7-2008

A pooled analysis of two placebo-controlled trials of desvenlafaxine in major depressive disorder.

Daniel Z Lieberman

Stuart A Montgomery

Karen A Tourian

Claudine Brisard

Gregory Rosas

See next page for additional authors

APA Citation

Lieberman, D., Montgomery, S., Tourian, K., Brisard, C., Rosas, G., Padmanabhan, K., Germain, J., & Pitrosky, B. (2008). A pooled analysis of two placebo-controlled trials of desvenlafaxine in major depressive disorder.. *International clinical psychopharmacology, 23* (4). http://dx.doi.org/10.1097/YIC.0b013e32830263de

Editorial Manager(tm) for International Clinical Psychopharmacology
Manuscript Draft

Manuscript Number:

Title: A Pooled Analysis of Two Placebo-Controlled Trials of Desvenlafaxine Succinate in Major Depressive Disorder

Article Type: Original Study

Section/Category:

Keywords: Desvenlafaxine; major depressive disorder; MMRM; venlafaxine.

Corresponding Author: Dr. Daniel Z Lieberman, M.D.

Corresponding Author's Institution: George Washington University School of Medicine

First Author: Daniel Lieberman, MD

Order of Authors: Daniel Lieberman, MD; Stuart A Montgomery, MD; Karen A Tourian, MD; Claudine Brisard, MD; Gregory Rosas, PhD; Krishna S Padmanabhan, MS; Jean-Michel Germain, PhD; Bruno Pitrosky, PhD

Manuscript Region of Origin: UNITED STATES

Abstract: The antidepressant efficacy and safety of desvenlafaxine succinate were evaluated in two, phase III, double-blind, placebo-controlled, flexible-dose studies. Outpatients with a primary diagnosis of major depressive disorder were treated with desvenlafaxine succinate or venlafaxine extended release. The primary outcome measure was the change from baseline on the 17-item Hamilton Rating Scale for Depression. Secondary outcome measures included the Clinical Global Impressions-Improvement Item scores, Montgomery-Åsberg Depression Rating Scale score, Clinical Global Impressions Scale, Severity of Illness score, 17-item Hamilton Rating Scale for Depression response rate, percentage of patients in remission, visual analog scale-pain intensity overall pain and subscale scores, 6-item Hamilton Rating Scale total score, Covi Anxiety Scale total score, and the response rates on the Montgomery-Åsberg Depression Rating Scale and Clinical Global Impressions Scale-Improvement Item Scale. At the end of eight weeks of

treatment, the pooled analyses revealed that desvenlafaxine was significantly better than placebo on the 17-item Hamilton Rating Scale and the Clinical Global Impressions Scale-Improvement-Item scores. Adverse events were comparable to those found with other drugs sharing a similar mechanism of action. These data provide support for the efficacy and safety of desvenlafaxine in the treatment of major depressive disorder.

A Pooled Analysis of Two Placebo-Controlled Trials of Desvenlafaxine Succinate in Major Depressive Disorder

Daniel Z. Lieberman, MD[1], Stuart A. Montgomery, MD[2], Karen A. Tourian, MD[3], Claudine Brisard, MD[4], Gregory Rosas, PhD[3], Krishna Padmanabhan, MS[3], Jean-Michel Germain PhD[4], Bruno Pitrosky, PhD[4]

[1]George Washington University Clinical Psychiatric Research Center, Washington, DC

[2] Imperial College School of Medicine, London, UK

[3]Wyeth Research, Collegeville, Pennsylvania

[4]Wyeth Research, Paris, France

Corresponding Author:
Daniel Z. Lieberman, MD
George Washington University Clinical Psychiatric Research Center
2150 Pennsylvania Avenue, NW
Washington, DC 20037
Phone: 202-741-2899
Fax: 202-741-2891
Email: cfrdzl@gwumc.edu

Running title: Desvenlafaxine Succinate in the Treatment of Major Depressive Disorder

Key Words: Desvenlafaxine, major depressive disorder, MMRM, venlafaxine.

Funding: Wyeth Research

Clinical Trials.gov Registry: NCT00087737 (US), NCT00090649 (EU)

Word Count (abstract 195; allowed 200)

Word Count (text only: 3,318; no limit)

Tables: 6

Figures: 3

ABSTRACT

The antidepressant efficacy and safety of desvenlafaxine succinate were evaluated in two, phase III, double-blind, placebo-controlled, flexible-dose studies. Outpatients with a primary diagnosis of major depressive disorder were treated with desvenlafaxine succinate or venlafaxine extended release. The primary outcome measure was the change from baseline on the 17-item Hamilton Rating Scale for Depression. Secondary outcome measures included the Clinical Global Impressions-Improvement Item scores, Montgomery–Åsberg Depression Rating Scale score, Clinical Global Impressions Scale, Severity of Illness score, 17-item Hamilton Rating Scale for Depression response rate, percentage of patients in remission, visual analog scale-pain intensity overall pain and subscale scores, 6-item Hamilton Rating Scale total score, Covi Anxiety Scale total score, and the response rates on the Montgomery–Åsberg Depression Rating Scale and Clinical Global Impressions Scale-Improvement Item Scale. At the end of eight weeks of treatment, the pooled analyses revealed that desvenlafaxine was significantly better than placebo on the 17-item Hamilton Rating Scale and the Clinical Global Impressions Scale-Improvement-Item scores. Adverse events were comparable to those found with other drugs sharing a similar mechanism of action. These data provide support for the efficacy and safety of desvenlafaxine in the treatment of major depressive disorder.

INTRODUCTION

Depression, a common mental disorder, is a major cause of disability throughout the world, and a serious public health concern. Worldwide, more than 150 million people suffer from depression, and nearly 1 million commit suicide every year. (WHO, 2001) Even with treatment, a large percentage of patients who receive currently available therapies recover only partially, often with continued functional impairment due to residual symptoms, underscoring the importance of and need for novel antidepressants. (Nelson et al., 2004, Thase et al., 2001, Steffens et al., 1997, Faravelli et al., 2003, Segal et al., 2003)

Desvenlafaxine (O-desmethylvenlafaxine) is the major active metabolite of the structurally novel antidepressant, venlafaxine. The succinate salt of desvenlafaxine is being developed as a drug candidate for the treatment of major depressive disorder (MDD). Desvenlafaxine succinate (desvenlafaxine) is chemically unrelated to tricyclic, tetracyclic, or other available antidepressants (with the exception of venlafaxine) and is classified as a dual-acting serotonin (5-HT) and norepinephrine (NE) reuptake inhibitor (SNRI) because pre-clinical studies have demonstrated that it inhibits the neuronal uptake of both 5-HT and NE and, to a lesser degree, dopamine reuptake. (Muth et al., 1991, Clement et al., 1998) It does not have any monoamine oxidase (MAO) inhibitory activity, and it shows virtually no affinity for rat brain muscarinic cholinergic, H_1-histaminergic, or α_1-adrenergic receptors. (Deecher et al., 2006)

Desvenlafaxine has been examined in a series of preclinical in vivo and in vitro tests and has been found to be active in multiple models used to predict antidepressant activity. (Alfinito et al., 2006) Results of 2 phase III clinical trials showed that desvenlafaxine had significantly better efficacy compared to placebo on the 17-item Hamilton Rating Scale for Depression ($HAM\text{-}D_{17}$), Clinical Global Impressions-Improvement scale scores (CGI-I), and the Montgomery–Åsberg Depression Rating Scale (MADRS). (DeMartinis et al., 2007) (Septien-Velez L, 2007) (Montgomery and Asberg, 1979)

Both phase III studies discussed herein, which compared the antidepressant efficacy of desvenlafaxine and placebo in MDD were, in retrospect, underpowered, largely due to the high placebo response rate observed in both studies. To examine the efficacy of desvenlafaxine in an adequately powered analysis, the data from both of these studies were pooled post-hoc. Performing pooled analyses is in accordance with European standards.

