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PROPRIETARY DRUG NAME® / GENERIC DRUG NAME:
Pristiq® / Desvenlafaxine Succinate

PROTOCOL NO.: 3151A1-309-EU (B2061075)

PROTOCOL TITLE: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Flexible-Dose Study of DVS-233 SR and Venlafaxine ER in Adult Outpatients With Major Depressive Disorder

Study Centers: A total of 44 centers took part in the study and randomized subjects: 11 in Poland, 9 in France, 6 in Germany, 4 in South Africa, 2 in Belgium, 3 each in Estonia, Latvia and Lithuania, and 1 each in Serbia, Croatia and Serbia and Montenegro.

Study Initiation and Final Completion Dates: 08 April 2004 to 11 March 2005

Phase of Development: Phase 3

Study Objective: The study objective was to compare the anti-depressant efficacy and safety of desvenlafaxine-233 sustained release (DVS-233 SR) with those of placebo in adult outpatients with major depressive disorder (MDD).

METHODS

Study Design:

This was a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group, flexible-dose trial conducted in outpatients with a primary diagnosis of MDD. Subjects were randomized to 1 of 3 treatment Groups: DVS SR 200 to 400 mg, venlafaxine extended release (ER) 75 to 150 mg, or placebo. After a screening period of 6 to 14 days, eligible subjects were treated for approximately 8 weeks +2 additional weeks for tapering the study medication dose. Subjects returned for a follow-up visit approximately 7 days after discontinuing use of study medication. This study was followed by an optional 10-month open-label extension study (A 10 Month Open-Label Evaluation of the Long-Term Safety of DVS-233 SR in Outpatients With Major Depressive Disorder [NCT01309542]).

Subjects who completed the 8-week double-blind study period and continued into the long-term extension study proceeded directly into the long-term study and did not have study drug doses tapered or follow-up evaluations. The study flow chart presented in Table 1 lists the procedures performed at each visit.

Table 1. Study Flow Chart

Study Days	Screening	Baseline	Full-Dose Double-Blind							Taper					Follow-Up
	10 ±4 days	(-1)	1	7[a]	14[a]	21[a]	28[a]	42[a]	56[a,b,c]	60[a]	63[a]	67[a]	70[a]	74[a]	77[a,d]
Obtain informed consent	X														
Medical history	X														
Psychiatric history and diagnosis	X														
Modified Mini International Neuropsychiatric Interview	X														
Eligibility assessment	X								X[e]						
Dispense double-blind study drug		X[f]		X	X	X	X	X	X		X		X		
Subject begins taking study drug			X												
Telephone contact[g]										X		X		X	
Completion of dosage record				X	X	X	X	X	X		X		X		
Recording of prior/concomitant medications	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Efficacy determinations															
HAM-D_{17}	X	X		X	X	X	X	X	X						
MADRS		X			X		X		X						
CGI-S	X	X		X	X	X	X	X	X						
CGI-I				X	X	X	X	X	X						
Raskin Depression Scale	X	X													
Covi Anxiety Scale	X	X			X		X		X						
Sheehan Disability Scale		X			X		X		X						
WHO-5 item well-being index		X			X		X		X						
VAS-PI		X			X		X		X						
Safety determinations															
Physical examination[h]	X								X						
Vital signs[i]	X	X		X	X	X	X	X	X		X		X		X
Weight	X	X		X	X	X	X	X	X		X		X		X
Laboratory tests[j]	X								X						
ECG[k]	X	X							X						
Recording of AEs[l]		X		X	X	X	X	X	X	X	X	X	X	X	X
DESS		X							X		X		X		X

Table 1. Study Flow Chart

AEs = adverse events; BP = blood pressure; CGI-I = Clinical Global Impressions Scale-Improvement; CGI-S = Clinical Global Impressions Scale-Severity of Illness; DESS = discontinuation-emergent signs and symptoms; ECG = electrocardiogram; HAM-D_{17} = Hamilton Rating Scale for Depression, 17-item; MADRS = Montgomery and Asberg Depression Rating Scale; PR = pulse rate; T_3 = triiodothyronine; T_4 = thyroxine; VAS-PI = Visual Analog Scale, Pain Intensity; WHO-5 = World Health Organization 5-item Well-Being Index; β-HCG = serum beta-human chorionic gonadotropin.

a. Every effort was made to bring the subject back on the designated study days; however, office visits had a ±3-day visit window to allow for slight variations in subject schedules, and telephone contacts designated for Days 60, 67, and 74 had a ±2-day window to allow for weekends and slight variations in subject schedules.
b. For subjects who withdrew early, the safety determinations designated for Day 56 were obtained on the last day on which the subject took a full dose of study medication (ie, before taper) or as soon as possible thereafter. The efficacy determinations designated for Day 56 were obtained on the last day on which the subject took a full dose of study medication (ie, before taper) or as soon as possible thereafter.
c. Those subjects entering the long-term, open-label extension study did not receive taper study medication or have any evaluation after the Day 56 visit.
d. For subjects not entering the long-term, open-label extension study, the follow-up determinations were obtained 7±3 days after the last dose of tapered double-blind study medication, or the last dose of double-blind study medication if taper was omitted, for all subjects who had received study medication regardless of the duration of treatment administration.
e. Eligibility assessment at this visit was for entry into the long-term, open-label extension study.
f. Subjects began dose administration on study Day 1.
g. Information recorded during these telephone contacts was reported for the subsequent visit.
h. Height was measured at the Screening physical examination only.
i. Supine and standing PR and supine and standing BP.
j. Subjects fasted for a minimum of 12 hours before testing. Hematology, blood chemistry, and urinalysis data were obtained at Screening and on study Day 56. The urine drug screen was performed at Screening only. Free T_4 index, including T_4 and T_3 uptake, and β-HCG (for women of childbearing potential) were performed at Screening and on study Day 56.
k. At Screening, only a single 12-lead ECG recording was made. On study Days -1 and 56, 3 separate 12-lead ECG recordings were recorded approximately 8 minutes apart over approximately a 15- to 20-minute period.
l. Concomitant treatments and AEs reported by the subject during the telephone contacts were recorded for the next office visit.

Number of Subjects (Planned and Analyzed): The planned enrollment was 360 subjects (120 subjects per treatment group). A total of 369 subjects were enrolled in the study, with 118, 128, and 123 subjects randomly assigned to receive DVS SR 200 to 400 mg, venlafaxine ER 75 to 150 mg, and placebo, respectively; 364 subjects received at least 1 dose of study drug.

Diagnosis and Main Criteria for Inclusion: Men and women 18 to 75 years of age, inclusive; outpatients; subjects must have had a primary diagnosis of MDD based on the criteria in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, single or recurrent episode, without psychotic features. If other allowable psychiatric diagnoses were present, MDD must have been the predominant psychiatric disorder present. At the Screening and Baseline visits, subjects were required to have depressive symptoms for at least 30 days, a score of at least 22 on the Hamilton Psychiatric Rating Scale for Depression, 17-items ($HAM\text{-}D_{17}$), a score of at least 2 on item 1 (depressed mood) of the $HAM\text{-}D_{17}$, and a score of at least 4 on the Clinical Global Impressions Scale-Severity of Illness (CGI-S). Sexually active subjects had to use a medically acceptable form of contraception during the study and for at least 15 days after the last dose of study drug.

Main Exclusion Criteria: Subjects treated with DVS SR at any time in the past, treated with venlafaxine (immediate release [IR] or ER) within 90 days of study Day 1, and subjects with know hypersensitivity to venlafaxine (IR or ER) were excluded from the study.

