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

PROTOCOL NO.: 3151A1-333-EU (B2061085)

PROTOCOL TITLE: A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of 2 Fixed Doses (50 mg, 100 mg) of Desvenlafaxine Sustained-Release Tablets in Adult Outpatients With Major Depressive Disorder

Study Centers: Forty-three (43) centers took part in the study and randomized subjects; 3 each in Croatia, Estonia, Lativa, Lithuania, Poland and Slovakia, 11 in Finland, 8 in France, 2 in Romania and 4 in South Africa.

Study Initiation and Final Completion Dates: 20 March 2006 to 22 January 2007

Phase of Development: Phase 3

Study Objectives:

The primary objective was to compare the anti-depressant efficacy, safety and tolerability of desvenlafaxine succinate sustained-release formulation (DVS SR) in subjects receiving daily doses of 50 mg or 100 mg of DVS SR versus subjects receiving placebo.

Additional objectives included testing both general and functional quality-of-life outcomes and satisfaction with therapy reported by the subject.

METHODS

Study Design: This was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in adult outpatients with major depressive disorder (MDD). After a screening period of 6 to 14 days, eligible subjects were treated for approximately 8 weeks plus 1 additional week for tapering the study drug. Subjects assigned to the 100-mg dose group had their dose titrated to 50 mg/day during Week 1. Subjects returned for a poststudy/follow-up visit (Day 70) approximately 7 days after discontinuing use of the study drug. The study flow chart is presented in Table 1.

Table 1. Study Flowchart

Study Procedures	Screening (10±4 Days)	Baseline	Double-Blind On-Therapy Period (Days 1 to 56±3 Days)[a]							Taper (±3 Days)[a]		Poststudy/Follow-Up (±3 Days)[a]	
Study Day	**-14 to -6**	**-1**	**1**	**7**	**14**	**21**	**28**	**42**	**56[b]**	**59[c]**	**63[c]**	**66[d]**	**70[d]**
Obtain informed consent	X												
Eligibility assessment	X	X											
Medical history	X												
Psychiatric history and diagnosis	X												
Modified Mini International Neuropsychiatric Interview	X												
DMS-IV Diagnostic Criteria for Major Depressive Disorder	X												
Randomization		X											
Dispense double-blind study drug		X		X	X	X	X	X					
Dispense taper study drug[e]									X				
First dose of double-blind study drug			X										
Telephone contact[a]										X		X	
Completion of dosage record				X	X	X	X	X	X		X		
Recording of prior/concomitant treatments	X	X		X	X	X	X	X	X	X[f]	X	X[f]	X
Safety determinations													
Physical examination	X								X				
Height	X												
Blood pressure and pulse rate[g]	X	X		X	X	X	X	X	X		X		X
Weight	X	X		X	X	X	X	X	X		X		X
Laboratory evaluation[h]	X								X				
Electrocardiogram[i]	X	X							X				
Adverse events[j]	X	X		X	X	X	X	X	X	X[f]	X	X[f]	X
DESS checklist									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											

Table 1. Study Flowchart

Study Procedures	Screening (10±4 Days)	Baseline	Double-Blind On-Therapy Period (Days 1 to 56±3 Days)[a]							Taper (±3 Days)[a]		Poststudy/Follow-Up (±3 Days)[a]	
Study Day	**-14 to -6**	**-1**	**1**	**7**	**14**	**21**	**28**	**42**	**56[b]**	**59[c]**	**63[c]**	**66[d]**	**70[d]**
Covi Anxiety Scale	X	X			X		X		X				
VAS-PI		X			X		X		X				
Health Outcome Assessments													
SDS		X			X		X		X				
WHO-5		X			X		X		X				

β-HCG = beta-human chorionic gonadotropin; CGI-I = Clinical Global Impressions Scale–Improvement; CGI-S = Clinical Global Impressions Scale–Severity of Illness; CRF = case report form; DESS = Discontinuation-Emergent Signs and Symptoms; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; ECG = electrocardiogram; HAM-D_{17} = Hamilton Rating Scale for Depression, 17-item; MADRS = Montgomery and Asberg Depression Rating Scale; SDS = Sheehan Disability Scale; VAS-PI = visual analog scale-pain intensity; WHO-5 = World Health Organization 5-Item Well-Being Index.

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. Telephone contacts designated for Days 59 and 66 had a ±2-day window to allow for weekends and slight variations in subject schedules.
b. For subjects who discontinued from the study, safety and efficacy determinations scheduled for Day 56 were obtained on the last day on which the subject took a full dose of study drug (ie, before taper) or as soon as possible thereafter.
c. The visits associated with the taper period should have occurred even if the taper period was omitted.
d. The follow-up telephone contact and visit occurred for all subjects who received study drug regardless of the duration of treatment.
e. A 7-day taper period was recommended but could be omitted, shortened, or extended if clinically indicated. If the taper period was omitted, study drug was not dispensed.
f. Information recorded during telephone contacts was recorded on the CRF for the subsequent office visit.
g. Supine and standing blood pressure and pulse rate.
h. Subjects were instructed to fast for a minimum of 12 hours before testing. Hematology, blood chemistry, and urinalysis samples were obtained at Screening and on Study Day 56. The urine drug screen and thyroid-stimulating hormone, free thyroxine index (including total thyroxine and triiodothyronine uptake), serum β-HCG (women of childbearing potential) tests were performed at Screening only.
i. A single 12-lead ECG recording was made at Screening only. On Study Days -1 and 56, 3 separate 12-lead ECG recordings were made approximately 8 minutes apart over approximately a 15- to 20-minute period.
j. Collected from the signing of the informed consent form to the poststudy/follow-up visit (Day 70).

Number of Subjects (Planned and Analyzed): Approximately 480 subjects (160 in each group) were planned to be enrolled in the study. A total of 485 subjects were randomly assigned to treatment (38 to Croatia, 40 in Estonia, 143 in Finland, 90 in France, 27 in Latvia, 45 in Lithuania, 30 in Poland, 8 in Romania, 28 in Slovakia and 36 in South Africa). A total of 161 subjects were assigned to placebo, 166 to the DVS SR 50-mg treatment group and 158 to the DVS SR 100-mg treatment group.

Diagnosis and Main Criteria for Inclusion and Exclusion: Male and female subjects aged ≥18 years were included in the study. Subjects who were primarily diagnosed with MDD and were found to have depressive symptoms for ≥30 days before the screening visit were included in the study. Subjects who were subjected to DVS SR treatment in past, who were known to have hypersensitivity to venlafaxine and subjects with significant risk of suicide based on clinical judgment were excluded from the study.