The results of both the pooled analysis using mixed-effect model for repeated measures (MMRM) and the results of the individual studies are presented in this article.

METHODS

Two similar studies were performed—one in Europe (EU) and one in the United States (US). Each was a double-blind, multi-site, placebo-controlled, parallel-group, venlafaxine extended release (ER) referenced flexible-dose trial designed to compare the antidepressant efficacy and safety of desvenlafaxine with placebo. After a screening

period of 6 to 14 days, eligible patients received up to 8 weeks of treatment. The use of placebo was necessary to provide reliable scientific evidence of efficacy.

The designs of the EU and US protocols allowed for a 4-arm pooled analysis. The entry criteria treatment protocol and other aspects of the study were similar with the exception of the dosing of the active control. In both studies, desvenlafaxine was dosed from 200 to 400 mg daily, whereas the venlafaxine ER dosing in the EU study was 75 to 150 mg daily and 150 to 225 mg daily in the US study. Because each study was designed to compare desvenlafaxine to placebo, the differences in the dosing of the active control did not affect the data analysis of the efficacy of desvenlafaxine.

The studies were approved by independent ethics committee (IEC) or Institutional Review Board (IRB) and were consistent with Principles of Good Clinical Practice and applicable regulatory requirements in each participating country. All participants provided written informed consent before enrollment.

Selection of Study Population

Men and women, outpatients 18 to 75 years of age with a primary diagnosis of MDD, based on a psychiatric interview using the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) criteria, single or recurrent episode, without psychotic features were eligible for study participation. At baseline and screening, patients were also required to have a minimum HAM-D_{17} score of 22 and score at least 2 on item 1 (depressed mood) of HAM-D_{17}, a Clinical Global Impressions Scale Severity

of Illness (CGI-S) score of at least 4, and a Raskin Depression Scale score greater than the Covi Anxiety Scale score.

The screening evaluation included a medical history and a psychiatric history. The modified Mini International Neuropsychiatric Interview (MINI) was used as a secondary confirmation of the primary diagnosis of MDD and any comorbid psychiatric disorders that may have been present. Patients with comorbid substance use disorders were excluded; however, patients with comorbid generalized anxiety disorder, panic disorder, or social anxiety disorder were allowed to participate as long as MDD was the primary diagnosis. Patients at high risk for suicidal behaviors were excluded.

Dosing Schedule

Patients were randomly assigned to one of the treatment groups (desvenlafaxine, venlafaxine ER, or placebo). Patients randomized to desvenlafaxine were treated with an initial target dose of 200 mg. Patients in the EU study were started on the initial target dose on day 1, while those in the US study received four days of 100 mg before reaching the target dose. Each study had an optional increase to 400 mg after day 28 or decrease back to 200 mg at any time, based on the investigator's judgment. At the end of the study, patients underwent a taper period based on their final dose.

Venlafaxine ER was used as an active control. In the EU study, patients assigned to venlafaxine ER received 75 mg for 28 days, with an optional increase to 150 mg after day 28 based on the investigator's judgment. In the US study, patients received a daily dose

of 75 mg daily for 4 days. This dose was increased to 150 mg on day 5, and there was an optional increase to 225 mg after day 28. At the end of the study period, patients underwent a taper period based on their final dose.

Study drug included 100 mg and 200 mg desvenlafaxine tablets, 75 mg venlafaxine ER capsules, and matching placebo for each. Each patient received the assigned treatment in individualized blister packs, using double dummy tablets and capsules.

Efficacy and Safety Evaluations

The primary efficacy measure was the HAM-D_{17} total score ascertained at each visit. Secondary efficacy measures included the CGI-I score, the response rate as measured by a 50% or greater decrease in the score on the HAM-D_{17}, the percentage of patients in remission (HAM-D_{17} scores of 7 or less), MADRS total score, CGI-S score, the visual analog scale-pain intensity (VAS-PI) overall pain and subscale scores, HAM-D_6 (Bech version) total score, Covi Anxiety Scale total score, and the response rates on the MADRS (decrease of 50% or more on the total score from baseline) and CGI-I.

Safety was determined using the following assessments: monitoring of adverse events (AEs), discontinuation because of AEs, physical examination, standard 12-lead electrocardiogram (ECG), vital signs (weight, pulse, and blood pressure), and laboratory determinations (hematology, blood chemistry, and urinalysis).

Statistical Methods

Although the study designs of the US and EU studies were similar with the same duration and efficacy measures, the dosing schedules of desvenlafaxine and venlafaxine ER were different. The flexible dosing schedule of desvenlafaxine and placebo data allowed for pooling. However, the venlafaxine ER dosing schedule was lower in the EU study (75 mg to 150 mg/day) than the US study (150 mg to 225 mg/day) and therefore, the venlafaxine ER data are presented as 2 groups.

All efficacy analyses were based on the intent-to-treat (ITT) population, and the safety analyses were based on the safety population.

The ITT population, or efficacy population, consisted of all randomized patients who had a baseline primary evaluation, who took at least 1 dose of study drug and who had at least 1 primary efficacy evaluation after the first dose of study drug. The safety population included all randomized patients who had taken at least 1 dose of study drug.

Longitudinal changes from baseline on pooled data for the primary efficacy measure (HAM-D_{17} total) and the secondary measure CGI-I were analyzed using a MMRM analysis. The change from baseline on the HAMD-$_{17}$ was analyzed as the outcome variable with treatment group, week, and the treatment group by week interaction as fixed factors, center as a random factor, and baseline as a covariate. The CGI-I score was analyzed as the outcome with treatment group, week, and the treatment group by week interaction as fixed factors and center as a random factor. An autoregressive first order [AR (1)] correlation structure was used to model the within subject correlations. The

MMRM analyzes all the data, taking into account the correlations between observations for each patient and is unaffected by randomly missing data. As a secondary analysis, changes from baseline to endpoint for both last observation carried forward (LOCF) and observed cases were analyzed using an analysis of covariance (ANCOVA) with terms of treatment, protocol, and baseline scores. A logistic regression model was used for binary outcome variables (response and remission measured by the HAM-D_{17} and CGI-I).