Study Treatment: DVS SR tablets (100 or 200 mg), venlafaxine ER encapsulated tablets (75 mg), or placebo, were administered orally. From study Days 1 through 28; subjects were instructed to take 1 tablet and 1 capsule per day (1 dosage unit = 200 mg of DVS SR or 75 mg of venlafaxine ER or placebo). From Day 29 onward, based on the Investigator's judgment, the total daily dose could have been adjusted to 2 tablets and 2 capsules per day (2 dosage units = 400 mg of DVS SR or 150 mg of venlafaxine ER or placebo). Subjects were treated for 8 weeks followed by up to a 2-week taper period, and a poststudy evaluation period 7 days after the last dose of study medication.

Efficacy Endpoints:

Primary Efficacy Endpoint: The primary efficacy endpoint was the change from Baseline in the $HAM\text{-}D_{17}$ total score at the final on-therapy evaluation.

Key Secondary Efficacy Endpoint: The key secondary efficacy endpoint was the change from Baseline in the Clinical Global Impression Scale–Improvement (CGI-I) score at the final on-therapy evaluation.

Other Secondary Efficacy Endpoints:

The other secondary efficacy endpoints were the Montgomery And Asberg Depression Rating Scale (MADRS) total score, Hamilton Psychiatric Rating Scale for Depression, 6-items ($HAM\text{-}D_6$) [Bech version: HAM-D items 1, 2, 7, 8, 10, and 13] total score, CGI-S score, the response rate on the $HAM\text{-}D_{17}$, the percentage of subjects in remission ($HAM\text{-}D_{17}$ score of ≤ 7), the Covi Anxiety Scale total score, Sheehan Disability Scale (SDS) total score

and subscale scores, the World Health Organization 5-item Well-Being Index (WHO-5) total score, the Visual Analog Scale, Pain Intensity (VAS-PI) overall pain and subscale scores, and the response rates on the MADRS and CGI-I. For all of the secondary efficacy endpoints, the final evaluation was the primary endpoint.

Safety Evaluations: The safety of DVS SR was determined using the following assessments: monitoring of adverse events (AEs), discontinuations because of AEs, physical examination, standard 12-lead electrocardiogram (ECG), vital signs (supine and standing pulse rate [PR] and blood pressure [BP]), laboratory determinations (hematology, blood chemistry, and urinalysis), and the discontinuation-emergent signs and symptoms checklist.

Statistical Methods:

Analysis Sets:

Intent-To-Treat Population (ITT): The primary population for the efficacy analysis was the ITT population. The ITT population comprised all randomized subjects who had a baseline primary efficacy evaluation, took at least 1 dose of double-blind study medication, and had at least 1 primary efficacy evaluation after the first dose of double-blind study medication. The ITT population was the primary population for efficacy analysis.

Per-Protocol Population (PPP): The PPP comprised all randomized subjects who had a baseline primary efficacy evaluation, who took at least 1 dose of double-blind study medication and had at least 1 primary efficacy evaluation after the first dose of double-blind study medication and had no major protocol violations.

Safety Population: All randomized subjects with documented use of at least 1 dose of double-blind study medication were included in the safety population.

All Randomized Population (ARP): A subject who had a randomization number assigned and had at least a baseline efficacy evaluation was included in the ARP.

The efficacy analyses were done based on ITT, PPP and ARP, and the safety analyses were done based on the safety population. ETRANK method was used to analyze the ARP for the primary efficacy variable.

Efficacy Analyses:

For all primary and secondary efficacy endpoints, the final on-therapy evaluation was the primary endpoint. Analyses were performed at each evaluation period by using the last observation carried forward (LOCF) technique and the observed-cases analysis.

The primary analysis was the change from Baseline on the HAM-D_{17} score at the final on-therapy evaluation and was tested by using analysis of covariance (ANCOVA) with treatment and site as the factors and baseline HAM-D_{17} scores as the covariate. The assumptions of the ANCOVA models were checked at the final evaluation based on the primary efficacy variable. The test of homoscedasticity was performed with the Levene test. An interaction term using the covariate and treatment was added to the primary model to test

parallelism. Normality was tested using the Shapiro-Wilk`s test. If assumptions of ANCOVA were not met, an analysis of variance (ANOVA) or a nonparametric ANCOVA based on ranks was performed.

Mean scores on the CGI-I were analyzed with ANOVA with treatment and site as the factors. A treatment-by-site interaction term was added into the primary and key secondary efficacy analysis models to explore the possibility of qualitative or quantitative treatment-by-site interaction. If the interaction was significant ($p \leq 0.10$), an assessment of the magnitude and direction of the interaction term was made.

Other secondary variables included the MADRS total score, the CGI-S score, and the overall pain score and each subcomponent of the VAS-PI. Health outcomes assessments included SDS and the WHO-5. These variables were evaluated by using ANCOVA on changes from baseline, with treatment and site as the main factors and baseline value as the covariate in the primary model.

Two (2) additional secondary variables were response rate based on the HAM-D_{17} total score and remission based on HAM-D_{17} score ≤ 7. Response on the HAM-D_{17} was defined as a decrease of 50% or more on the total score from baseline. Response rate on the HAM-D_{17} was analyzed with the logistic regression model, with treatment and site as the factors and baseline score as a covariate. Remission (HAM-$D_{17} \leq 7$) was analyzed using logistic regression.

Ancillary efficacy variables included the HAM-D_6 total score, the Covi Anxiety Scale score, response rates based on the MADRS score, response rates based on the CGI-I score, and response rates based on the SDS score. The HAM-D_6 total score and the Covi Anxiety Scale score were evaluated by using ANCOVA on changes from baseline with treatment and site as the main factors and baseline value as the covariate in the primary model.

Subjects who had CGI-I scores of 1 or 2 were classified as responders. These data were analyzed with the logistic regression model with treatment and site as the factors. A second model with treatment-by-site interaction as an additional factor was performed to explore the possibility of treatment-by-site interaction.

Response on the MADRS was defined as a decrease of 50% or more on the total score from Baseline. Response rate on the MADRS was analyzed with the logistic regression model with treatment and site as the factors and baseline score as the covariate.

If there was a significant difference between the DVS SR and placebo groups in the results of the ANCOVA analysis on the primary efficacy variable, $HAMD_{17}$, additional analyses to correct for patterns of missing data were performed with the HAM-D_{17}. These longitudinal methods were the RANDOM effect mixed model and/or the ETRANK method.

RESULTS

Subject Disposition and Demography: A total of 437 subjects were screened for the study; 68 subjects were screen failures, and 369 subjects were enrolled in the study, with 118, 128,

and 123 subjects randomly assigned to receive DVS SR 200 to 400 mg, venlafaxine ER 75 to 150 mg, and placebo, respectively. Of the subjects enrolled in the study, 364 subjects received at least 1 dose of study medication and were included in the safety population, and 363 subjects were included in the ITT population. Table 2 summarizes the number of subjects in each population subset for each treatment group. Six (6) subjects were excluded from the ITT population because they did not take any study medication, did not have any post-baseline data, or did not have a primary efficacy evaluation (HAM-D_{17}) on therapy.

Table 2. Summary of Subject Status: Number of Subjects by Population Subset

Population Subset	Placebo	DVS SR 200 to 400 mg	Venlafaxine ER 75 to 150 mg	Total
Randomly assigned to study	123	118	128	369
No data after baseline (no study drug used)	3	1	1	5
Safety population[a]	120	117	127	364
Total ITT population[b]	120	116	127	363
Non-ITT (includes no-data subjects)	3	2	1	6
PPP for efficacy[c]	112	99	114	325
Completed double-blind period[d]	106	89	108	303

CDR = clinical data report; DVS SR = desvenlafaxine succinate sustained release; ER = extended release; ITT = intent-to-treat; PPP = per-protocol population.

a. Safety population included all randomly assigned subjects who received at least 1 dose of study medication.