Study Treatment: DVS SR was provided as 50-mg DVS SR pyramid-shaped tablets; matching placebo tablets were also provided. Each subject received the assigned treatment in individual blister packs. Each blister pack contained 2 tablets per day.

On Study Day -1 (Baseline), each subject was randomly assigned to 1 of 2 fixed doses of DVS SR (50 mg or 100 mg) or placebo. Subjects assigned to the DVS SR 50-mg dose group received their maintenance dose beginning on Study Day 1 and continued this regimen until Study Day 56 or early withdrawal. For the taper period (Days 1 through 7 after the end of the double-blind treatment period), they received 0 mg. Subjects assigned to the DVS SR 100-mg dose group were titrated to their maintenance dose. On Study Days 1 through 7 they received DVS SR 50 mg/day. Beginning on Study Day 8, they received their assigned dose of DVS SR 100 mg/day and continued on this regimen until Study Day 56 or early withdrawal. For the taper period (Days 1 through 7 after the end of the double-blind treatment period), they received DVS SR 50 mg/day. Subjects assigned to placebo received their maintenance dose (0 mg) from Study Day 1 through Day 56 or early withdrawal, and also received 0 mg during the taper period.

The dosage summary for each of the 3 dose groups is provided in Table 2.

Table 2. Dosage Summary

Treatment Study Schedule	Tablet A (mg)	Tablet B (mg)	Total Daily Dose (mg)
DVS SR 50 mg/day			
Days 1-56	50	PB 50	50
Taper Days 1-7	PB 50	PB 50	0
DVS SR 100 mg/day			
Days 1-7	50	PB 50	50
Days 8-56	50	50	100
Taper Days 1-7	50	PB 50	50
Placebo			
Days 1-56	PB 50	PB 50	0
Taper Days 1-7	PB 50	PB 50	0

DVS SR = desvalafaxine succinate sustained release; PB 50 = placebo tablet to match 50-mg tablet of DVS SR.

Eligible subjects received up to 56 days of treatment. A 7-day taper period was recommended. Alterations to the taper period were permitted at the discretion of the Investigator if a subject experienced safety and/or tolerability issues. Subjects returned for a follow-up visit 7 (±3) days after discontinuing study medication.

Efficacy and Health Outcomes Endpoints:

Primary Endpoint:

- Hamilton Rating Scale for Depression, 17-Item ($HAM\text{-}D_{17}$) total score.

Key Secondary Endpoints:

- Clinical Global Impression Scale Improvement scale (CGI-I) score.

Other Secondary Endpoints:

- Sheehan Disability Scale (SDS) - Total score and subscales,
- Remission rate (percentage of subjects with $HAM\text{-}D_{17} \leq 7$),
- $HAM\text{-}D_6$ (Bech version: HAM-D items 1, 2, 7, 8, 10, and 13) total score,
- Montgomery Asberg Depression Rating Scale (MADRS) total score,
- CGI severity scale (CGI-S) score,
- Covi Anxiety Scale total score,
- Visual Analog Scale-Pain Intensity (VAS-PI) - Overall pain score and individual subscales,
- World Health Organization 5-item Well Being Index (WHO-5) total score.

Safety Evaluations: Subjects were monitored for adverse events (AEs), vital sign measurements, and weight at all visits. Height, physical examination, 12-lead ECG, laboratory data parameters and the Discontinuation-Emergent Signs and Symptoms (DESS) Checklist were performed at scheduled intervals during the study.

Statistical Methods: The populations sets used in the analyses were:

Intent-To-Treat (ITT) Population: The ITT population included all randomly assigned subjects who had a baseline primary efficacy evaluation, who had taken at ≥1 dose of double-blind test article, and had ≥ 1 primary efficacy evaluation after the first dose of double-blind test article. The ITT population was the primary population for efficacy analysis.

Safety Population: All randomized subjects with documented use of ≥1 dose of double-blind test article were included in the safety population. Subjects who were dispensed test article but have no documented use of ≥1 dose were not included in the safety population.

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

Per-Protocol Population (PP): The PP population included all randomly assigned subjects who had a baseline primary efficacy evaluation, who had taken at least 1 dose of double-blind test article, and had at least 1 primary efficacy evaluation after the first dose of double-blind test article and had no major protocol violations. The criteria of major violations were determined by the Medical Monitor, after a blinded review of all data from the study.

Statistical analyses were based on the data from all individual clinical study sites. Unless otherwise stated, the use of the word "significant" in conjunction with the results refers to p-values ≤0.05. All tests were 2-tailed. Because of the large number of sites with few subjects, data from individual sites were pooled (before the study was unblinded) to form groups with a greater number of subjects. Each pooled group was referred to as a site for the purposes of the analysis.

The primary efficacy variable was the change from Baseline in the HAM-D_{17} total score, which was analyzed using analysis of covariance (ANCOVA) at the final on-therapy (FOT) evaluation (last observation carried forward [LOCF] technique). Closed testing procedures were performed to compare the 2 doses (50 and 100 mg/day) of DVS SR with placebo based on the primary efficacy variable, the change in HAM-D_{17} total score from Baseline. A general linear model with multiple contrast statements was used to calculate F-statistics for the global null hypotheses and all intersection hypotheses. The closure principle was used to determine which hypothesis should have been retained or rejected at α=0.05. If a significant difference was detected for 1 or both doses of DVS SR, then a sequential testing method was applied to that/those dose(s) as follows: for 1 or both DVS SR dose group(s), if a significant difference from placebo on the primary efficacy variable was noted based on the closed testing procedure, the key secondary efficacy variable was tested at the 0.05 level to compare the DVS SR dose(s) with placebo. The HAM-D_{17} change from Baseline was also analyzed using a mixed effects model with treatment, time, and the interaction of treatment and time as fixed effects, baseline HAM-D_{17} total score as covariate, and site as a random effect. An autoregression of the first order covariance matrix was used to model the within subject errors. The ETRANK method, which corrects for missing data patterns, was also used to analyze changes in the HAM-D_{17} scores from Baseline (the primary efficacy variable).