When the studies were analyzed individually, the HAM-D_{17} total score was evaluated by using ANCOVA on changes from baseline with treatment and site as the factors and baseline scores as the covariate. LOCF and observed-cases analyses were both performed. The CGI-I score was analyzed by using analysis of variance (ANOVA) with treatment and site as the factors. Response and remission rates on the HAM-D_{17} were analyzed with the logistic regression model, with treatment and site as the factors and baseline score as a covariate. The HAM-D_6 total score and Covi Anxiety Scale score were evaluated by using ANCOVA on changes from baseline. Treatment effects were tested at a two-sided significance level of 0.05.

STUDY PATIENTS

Disposition

A total of 738 patients (250 randomized to placebo, 239 to desvenlafaxine, 128 to venlafaxine ER 75-150 mg, and 121 to venlafaxine ER 150-225 mg) were included in this pooled analysis. Eighteen (18) patients had no data after baseline and were not included in the safety population. The remaining 720 patients who completed the

prestudy period and took randomly assigned study drug under double-blind conditions were included in the safety analyses. Seven patients of the safety population did not meet criteria for the Intent-to-Treat (ITT) population, which included 713 patients. **(Table 1)**

Demographic and Other Baseline Characteristics

In the pooled analyses, 226, 127, 115 and 245 patients were evaluated in the desvenlafaxine, venlafaxine ER 75 to 150 mg, venlafaxine ER 150 to 225 mg, and placebo groups, respectively, with a mean age of 42 to 46 years. **(Table 2)** Reflecting the geographic differences between the two pooled studies, minor differences in demographic characteristics were seen among the patients. Individuals in the EU study had a lower mean weight than those in the US study, and a greater percentage of patients were non-Hispanic Caucasians. Because the magnitude of these differences was small, they did not interfere with the use of the pooled analysis. Mean baseline severity on the HAM-D_{17} ranged from 25.1 to 25.8 and did not show statistically significant differences between groups.

RESULTS

Efficacy Evaluations

In the pooled analyses using MMRM**,** desvenlafaxine showed superior efficacy versus placebo as measured by the change from baseline in the HAM-D_{17} score and the CGI-I mean scores. A significant difference was observed at week 3 and was maintained throughout the treatment period. **(Figure 1)** By the week 8 evaluation, desvenlafaxine was significantly better than placebo in reducing MDD severity as measured by the

change from baseline in the HAM-D_{17} total scores (–14.21 versus –11.87 for desvenlafaxine and placebo, respectively, p value <0.001). The magnitude of effect at week 8 on MMRM was clinically significant at –2.34. Desvenlafaxine was also significantly better than placebo as measured by the CGI-I (mean score of 1.9 versus 2.3, respectively at week 8). **(Figure 2)**

Although the EU study failed on the primary efficacy endpoint using ANCOVA (LOCF), desvenlafaxine and venlafaxine ER were significantly better than placebo at week 8 for ANCOVA (OC data; p<0.001 and p=0.027, respectively) and MMRM (p<0.001 and p=0.005, respectively), whereas in the US study, only venlafaxine ER separated from placebo, using both ANCOVA (LOCF and OC) and MMRM.

At the final evaluation (ANCOVA), 55% of desvenlafaxine patients were HAM-D_{17} responders (≥50% reduction in HAM-D_{17} total score) compared with 47% of patients who had received placebo. Thirty percent (30%) of patients on desvenlafaxine achieved remission (HAM-D_{17} total score ≤7) compared with 23% of patients on placebo. (**Figure 3)** Final on therapy comparison between treatment groups showed desvenlafaxine was significantly superior to placebo on the HAM-D_6 Total and the back pain subscale score. Venlafaxine ER 75-150 mg was superior to placebo on symptom improvement as measured by the back pain and joint pain subscales as well as the and overall pain score. Venlafaxine ER 150-225 mg was better than placebo for HAM-D_6, MADRS total and overall pain. **(Table 3)** Individual study results are presented in **Tables 4 and 5**.

Safety Results

The most common treatment emergent adverse events (TEAEs) included nausea, somnolence, dry mouth, and sweating. The type and frequency of TEAEs reported were similar to those reported with other SNRIs. **(Table 6)** In the desvenlafaxine group, there were increases in mean serum lipids, blood pressure, and pulse compared to placebo and decreases in mean weight. No deaths occurred in either study.

DISCUSSION

The results of this study confirm and extend results of 2 previous phase III studies of desvenlafaxine. (DeMartinis et al., 2007) (Septien-Velez L, 2007) The first trial (N=461) showed significant reduction in the HAM-D_{17} scores for the desvenlafaxine 100 mg ($p=0.0038$) and 400 mg ($p=0.0023$) dose groups versus the placebo group. In the 200 mg dose group, reduction in the HAM-D_{17} trended towards significance ($p=0.0764$). All desvenlafaxine dose groups showed significant improvement on the CGI-I scale, a secondary efficacy measure, compared with placebo ($p< 0.05$). (Septien-Velez L, 2007) In the second phase III trial (N= 369), the adjusted mean change from baseline in the HAM-D_{17} total score, the primary efficacy measure, was significantly greater for the desvenlafaxine 200 mg ($p=0.002$) and 400 mg ($p=0.008$) dose groups versus placebo. ($p=0.053$). (DeMartinis et al., 2007)

In the pooled analysis of the 2 underpowered studies described in this report, desvenlafaxine was found to be effective compared with placebo on both the primary and secondary efficacy measures. The efficacy of desvenlafaxine was also reflected in the

positive responder and remission analyses. Pooling of data from inconclusive placebo-controlled studies provides a useful method of establishing whether the treatment effect observed was significant. The pooled analysis could only be carried out provided the studies were comparable. In this case, the design of the studies was similar with the same duration and the same primary and secondary scales. The flexible dosage regime for desvenlafaxine was the same with the target treatment dose dependant on efficacy and tolerability, and this allowed for pooling of data on desvenlafaxine and placebo. By contrast, the dosage regime for the comparator, venlafaxine ER, was different in each study, with a low dose of 75 mg to 150 mg a day in the EU study and a higher dose of 150 mg to 225 mg a day in the US study. The pooling of data allowed for valid conclusions for the efficacy of desvenlafaxine but not for venlafaxine ER as a whole.

