SYNOPSIS

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

Title: An Open Label Study of the Long-term Safety of Dapoxetine HCl in the Treatment of Rapid Ejaculation	
Investigator(s)/Study Center: Multicenter	
Publication (reference): none	
Study period: **First participant treated:** 16 September 2003 **Last participant completed:** 14 April 2005	**Phase of Development:** 3a

Objectives:

- To determine the long-term safety of dapoxetine HCl (dapoxetine) in the treatment of PE
- To evaluate the participant's perception of efficacy of dapoxetine in the treatment of PE

Methodology: This is a multicenter, open label study that evaluated the long-term safety and efficacy of dapoxetine therapy in adult males with PE. After participation in a 14-week, randomized, placebo-controlled trial of dapoxetine, participants were allowed to enter this open-label extension trial of dapoxetine. Participants were provided a supply of 60 mg tablets of dapoxetine to be taken on an as needed (prn) basis approximately 1-3 hours prior to sexual intercourse. Doses could be decreased to dapoxetine 30 mg if needed clinically. Treatment duration in this open-label study was 9 months. Participants were evaluated for safety and efficacy at Months 1, 2, 3, 6, and 9.

Number of participants: Treated: 1774 (615, 607, and 552 from placebo, dapoxetine 30 mg, and dapoxetine 60 mg treatment groups in the Phase 3 controlled study, respectively); Completed: 962; Discontinued: 812.

1250 participants received dapoxetine for at least 6 months; 962 participants received dapoxetine for at least 9 months; and 654 participants completed the study and had received dapoxetine treatment for approximately 12 months.

Diagnosis and main criteria for inclusion: Males who completed 1 of the 2 Phase 3 controlled studies (Study C-2002-012 or Study C-2002-013) could elect to enroll within 30 days in Study CR005041, if: 1) in the opinion of the Investigator, the participant could safely continue dapoxetine treatment; 2) the participant had systolic and diastolic blood pressures less than or equal to 180 mm Hg and 100 mm Hg, respectively; and 3) the participant whose sexual partner was of childbearing potential agreed to ensure use of a medically acceptable method of contraception for the study duration. Participants were not eligible to enroll if they were taking any protocol-defined prohibited medications, reported a new diagnosis of any sexually transmitted disease, had a new allergy or hypersensitivity to dapoxetine or other selective serotonin reuptake inhibitors, or if in the opinion of the Investigator should not participate or were not capable of following the study schedule for any reason.

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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 were 03F04/F006, 03F05/F006, 03F10/F006, and 03G04/F006 for the 60 mg tablet, and 03I16/F005 and 02E06/F005 for the 30 mg tablet.

Duration of trial: Approximately 14 months

Duration of individual participation: Approximately 9 months

Reference therapy: No reference therapy was used during this extension study.

Criteria for Evaluation:

Safety:

Clinical laboratory assessments (complete blood count, chemistry, and urinalysis) were performed at Months 1, 3 and 9 or termination visit. The baseline laboratory assessments for this study were the laboratory assessments from the termination visit of the prior Phase 3 controlled study. Vital signs were measured at interim safety clinic visits (Months 1, 2, and 6). Physical examinations (including vital signs) and electrocardiograms (ECGs) were performed at the baseline visit (termination visit of Study C-2002-012 or C-2002-013), Month 3, and Month 9 or termination visit. Adverse events experienced by the participants were assessed throughout study participation.

Efficacy:

The participant's perception of sexual function during dapoxetine use was evaluated at each visit using the following patient reported outcomes (PROs): satisfaction with sexual intercourse, control over ejaculation, symptom severity, medication helpfulness, and firmness of erections.

Statistical Methods:

Analysis Populations: Available data from all participants who were dispensed study drug in this extension study were included in data summaries for this final report.

***Safety Analysis*:** The incidence of adverse events (AEs) were summarized by prior study treatment group in the Phase 3 controlled study and sorted by body system, preferred term, severity, seriousness, and relationship to study drug. Laboratory test results and changes from baseline were summarized. The incidences of clinically relevant abnormalities in vital signs were also summarized.

***Efficacy Analysis*:**

PRO responses were summarized. Ratings on patient reported outcome questions were analyzed in terms of changes from the baseline score using a paired t-test. A separate comparison was made for each of the 3 possible treatments: placebo, dapoxetine 30 mg, and dapoxetine 60 mg. Participants could roll over from participation in the double-blind studies.

