapoxetine than with placebo treatment.
- Partner perception of satisfaction with sexual intercourse was statistically significantly better with dapoxetine than with placebo treatment.

The response across all of these endpoints consistently demonstrates that both doses of dapoxetine are superior to placebo.

In addition, between-group effect sizes indicate that dapoxetine treatment leads to moderate to large changes in IELT and in participant perception of control over ejaculation and satisfaction with sexual intercourse.

Pharmacokinetic/Pharmacodynamic Results Summary: A population pharmacokinetic model was developed to describe the dapoxetine concentration-time data. The mean population apparent clearance was 23.3 L/h. CYP2D6 genotype appeared to have an impact on apparent clearance ($p=0.0317$). The mean post hoc estimated clearance values were significantly lower in CYP2D6 poor metabolizers (19.6 ± 12.9 L/hr) than in CYP2D6 extensive metabolizers (27.5 ± 13.1 L/hr). This is consistent with the fact that this isozyme plays a role in the metabolism of dapoxetine.

Safety Results Summary: No deaths occurred during this study. An SAE was reported in 4 (0.9%), 2 (0.5%), and 3 (0.7%) participants in the placebo, dapoxetine 30 mg, and 60 mg groups, respectively; all were associated with an intercurrent illness, pre-existing condition, or accident and were assessed as not related to study treatment. Early study terminations due to an AE occurred in 2 (0.5%), 21 (4.9%), and 37 (8.7%) participants in the placebo, dapoxetine 30 mg, and dapoxetine 60 mg groups, respectively. Nausea was the AE most commonly cited for early study termination in the dapoxetine 30 mg and 60 mg groups, occurring in 1.2% and 3.3% of participants, respectively. No participants in the placebo group discontinued early because of nausea.

SYNOPSIS

(Page 5 of 5)

Company: ALZA Corporation **Investigational Product:** Dapoxetine HCl **Active ingredient:** dapoxetine		

Safety Results Summary continued: Treatment-emergent AEs were reported by 36%, 49%, and 60% of participants in the placebo, dapoxetine 30 mg, and dapoxetine 60 mg groups, respectively, and certain ones appeared to increase with the dapoxetine dose. Most of the AEs reported for each of the 3 treatments were of mild followed by moderate severity, and for participants in the dapoxetine treatment groups the majority of AEs were assessed as treatment related.

Nausea, diarrhea, dizziness, and headache were the most common AEs reported during dapoxetine treatment: nausea (2.7% on placebo, 9.3% on dapoxetine 30 mg, 19.8% on dapoxetine 60 mg), diarrhea (1.6%, 4.6%, and 7.3%), dizziness (0.9%, 2.8%, and 5.4%), and headache (2.7%, 5.3%, and 4.9%). Nausea, diarrhea, and dizziness appear dose related and often started with the first dose of dapoxetine administered. Other AEs reported in ≥2% of participants and more common on dapoxetine than placebo treatment were: impotence, asthenia, dyspepsia, somnolence, insomnia, vomiting, and dry mouth. In addition to evaluating the most common AEs, this report evaluates AEs known to be associated with other drugs with similar serotonin activities. AEs of potential concern relating to mood and affect, which are both effects associated with commercially available SSRI antidepressants, were reported infrequently. In this study, there was no evidence of hypotensive or cardiac effects with dapoxetine.

Conclusions: Both the 30 mg and 60 mg prn dapoxetine treatments showed significant improvement in PE compared with placebo, and the 60 mg dose gave consistently better results than the 30 mg dose. IELT was significantly increased for both dapoxetine doses compared with placebo from the first dose through all evaluations to study endpoint. Moreover, increases in latency time were accompanied by better ratings on key secondary endpoints (participant perceptions of control over ejaculation and satisfaction with sexual intercourse). These data and the between-group effect sizes strongly support the benefit of dapoxetine in the treatment of PE.

In the pharmacokinetic analysis, the mean post hoc estimated clearance values were significantly lower in CYP2D6 poor metabolizers than in CYP2D6 extensive metabolizers, and a marginal decrease in clearance was seen with age.

The safety findings from this placebo-controlled study indicate that dapoxetine taken prn in men with PE is generally safe and well tolerated. Certain treatment-emergent AEs appeared to increase with the dapoxetine dose. The most common AEs were nausea, diarrhea, dizziness, and headache during dapoxetine 30 mg or 60 mg treatment, and these often started with the first dose. Aside from the gastrointestinal and CNS side effects, no other patterns emerged for AEs associated with other body systems.

Date of the report: 1 November 2004

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.