The CGI-I score was the key secondary efficacy variable. Sequential testing was applied to the CGI-I. The order of testing was to first test the HAM-D_{17}. If a DVS SR treatment group was significantly different from placebo for the HAM-D_{17}, then the CGI-I was tested. The CGI-I score was analyzed as a categorical variable via the Cochran Mantel-Haenszel test with treatment as the factor, controlling for site. The RIDIT scoring scheme, which yields a nonparametric analysis, was used. Mean scores on the CGI-I were also analyzed by analysis of variance with treatment and site as factors. Other secondary variables include HAM-D_6

total score, MADRS total score, Covi Anxiety Scale total score, CGI-S score, and the overall pain score and each subcomponent of the VAS-PI. These variables were evaluated using ANCOVA on changes from Baseline with treatment and site as factors and baseline value as the covariate. Remission, defined as a HAM-D_{17} total score of ≤7, was analyzed using a logistic regression model with treatment and site as factors and the baseline HAM-D_{17} total score value as the covariate. Response, defined as a decrease of ≥50% on the HAM-D_{17} total score from Baseline, was analyzed with the logistic regression model with treatment and site as factors and baseline HAM-D_{17} score as a covariate. 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 factors. Response on the MADRS, defined as a decrease of ≥50% on the total score from Baseline, was analyzed with the logistic regression model with treatment and site as factors and baseline MADRS score as a covariate.

Efficacy analyses for the secondary variables were conducted at each time point using the LOCF technique and observed-cases data. No adjustment for multiplicity was made for the secondary efficacy

RESULTS

Subject Disposition and Demography: A total of 565 subjects were screened for participation in this study; 80 were screen failures, and 485 subjects were randomly assigned to treatment: 161 were assigned to receive placebo, 166 were assigned to receive DVS SR 50 mg, and 158 were assigned to receive DVS SR 100 mg. None of these 485 subjects were considered "no-data subjects" and all were, therefore, included in the safety population. The ITT population included 483 subjects. Two (2) subjects were excluded from the ITT population because they did not have a primary efficacy evaluation (HAM-D_{17}) while on therapy. Table 3 summarizes the number of subjects in each population subset by treatment group.

Table 3. Subject Disposition

Population Subset	Placebo	DVS SR 50 mg	DVS SR 100 mg	Total
Randomly assigned	161	166	158	485
No-data subjects	0	0	0	0
Safety[a]	161	166	158	485
Total ITT[b]	161	164	158	483
Non-ITT	0	2	0	2
PP for efficacy[c]	145	148	147	440
Completed on-therapy period[d]	147	148	128	423

DVS SR = desvenlafaxine succinate sustained release; ITT = intent-to-treat; PP = per-protocol.

a. The safety population included all randomly-assigned subjects who completed the prestudy period and received at least 1 dose of study drug.

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

c. The PP population included all randomly-assigned subjects who took ≥1 dose of double-blind study drug, had a baseline primary efficacy evaluation, had ≥1 primary efficacy evaluation after the first dose of double-blind study drug, and had no major protocol violations. Evaluations were done within 3 days after the subject's last full-dose of on-therapy study drug.

d. Completers were defined as subjects who had at least 53 days of exposure to the study drug. Completers were defined independently of whether subjects discontinued from the on-therapy period of the study.

Table 4 summarizes the number of subjects who discontinued treatment by reasons for withdrawal in each treatment group.

Table 4. Number (%) of Subjects Who Discontinued During the On-Therapy Period by Reason for Withdrawal

Reason	Placebo n=161	DVS SR 50 mg n=166	DVS SR 100 mg n=158	Total N=485
Total[a]	13 (8.1)	17 (10.2)	20 (12.7)	50 (10.3)
Adverse event	5 (3.1)	8 (4.8)	11 (7.0)	24 (4.9)
Failed to return	0	0	2 (1.3)	2 (0.4)
Investigator request	0	0	2 (1.3)	2 (0.4)
Other	1 (0.6)	0	0	1 (0.2)
Protocol violation	1 (0.6)	4 (2.4)	0	5 (1.0)
Subject request unrelated to study	1 (0.6)	3 (1.8)	4 (2.5)	8 (1.6)
Unsatisfactory response–efficacy	5 (3.1)	2 (1.2)	1 (0.6)	8 (1.6)

DVS SR = desvenlafaxine succinate sustained release; n = number of subjects per treatment group; N = total number of subjects.

a. Total discontinued is the sum of individual reasons because the reasons are mutually exclusive by subject.

Tapering was scheduled for subjects who were withdrawn and for subjects who completed the Day 56 evaluations. The disposition of subjects with regard to the taper period is shown in Table 5.

Table 5. Disposition of Safety Population With Regard to the Taper Period

Population	DVS SR
Subjects in safety population	485
Subjects who did not participate in the taper period[a]	4
Subjects who withdrew prematurely and were not available for a taper period[b]	3[c]
Subject who completed the study but who did not participate in the taper period[b]	1[d]
Subjects who participated in the taper period[a]	481
Subjects who had elective modifications to taper period	69
Taper period was omitted per Investigator	56
Taper period was shortened per Investigator	13
Taper period was extended per Investigator	0
Subjects who participated in the taper period, as per study requirements[e]	412

DVS SR = desvenlafaxine succinate sustained release.

a. Subjects with taper data collected, taper status known (ie taper period modified [omitted, shortened, or extended] or dose tapered as per study requirements).
b. Subjects without taper data, taper status unknown.
c. This includes 1 subject in the DVS SR 50-mg group and 2 subjects in DVS SR 100-mg group.
d. This includes 1 subject in DVS SR 50-mg group.
e. This includes all subjects who electively participated in the taper period whether they withdrew prematurely or they completed the Day 56 evaluations

The demographic and baseline characteristics are presented in Table 6.

Table 6. Demographic and Baseline Characteristics, Safety Population

Characteristic	Placebo (N=161)	DVS SR 50 mg (N=166)	DVS SR 100 mg (N=158)
Age (years)			
Mean	45.62	43.93	45.70
Standard deviation	11.55	13.54	12.59
Minimum	19.00	18.00	19.00
Maximum	75.00	78.00	77.00
Age group (years), n (%)			
18-29	18 (11.18)	31 (18.67)	18 (11.39)
30-49	83 (51.55)	77 (46.39)	80 (50.63)
50-64	52 (32.30)	48 (28.92)	48 (30.38)
≥65	8 (4.97)	10 (6.02)	12 (7.59)
Sex, n (%)			
Female	109 (67.70)	116 (69.88)	112 (70.89)
Male	52 (32.30)	50 (30.12)	46 (29.11)
Race, n (%)			
Black or African American	1 (0.62)	0	0
Other: mixed	2 (1.24)	1 (0.60)	2 (1.27)
White	158 (98.14)	165 (99.40)	156 (98.73)
Ethnic origin, n (%)			
Hispanic or Latino	2 (1.24)	2 (1.20)	1 (0.63)
Non-Hispanic	0	0	1 (0.63)
Non-Hispanic and non-Latino	159 (98.76)	164 (98.80)	156 (98.73)
Height (cm)			
Mean	168.50	167.07	167.72
Standard deviation	8.59	9.98	8.95
Minimum	149.00	109.50	144.00
Maximum	200.00	191.00	192.00
Weight (kg)			
Mean	76.07	74.54	73.08
Standard deviation	17.78	16.18	17.56
Minimum	45.00	40.00	40.00
Maximum	139.00	126.90	131.80

DVS SR = desvenlafaxine sustained release; n = number of subjects in specified category; N = number of subjects.