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

c. The PPP included all randomly assigned subjects who had a baseline primary efficacy evaluation, had taken at least 1 dose of double-blind study medication, had at least 1 primary efficacy evaluation after the first dose of double-blind study medication, and had no major protocol violation.

d. Completers were defined as subjects who had a duration of therapy of ≥53 days or (56±3 days).

A total of 54 (15%) subjects discontinued treatment during the double-blind period: 13 (11%), 25 (21%), and 16 (13%) in the placebo, DVS SR, and venlafaxine ER groups, respectively. Table 3 summarizes the number of subjects who discontinued treatment by the primary reasons for withdrawal in each treatment group. The most common reason for discontinuation was AE in either DVS SR or venlafaxine ER groups, while it was unsatisfactory response in the placebo group.

Table 3. Number (%) of Subjects Who Discontinued Treatment During the Double-Blind Period by Primary Reason for Withdrawal

Reason	Placebo N=120	DVS SR 200 to 400 mg N=117	Venlafaxine ER 75 to 150 mg N=127
Total	13 (11)	25 (21)	16 (13)
AE	1 (<1)	19 (16)	7 (6)
Failed to return	1 (<1)	1 (<1)	1 (<1)
Other event	1 (<1)	1 (<1)	3 (2)
Subject request unrelated to study	1 (<1)	1 (<1)	1 (<1)
Protocol violation	3 (3)	1 (<1)	1 (<1)
Unsatisfactory response - efficacy	6 (5)	2 (2)	3 (2)

AE = adverse event; DVS SR = desvenlafaxine succinate sustained release; ER = extended release; N = number of subjects.

Table 4 shows the demographic characteristics for the safety population. Most of the subjects were White (99%) and women (70%). The mean baseline severity of MDD based on the HAM-D_{17} total score was 26, and the mean duration of current depressive episode was 7 months. There were no significant differences among treatment groups for demographic characteristics. The characteristics for the safety and ITT populations were similar.

Table 4. Demographic Characteristics, Safety Population

Characteristic	Placebo N=120	DVS SR 200 to 400 mg N=117	Venlafaxine ER 75 to 150 mg N=127
Age, years			
Mean±SD	45.4±12.0	43.9±12.3	45.9±12.0
Range	21.0 to 72.0	18.0 to 73.0	23.0 to 70.0
Median	47.0	45.0	47.0
Sex, n (%)			
Female	80 (67)	84 (72)	92 (72)
Male	40 (33)	33 (28)	35 (28)

DVS SR = desvenlafaxine succinate sustained release; ER = extended release; N = total number of subjects; n = number of subjects in category; SD = standard deviation.

Efficacy Results:

Primary Efficacy Endpoint:

The results of the LOCF and observed-cases analyses at each scheduled time point for the primary efficacy variable (HAM-D_{17}) in the ITT population are displayed in Table 5.

Short-term outcomes for the primary comparison of interest, DVS SR against placebo, showed no significant differences (p=0.381) at the final on-therapy evaluation. At the final on-therapy evaluation, the adjusted mean change from Baseline on the HAM-D_{17} total score was -12.5 in the placebo group, -13.4 in the DVS SR group, and -13.8 in the venlafaxine ER group. No significant difference (p=0.171) was observed between the venlafaxine ER group and the placebo group at the final on-therapy evaluation. The lack of significant difference in

efficacy between active treatments and placebo appeared to result from a clinically important placebo effect.

In the observed-cases analysis at Week 8, significant differences in adjusted mean changes from Baseline were observed between DVS SR and placebo ($p<0.001$) and between venlafaxine ER and placebo ($p=0.027$). At Week 8, the observed cases adjusted mean change from Baseline in the HAM-D_{17} total score was -12.8 in the placebo group, -16.4 in the DVS SR group, and -14.9 in the venlafaxine ER group. No statistically significant difference was observed between the DVS SR and venlafaxine ER groups.

Table 5. Comparison of Changes From Baseline in HAM-D_{17} Total Score (ANCOVA) - ITT Population

Analysis Week on Therapy	Treatment Group	N	Raw Mean Score	Adjusted Mean Change From Baseline	Standard Error	Adjusted Means (95% CI)	Difference in Adjusted Means (95% CI) vs Placebo	p-Value vs DVS SR	p-Value vs Ven ER
LOCF									
Baseline	Placebo	120	26.0			25.9 (25.9, 25.9)			
	DVS SR	116	25.9			25.9 (25.9, 25.9)			
	Ven ER	127	25.8			25.9 (25.9, 25.9)			
Week 1	Placebo	119	23.0	-3.15	0.35	22.8 (22.1, 23.4)		0.227	0.458
	DVS SR	116	23.5	-2.56	0.35	23.3 (22.6, 24.0)	-0.6 (-1.5, 0.4)		0.624
	Ven ER	127	23.3	-2.79	0.34	23.1 (22.4, 23.8)	-0.4 (-1.3, 0.6)		
Week 2	Placebo	120	20.3	-5.86	0.49	20.0 (19.1, 21.0)		0.377	0.835
	DVS SR	116	19.6	-6.47	0.50	19.4 (18.5, 20.4)	0.6 (-0.7, 1.9)		0.490
	Ven ER	127	20.0	-6.00	0.48	19.9 (19.0, 20.8)	0.1 (-1.2, 1.4)		
Week 3	Placebo	120	17.6	-8.56	0.57	17.4 (16.2, 18.5)		0.904	0.580
	DVS SR	116	17.4	-8.66	0.58	17.3 (16.1, 18.4)	0.1 (-1.5, 1.7)		0.503
	Ven ER	127	17.9	-8.12	0.56	17.8 (16.7, 18.9)	-0.4 (-2.0, 1.1)		
Week 4	Placebo	120	16.1	-9.97	0.62	15.9 (14.7, 17.2)		0.650	0.891
	DVS SR	116	15.6	-10.4	0.64	15.5 (14.3, 16.8)	0.4 (-1.3, 2.1)		0.745
	Ven ER	127	15.8	-10.1	0.61	15.8 (14.6, 17.0)	0.1 (-1.6, 1.8)		
Week 6	Placebo	120	15.0	-11.1	0.67	14.8 (13.5, 16.1)		0.203	0.211
	DVS SR	116	13.7	-12.3	0.69	13.6 (12.3, 15.0)	1.2 (-0.6, 3.0)		0.959
	Ven ER	127	13.7	-12.2	0.66	13.7 (12.4, 14.9)	1.2 (-0.7, 3.0)		
Week 8	Placebo	120	13.9	-12.2	0.70	13.7 (12.3, 15.1)		0.275	0.121
	DVS SR	116	12.8	-13.3	0.72	12.6 (11.2, 14.0)	1.1 (-0.9, 3.0)		0.665
	Ven ER	127	12.3	-13.7	0.69	12.2 (10.8, 13.5)	1.5 (-0.4, 3.4)		
Week >8	Placebo	120	13.6	-12.5	0.71	13.4 (12.0, 14.8)		0.381	0.171
	DVS SR	116	12.7	-13.4	0.72	12.5 (11.1, 14.0)	0.9 (-1.1, 2.8)		0.639
	Ven ER	127	12.2	-13.8	0.69	12.1 (10.7, 13.4)	1.3 (-0.6, 3.2)		
Final evaluation	Placebo	120	13.6	-12.5	0.71	13.4 (12.0, 14.8)		0.381	0.171
	DVS SR	116	12.7	-13.4	0.72	12.5 (11.1, 14.0)	0.9 (-1.1, 2.8)		0.639
	Ven ER	127	12.2	-13.8	0.69	12.1 (10.7, 13.4)	1.3 (-0.6, 3.2)		