The ANCOVA, using LOCF method, which traditionally has been used as a primary analysis in registration studies in EU and the US, uses the last recorded data point to replace the missing points for a participant failing to complete the trial. This approach is believed to be the most conservative because it can reduce the apparent efficacy by assigning high scores for medications that are not well tolerated; however, recent comparisons of different methods have demonstrated that this approach might not be the best in all cases. (Mallinckrodt et al., 2004) The MMRM analysis is a type of likelihood-based mixed-effects methods in which missing points are estimated based on observed data. MMRM approaches are easy to implement, are more robust to the biases from missing data, and provide better control of type I and type II errors than LOCF ANOVA. (Mallinckrodt et al., 2004, Molenberghs et al., 2004)

The high placebo response observed in the 2 studies discussed herein reflects the increasing placebo response observed in many studies over recent years. It has been estimated that the proportion of patients in studies who respond to placebo has risen by approximately 7% per decade (Walsh et al., 2002). A high placebo response in a study makes it difficult, because of ceiling effects, to test for efficacy, as a larger number of patients would be required for a valid comparison. Unless the power calculations for the size of a study were constantly revised upwards to account for this difficulty, it is likely that studies will be underpowered.

Placebo response is a major issue in clinical trials for psychiatric disorders. The causes of a high placebo response in modern studies are many and varied and are the subject of controversy. It is often claimed that the increased number of assessment visits and increased non-specific contact and support, which are part of current high contact trial practice, automatically increases the response rate on both placebo and active treatment and raises the placebo response rate to a level where it is often difficult to distinguish from active treatment. Similarly, the use of many assessment instruments and the careful collection of adverse events have the consequence of increasing contact time with the treatment team, and this may need to be more carefully controlled.

There is also evidence that the placebo response is higher in patients with mild to moderate depression and lower in those with more severe depression; therefore the

inclusion of patients with more severe depression has been recommended as one means of controlling the placebo response. (Fava et al., 1997)

The treatment effect—the magnitude of change on the pivotal scale of 1 antidepressant compared to placebo—is also likely to be affected by the raised placebo response. The treatment effect of desvenlafaxine observed in this analysis is 2.3 points on the HAM-$D_{17,}$ which compares well with the treatment effect of between 2 and 3 points that has been reported in positive pivotal placebo-controlled studies of recently licensed antidepressants. (Khan et al., 2000, Storosum et al., 2001) The treatment effect of desvenlafaxine in this pooled analysis is also in line with that observed with the comparator venlafaxine ER, 75 mg to 150mg (2.4) and 150 mg to 225 mg (2.7) in individual studies. These results suggest that treatment effects of desvenlafaxine and venlafaxine ER in this analysis are clinically relevant. The clinical relevance of the significant difference of the treatment effect observed on desvenlafaxine and venlafaxine ER is also shown by the significant advantage compared to placebo measured on the CGI severity and improvement scores, which represent the view of the independent clinician who is making a clinical judgement of the individual patient under double-blind conditions.

While the univariate repeated-measures ANOVA is still the most commonly used statistical analysis tool for repeated measures in depression trials because of its simplicity and familiarity, mixed-effects models have distinct advantages, including greater

flexibility. The differences in results between analytic methods is clearly demonstrated in the EU and US studies, where in the pooled analyses, using MMRM, desvenlafaxine was significantly more effective than placebo as measured by the HAM-D_{17}, CGI-I, and CGI-S at week 8. These results suggest that the mixed-effects approach, the use of which has substantially increased over the last 10 years, may have important advantages over traditional methods and may yield unbiased and more valid estimates. (Gueorguieva and Krystal, 2004)

CONCLUSIONS

Desvenlafaxine was generally safe and well tolerated in this population. Pooled analyses of the data with MMRM models demonstrate that desvenlafaxine was efficacious in the treatment of MDD, despite the fact that the underpowered individual studies failed to reach statistical significance.

Conflict of Interest Statement:
D. Lieberman has received grant/research support from AstraZeneca, Bristol Myers Squibb, Comentis, The Dalio Family Foundation, Eli Lilly, Epix, GlaxoSmithKline, McNeil, Ono, Predix, The Richard Lounsbery Foundation, Sanofi Aventis, and Wyeth, and is on the speaker's bureau of GlaxoSmithKline. S. Montgomery is a consultant to almost all major pharmaceutical companies, including Wyeth. K. Tourian, K. Padmanabhan, and G. Rosas are employees of Wyeth Research, Collegeville, Pennsylvania. C. Brisard, J-M Germain, and B. Pitrosky are employees of Wyeth Research, Paris, France.

ACKNOWLEDGEMENTS

The clinical trials and analyses included in this report were sponsored by Wyeth Research, Collegeville, Pennsylvania, USA. The authors wish to thank Dorothy L. Tengler, Publications and External Communications at Wyeth for her professional writing and editorial assistance.

We also wish to thank the following co investigators in the desvenlafaxine 309 and 317 studies for their valuable involvement: Raisa Andresina, Andris Arajs, Dolores Backhaus, Bertrand Baranovsky, Bettina Bergtholdt, Leszek Bidzan, Ralf Bodenschatz, Richard Brown, Wlodzimierz Chrzanowski, Johannes Coppens, Andrew Cutler, Marek Cwiakala, Maciej Czerwinski, Didier Deroche, Vladimir Diligenski, Bernadette D'Souza, Christophe Dufour, David Louis Dunner, Louis Fabre, Michel Faure, Pavo Filakovic, Michel Floris, Antoni Florkowski, Vera Folnegovic-Smalc, Peter Franz, Carllo Gagiano, Francis Gheysen, Janusz Janczewski, Mieczyslaw Janiszewski, Riina Jents, Jacek Kacalak, Arifulla Khan, Louis Kirby, Irving Kolin, Peeter Lääne, Jaroslaw Laczkowski, Joel-Louis Langeard, Philippe Leclercq, Pierre LeGoubey, Andres Lehmets, Joseph Lejeune, Vanda Liesiene, James Lohr, Dieter Lohse Lutz, Ljiljana Moro, Peter Londborg, Robert Bruce Lydiard, Eric Perreard, Liaudginas Erdvilas Radavicius, Paresh Ramjee, Paulis Revelis, Christine Reynaert, Robert Riesenberg, Norman Rosenthal, Eckart Ruther, Alexander Schulze, Bruno Scottez, Jeffrey Simon, Martelle Slabber, Jaroslaw Strzelec, Emilis Subata, Ivana Timotijevic, Gerrit Christiaan Verster, Ryszard Wardenski, Hans-Peter Wunderlich.

REFERENCES

ALFINITO, P. D., HUSELTON, C., CHEN, X. & DEECHER, D. C. (2006) Pharmacokinetic and pharmacodynamic profiles of the novel serotonin and norepinephrine reuptake inhibitor desvenlafaxine succinate in ovariectomized Sprague-Dawley rats. *Brain Res,* 1098**,** 71-8.

CLEMENT, E. M., ODONTIADIS, J. & FRANKLIN, M. (1998) Simultaneous measurement of venlafaxine and its major metabolite, oxydesmethylvenlafaxine, in human plasma by high-performance liquid chromatography with coulometric detection and utilisation of solid-phase extraction. *J Chromatogr B Biomed Sci Appl,* 705**,** 303-8.