Efficacy and Health Outcomes Results: Table 7 shows the results of the primary efficacy endpoint, the adjusted mean change from Baseline in the HAM-D_{17} total score at the final on-therapy evaluation. At the final on-therapy evaluation, the adjusted mean change from Baseline in the HAM-D_{17} total score was significantly greater for subjects in the DVS SR 50-mg ($p=0.002$) and 100-mg ($p<0.001$) treatment groups compared with the placebo group. At the final on-therapy evaluation, the adjusted mean change from Baseline in the HAM-D_{17} total score was -13.2 in the DVS SR 50-mg group and -13.7 in the DVS SR 100-mg group compared with -10.7 in the placebo group.

Table 7. Comparison of Changes From Baseline for the ITT Population for the HAM-D_{17} (ANCOVA), LOCF and Observed-Cases Analyses

Analysis	Week of Therapy	Therapy Group	n	Raw Mean Score	Adjusted Change From Baseline	SE	Adjusted Mean (95% CI)	Difference in Adjusted Mean (95% CI) vs Placebo	Overall p-Value	p-Value vs DVS SR 50 mg	p-Value vs DVS SR 100 mg
LOCF	Baseline	Placebo	161	24.3	-	-	24.3 (24.3, 24.3)	-	-	-	-
		DVS SR 50 mg	164	24.3	-	-	24.3 (24.3, 24.3)	-	-	-	-
		DVS SR 100 mg	158	24.4	-	-	24.3 (24.3, 24.3)	-	-	-	-
	Week 1	Placebo	156	21.6	-2.64	0.29	21.7 (21.1, 22.3)	-	0.788	0.977	0.542
		DVS SR 50 mg	162	21.6	-2.63	0.29	21.7 (21.1, 22.3)	-0.0 (-0.8, 0.8)	-	-	0.557
		DVS SR 100 mg	156	22.0	-2.40	0.29	21.9 (21.4, 22.5)	-0.2 (-1.0, 0.5)	-	-	
	Week 2	Placebo	161	18.8	-5.53	0.42	18.8 (18.0, 19.6)		0.629	0.386	0.942
		DVS SR 50 mg	164	18.2	-6.03	0.42	18.3 (17.5, 19.1)	0.5 (-0.6, 1.6)	-	-	0.429
		DVS SR 100 mg	158	18.8	-5.57	0.42	18.8 (17.9, 19.6)	0.0 (-1.1, 1.2)	-	-	-
	Week 3	Placebo	161	16.3	-7.93	0.47	16.4 (15.5, 17.3)		0.252	0.168	0.136
		DVS SR 50 mg	164	15.4	-8.81	0.47	15.5 (14.6, 16.4)	0.9 (-0.4, 2.1)	-	-	0.898
		DVS SR 100 mg	158	15.4	-8.89	0.48	15.4 (14.5, 16.4)	1.0 (-0.3, 2.2)	-	-	-
	Week 4	Placebo	161	14.9	-9.17	0.52	15.2 (14.1, 16.2)		0.043	0.103	0.014
		DVS SR 50 mg	164	13.8	-10.3	0.51	14.0 (13.0, 15.0)	1.1 (-0.2, 2.5)	-	-	0.389
		DVS SR 100 mg	158	13.3	-10.9	0.52	13.4 (12.4, 14.4)	1.7 (0.4, 3.1)	-	-	-
	Week 6	Placebo	161	14.1	-10.0	0.57	14.3 (13.2, 15.4)		0.002	0.002	0.002
		DVS SR 50 mg	164	11.7	-12.4	0.56	11.9 (10.8, 13.0)	2.3 (0.8, 3.8)	-	-	0.937
		DVS SR 100 mg	158	11.8	-12.4	0.57	11.9 (10.8, 13.0)	2.4 (0.9, 3.9)	-	-	-
	Week 8	Placebo	161	13.3	-10.7	0.60	13.7 (12.5, 14.8)		<0.001	0.003	<0.001
		DVS SR 50 mg	164	10.9	-13.1	0.60	11.2 (10.0, 12.4)	2.4 (0.9, 4.0)	-	-	0.511
		DVS SR 100 mg	158	10.5	-13.7	0.61	10.7 (9.5, 11.9)	3.0 (1.4, 4.6)	-	-	-
Final on-therapy	Final	Placebo	161	13.3	-10.7	0.61	13.7 (12.5, 14.8)		<0.001	0.002	<0.001
		DVS SR 50 mg	164	10.9	-13.2	0.60	11.2 (10.0, 12.3)	2.5 (0.9, 4.1)	-	-	0.498
		DVS SR 100 mg	158	10.4	-13.7	0.61	10.6 (9.4, 11.8)	3.0 (1.4, 4.7)	-	-	-
Observed	Baseline	Placebo	161	24.3	-	-	24.3 (24.3, 24.3)	-	-	-	-
		DVS SR 50 mg	164	24.3	-	-	24.3 (24.3, 24.3)	-	-	-	-
		DVS SR 100 mg	158	24.4	-	-	24.3 (24.3, 24.3)	-	-	-	-
	Week 1	Placebo	156	21.6	-2.64	0.29	21.7 (21.1, 22.3)	-	0.788	0.977	0.542
		DVS SR 50 mg	162	21.6	-2.63	0.29	21.7 (21.1, 22.3)	-0.0 (-0.8, 0.8)	-	-	0.557
		DVS SR 100 mg	156	22.0	-2.40	0.29	21.9 (21.4, 22.5)	-0.2 (-1.0, 0.5)	-	-	-

Table 7. Comparison of Changes From Baseline for the ITT Population for the HAM-D_{17} (ANCOVA), LOCF and Observed-Cases Analyses