Table 5. Comparison of Changes From Baseline in HAM-D_{17} Total Score (ANCOVA) - ITT Population

Analysis Week on Therapy	Treatment Group	N	Raw Mean Score	Adjusted Mean Change From Baseline	Standard Error	Adjusted Means (95% CI)	Difference in Adjusted Means (95% CI) vs Placebo	p-Value vs DVS SR	p-Value vs Ven ER
Observed cases									
Baseline	Placebo	120	26.0			25.9 (25.9, 25.9)			
	DVS SR	116	25.9			25.9 (25.9, 25.9)			
	Ven ER	127	25.8			25.9 (25.9, 25.9)			
Week 1	Placebo	119	23.0	-3.15	0.35	22.8 (22.1, 23.4)		0.227	0.458
	DVS SR	116	23.5	-2.56	0.35	23.3 (22.6, 24.0)	-0.6 (-1.5, 0.4)		0.624
	Ven ER	127	23.3	-2.79	0.34	23.1 (22.4, 23.8)	-0.4 (-1.3, 0.6)		
Week 2	Placebo	118	20.2	-5.99	0.48	19.9 (18.9, 20.8)		0.062	0.441
	DVS SR	101	18.8	-7.28	0.52	18.6 (17.6, 19.6)	1.3 (-0.1, 2.6)		0.260
	Ven ER	117	19.5	-6.50	0.48	19.4 (18.4, 20.3)	0.5 (-0.8, 1.8)		
Week 3	Placebo	117	17.6	-8.56	0.56	17.3 (16.2, 18.4)		0.110	0.879
	DVS SR	95	16.1	-9.88	0.62	16.0 (14.7, 17.2)	1.3 (-0.3, 2.9)		0.082
	Ven ER	114	17.5	-8.44	0.57	17.4 (16.3, 18.5)	-0.1 (-1.6, 1.4)		
Week 4	Placebo	111	16.1	-10.0	0.62	15.8 (14.6, 17.0)		0.046	0.304
	DVS SR	98	14.1	-11.8	0.66	14.1 (12.8, 15.3)	1.8 (0.0, 3.5)		0.315
	Ven ER	112	14.9	-10.9	0.61	14.9 (13.7, 16.1)	0.9 (-0.8, 2.5)		
Week 6	Placebo	102	14.7	-11.5	0.68	14.3 (13.0, 15.7)		0.003	0.047
	DVS SR	92	11.6	-14.4	0.72	11.5 (10.0, 12.9)	2.9 (1.0, 4.8)		0.288
	Ven ER	105	12.6	-13.4	0.67	12.5 (11.2, 13.8)	1.9 (0.0, 3.7)		
Week 8	Placebo	95	13.2	-12.8	0.69	13.0 (11.6, 14.3)		<0.001	0.027
	DVS SR	87	9.4	-16.4	0.70	9.4 (8.1, 10.8)	3.5 (1.6, 5.4)		0.117
	Ven ER	101	11.0	-14.9	0.65	10.9 (9.6, 12.2)	2.0 (0.2, 3.9)		

ANCOVA = analysis of covariance; CI = confidence interval; DVS SR = desvenlafaxine succinate sustained release; HAM-D_{17} = Hamilton Rating Scale for Depression, 17-item; ITT = intent-to-treat; LOCF = last observation carried forward; N = number of subjects; Ven ER = venlafaxine, extended-release formulation; vs = versus.

Key Secondary Efficacy Endpoint:

Table 6 displays at each scheduled time point the ITT results of the LOCF and observed cases analyses for CGI-I scores.

No significant differences were observed between DVS SR and placebo (p=0.404), or between venlafaxine ER and placebo (p=0.107) at the final on-therapy evaluation. At this final on-therapy evaluation, the predicted mean CGI-I scores were 2.3 in the placebo group, 2.2 in the DVS SR group, and 2.0 in the venlafaxine ER group.

In the observed-cases analysis, significant differences in the predicted mean CGI-I score were observed between DVS SR and placebo from Week 2 to Week 8 ($p<0.001$ at Week 8) and between venlafaxine ER and placebo at Week 8 (p=0.014). At Week 8, the observed cases predicted mean CGI-I scores were 2.2 in the placebo group, 1.7 in the DVS SR group, and 1.9 in the venlafaxine ER group. No statistically significant difference was observed between DVS SR and venlafaxine ER.

Table 6. Comparison of Changes From Baseline in CGI-I Score (ANOVA), ITT Population

Analysis Week on Therapy	Treatment Group	N	Raw Mean Score	Standard Error	Predicted Means (95% CI)	Difference in Predicted Means (95% CI) vs Placebo	p-Value vs DVS SR	p-Value vs Ven ER
LOCF								
Week 1	Placebo	119	3.5	0.06	3.4 (3.3, 3.6)		0.077	0.044
	DVS SR	116	3.6	0.06	3.6 (3.5, 3.7)	-0.2 (-0.3, 0.0)		0.832
	Ven ER	127	3.7	0.06	3.6 (3.5, 3.7)	-0.2 (-0.3, -0.0)		
Week 2	Placebo	120	3.1	0.08	3.1 (2.9, 3.2)		0.249	0.671
	DVS SR	116	3.0	0.09	2.9 (2.8, 3.1)	0.1 (-0.1, 0.4)		0.454
	Ven ER	127	3.1	0.08	3.0 (2.9, 3.2)	0.0 (-0.2, 0.3)		
Week 3	Placebo	120	2.7	0.10	2.7 (2.5, 2.9)		0.822	0.296
	DVS SR	116	2.7	0.10	2.7 (2.5, 2.9)	0.0 (-0.2, 0.3)		0.206
	Ven ER	127	2.9	0.09	2.8 (2.6, 3.0)	-0.1 (-0.4, 0.1)		
Week 4	Placebo	120	2.5	0.10	2.5 (2.3, 2.7)		0.654	0.925
	DVS SR	116	2.5	0.10	2.4 (2.2, 2.6)	0.1 (-0.2, 0.3)		0.718
	Ven ER	127	2.5	0.10	2.5 (2.3, 2.7)	0.0 (-0.3, 0.3)		
Week 6	Placebo	120	2.4	0.11	2.4 (2.2, 2.6)		0.316	0.418
	DVS SR	116	2.3	0.11	2.2 (2.0, 2.5)	0.2 (-0.1, 0.4)		0.829
	Ven ER	127	2.3	0.10	2.3 (2.1, 2.5)	0.1 (-0.2, 0.4)		
Week 8	Placebo	120	2.3	0.11	2.3 (2.1, 2.5)		0.319	0.068
	DVS SR	116	2.2	0.11	2.2 (2.0, 2.4)	0.2 (-0.1, 0.4)		0.423
	Ven ER	127	2.1	0.11	2.1 (1.8, 2.3)	0.3 (-0.0, 0.6)		
Week >8	Placebo	120	2.3	0.11	2.3 (2.1, 2.5)		0.404	0.107
	DVS SR	116	2.2	0.11	2.2 (1.9, 2.4)	0.1 (-0.2, 0.4)		0.451
	Ven ER	127	2.1	0.11	2.0 (1.8, 2.3)	0.2 (-0.1, 0.5)		
Final evaluation	Placebo	120	2.3	0.11	2.3 (2.1, 2.5)		0.404	0.107
	DVS SR	116	2.2	0.11	2.2 (1.9, 2.4)	0.1 (-0.2, 0.4)		0.451
	Ven ER	127	2.1	0.11	2.0 (1.8, 2.3)	0.2 (-0.1, 0.5)		
Observed cases								
Week 1	Placebo	119	3.5	0.06	3.4 (3.3, 3.6)		0.077	0.044
	DVS SR	116	3.6	0.06	3.6 (3.5, 3.7)	-0.2 (-0.3, 0.0)		0.832
	Ven ER	127	3.7	0.06	3.6 (3.5, 3.7)	-0.2 (-0.3, -0.0)		
Week 2	Placebo	118	3.1	0.08	3.1 (2.9, 3.2)		0.011	0.289
	DVS SR	101	2.8	0.09	2.8 (2.6, 2.9)	0.3 (0.1, 0.5)		0.128
	Ven ER	117	3.0	0.08	2.9 (2.8, 3.1)	0.1 (-0.1, 0.3)		
Week 3	Placebo	117	2.7	0.09	2.7 (2.5, 2.9)		0.046	0.308

