Proprietary Drug Name: Pristiq®	**Generic Drug Name:** desvenlafaxine	**FDA approved indications:** Major depressive disorder

Name of Sponsor/Company: Wyeth

Title of the study: A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY OF 2 FIXED DOSES OF DVS-233 SR IN ADULT OUTPATIENTS WITH MAJOR DEPRESSIVE DISORDER. SYNOPSIS BASED ON FINAL REPORT. (Protocol 0600D3-223)

Study centers: 35 study centers in France, Poland, the United States, and South Africa.

Publication (reference): None as of this report date.

Study period: 19 Sep 2002 to 28 Mar 2003 **Clinical phase:** 2
(first subject randomized to last subject visit)

Objectives: The primary objective was to compare the antidepressant efficacy and safety of 2 fixed doses of desvenlafaxine with those of placebo. The secondary objectives were to compare the response rates using the Clinical Global Impressions scales, the 17-item Hamilton Rating Scale for Depression (HAM-D_{17}), and the Montgomery and Asberg Depression Rating Scale (MADRS) for subjects receiving desvenlafaxine with those receiving placebo, and to compare the percentage of subjects with a HAM-D_{17} total score ≤ 7 in the desvenlafaxine and placebo groups.

Methodology: Eligible subjects were randomly assigned to 1 of 3 treatment groups: desvenlafaxine 200 mg or 400 mg daily, or placebo. All subjects receiving desvenlafaxine began at 100 mg/day (days 1-3) and were titrated up to 200 mg/day on day 4. For subjects in the desvenlafaxine 400 mg group, the dose was increased to 400 mg/day on day 8. The total treatment duration was up to 8 weeks followed by a 1-week taper period.

Number of subjects: The planned enrollment was approximately 200 subjects; 227 subjects were randomly assigned to receive double-blind medication; 222 were analyzed for safety; 213 were analyzed for efficacy (intent-to-treat [ITT] population), and 161 completed the study.

Diagnosis and main criteria for inclusion: Men and postmenopausal or surgically sterile women aged 18 to 65 years were eligible if they weighed at least 50 kg (110 lbs). They had to be outpatients with a primary diagnosis of major depressive disorder (MDD) based on the criteria in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV), single or recurrent episode, without psychotic features. If other allowable Axis I and Axis II psychiatric diagnoses were present, MDD had to be the primary reason why the subject sought help.

Test product, dose and mode of administration: Desvenlafaxine (200 or 400 mg) was administered orally once a day. The drug was administered as 100 mg or 200 mg tablets.

Duration of treatment: Subjects were treated for 8 weeks followed by a 1-week taper period.

Reference therapy, dose and mode of administration: Placebo tablets (matching desvenlafaxine 100-mg and 200-mg) were administered orally once a day.

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Criteria for evaluation:

Efficacy assessment methods: The primary efficacy endpoint was the change from baseline on the HAM-D_{17} total score at the final evaluation, although the 21-item scale was administered.
The key secondary efficacy endpoints were the Clinical Global Impressions-Global Improvement (CGI-I) scores, the change from baseline on the HAM-D_6 subscale (Bech version, HAM-D items 1, 2, 7, 8, 10, and 13), the percentage of subjects with HAM-D_{17} ≤7, and the change from baseline on the MADRS at the final evaluation. Additional secondary efficacy variables were the response rate on the CGI-I, HAM-D_{17}, MADRS, and CGI-Severity of Illness (CGI-S) scales at the final evaluation. These scales were administered at screening (MADRS and CGI-S only) and on study days –1, 7, 14, 21, 28, 42, and 56. Every effort was made to administer the rating scales at the same time for each visit, and the same person was to perform all the ratings for a given individual. Beginning on study day 7, all visits had a ±3-day visit window to allow for slight variations in subject schedules; however, every effort was made to have the subject return on the designated study days.

Baseline evaluations were done on day –1 (before test article administration). The subject began to take test article the following day (day 1). If the subject did not complete 56 days of double-blind test article, all of the above measurements were obtained on the last day on which the subject took a full dose of test article, ie, before the dose was tapered, or as soon as possible thereafter. A subject was to complete all visits up to and including day 56, to be considered as completing the study.