Analysis	Week of Therapy	Therapy Group	n	Raw Mean Score	Adjusted Change From Baseline	SE	Adjusted Mean (95% CI)	Difference in Adjusted Mean (95% CI) vs Placebo	Overall p-Value	p-Value vs DVS SR 50 mg	p-Value vs DVS SR 100 mg
	Week 2	Placebo	155	18.6	-5.75	0.43	18.6 (17.7, 19.4)		0.571	0.291	0.648
		DVS SR 50 mg	155	18.0	-6.36	0.43	18.0 (17.1, 18.8)	0.6 (-0.5, 1.7)	-	-	0.562
		DVS SR 100 mg	144	18.5	-6.02	0.44	18.3 (17.4, 19.2)	0.3 (-0.9, 1.4)	-	-	-
	Week 3	Placebo	154	16.3	-8.09	0.48	16.3 (15.4, 17.3)		0.091	0.042	0.090
		DVS SR 50 mg	148	15.0	-9.42	0.49	15.0 (14.0, 15.9)	1.3 (0.1, 2.6)	-	-	0.729
		DVS SR 100 mg	149	15.3	-9.19	0.48	15.2 (14.3, 16.2)	1.1 (-0.2, 2.4)	-	-	-
	Week 4	Placebo	151	14.8	-9.61	0.51	14.8 (13.8, 15.8)		0.004	0.006	0.004
		DVS SR 50 mg	147	12.8	-11.5	0.52	12.9 (11.9, 13.9)	1.9 (0.6, 3.3)	-	-	0.851
		DVS SR 100 mg	140	12.9	-11.6	0.53	12.8 (11.7, 13.8)	2.0 (0.7, 3.4)	-	-	-
	Week 6	Placebo	137	13.7	-10.9	0.57	13.5 (12.4, 14.6)		<0.001	<0.001	<0.001
		DVS SR 50 mg	144	10.6	-13.9	0.56	10.5 (9.4, 11.6)	3.0 (1.5, 4.4)	-	-	0.895
		DVS SR 100 mg	133	11.0	-13.8	0.58	10.6 (9.5, 11.8)	2.9 (1.4, 4.4)	-	-	-
	Week 8	Placebo	138	12.8	-11.6	0.61	12.8 (11.6, 14.0)		<0.001	<0.001	<0.001
		DVS SR 50 mg	145	9.7	-14.7	0.59	9.7 (8.6, 10.9)	3.1 (1.5, 4.6)	-	-	0.533
		DVS SR 100 mg	126	9.4	-15.2	0.63	9.2 (8.0, 10.5)	3.6 (2.0, 5.2)	-	-	-
	Week >8	Placebo	10	10.3	-	-	-	-	-	-	-
		DVS SR 50 mg	5	13.0	-	-	-	-	-	-	-
		DVS SR 100 mg	5	7.4	-	-	-	-	-	-	-

ANCOVA = analysis of covariance; CI = confidence interval; DVS SR = desvenlafaxine succinate sustained-release formulation; HAM-D_{17} = Hamilton Rating Scale for Depression, 17-item; ITT = intent-to-treat; LOCF = last observation carried forward; n = number of subject; SE = standard error; vs = versus.

Table 8 presents the results of the key secondary efficacy endpoint, the percentage of subjects with each CGI-I score at the final on-therapy evaluation. At the final on-therapy evaluation, the CGI-I scores differed significantly for subjects in the DVS SR 50-mg ($p=0.002$) and 100-mg ($p<0.001$) treatment groups compared with the placebo group. At the final on-therapy evaluation, the percentage of subjects with CGI-I scores of 1 (very much improved) or 2 (much improved) was 73% in the DVS SR 50-mg and DVS SR 100-mg groups compared with 53% in the placebo group.

Table 8. Cochran-Mantel-Haenszel Test for CGI-I, LOCF and Observed-Cases Analyses, ITT Population

Analysis	Week of Therapy	Therapy Group	n	1 n (%)	2 n (%)	3 n (%)	4 n (%)	5 n (%)	6 n (%)	Overall p-Value (CMH)[a]	p-Value vs DVS SR 50 mg[a]	p-Value vs DVS SR 100 mg[a]
LOCF	Week 1	Placebo	156	1 (0.6)	14 (9.0)	46 (29.5)	92 (59.0)	2 (1.3)	1 (0.6)	0.541	0.856	0.280
		DVS SR 50 mg	162	2 (1.2)	9 (5.6)	54 (33.3)	91 (56.2)	6 (3.7)	-	-	-	0.404
		DVS SR 100 mg	156	3 (1.9)	5 (3.2)	50 (32.1)	88 (56.4)	10 (6.4)	-	-	-	-
	Week 2	Placebo	161	7 (4.3)	39 (24.2)	54 (33.5)	56 (34.8)	4 (2.5)	1 (0.6)	0.683	0.359	0.657
		DVS SR 50 mg	164	7 (4.3)	40 (24.4)	70 (42.7)	37 (22.6)	9 (5.5)	1 (0.6)	-	-	0.737
		DVS SR 100 mg	158	10 (6.3)	36 (22.8)	57 (36.1)	48 (30.4)	7 (4.4)	-	-	-	-
	Week 3	Placebo	161	19 (11.8)	52 (32.3)	48 (29.8)	39 (24.2)	2 (1.2)	1 (0.6)	0.267	0.145	0.176
		DVS SR 50 mg	164	25 (15.2)	56 (34.1)	54 (32.9)	21 (12.8)	5 (3.0)	3 (1.8)	-	-	0.983
		DVS SR 100 mg	158	23 (14.6)	57 (36.1)	48 (30.4)	25 (15.8)	5 (3.2)	-	-	-	-
	Week 4	Placebo	161	28 (17.4)	53 (32.9)	49 (30.4)	27 (16.8)	2 (1.2)	2 (1.2)	0.032	0.053	0.012
		DVS SR 50 mg	164	40 (24.4)	62 (37.8)	37 (22.6)	16 (9.8)	5 (3.0)	4 (2.4)	-	-	0.597
		DVS SR 100 mg	158	40 (25.3)	63 (39.9)	32 (20.3)	19 (12.0)	4 (2.5)	-	-	-	-
	Week 6	Placebo	161	41 (25.5)	47 (29.2)	41 (25.5)	24 (14.9)	4 (2.5)	4 (2.5)	0.001	<0.001	0.002
		DVS SR 50 mg	164	69 (42.1)	46 (28.0)	26 (15.9)	16 (9.8)	4 (2.4)	3 (1.8)	-	-	0.782
		DVS SR 100 mg	158	61 (38.6)	49 (31.0)	28 (17.7)	17 (10.8)	3 (1.9)	-	-	-	-
	Week 8	Placebo	161	56 (34.8)	31 (19.3)	40 (24.8)	24 (14.9)	5 (3.1)	5 (3.1)	<0.001	0.003	<0.001
		DVS SR 50 mg	164	78 (47.6)	41 (25.0)	22 (13.4)	14 (8.5)	6 (3.7)	3 (1.8)	-	-	0.407
		DVS SR 100 mg	158	82 (51.9)	34 (21.5)	22 (13.9)	17 (10.8)	3 (1.9)	-	-	-	-
Final on-therapy	Final	Placebo	161	56 (34.8)	30 (18.6)	40 (24.8)	25 (15.5)	5 (3.1)	5 (3.1)	<0.001	0.002	<0.001
		DVS SR 50 mg	164	79 (48.2)	40 (24.4)	21 (12.8)	15 (9.1)	6 (3.7)	3 (1.8)	-	-	0.440
		DVS SR 100 mg	158	82 (51.9)	34 (21.5)	22 (13.9)	17 (10.8)	3 (1.9)	-	-	-	-
Observed	Week 1	Placebo	156	1 (0.6)	14 (9.0)	46 (29.5)	92 (59.0)	2 (1.3)	1 (0.6)	0.541	0.856	0.280
		DVS SR 50 mg	162	2 (1.2)	9 (5.6)	54 (33.3)	91 (56.2)	6 (3.7)	-	-	-	0.404
		DVS SR 100 mg	156	3 (1.9)	5 (3.2)	50 (32.1)	88 (56.4)	10 (6.4)	-	-	-	-