Table 6. Comparison of Changes From Baseline in CGI-I Score (ANOVA), ITT Population

Analysis Week on Therapy	Treatment Group	N	Raw Mean Score	Standard Error	Predicted Means (95% CI)	Difference in Predicted Means (95% CI) vs Placebo	p-Value vs DVS SR	p-Value vs Ven ER
	DVS SR	95	2.4	0.10	2.4 (2.2, 2.6)	0.3 (0.0, 0.5)		0.003
	Ven ER	114	2.8	0.09	2.8 (2.6, 3.0)	-0.1 (-0.4, 0.1)		
Week 4	Placebo	111	2.5	0.10	2.5 (2.3, 2.7)		0.030	0.435
	DVS SR	98	2.2	0.11	2.2 (2.0, 2.4)	0.3 (0.0, 0.6)		0.154
	Ven ER	112	2.4	0.10	2.4 (2.2, 2 .6)	0.1 (-0.2, 0.4)		
Week 6	Placebo	102	2.3	0.10	2.3 (2.1, 2.5)		0.015	0.215
	DVS SR	92	2.0	0.11	1.9 (1.7, 2.1)	0.4 (0.1, 0.7)		0.208
	Ven ER	105	2.1	0.10	2.1 (1.9, 2.3)	0.2 (-0.1, 0.5)		
Week 8	Placebo	95	2.2	0.11	2.2 (2.0, 2.4)		<0.001	0.014
	DVS SR	87	1.8	0.11	1.7 (1.5, 1.9)	0.5 (0.2, 0.8)		0.323
	Ven ER	101	1.9	0.10	1.9 (1.7, 2.1)	0.4 (0.1, 0.6)		

ANOVA = analysis of covariance; CI = confidence interval; CGI-I = Clinical Global Impressions Scale-Improvement; DVS SR = desvenlafaxine succinate sustained release; ITT = intent-to-treat; LOCF = last observation carried forward; N = number of subjects; Ven ER = venlafaxine, extended-release formulation; vs = versus.

Other Secondary Efficacy Endpoints: Results for the MADRS total score, CGI-S score, VAS-PI overall score and VAS-PI component scores are presented in Table 7 for the final on-therapy evaluation and Table 8 for the observed-cases analysis at Week 8.

Table 7. Secondary Efficacy Parameters: Adjusted Mean (95% CI), Final On-Therapy Evaluation, ITT Population

Parameter Time Point	Placebo		DVS SR 200 to 400 mg		Venlafaxine ER 75 to 150 mg	
	N	Adjusted Mean	N	Adjusted Mean	N	Adjusted Mean
MADRS total score						
Baseline	120	30.9	116	30.9	127	30.9
Final on-therapy evaluation	120	16.3 (14.5, 18.1)	116	14.3 (12.5, 16.2)	125	13.8 (12.0, 15.5)*
CGI-S						
Baseline	120	4.8	116	4.8	127	4.8
Final on-therapy evaluation	120	3.1 (2.9, 3.3)	116	2.9 (2.6, 3.1)	127	2.8 (2.6, 3.1)
VAS-PI overall pain						
Baseline	120	37.6	115	37.6	126	37.6
Final on-therapy evaluation	120	27.0 (23.3, 30.6)	114	21.9 (18.1, 25.7)	124	18.8 (15.2, 22.5)*
VAS-PI stomach pain						
Baseline	120	23.2	115	23.2	126	23.2
Final on-therapy evaluation	120	16.1 (12.5, 19.7)	114	14.6 (10.9, 18.3)	124	12.5 (9.0, 16.1)
VAS-PI back pain						
Baseline	120	33.3	115	33.3	126	33.3
Final on-therapy evaluation	120	25.5 (21.9, 29.1)	114	17.5 (13.8, 21.2)*	124	17.8 (14.3, 21.4)*
VAS-PI chest pain						
Baseline	120	22.8	114	22.8	126	22.8
Final on-therapy evaluation	120	16.4 (13.1, 19.7)	113	10.2 (6.8, 13.6)*	124	11.8 (8.6, 15.1)*
VAS-PI arms/legs/joints pain						
Baseline	120	33.9	115	33.9	126	33.9
Final on-therapy evaluation	120	24.7 (20.9, 28.4)	114	20.6 (16.8, 24.5)	124	18.3 (14.6, 22.0)*

* Significantly different from placebo ($p \leq 0.05$) on the pairwise comparison; ANCOVA.
ANCOVA = analysis of covariance; CI = confidence interval; CGI-S = Clinical Global Impressions Scale-Severity of Illness; DVS SR = desvenlafaxine succinate sustained release; ER = extended-release ; ITT = intent-to-treat; MADRS = Montgomery And Asberg Depression Rating Scale; N = number of subjects; VAS-PI = Visual Analog Scale, Pain Intensity.

Table 8. Secondary Efficacy Parameters: Adjusted Mean (95% CI), Observed-Cases Analysis, ITT Population

Parameter Time Point	Placebo		DVS SR 200 to 400 mg		Venlafaxine ER 75 to 150 mg	
	N	Adjusted Mean	N	Adjusted Mean	N	Adjusted Mean
MADRS total score						
Baseline	120	30.9	116	30.9	127	30.9
Week 8	95	16.0 (14.2, 17.7)	87	10.4 (8.6, 12.2)*	101	12.8 (11.1, 14.5)*
CGI-S						
Baseline	120	4.8	116	4.8	127	4.8
Week 8	95	3.0 (2.7, 3.2)	87	2.4 (2.1, 2.7)*	101	2.7 (2.4, 2.9)
VAS-PI overall pain						
Baseline	120	37.6	115	37.6	126	37.6
Week 8	95	25.9 (22.1, 29.7)	86	14.8 (10.8, 18.8)*	101	17.1 (13.5, 20.8)*
VAS-PI stomach pain						
Baseline	120	23.2	115	23.2	126	23.2
Week 8	95	14.8 (11.5, 18.1)	86	8.5 (5.1, 12.0)*	101	11.0 (7.9, 14.2)
VAS-PI back pain						
Baseline	120	33.3	115	33.3	126	33.3
Week 8	95	24.3 (20.2, 28.4)	86	14.9 (10.6, 19.1)*	101	18.1 (14.2, 22.1)*
VAS-PI chest pain						
Baseline	120	22.8	114	22.8	126	22.8
Week 8	95	16.1 (12.6, 19.5)	86	8.6 (4.9, 12.3)*	101	10.2 (6.9, 13.5)*
VAS-PI arms/legs/joints pain						
Baseline	120	33.9	115	33.9	126	33.9
Week 8	95	24.3 (20.2, 28.4)	86	17.6 (13.3, 21.9)*	101	17.1 (13.2, 21.1)*

* Significantly different from placebo ($p \leq 0.05$) on the pairwise comparison; ANCOVA.
ANCOVA = analysis of covariance; CI = confidence interval; CGI-S = Clinical Global Impressions Scale-Severity of Illness; DVS SR = desvenlafaxine succinate sustained release; ER = extended-release; ITT = intent-to-treat; MADRS = Montgomery And Asberg Depression Rating Scale; N = number of subjects; VAS-PI = Visual Analog Scale, Pain Intensity.