DEECHER, D. C., BEYER, C. E., JOHNSTON, G., BRAY, J., SHAH, S., ABOU-GHARBIA, M. & ANDREE, T. H. (2006) Desvenlafaxine Succinate: A New Serotonin and Norepinephrine Reuptake Inhibitor. *J Pharmacol Exp Ther,* 318**,** 657-65.

DEMARTINIS, N. A., YEUNG, P. P., ENTSUAH, R. & MANLEY, A. L. (2007) A double-blind, placebo-controlled study of the efficacy and safety of desvenlafaxine succinate in the treatment of major depressive disorder. *Journal of Clinical Psychiatry,* 68**,** 677-88.

FARAVELLI, C., COSCI, F., CIAMPELLI, M., SCARPATO, M. A., SPITI, R. & RICCA, V. (2003) A self-controlled, naturalistic study of selective serotonin reuptake inhibitors versus tricyclic antidepressants. *Psychother Psychosom,* 72**,** 95-101.

FAVA, M., UEBELACKER, L. A., ALPERT, J. E., NIERENBERG, A. A., PAVA, J. A. & ROSENBAUM, J. F. (1997) Major depressive subtypes and treatment response. *Biological Psychiatry,* 42**,** 568-76.

GUEORGUIEVA, R. & KRYSTAL, J. H. (2004) Move over ANOVA: progress in analyzing repeated-measures data and its reflection in papers published in the Archives of General Psychiatry. *Arch Gen Psychiatry,* 61**,** 310-7.

KHAN, A., WARNER, H. A. & BROWN, W. A. (2000) Symptom Reduction and Suicide Risk in Patients Treated With Placebo in Antidepressant Clinical Trials: An Analysis of the Food and Drug Administration Database. *Arch Gen Psychiatry,* 57**,** 311-7.

MALLINCKRODT, C. H., KAISER, C. J., WATKIN, J. G., MOLENBERGHS, G. & CARROLL, R. J. (2004) The effect of correlation structure on treatment contrasts estimated from incomplete clinical trial data with likelihood-based repeated measures compared with last observation carried forward ANOVA. *Clin Trials,* 1**,** 477-89.

MOLENBERGHS, G., THIJS, H., JANSEN, I., BEUNCKENS, C., KENWARD, M. G., MALLINCKRODT, C. & CARROLL, R. J. (2004) Analyzing incomplete longitudinal clinical trial data. *Biostat,* 5**,** 445-64.

MONTGOMERY, S. A. & ASBERG, M. (1979) A new depression scale designed to be sensitive to change. *Br J Psychiatry,* 134**,** 382-9.

MUTH, E. A., MOYER, J. A., HASKINS, J. T., ANDREE, T. H. & HUSBANDS, G. E. M. (1991) Biochemical, neurophysiological and behavioral effects of Wy-45,233 and other identified metabolites of the antidepressant venlafaxine. *Drug Dev Res,* 23**,** 191-9.

NELSON, J. C., MAZURE, C. M., JATLOW, P. I., BOWERS, J. M. B. & PRICE, L. H. (2004) Combining norepinephrine and serotonin reuptake inhibition mechanisms for treatment of depression: a double-blind, randomized study. *Biol Psychiatry,* 55**,** 296-300.

SEGAL, Z. V., PEARSON, J. L. & THASE, M. E. (2003) Challenges in preventing relapse in major depression. Report of a National Institute of Mental Health Workshop on state of the science of relapse prevention in major depression. *J Affect Disord,* 77**,** 97-108.

SEPTIEN-VELEZ L., P. B., PADMANABHAN SK, GERMAIN JM, TOURIAN KA (2007) A randomized, double-blind, placebo-controlled trial of desvenlafaxine succinate in the treatment of major depressive disorder. *Int Clin Psychopharmacol,* 22**,** 338-347.

STEFFENS, D. C., KRISHNAN, K. R. & HELMS, M. J. (1997) Are SSRIs better than TCAs? Comparison of SSRIs and TCAs: a meta-analysis. *Depress Anxiety,* 6**,** 10-8.

STOROSUM, J. G., ELFERINK, A. J., VAN ZWIETEN, B. J., VAN DEN BRINK, W., GERSONS, B. P., VAN STRIK, R. & BROEKMANS, A. W. (2001) Short-term efficacy of tricyclic antidepressants revisited: a meta-analytic study.[erratum appears in Eur Neuropsychopharmacol 2001 Aug;11(4):325]. *Eur Neuropsychopharmacol,* 11**,** 173-80.

THASE, M. E., ENTSUAH, A. R. & RUDOLPH, R. L. (2001) Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. *Br J Psychiatry,* 178**,** 234-41.

WALSH, B. T., SEIDMAN, S. N., SYSKO, R. & GOULD, M. (2002) Placebo response in studies of major depression: variable, substantial, and growing. *JAMA,* 287**,** 1840-7.

WHO (2001) The World Health Organization. The World Health Report 2001--Mental Health: New Understanding, New Hope. Geneva, Switzerland.

Table 1.

Summary of Patient Status: Number of Patients by Population Subset					
Population Subset	**Placebo**	**DVS 200-400mg**	**VEN ER 75- 150mg**	**VEN ER 150-225mg**	**Total**
Randomized to studies	250	239	128	121	**738**
No data after baseline	5	8	1	4	**18**
Safety population[a]	245	231	127	117	**720**
Total ITT[b]	245	226	127	115	**713**
Non-ITT (includes no-data patients	5	13	1	6	**25**
Completed double-blind period	210	166	108	90	**574**

Abbreviations: ITT=Intent to treat; DVS=desvenlafaxine ; VEN ER=venlafaxine ER

a. Safety population included all randomly assigned patients who received at least 1 dose of study drug.
b. The ITT population included all randomly assigned patients who received at least 1 dose of double-blind study drug, had a baseline primary efficacy evaluation, and had a least 1 primary efficacy evaluation after the first dose of double-blind study drug.

Table 2

Demographic and Baseline Characteristics: ITT Pooled Population

Characteristics	Placebo n=245	DVS 200-400mg n=226	VEN ER 75-150 mg n=127	VEN ER 150-225mg n=115
Age, mean (SD), years	42 (12)	43 (12)	46 (12)	42 (12)
Female, n (%)	160 (65%)	153 (68%)	92 (72%)	80 (70%)
Ethnicity/race, n (%)				
White	202 (82%)	202 (89%)	125 (98%)	89 (77%)
Weight, mean (SD), kg	80 (19.9)	77 (21)	72 (15)	83 (22)
Baseline HAM-D_{17}, total, mean (SD)	25.5 (2.8)	25.4 (2.9)	25.8 (3.0)	25.1 (2.4)
Baseline CGI-S, mean (SD)	4.6 (0.6)	4.6 (0.6)	4.8 (0.6)	4.3 (0.5)

HAM-D_{17}=17-item Hamilton Rating Scale for Depression; CGI-S= Clinical Global Impression-Severity of Illness

DVS =desvenlafaxine ; VEN ER=venlafaxine ER

Table 3.