Table 8. Cochran-Mantel-Haenszel Test for CGI-I, LOCF and Observed-Cases Analyses, ITT Population

Analysis	Week of Therapy	Therapy Group	n	1 n (%)	2 n (%)	3 n (%)	4 n (%)	5 n (%)	6 n (%)	Overall p-Value (CMH)[a]	p-Value vs DVS SR 50 mg[a]	p-Value vs DVS SR 100 mg[a]
	Week 2	Placebo	155	7 (4.5)	39 (25.2)	52 (33.5)	53 (34.2)	4 (2.6)	-	0.554	0.339	0.353
		DVS SR 50 mg	155	6 (3.9)	39 (25.2)	69 (44.5)	33 (21.3)	7 (4.5)	1 (0.6)	-	-	0.928
		DVS SR 100 mg	144	10 (6.9)	36 (25.0)	54 (37.5)	37 (25.7)	7 (4.9)	-	-	-	-
	Week 3	Placebo	154	19 (12.3)	51 (33.1)	44 (28.6)	38 (24.7)	2 (1.3)		0.111	0.037	0.153
		DVS SR 50 mg	148	24 (16.2)	55 (37.2)	49 (33.1)	16 (10.8)	2 (1.4)	2 (1.4)	-	-	0.619
		DVS SR 100 mg	149	22 (14.8)	56 (37.6)	46 (30.9)	20 (13.4)	5 (3.4)	-	-	-	-
	Week 4	Placebo	151	28 (18.5)	51 (33.8)	48 (31.8)	22 (14.6)	1 (0.7)	1 (0.7)	0.009	0.010	0.007
		DVS SR 50 mg	147	38 (25.9)	61 (41.5)	35 (23.8)	11 (7.5)	1 (0.7)	1 (0.7)	-	-	0.901
		DVS SR 100 mg	140	36 (25.7)	60 (42.9)	31 (22.1)	11 (7.9)	2 (1.4)	-	-	-	-
	Week 6	Placebo	137	38 (27.7)	39 (28.5)	38 (27.7)	18 (13.1)	3 (2.2)	1 (0.7)	<0.001	<0.001	<0.001
		DVS SR 50 mg	144	66 (45.8)	42 (29.2)	24 (16.7)	12 (8.3)	-	-	-	-	0.782
		DVS SR 100 mg	133	57 (42.9)	42 (31.6)	26 (19.5)	7 (5.3)	1 (0.8)	-	-	-	-
	Week 8	Placebo	138	51 (37.0)	28 (20.3)	35 (25.4)	18 (13.0)	4 (2.9)	2 (1.4)	<0.001	<0.001	<0.001
		DVS SR 50 mg	145	75 (51.7)	38 (26.2)	19 (13.1)	11 (7.6)	2 (1.4)	-	-	-	0.377
		DVS SR 100 mg	126	72 (57.1)	28 (22.2)	19 (15.1)	6 (4.8)	1 (0.8)	-	-	-	-
	Week >8	Placebo	10	5 (50.0)	1 (10.0)	3 (30.0)	1 (10.0)	-	-	0.546	0.447	0.503
		DVS SR 50 mg	5	2 (40.0)	1 (20.0)	1 (20.0)	1 (20.0)	-	-	-	-	0.386
		DVS SR 100 mg	5	3 (60.0)	1 (20.0)	1 (20.0)	-	-	-	-	-	-

CGI-I = Clinical Global Impressions Scale-Improvement; CHM = Cochran-Mantel-Haenszel; DVS SR = desvenlafaxine succinate sustained-release formulation; ITT = intent-to-treat; LOCF = last observation carried forward; n = number of subject; vs = versus.

a. The p-value obtained from alternative hypothesis: 'row mean scores differ'.

At the final on-therapy evaluation, the adjusted mean change from Baseline in the MADRS total score was significantly greater for subjects in the DVS SR 50-mg ($p=0.004$) and 100-mg ($p<0.001$) treatment groups compared with the placebo group. At the final on-therapy evaluation, the adjusted mean change from Baseline in the MADRS total score was -16.4 in the DVS SR 50-mg group and -17.5 in the DVS SR 100-mg group compared with -13.3 in the placebo group. The results of the LOCF and observed-cases analyses at each scheduled time point for MADRS scores are presented in Table 9.

Table 9. Comparison Between Treatment Groups for the MADRS Total Score, ITT Population