Results for remission and response to treatment (defined using HAM-D_{17}, MADRS, or CGI-I) are summarized for both the final on-therapy evaluation and at Week 8 using the observed-cases analysis in Table 9.

Table 9. Comparison of Remission and Response Between Treatment Groups: Number (%) of Subjects, ITT Population

Analysis, Time Point Responder Type	Placebo	DVS SR 200 to 400 mg	Venlafaxine ER 75 to 150 mg
Final on-therapy evaluation			
Remission[a]	30 (25.0)	39 (33.6)	43 (33.9)
HAM-D_{17} responders[b]	60 (50.0)	69 (59.5)	81 (63.8)*
MADRS responders[c]	55 (45.8)	68 (58.6)*	74 (59.2)*
CGI-I responders[d]	76 (63.3)	75 (64.7)	93 (73.2)
Observed cases, Week 8			
Remission	23 (24.2)	37 (42.5)*	36 (35.6)
HAM-D_{17} responders	50 (52.6)	65 (74.7)*	71 (70.3)*
MADRS responders	45 (47.4)	65 (74.7)*	65 (64.4)*
CGI-I responders	62 (65.3)	71 (81.6)*	82 (81.2)*

* Significantly different from placebo ($p \leq 0.05$) on the logistic regression analysis.
CGI-I = Clinical Global Impressions Scale-Improvement; DVS SR = desvenlafaxine succinate sustained release; ER = extended-release; HAM-D_{17} = Hamilton Rating Scale for Depression, 17-item; ITT = intent-to-treat; MADRS = Montgomery and Asberg Depression Rating Scale.

a. Remission defined as HAM-D_{17} total score ≤7.
b. A HAM-D_{17} responder was defined as a subject with a decrease of ≥50% from Baseline in HAM-D_{17} score.
c. A MADRS responder was defined as a subject with a decrease of ≥50% from the Baseline score.
d. A CGI-I responder was defined as a subject with CGI-I scores of 1 or 2.

The HAM-D_6 total scores and the Covi Anxiety Scale results at the final on-therapy evaluation and at Week 8 (observed cases) are summarized in Table 10.

Table 10. Ancillary Efficacy Variables: Adjusted Mean (95% CI), ITT Population

Parameter Time Point	Placebo		DVS SR 200 to 400 mg		Venlafaxine ER 75 to 150 mg	
	N	Adjusted Mean	N	Adjusted Mean	N	Adjusted Mean

Table 10. Ancillary Efficacy Variables: Adjusted Mean (95% CI), ITT Population

Parameter Time Point	Placebo		DVS SR 200 to 400 mg		Venlafaxine ER 75 to 150 mg	
	N	Adjusted Mean	N	Adjusted Mean	N	Adjusted Mean
HAM-D_6 total score						
Baseline	120	12.9	116	12.9	127	12.9
Final on-therapy evaluation	120	7.0 (6.2, 7.7)	116	6.1 (5.3, 6.8)	127	6.0 (5.3, 6.7)
Covi Anxiety Scale total score						
Baseline	120	6.5	116	6.5	127	6.5
Final on-therapy evaluation	120	5.2 (5.0, 5.5)	116	4.8 (4.5, 5.1)*	127	4.8 (4.5, 5.1)*
Observed-cases analysis						
HAM-D_6 total score						
Baseline	120	12.9	116	12.9	127	12.9
Week 8	95	6.7 (6.0, 7.4)	87	4.5 (3.8, 5.3)*	101	5.5 (4.8, 6.1)*
Covi Anxiety Scale total score						
Baseline	120	6.5	116	6.5	127	6.5
Week 8	95	5.2 (4.9, 5.5)	87	4.5 (4.2, 4.8)*	101	4.7 (4.4, 5.0)*

* Significantly different from placebo ($p \leq 0.05$) on the pairwise comparison; ANCOVA.
ANCOVA = analysis of covariance; CI = confidence interval; HAM-D_6 = Hamilton Rating Scale for Depression, 6-item; DVS SR = desvenlafaxine succinate sustained release; ER = extended-release; ITT = intent-to-treat; N = number of subjects.

Table 11 summarizes the final on-therapy evaluation results for the SDS and the WHO-5 scales.

Table 11. Health Outcomes Assessments: Adjusted Mean (95% CI)

Parameter Time Point	Placebo		DVS SR 200 to 400 mg		Venlafaxine ER 75 to 150 mg	
	N	Adjusted Mean	N	Adjusted Mean	N	Adjusted Mean

Table 11. Health Outcomes Assessments: Adjusted Mean (95% CI)

Parameter Time Point	Placebo		DVS SR 200 to 400 mg		Venlafaxine ER 75 to 150 mg	
	N	Adjusted Mean	N	Adjusted Mean	N	Adjusted Mean
SDS-1 work						
Baseline	109	6.9	105	6.9	115	6.9
Final on-therapy evaluation	108	4.9 (4.4, 5.4)	102	4.3 (3.7, 4.8)	113	4.4 (3.9, 4.9)
SDS-2 social						
Baseline	120	7.5	116	7.5	127	7.5
Final on-therapy evaluation	120	5.2 (4.7, 5.7)	115	4.4 (3.9, 4.9)*	125	4.6 (4.1, 5.1)
SDS-3 family						
Baseline	120	6.9	116	6.9	127	6.9
Final on-therapy evaluation	120	4.8 (4.4, 5.3)	115	4.2 (3.7, 4.7)	125	4.3 (3.8, 4.7)
SDS-4 work and social disability						
Baseline	120	4.2	116	4.2	127	4.2
Final on-therapy evaluation	120	3.3 (3.1, 3.5)	114	3.1 (2.9, 3.3)	125	3.1 (2.9, 3.2)
SDS total score						
Baseline	120	25.5	116	25.5	127	25.5
Final on-therapy evaluation	120	18.1 (16.6, 19.6)	115	16.1 (14.6, 17.7)	125	16.2 (14.7, 17.7)
WHO-5 total score						
Baseline	120	4.5	116	4.5	127	4.5
Final on-therapy evaluation	120	10.4 (9.3, 11.5)	115	12.1 (10.9, 13.2)*	125	11.3 (10.3, 12.4)

* Significantly different from placebo ($p \leq 0.05$) on the pairwise comparison; ANCOVA.
ANCOVA = analysis of covariance; CI = confidence interval; DVS SR = desvenlafaxine succinate sustained release; ER = extended-release; N = number of subjects; SDS = Sheehan Disability Scale; WHO-5 = World Health Organization 5-Item Well-Being Index.

Safety Results:

The common treatment-emergent adverse events (TEAEs) reported by at least 5% of the subjects in any treatment group during the double-blind period are shown in Table 12. The number and percentage of subjects with AEs that emerged during the taper period and poststudy period are presented in Table 13.