Secondary Efficacy Endpoints (LOCF, ANCOVA), Final Evaluation: Pooled Population

Efficacy Variable	Therapy Group	n	Adjusted Change From Baseline	Adjusted Means (95%CI)	P Value Versus Placebo
MADRS Total score	Placebo	244	-13.5	17.5 (16.2,18.8)	-
	DVS 200-400mg	223	-15.5	15.5 (14.2,16.9)	0.088
	VEN ER 75-150mg	125	-16.0	15.0 (13.1.17.0)	0.108
	VEN ER 150-225mg	113	-17.5	13.6 (11.4,15.7)	0.004
CGI-S	Placebo	245	-1.5	3.1 (2.9,3.3)	-
	DVS 200-400 mg	226	-1.7	2.9 (2.8,3.1)	0.368
	VEN ER 75-150mg	127	-1.7	-2.9 (2.6,3.1)	0.326
	VEN ER 150-225mg	115	-2.0	2.6 (2.3,2.9)	0.005
HAM-D_6 Total	Placebo	245	-5.7	7.6 (7.0,8.1)	-
	DVS 200-400mg	226	-6.6	6.6 (6.0,7.2)	0.049
	VEN ER 75-150mg	127	-6.6	6.6 (5.8,7.5)	0.175
	VEN ER 150-225mg	115	-7.8	5.4 (4.5,63)	<0.001
COVI Total	Placebo	244	-1.3	5.2 (5.0,5.3)	-
	DVS SR 200-400mg	223	-1.4	5.0 (4.8,5.2)	0.782
	VEN ER 75-150mg	125	-1.6	4.9 (4.6,5.2)	0.359
	VENER 150225mg	113	-1.6	4.9 (4.6,5.2)	0.431
VAS Back Pain	Placebo	244	-1.3	21.3 (18.8,23.8)	-
	DVS 200-400mg	223	-1.4	15.4 (12.8,18.0)	0.782
	VEN ER 75-150mg	125	-1.6	14.5 (10.7,18.4)	0.359
	VEN ER 150-225mg	113	-1.6	16.9 (11.9,20.1)	0.431

Secondary Efficacy Endpoints (LOCF, ANCOVA), Final Evaluation: Pooled Population (continued)

Efficacy Variable	Therapy Group	n	Adjusted Change From Baseline	Adjusted Means (95%CI)	P Value Versus Placebo
VAS Arms, Legs, Joint Pain	Placebo	244	-9.2	20.5 (18.0,23.1)	-
	DVS 200-400mg	221	-11.9	17.7(15.1,20.4)	0.321
	VEN ER 75-100mg	125	-15.0	14.6 (10.7,18.5)	0.039
	VEN ER 150-225mg	113	-15.2	14.5(10.3,18.7)	0.037
VAS-PI Overall Pain	Placebo	244	-9.5	22.0(19.5,24.6)	-
	DVS 200-400mg	221	-11.8	19.8 (17.1,22.4)	0.478
	VEN ER 75-100mg	125	-16.3	15.3 (11.4,19.1)	0.011
	VEN ER 150-225mg	113	-13.9	17.7 (13.6,21.8)	0.178

MADRS=Montgomery-Åshberg Depression Rating Scale; CGI-S=Clinical Global Impression-Severity of Illness; HAM-D_6=Bech version of HAM-D_{17}; VAS-PI=Visual Analog Scale Pain Intensity; DVS=desvenlafaxine; VEN ER=venlafaxine ER

Table 4.

Efficacy Results (LOCF), Final Evaluation: ITT Individual Studies

Efficacy Variable	Therapy Group	n	Adjusted Mean Change from Baseline	Difference in Adjusted Means (95% CI) versus Placebo	*P* Value versus DVS SR	*P* Value versus VEN ER
HAM-D_{17} total score (ANCOVA)	**EU**					
	Placebo	120	-12.5	–	0.381	0.171
	DVS 200-400mg	116	-13.4	0.9 (-1.1, 2.8)		
	VEN ER 75-100mg	127	-13.8	1.3 (-0.6, 3.2)		
	US					
	Placebo	125	-9.78	–	0.488	0.005
	DVS 200-400mg	110	-10.5	0.7 (-1.3, 2.7)		
	VEN 150-225mg	115	-12.6	2.9 (0.9, 4.9)		
CGI-I Score (ANOVA)	**EU**					
	Placebo	120	2.3 (2.1, 2.5)	–	0.404	0.107
	DVS 200-400mg	116	2.2 (1.9, 2.4)	0.1 (-0.2, 0.4)		
	VEN ER 75-100mg	127	2.0 (1.8, 2.3)	0.2 (-0.1, 0.5)		
	US					
	Placebo	125	2.5 (2.3, 2.8)	-0.1 (-0.2, 0.4)	0.604	0.011
	DVS 200-400mg	110	2.5 (2.2, 2.7)	0.4 (0.1, 0.7)		
	VEN ER 150-225mg	115	2.1 (1.9, 2.4)			

Abbreviations: ANCOVA=analysis of covariance; ANOVA=analysis of variance; CI=confidence intervals; HAM-D_{17}=17-item Hamilton Rating Scale for Depression; CGI-I=Clinical Global Impressions Scale-Improvement; LOCF= last observation carried forward; DVS =desvenlafaxine ; VEN ER=venlafaxine ER

Table 5.

HAM-D_{17} Response and Remission Rates, Final Evaluation: Individual Studies

Efficacy Variable	Therapy Group	Proportion of Responders (%)	OR (Adjusted Odds Ratio 95% CI)	*P* Value versus Placebo
HAM-D_{17} Response	**EU**			
	Placebo	60 (50)	–	–
	DVS 200-400mg	69 (59)	1.507 (0.89, 2.55)	0.126
	VEN ER 75-100mg	81 (64)	1.772 (1.06, 2.97)	0.03
	US			
	Placebo	55 (44)	–	–
	DVS 200-400mg	55 (50)	1.248 (0.74, 2.11)	0.408
	VEN ER 150-225mg	66 (57)	1.738 (1.03, 2.93)	0.038
HAM-D_{17} Remission	**EU**			
	Placebo	30 (25)	–	–
	DVS 200-400mg	39 (34)	1.549 (0.87, 2.76)	0.138
	VEN ER 75-100mg	43 (34)	1.553 0.88, 2.73)	0.127
	US			
	Placebo	26 (21)	–	–
	DVS 200-400mg	29 (26)	1.331 (0.71, 2.48)	0.369
	VEN ER 150-225mg	41 (36)	2.191 (1.21, 3.98)	0.01

HAM-D_{17}=17-item Hamilton Rating Scale for Depression; CI=confidence interval; DVS =desvenlafaxine
VEN ER=venlafaxine ER

Table 6.