Analysis	Week of Therapy	Therapy Group	n	Raw Mean Score	Adjusted Change From Baseline	SE	Adjusted Mean (95% CI)	Difference in Adjusted Mean (95% CI) vs Placebo	Overall p-Value	p-Value vs DVS SR 50 mg	p-Value vs DVS SR 100 mg
LOCF	Baseline	Placebo	161	29.2	-	-	29.4 (29.4, 29.4)	-	-	-	-
		DVS SR 50 mg	164	29.4	-	-	29.4 (29.4, 29.4)	-	-	-	-
		DVS SR 100 mg	158	29.6	-	-	29.4 (29.4, 29.4)	-	-	-	-
	Week 2	Placebo	154	23.3	-5.95	0.57	23.5 (22.4, 24.6)	-	0.150	0.076	0.114
		DVS SR 50 mg	160	22.1	-7.31	0.56	22.1 (21.0, 23.2)	1.4 (-0.1, 2.8)	-	-	0.869
		DVS SR 100 mg	150	22.4	-7.18	0.57	22.2 (21.1, 23.4)	1.2 (-0.3, 2.7)	-	-	-
	Week 4	Placebo	161	18.7	-10.5	0.67	19.0 (17.6, 20.3)		0.013	0.036	0.004
		DVS SR 50 mg	164	16.9	-12.4	0.66	17.1 (15.8, 18.4)	1.9 (0.1, 3.7)	-	-	0.429
		DVS SR 100 mg	157	16.3	-13.1	0.67	16.3 (15.0, 17.7)	2.6 (0.8, 4.4)	-	-	-
	Week 8	Placebo	161	15.8	-13.3	0.79	16.2 (14.6, 17.7)		<0.001	0.004	<0.001
		DVS SR 50 mg	164	12.9	-16.3	0.78	13.1 (11.6, 14.6)	3.1 (1.0, 5.1)	-	-	0.293
		DVS SR 100 mg	157	11.8	-17.5	0.79	12.0 (10.4, 13.5)	4.2 (2.1, 6.3)	-	-	
Final on-therapy	Final	Placebo	161	15.8	-13.3	0.79	16.1 (14.6, 17.7)		<0.001	0.004	<0.001
		DVS SR 50 mg	164	12.8	-16.4	0.78	13.0 (11.5, 14.6)	3.1 (1.0, 5.2)	-	-	0.311
		DVS SR 100 mg	157	11.8	-17.5	0.79	11.9 (10.4, 13.5)	4.2 (2.1, 6.3)	-	-	
Observed	Baseline	Placebo	161	29.2	-	-	29.4 (29.4, 29.4)	-	-	-	-
		DVS SR 50 mg	164	29.4	-	-	29.4 (29.4, 29.4)	-	-	-	-
		DVS SR 100 mg	158	29.6	-	-	29.4 (29.4, 29.4)	-	-	-	-
	Week 2	Placebo	153	23.2	-6.10	0.57	23.4 (22.2, 24.5)	-	0.124	0.080	0.075
		DVS SR 50 mg	154	22.0	-7.44	0.57	22.0 (20.9, 23.1)	1.3 (-0.2, 2.9)	-	-	0.947
		DVS SR 100 mg	142	22.3	-7.50	0.59	22.0 (20.8, 23.1)	1.4 (-0.1, 2.9)	-	-	-
	Week 4	Placebo	143	18.4	-11.1	0.69	18.5 (17.1, 19.8)	-	0.001	0.001	0.002
		DVS SR 50 mg	140	15.5	-14.1	0.70	15.5 (14.1, 16.8)	3.0 (1.2, 4.8)	-	-	0.971
		DVS SR 100 mg	137	15.6	-14.1	0.71	15.5 (14.1, 16.9)	3.0 (1.1, 4.8)	-	-	-
	Week 8	Placebo	138	15.2	-14.5	0.81	15.1 (13.5, 16.7)	-	<0.001	<0.001	<0.001
		DVS SR 50 mg	144	11.4	-18.2	0.79	11.3 (9.8, 12.9)	3.7 (1.7, 5.8)	-	-	0.395
		DVS SR 100 mg	126	10.6	-19.1	0.84	10.4 (8.8, 12.0)	4.7 (2.5, 6.8)	-	-	-

CI = confidence interval; DVS SR = desvenlafaxine succinate sustained-release formulation; ITT = intent-to-treat; LOCF = last observation carried forward; MADRS = Montgomery and Asberg Depression Rating Scale; n = number of subject; SE = standard error; vs = versus.

At the final on-therapy evaluation, the adjusted mean change from Baseline in the CGI-S score was significantly greater for subjects in the DVS SR 50-mg ($p=0.003$) and 100-mg ($p<0.001$) treatment groups compared with the placebo group. At the final on-therapy evaluation, the adjusted mean change from baseline in the CGI-S score was -2.1 in the DVS SR 50-mg group and -2.2 in the DVS SR 100-mg group compared with -1.6 in the placebo group. The results of the LOCF and observed-cases analyses at each scheduled time point for the CGI-S are provided in Table 10.

Table 10. Comparison Between Treatment Groups for the CGI-S, ITT Population

Analysis	Week of Therapy	Therapy Group	n	Raw Mean Score	Adjusted Change From Baseline	SE	Adjusted Mean (95% CI)	Difference in Adjusted Mean (95% CI) vs Placebo	Overall p-Value	p-Value vs DVS SR 50 mg	p-Value vs DVS SR 100 mg
LOCF	Baseline	Placebo	161	4.7	-	-	4.7 (4.7, 4.7)	-	-	-	-
		DVS SR 50 mg	164	4.7	-	-	4.7 (4.7, 4.7)	-	-	-	-
		DVS SR 100 mg	158	4.8	-	-	4.7 (4.7, 4.7)	-	-	-	-
	Week 1	Placebo	156	4.4	-0.33	0.05	4.4 (4.3, 4.5)	-	0.263	0.386	0.446
		DVS SR 50 mg	162	4.3	-0.38	0.05	4.3 (4.2, 4.4)	0.1 (-0.1, 0.2)	-	-	0.103
		DVS SR 100 mg	156	4.5	-0.28	0.05	4.4 (4.3, 4.5)	-0.0 (-0.2, 0.1)	-	-	-
	Week 2	Placebo	161	4.0	-0.75	0.07	4.0 (3.8, 4.1)	-	0.860	0.647	0.972
		DVS SR 50 mg	164	3.9	-0.79	0.07	3.9 (3.8, 4.1)	0.0 (-0.1, 0.2)	-	-	0.624
		DVS SR 100 mg	158	4.0	-0.74	0.07	4.0 (3.8, 4.1)	-0.0 (-0.2, 0.2)	-	-	-
	Week 3	Placebo	161	3.7	-1.08	0.08	3.6 (3.5, 3.8)		0.251	0.134	0.170
		DVS SR 50 mg	164	3.5	-1.24	0.08	3.5 (3.3, 3.6)	0.2 (-0.0, 0.4)	-	-	0.910
		DVS SR 100 mg	158	3.5	-1.23	0.08	3.5 (3.3, 3.6)	0.2 (-0.1, 0.4)	-	-	-
	Week 4	Placebo	161	3.4	-1.31	0.09	3.4 (3.2, 3.6)	-	0.060	0.066	0.027
		DVS SR 50 mg	164	3.2	-1.53	0.09	3.2 (3.0, 3.4)	0.2 (-0.0, 0.5)	-	-	0.691
		DVS SR 100 mg	158	3.1	-1.58	0.09	3.1 (3.0, 3.3)	0.3 (0.0, 0.5)	-	-	-
	Week 6	Placebo	161	3.2	-1.51	0.10	3.2 (3.0, 3.4)	-	0.004	0.002	0.008
		DVS SR 50 mg	164	2.7	-1.93	0.10	2.8 (2.6, 3.0)	0.4 (0.2, 0.7)	-	-	0.677
		DVS SR 100 mg	158	2.8	-1.87	0.10	2.8 (2.6, 3.0)	0.4 (0.1, 0.6)	-	-	-
	Week 8	Placebo	161	3.0	-1.64	0.11	3.1 (2.9, 3.3)	-	<0.001	0.003	<0.001
		DVS SR 50 mg	164	2.6	-2.09	0.11	2.6 (2.4, 2.9)	0.4 (0.2, 0.7)	-	-	0.522
		DVS SR 100 mg	158	2.5	-2.18	0.11	2.5 (2.3, 2.8)	0.5 (0.2, 0.8)	-	-	-
Final on-therapy	Final	Placebo	161	3.0	-1.64	0.11	3.1 (2.9, 3.3)	-	<0.001	0.003	<0.001
		DVS SR 50 mg	164	2.6	-2.09	0.11	2.6 (2.4, 2.8)	0.4 (0.2, 0.7)	-	-	0.494
		DVS SR 100 mg	158	2.5	-2.19	0.11	2.5 (2.3, 2.7)	0.5 (0.3, 0.8)	-	-	-
Observed	Baseline	Placebo	161	4.7	-	-	4.7 (4.7, 4.7)	-	-	-	-
		DVS SR 50 mg	164	4.7	-	-	4.7 (4.7, 4.7)	-	-	-	-