Table 12. Number (%) of Subjects With TEAEs Reported by ≥5% of Subjects in Any Treatment Group During the Double-Blind Period (Excluding Taper) - Safety Population

Body System[a] AEs	Placebo (N=120)	DVS SR 200 to 400 mg (N=117)	Venlafaxine ER 75 to 150 mg (N=127)
Any AE	77 (64)	92 (79)	92 (72)
Body as a whole	50 (42)	40 (34)	47 (37)
Abdominal pain	11 (9)	6 (5)	8 (6)
Asthenia	2 (2)	12 (10)	10 (8)
Back pain	6 (5)	3 (3)	3 (2)
Headache	34 (28)	25 (21)	29 (23)
Infection	10 (8)	0	2 (2)
Cardiovascular system	3 (3)	12 (10)	7 (6)
Tachycardia	0	7 (6)	0
Digestive system	29 (24)	66 (56)	51 (40)
Anorexia	2 (2)	8 (7)	6 (5)
Constipation	5 (4)	12 (10)	6 (5)
Diarrhea	6 (5)	8 (7)	3 (2)
Dry mouth	1 (<1)	19 (16)	17 (13)
Nausea	14 (12)	39 (33)	27 (21)
Vomiting	2 (2)	9 (8)	3 (2)
Musculoskeletal system	4 (3)	6 (5)	5 (4)
Nervous system	33 (28)	43 (37)	39 (31)
Dizziness	7 (6)	9 (8)	6 (5)
Insomnia	8 (7)	10 (9)	14 (11)
Somnolence	3 (3)	10 (9)	12 (9)
Tremor	3 (3)	7 (6)	4 (3)
Vertigo	5 (4)	5 (4)	9 (7)
Respiratory system	6 (5)	9 (8)	11 (9)
Skin and appendages	8 (7)	24 (21)	16 (13)
Sweating	4 (3)	22 (19)	12 (9)
Special senses	5 (4)	12 (10)	7 (6)
Abnormal vision	0	7 (6)	3 (2)
Urogenital system	3 (3)	7 (6)	9 (7)
Impotence	0	1 (3)	2 (6)

Non-serious AEs and serious AEs are not separated out.
AEs = adverse events; DVS SR = desvenlafaxine succinate sustained release; ER = extended-release; N = number of subjects; TEAE=treatment-emergent adverse event.
a. Body system totals are not necessarily the sum of the individual AEs since a subject might have reported ≥2 different AEs in the same body system.

Table 13. Number (%) of Subjects Reporting AEs - Safety Population – (Taper/Poststudy Emergent)

Body System[a] AEs	Placebo Taper (N=27)	DVS SR Taper (N=35)	Venlafaxine ER Taper (N=27)
Any AE	4 (15)	10 (29)	6 (22)
Body as a whole	1 (4)	5 (14)	2 (7)
Accidental injury	0	0	1 (4)
Discontinuation symptoms	0	1 (3)	0
Headache	1 (4)	3 (9)	1 (4)
Infection	0	0	1 (4)
Lab test abnormal	0	1 (3)	0
Malaise	0	1 (3)	0
Digestive system	1 (4)	3 (9)	3 (11)
Abdominal distension	0	1 (3)	0
Diarrhea	1 (4)	0	0
Dry mouth	0	1 (3)	0
Dyspepsia	0	0	1 (4)
Gastroenteritis	0	0	1 (4)
Gastroesophageal reflux - disease	0	0	1 (4)
Nausea	0	1 (3)	1 (4)
Metabolic and nutritional	0	0	1 (4)
Hyperglycemia	0	0	1 (4)
Musculoskeletal system	0	0	2 (7)
Arthralgia	0	0	1 (4)
Musculoskeletal stiffness	0	0	1 (4)
Nervous system	1 (4)	3 (9)	3 (11)
Abnormal dreams	0	1 (3)	0
Agitation	1 (4)	0	0
Anxiety	0	1 (3)	1 (4)
Dizziness	0	0	1 (4)
Emotional lability	0	2 (6)	0
Hostility	0	1 (3)	1 (4)
Incoordination	0	1 (3)	0
Vertigo	0	1 (3)	2 (7)
Respiratory system	0	3 (9)	0
Dyspnea	0	1 (3)	0
Pharyngitis	0	2 (6)	0
Skin and appendages	0	1 (3)	0
Sweating	0	1 (3)	0
Special senses	1 (4)	0	0
Abnormal vision	1 (4)	0	0
Eye pain	1 (4)	0	0
Urogenital system	1 (4)	1 (3)	1 (4)
Hematuria	0	0	1 (4)
Unintended pregnancy	1 (5)	1 (4)	0
AEs associated with miscellaneous factors	0	1 (3)	0
Laboratory events not classified	0	1 (3)	0

Non-serious AEs and serious AEs are not separated out.
AEs = adverse events; DVS SR = desvenlafaxine succinate sustained release; ER = extended-release; N = number of subjects.
a. Body system totals are not necessarily the sum of the individual AEs since a subject might have reported ≥2 different AEs in the same body system.

The common treatment-related TEAEs reported by at least 5% of the subjects in any treatment group are presented in Table 14.

Table 14. Number (%) of Subjects Reporting Treatment-Related TEAEs (≥5%)-Safety Population (On Therapy)

Body System[a] AEs	Treatment-Related		
	Placebo N=120	DVS SR 200 to 400 mg N=117	Venlafaxine ER 75 to 150 mg N=127
Any AE	44 (36.7)	75 (64.1)	74 (58.3)
Body as a whole	28 (23.3)	25 (21.4)	29 (22.8)
Abdominal pain	7 (5.8)	4 (3.4)	5 (3.9)
Asthenia	2 (1.7)	10 (8.5)	8 (6.3)
Headache	24 (20.0)	18 (15.4)	24 (18.9)
Cardiovascular system	3 (2.5)	10 (8.5)	7 (5.5)
Tachycardia	0	6 (5.1)	0
Digestive system	21 (17.5)	59 (50.4)	47 (37.0)
Anorexia	2 (1.7)	8 (6.8)	6 (4.7)
Constipation	4 (3.3)	10 (8.5)	5 (3.9)
Diarrhea	3 (2.5)	6 (5.1)	1 (<1.0)
Dry mouth	1 (<1.0)	18 (15.4)	17 (13.4)
Nausea	11 (9.2)	38 (32.5)	25 (19.7)
Vomiting	1 (<1.0)	9 (7.7)	2 (1.6)
Nervous system	23 (19.2)	40 (34.2)	37 (29.1)
Dizziness	7 (5.8)	8 (6.8)	6 (4.7)
Insomnia	4 (3.3)	8 (6.8)	12 (9.4)
Somnolence	3 (2.5)	10 (8.5)	12 (9.4)
Tremor	2 (1.7)	7 (6.0)	4 (3.1)
Vertigo	4 (3.3)	5 (4.3)	9 (7.1)
Skin and appendages	6 (5.0)	23 (19.7)	13 (10.2)
Sweating	4 (3.3)	22 (18.8)	11 (8.7)
Special senses	3 (2.5)	10 (8.5)	5 (3.9)
Abnormal vision	0	6 (5.1)	3 (2.4)
Impotence	0	1 (3.0)	2 (5.7)

Non-serious AEs and serious AEs are not separated out.
AEs = adverse events; DVS SR = desvenlafaxine succinate sustained release; ER = extended-release; N = number of subjects; TEAE=treatment-emergent adverse event.
a. Body system totals are not necessarily the sum of the individual AEs since a subject might have reported ≥2 different AEs in the same body system.

Serious Adverse Events (SAEs): Seven (7) subjects (4 in the DVS SR group, 2 in the venlafaxine ER group, and 1 in the placebo group) reported a SAE during the study (Table 15); Additionally, 4 subjects had a reportable event of interest: 2 accidental overdoses (both in the placebo group) and 2 unintended pregnancies (1 in the placebo group and 1 in the DVS SR group).