Most Common TEAEs (≥5% and at Least 2 Times Greater with DVS Than with Placebo): Pooled and Individual Populations				
Adverse Event	**Placebo n=245**	**DVS 200-400 mg n=231**	**VEN ER 75-150 mg n=127**	**VEN ER 150-225 mg n=117**
Nausea	30 (12)	87 (38)	27 (21)	34 (29)
Somnolence	16 (7)	31 (13)	12 (9)	22 (19)
Dry mouth	10 (4)	47 (20)	17 (13)	30 (26)
Sweating	10 (4)	45 (20)	12 (9)	21 (18)
Asthenia	10 (4)	21 (9)	10 (8)	7 (6)
Constipation	7 (3)	32 (14)	6 (5)	9 (8)
Abnormal vision	3 (1)	13 (6)	3 (2)	5 (4)
Anorexia	3 (1)	23 (10)	6 (5)	18 (15)
Vomiting	2 (1)	17 (7)	3 (2)	3 (3)
Tachycardia	2 (1)	13 (6)	0	5 (4)
Impotence∗ (men only)	1 (1)	7 (9)	2 (6)	4 (11)

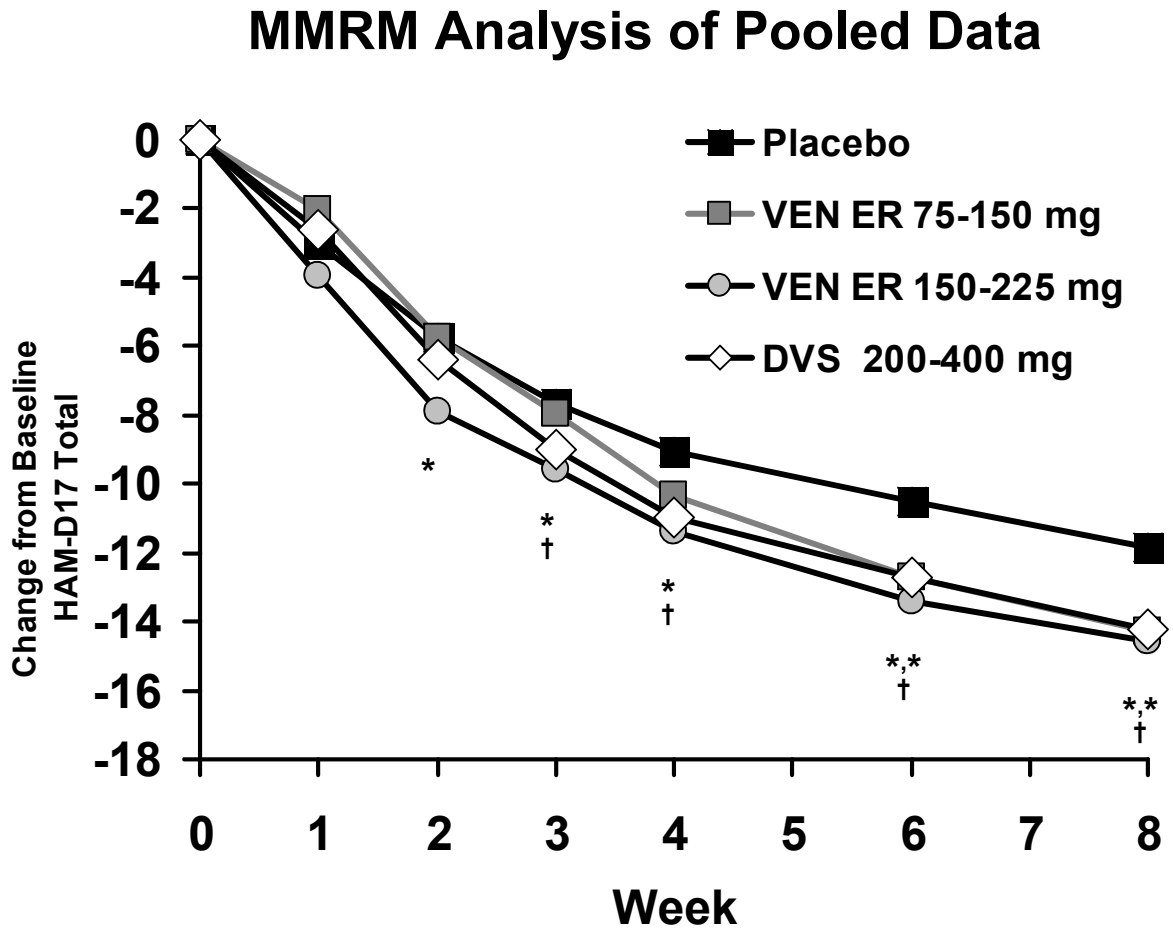
TEAEs = treatment-emergent adverse events
DVS = desvenlafaxine; VEN ER=venlafaxine ER
∗ Incidence based on the number of men: placebo=85, desvenlafaxine =75, and venlafaxine ER=71

LEGENDS

Figure 1. Mean Change from Baseline of HAM-D_{17} Total Score Over Time, MMRM: Pooled Population

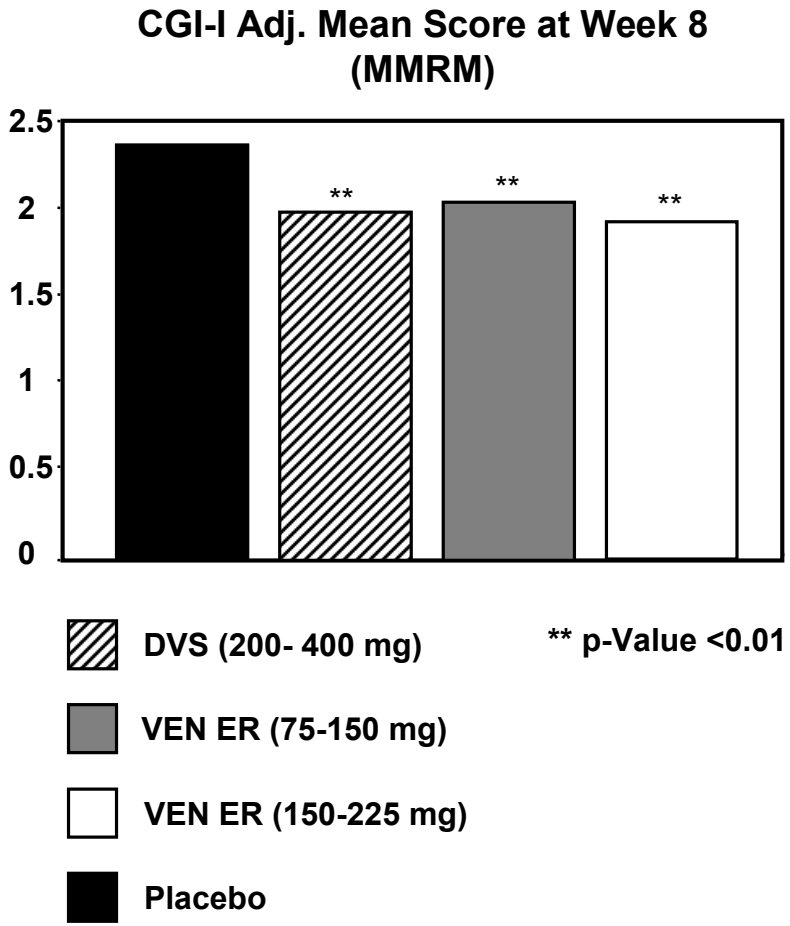
Figure 2. Efficacy Results, MMRM, Week 8 Evaluation: Pooled Population