Safety assessment methods: Safety was determined by the following evaluations at the prestudy visit and on study day 56: physical examination, a 12-lead electrocardiogram (ECG), and laboratory determinations (hematology, blood chemistry, urinalysis). The free thyroxine index, including total T4 and T-uptake, and urine drug screen were only done at the prestudy visit. In addition, hematology and blood chemistry evaluations were performed on study days 14 and 28. Weight and vital signs (supine pulse and supine and standing blood pressure measurements were taken at the prestudy visit and all subsequent visits, including the poststudy visit). Prior and concomitant medications and adverse events were recorded at the screening visit and all subsequent visits. Baseline determinations were done on day –1 (before test article administration). The subject began taking test article the following day (day 1). If the subject did not complete 56 days of double-blind test article, all day 56 determinations were obtained on the last day the subject took a full dose of test article, ie, before the dose was tapered, or as soon as possible thereafter.

Pharmacokinetic assessment methods: Plasma drug levels were measured on study days 14 and 56, or upon early withdrawal. If the subject discontinued before study day 56, plasma drug levels were to be measured on the last day on which the subject took a full dose of test article (ie, before taper), or as soon as possible thereafter, but within 3 days of the last full dose in any case.

Statistical methods: Statistical analyses were based on pooling of all data from individual study sites. The use of the word "significant" in conjunction with the results refers to p-values ≤0.05. All tests were 2-sided. Three (3) populations were analyzed. The ITT population, which was the primary population for the efficacy analysis, included all randomized subjects who had a baseline HAM-D_{17} total score, had taken at least 1 dose of double-blind test article, and had at least 1 HAM-D_{17} total score evaluation after the first dose of double-blind test article. The per-protocol (PP) population included all randomized subjects who had a baseline HAM-D_{17} total score, had taken at least 1 dose of double-blind test article, and had at least 1 HAM-D_{17} total score evaluation after the first dose of double-blind test article within 3 days of stopping full-dose double-blind test article. The all-randomized population included all randomized subjects with at least 1 baseline HAM-D_{17} total score. All analyses were done at each evaluation period by using the last-observation-carried-forward (LOCF) technique and the observed-cases analysis.

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The primary analysis was the change from baseline on the HAM-D_{17} total score at the final evaluation and was tested using analysis of covariance (ANCOVA) with treatment and center as main factors and baseline value as a covariate. Because many centers had few subjects, the center term was replaced by 10 pooled centers based on country (France, Poland, South Africa), and geographic regions within the United States. Closed testing procedures were performed to compare the 2 doses (200 and 400 mg/day) of desvenlafaxine with placebo based on the primary efficacy variable. A general linear model with multiple contrast statements was used to calculate F-statistics for global null hypotheses and all intersection hypotheses. The closure principle was used to determine which hypothesis should be retained or rejected at α=0.05. If a significant difference was detected for 1 or both doses of desvenlafaxine, then the sequential testing method would be applied to that dose(s) to test the key secondary efficacy endpoints.

If significant differences from placebo were found on the primary efficacy variable based on the closed testing procedure, the key secondary efficacy variables were to be tested at the α=0.05 level in ranking order. Each desvenlafaxine dose was to be compared with placebo. The ranking of the key secondary efficacy endpoints was as follows: scores on the CGI-I, changes from baseline on HAM-D_6 subscale (Bech version, HAM-D items 1, 2, 7, 8, 10, and 13), the percentage of subjects with HAM-D_{17} $\leq$7, and the changes from baseline on the MADRS. The CGI-I scores were analyzed by using ANOVA with treatment and pooled center as the factors.

The HAM-D_6 total score was evaluated using ANCOVA on changes from baseline with treatment and pooled center as factors and the baseline value as a covariate. The percentage of subjects with HAM-D_{17} $\leq$7 was compared between each desvenlafaxine treatment group and the placebo group by using logistic regression. The model included treatment and center as main factors and baseline score as a covariate. Results of these analyses are reported as percentage of remitters, odds ratios, and 95% confidence interval (CI) of the odds ratio. The MADRS total score was analyzed using methods similar to those applied for HAM-D_6.

Response rates were also analyzed. Response was defined as a score of 1 or 2 for CGI-I or CGI-S, or a decrease of 50% or more from baseline to the specific time point for HAM-D_{17} or MADRS. Response rate was compared between desvenlafaxine and placebo by using logistic regression. The model included treatment and pooled center as main factors and baseline score as a covariate. Results of these analyses are reported as percentage of responders, odds ratios, and 95% CI of the odds ratio.