Table 15. Subjects With SAEs and Other Reportable Events

Treatment Body System Serial Number	Mean Daily Dose (mg)[a]	Days on Therapy at Onset	SAE or Other RE	AE Preferred Term (Verbatim)	Relation to Study Medication	Discontinued Because of Identified AEs
Placebo						
Body as a whole						
1	0	28	Other RE	Accidental overdose	No	No
2	0	52	Other RE	Accidental overdose	No	No
Urogenital system						
3	0	NA[b]	Other RE	Unintended pregnancy	No	Yes[c]
Nervous system						
4	0	35	SAE	Anxiety (panic attack)	No	No
DVS SR 200 to 400 mg						
Body as a whole						
5	363.6	33	SAE	Intentional overdose/suicide attempt[d]	Possibly[e]	Yes
Digestive system						
6	294.5	41	SAE	Gastroenteritis	No	No
7	272.7	25	SAE	Abscess/cholecystitis (acute)	No	No
Nervous system						
8	200.0	1	SAE	Dizziness	Probably	Yes
Urogenital system						
9	280.9	52	Other RE	Unintended pregnancy	No	Yes
Venlafaxine ER 75 to 150 mg						
Urogenital system						
10	73.7	14	SAE	Pregnancy disorder (extra uterine)	No	No
11	115.6	54	SAE	Cervix carcinoma	No	No

AEs = adverse events; DVS SR = desvenlafaxine succinate sustained release; ER = extended-release; NA = not available; RE = reportable event; SAEs = serious adverse events.

a. Including missed doses.
b. Between Day 40 and post-study. The pregnancy test was done 1 week after last dose intake (placebo).
c. The subject was previously withdrawn from the study due to AE (irritability, insomnia, and manic reaction).
d. This subject was already hospitalized for depression at the beginning of the study.
e. The Investigator judged the SAE to be not drug-related; the Sponsor judged the SAE to be possibly drug-related and possibly related to the underlying depression.

Discontinuations due to Adverse Events: During the double-blind period, AEs led to discontinuation of treatment for 27 subjects: 19 (16%) in the DVS SR group, 7 (6%) in the venlafaxine ER group, and 1 (<1%) in the placebo group. Table 16 summarizes the AEs that caused premature discontinuation of treatment. Vomiting and nausea were the most frequent causes for discontinuation of treatment in the DVS SR group, reported by 6 (5%) and 5 (4%) subjects, respectively.

In addition, 7 (20%) subjects in the DVS SR group, 2 (7%) subjects in the venlafaxine ER group, and 1 (4%) subject in the placebo group had modifications to the taper period because of AEs; all of these subjects had the taper period omitted.

Table 16. Number (%) of Subjects Who Discontinued Treatment Because of AEs During the Double Blind Period

Body System[a] AEs	Placebo N=120	DVS SR 200 to 400 mg N=117	Venlafaxine ER 75 to 150 mg N=127
Any AE	1 (<1)	19 (16)	7 (6)
Body as a whole	0	9 (8)	4 (3)
Abdominal pain	0	3 (3)	0
Asthenia	0	3 (3)	1 (<1)
Chest pain	0	0	1 (<1)
Chills	0	1 (<1)	0
Discontinuation symptoms	0	1 (<1)	0
Headache	0	2 (2)	3 (2)
Intentional overdose	0	1 (<1)	0
Suicide attempt	0	1 (<1)	0
Cardiovascular system	0	1 (<1)	1 (<1)
ECG abnormal	0	1 (<1)	0
Hypertension	0	0	1 (<1)
ST depressed	0	1 (<1)	0
T inverted	0	1 (<1)	0
Digestive system	0	12 (10)	4 (3)
Abdominal distension	0	2 (2)	0
Anorexia	0	1 (<1)	0
Constipation	0	0	1 (<1)
Diarrhea	0	3 (3)	1 (<1)
Nausea	0	4 (3)	3 (2)
Nausea and vomiting[b]	0	1 (<1) [b]	0
Vomiting	0	5 (4)	0
Metabolic and nutritional	0	0	1 (<1)
Hyperglycemia	0	0	1 (<1)
Musculoskeletal system	0	1 (<1)	0
Muscle spasms	0	1 (<1)	0
Nervous system	1 (<1)	5 (4)	3 (2)
Depression	0	1 (<1)	0
Dizziness	0	1 (<1)	1 (<1)
Hostility	1 (<1)	1 (<1)	0
Insomnia	1 (<1)	0	2 (2)
Manic reaction	1 (<1)	0	0
Somnolence	0	2 (2)	0
Thinking abnormal	0	1 (<1)	0
Respiratory system	0	1 (<1)	0
Dyspnea	0	1 (<1)	0
Skin and appendages	0	1 (<1)	1 (<1)
Sweating	0	1 (<1)	1 (<1)
Special senses	0	3 (3)	1 (<1)
Abnormal vision	0	1 (<1)	1 (<1)
Eye disorder	0	1 (<1)	0
Tinnitus	0	1 (<1)	0
Urogenital system	0	1 (<1)	1 (<1)
Hematuria	0	0	1 (<1)
Testis disorder[c]	0	1 (3)	0

Table 16. Number (%) of Subjects Who Discontinued Treatment Because of AEs During the Double Blind Period

AEs = adverse events; DVS SR = desvenlafaxine succinate sustained release; ECG = electrocardiogram; ER = extended-release; N = number of subjects.

a. This table lists AEs that were a primary or secondary reason for discontinuation. The number of subjects who discontinued for "any event" did not equal the number of AEs listed because some subjects had multiple AEs listed as reasons for discontinuation.

b. This incidence of discontinuation due to "nausea and vomiting" is to be added to incidences of discontinuation for each of these AEs.

c. Percentages are calculated based on males only; n=33 in the DVS group and n=35 in the venlafaxine group.

Deaths: No deaths were reported during the study.

Clinical Laboratory Evaluations: In the DVS SR group, there was a statistically significant increase from Baseline in the mean gamma-glutamyl transpeptidase (GGT) level, total cholesterol level, low density lipoprotein-cholesterol level, triglyceride level, and mean thyroxine (T_4) level at Week 8 and the final-on-therapy evaluation. Although statistically significant, the increases in triglyceride, GGT, and T_4 levels did not reach clinical significance.

Vital Signs: Mean weight was statistically significantly lower in the DVS SR group at Weeks 1 through 8 and at the final evaluation. Statistically significant different increases from Baseline were observed in the DVS SR group for the supine systolic BP (Week 2 through 6), for the supine diastolic BP (Weeks 4, 6, and 8), and for the supine PR (Weeks 1 through 8 and at the final-on-therapy evaluation). These mean changes did not reach clinical significance, but suggest a potential effect on BP that is consistent with the mechanism of action of drugs in this class.

Electrocardiograms: Mean heart rate was significantly higher in the DVS SR group at Week 7 and 8 and at the final evaluation, and QT and PR intervals were significantly shorter at Week 8 and at the final evaluation, than in the placebo group. These changes reached statistical significance but were not clinically significant.

CONCLUSIONS:

The primary comparison of interest (HAM-D_{17} score) and the key secondary comparison (CGI-I score) between DVS SR and placebo at the final on-therapy evaluation revealed no significant differences in the measures of short-term efficacy for the LOCF analysis. No significant difference was seen between venlafaxine ER and placebo for either HAM-D_{17} or CGI-I scores. Nevertheless, in the observed-cases analysis, significant differences were observed between active groups and placebo at Week 8. This suggests that the lack of separation between the active and placebo groups in the LOCF analysis may have been due to withdrawal of subjects before completion of the study. The lack of separation may have been exacerbated by a high placebo response rate.

Although no significant differences were observed with the primary efficacy endpoint, a number of observed-cases and secondary efficacy parameter results provide supportive evidence of the efficacy of DVS SR in the treatment of MDD.

The safety data in this study did not raise unexpected issues. Nausea, vomiting, dry mouth, asthenia, tachycardia, somnolence, sweating, and abnormal vision were significantly more common in the DVS SR group than in the placebo group, and are likely to reflect the mechanism of action for drugs in this class. Statistically significant adverse effects were noted with some laboratory measures (GGT, lipids, measures of thyroid function), but these were not clinically important. Increases in mean BP and heart rate were noted but not deemed clinically significant and are considered to be consistent with the mechanism of action.