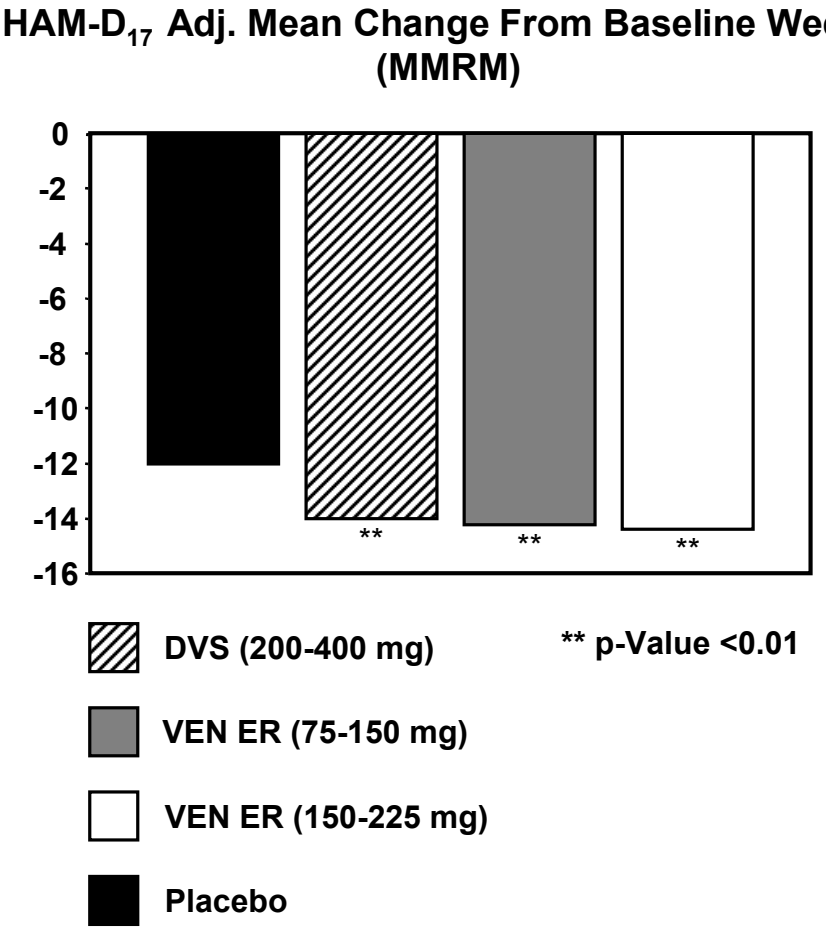
Figure 3. HAM-D_{17} Response and Remission Rates, Final Evaluation: Pooled Population

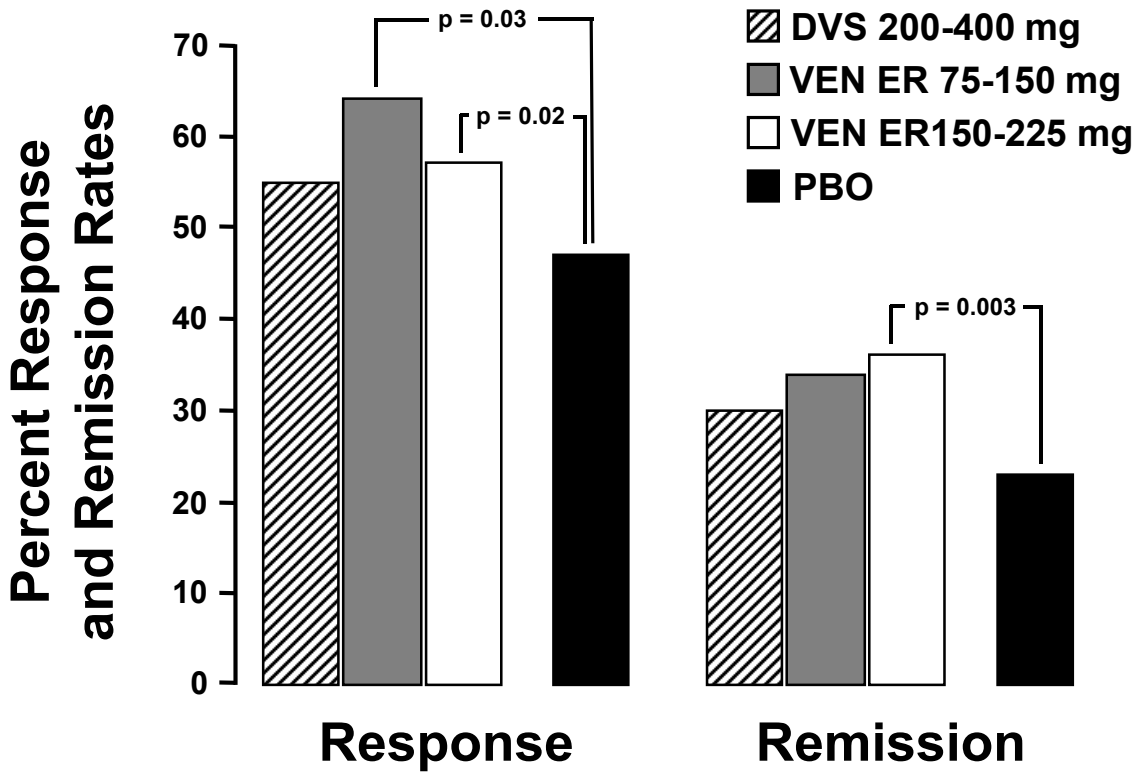


Mean doses:
Study 309: 302 mg DVS; 118 mg Ven ER
Study 317: 336 mg DVS; 206 mg Ven ER

*P<0.05 venlafaxine ER vs. placebo; †P<0.05 DVS vs. placebo.


CGI-I Adj. Mean Score at Week 8
(MMRM)
2.5
2
1.5
1
0.5
0
**
**
**
DVS (200- 400 mg)
VEN ER (75-150 mg)
VEN ER (150-225 mg)
Placebo
** p-Value <0.01


HAM-D17 Adj. Mean Change From Baseline Week 8 (MMRM)
0
-2
-4
-6
-8
-10
-12
-14
-16
**
**
**
DVS (200-400 mg)
VEN ER (75-150 mg)
VEN ER (150-225 mg)
Placebo
** p-Value <0.01



Response = ≥ 50% reduction in HAM-D_{17} total score.
Remission = HAM-D_{17} total score ≤ 7.