Summary of Results:

***Demographics and Baseline Characteristics*:** As participants in this study had to have completed 1 of the 2 Phase 3 controlled studies, participant demographics in this study were similar to the prior studies. The 1774 men who enrolled in this study were between 18 and 77 years of age (mean: 41.1 years) and predominately Caucasian (89%; 1571/1774).

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***Extent of Exposure*:** Based on dapoxetine exposure in both the Phase 3 controlled study and this study, 1250 participants have received dapoxetine (30 mg or 60 mg) for at least 6 months and 962 participants for at least 9 months. A total of 654 participants completed approximately 12 months of exposure to dapoxetine. Eleven percent (194) of the 1774 participants have had a dose reduction from 60 mg to 30 mg; all but 2 because of an AE.

***Safety Results*:**

No new safety concerns that could be attributed to longer-term use of prn dapoxetine were observed in this study. No deaths were reported during this study. Twenty-five (1.4%) participants experienced serious adverse events (SAEs) in this study; 22 of the 25 participants had SAEs associated with an intercurrent illness, pre-existing condition, or accident. These SAEs were assessed as not related to study treatment. Three (0.2%) of the 1774 participants had SAEs that were considered related to study treatment (1 had a seizure and 2 had syncope). A total of 119 (6.7%) participants discontinued early from the study due to an AE. Nausea was the AE most commonly cited for early study termination, cited by 29 (1.6%) participants.

Similar to the Phase 3 controlled studies, most participants in this study had AEs of mild to moderate severity; AEs were severe in 79 (4.5%) participants. Nausea (15.4%), diarrhea (5.5%), URTI (5.5%), dizziness (5.2%), headache (4.8%), and accidental injury (4.8%) were the most common AEs reported in this study, and, except for accidental injury and URTI, were generally considered possibly or probably related to study drug. These results are consistent with those from the 2 Phase 3 controlled studies (C-2002-012 and C-2002-013) and these AEs were reported at a similar rate as in the Phase 3 controlled studies. The percentage of participants who reported at least 1 AE with an onset in this study and the percentage reporting the most common AEs with onset in this study tended to be highest in participants who had previously been assigned placebo treatment in a Phase 3 controlled study and lowest in those continuing on dapoxetine 60 mg. Based on AEs with onset in this study and ongoing AEs from the Phase 3 controlled study, the incidence of specific AEs was similar for all 3 prior treatment groups.

The most common AEs reported and the proportion of participants reporting these AEs were consistent across the other analyses: participants who reported the specific AE in this study but not in a Phase 3 controlled study; participants who reported the specific AE in a Phase 3 controlled study but not in this study; and AEs reported by these participants in the Phase 3 controlled study and in this study. Participants previously assigned placebo tended to report these common AEs for the first time in this study, while participants continuing on dapoxetine 60 mg tended to have more of these specific AEs ongoing from the prior study and tended not to report them as new onsets in this study.

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Safety Results (continued):

In terms of AEs mapped to the cardiovascular and nervous systems, which were identified as areas of special interest in the dapoxetine Phase 3 controlled studies, 4 SAEs were reported by 3 participants in the study that were not reported in the controlled phase: an isolated case of convulsion (seizure) in 1 participant, cardiomyopathy and supraventricular tachycardia that occurred 35 days after the last dose of study medication in a participant with extensive pre-existing congenital heart disease, and cerebrovascular accident (CVA) in a participant with significant risk factors.

No clinically relevant mean changes were observed between baseline and termination for clinical laboratory tests, vital sign measurements, ECG tracings, or physical examination findings.

Efficacy Results:

After 1 month of treatment with dapoxetine in this study, participants previously assigned placebo in the double-blind studies noted improvements in satisfaction with sexual intercourse, control over ejaculation, symptom severity, and medication helpfulness that were comparable with the efficacy results for participants who initially received dapoxetine 60 mg in the double-blind studies. Efficacy was also maintained for the duration of this study for all enrolled participants and for those that completed approximately 12 months of dapoxetine treatment.

Conclusions: In this longer term extension study, 1250 participants received dapoxetine (30 mg or 60 mg) for at least 6 months, 962 for at least 9 months, and 654 completed the study and had approximately 12 months of dapoxetine treatment. Safety results in this study were consistent with what was reported in the double-blind studies. The most common treatment-related side effects with longer-term use have been the same as those reported after 12-weeks of use: nausea, diarrhea, dizziness, and headache. Efficacy was maintained throughout this 9-month study

Date of the report: 27 June 2005

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