SUMMARY – CONCLUSIONS:

Efficacy results: In this first efficacy trial of desvenlafaxine in subjects with MDD, the primary and secondary efficacy endpoints did not show a statistical difference between placebo and desvenlafaxine at either the 200- or 400-mg/day dosages. For 2 of the endpoints, response rates based on a 50% decrease from baseline in the HAM-D_{17} total scores and response rates based on a 50% decrease from baseline in the MADRS scores, the difference between placebo and desvenlafaxine 200 mg approached significance at week 8 in the observed-cases analyses (HAM-D_{17} p=0.055; MADRS p=0.069). Although the efficacy results were not significant, this study was useful in selecting dosages for the proposed phase 3 studies in subjects with MDD.

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Safety Results: There were no deaths. The most common treatment-emergent adverse events (TEAEs), ie, those reported by at least 5% of the desvenlafaxine-treated subjects in either dose group and at a frequency at least twice the rate for placebo-treated subjects during the double-blind period, were anorexia, constipation, nausea, dizziness, nervousness, upper respiratory infection, yawn, sweating, abnormal ejaculation/orgasm, anorgasmia, and impotence. In most cases, these adverse events were mild or moderate in severity. The incidence of nausea was 25% in both the desvenlafaxine 200-mg and 400-mg groups and 12% in the placebo group. The mean nausea duration was similar in the placebo and desvenlafaxine groups.

Three (3) subjects had serious adverse events. Two (2) of these subjects had liver enzyme elevations (alanine aminotransferase, aspartate aminotransferase, gamma-glutamyltransferase [GGT]), that would not be considered serious according to the FDA definition of serious adverse events. In both cases, the liver enzyme elevations resolved after desvenlafaxine was discontinued and did not require further treatment. The serious adverse events in the third subject) were unrelated to desvenlafaxine treatment.

During the double-blind period, an adverse event was the primary reason for withdrawal for 4 (5%) subjects in the placebo group, 9 (13%) in the desvenlafaxine 200-mg group, and 11 (14%) of the desvenlafaxine 400-mg group. The adverse events that most frequently led to discontinuation of treatment in desvenlafaxine-treated subjects (asthenia, nausea, depersonalization, and insomnia) were not unexpected; these adverse events had been observed in the desvenlafaxine phase 1 studies. The adverse events of clinical interest included hypertension, which had also been reported in the phase 1 studies.

Desvenlafaxine treatment was associated with few clinically important changes in laboratory test results, vital signs, or ECG assessments. The desvenlafaxine-treated groups had statistically significant mean increases from baseline in GGT and alkaline phosphatase at week 8; the differences between the placebo group and each desvenlafaxine group were significant. Mean total cholesterol showed an increase of 0.271 mmol/L and 0.117 mmol/L at the week 8 evaluation for the desvenlafaxine 200-mg and 400-mg groups, respectively, compared with a decrease of 0.034 mmol/L in the placebo group.

At week 8, mean increases from baseline in supine pulse rate were 0.55 and 5.01 beats/min for the desvenlafaxine 200- and 400-mg groups, respectively, compared with a decrease of 1.49 beats/min in the placebo group. Mean supine diastolic blood pressure increased 0.24 and 2.69 mm Hg at the week 8 evaluation for the desvenlafaxine 200- and 400 mg groups, respectively, compared with a decrease of 1.67 mm Hg in the placebo group.

At week 8, change from baseline for mean heart rate showed a trend towards a dose-related increase with desvenlafaxine treatment. In the desvenlafaxine 200- and 400-mg treatment groups, the increases were 5.10 and 6.19 beats/min, respectively, compared with a decrease of 0.05 beats/min in the placebo group. Mean values for QTc changed by -0.65, -3.00, and -1.45 msec at the week 8 evaluations for desvenlafaxine 200 mg, 400 mg, and placebo, respectively. These results were based on Fridericia's correction, which was chosen because the Bazett's formula tends to overcorrect when there is an increase in heart rate. QTc mean changes from baseline with Bazett's correction were 4.21, 2.60, and -1.41 msec for desvenlafaxine 200 mg, 400 mg, and placebo, respectively.

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Conclusion: In this study, the 200- and 400-mg/day dosages of desvenlafaxine were not statistically different from placebo for the primary and secondary efficacy endpoints in subjects with MDD. This was the first study to evaluate the safety of 2 doses of desvenlafaxine in subjects with MDD and was useful in understanding the desvenlafaxine safety profile. Desvenlafaxine was well tolerated in this population in this study. In this study, the TEAEs observed with desvenlafaxine and the adverse events that led subjects to discontinue treatment were not unexpected; some of these adverse events had been observed in the desvenlafaxine phase 1studies. **Date of report:** 05 Jul 2005		