Table 10. Comparison Between Treatment Groups for the CGI-S, ITT Population

Analysis	Week of Therapy	Therapy Group	n	Raw Mean Score	Adjusted Change From Baseline	SE	Adjusted Mean (95% CI)	Difference in Adjusted Mean (95% CI) vs Placebo	Overall p-Value	p-Value vs DVS SR 50 mg	p-Value vs DVS SR 100 mg
		DVS SR 100 mg	158	4.8	-	-	4.7 (4.7, 4.7)	-	-	-	-
	Week 1	Placebo	156	4.4	-0.33	0.05	4.4 (4.3, 4.5)	-	0.263	0.386	0.446
		DVS SR 50 mg	162	4.3	-0.38	0.05	4.3 (4.2, 4.4)	0.1 (-0.1, 0.2)	-	-	0.103
		DVS SR 100 mg	156	4.5	-0.28	0.05	4.4 (4.3, 4.5)	-0.0 (-0.2, 0.1)	-	-	
	Week 2	Placebo	155	4.0	-0.78	0.07	3.9 (3.8, 4.1)	-	0.933	0.759	0.740
		DVS SR 50 mg	155	3.9	-0.81	0.07	3.9 (3.8, 4.0)	0.0 (-0.2, 0.2)	-	-	0.975
		DVS SR 100 mg	144	4.0	-0.82	0.07	3.9 (3.8, 4.0)	0.0 (-0.2, 0.2)	-	-	-
	Week 3	Placebo	154	3.6	-1.10	0.08	3.6 (3.5, 3.8)	-	0.084	0.031	0.125
		DVS SR 50 mg	148	3.4	-1.34	0.08	3.4 (3.2, 3.6)	0.2 (0.0, 0.5)	-	-	0.530
		DVS SR 100 mg	149	3.5	-1.27	0.08	3.5 (3.3, 3.6)	0.2 (-0.0, 0.4)	-	-	-
	Week 4	Placebo	151	3.3	-1.42	0.09	3.3 (3.2, 3.5)	-	0.025	0.019	0.020
		DVS SR 50 mg	147	3.0	-1.70	0.09	3.0 (2.9, 3.2)	0.3 (0.0, 0.5)	-	-	0.981
		DVS SR 100 mg	140	3.1	-1.70	0.09	3.0 (2.9, 3.2)	0.3 (0.0, 0.5)	-	-	-
	Week 6	Placebo	137	3.1	-1.65	0.10	3.1 (2.9, 3.3)	-	<0.001	<0.001	0.002
		DVS SR 50 mg	144	2.6	-2.15	0.10	2.6 (2.4, 2.8)	0.5 (0.2, 0.8)	-	-	0.638
		DVS SR 100 mg	133	2.7	-2.09	0.11	2.6 (2.4, 2.8)	0.4 (0.2, 0.7)	-	-	-
	Week 8	Placebo	138	2.9	-1.80	0.11	2.9 (2.7, 3.1)	-	<0.001	<0.001	<0.001
		DVS SR 50 mg	145	2.4	-2.32	0.11	2.4 (2.2, 2.6)	0.5 (0.2, 0.8)	-	-	0.391
		DVS SR 100 mg	126	2.3	-2.45	0.12	2.3 (2.0, 2.5)	0.6 (0.3, 0.9)	-	-	-
	Week >8	Placebo	10	2.5	-	-	-	-	-	-	-
		DVS SR 50 mg	5	3.0	-	-	-	-	-	-	-
		DVS SR 100 mg	5	2.0	-	-	-	-	-	-	-

CGI-S = Clinical Global Impressions Scale-Severity; CI = confidence interval; DVS SR = desvenlafaxine succinate sustained-release formulation; ITT = intent-to-treat; LOCF = last observation carried forward; n = number of subject; SE = standard error; vs = versus.

At the final on-therapy evaluation for the logistic regression analysis of the HAM-D_{17} remission rate, the adjusted odds ratio to placebo was 1.488 (p=0.099; 95% CI=0.93, 2.38) in the DVS SR 50-mg group and 2.117 (p=0.002; 95% CI=1.32, 3.39) in the DVS SR 100-mg group. At the Week 8 observed-cases evaluation for the logistic regression analysis of the HAM-D_{17} remission rate, the adjusted odds ratio to placebo was 1.723 (p=0.033; 95% CI=1.04, 2.84) in the DVS SR 50-mg group and 2.349 (p=0.001; 95% CI=1.40, 3.94) in the 100-mg group. The results of the logistic regression analysis of the HAM-D_{17} remission rate, including the LOCF and observed-cases analyses at each scheduled time point, are provided in Table 11.

Table 11. Logistic Regression Analysis of Remission From the HAM-D_{17} Score, ITT Population

Analysis	Week of Therapy	Therapy	Proportion of Remitters n (%)	Odds Ratio	Wald 95% CI Adjusted Odds Ratio	p-Value vs Placebo
LOCF	Week 1	Placebo	1 (0.6)	-	-	-
		DVS SR 50 mg	1 (0.6)	0.805	(0.04, 14.41)	0.883
		DVS SR 100 mg	1 (0.6)	1.056	(0.06, 17.76)	0.970
	Week 2	Placebo	4 (2.5)	-	-	-
		DVS SR 50 mg	5 (3.0)	1.179	(0.29, 4.79)	0.818
		DVS SR 100 mg	5 (3.2)	1.418	(0.35, 5.75)	0.625
	Week 3	Placebo	9 (5.6)	-	-	-
		DVS SR 50 mg	12 (7.3)	1.335	(0.54, 3.30)	0.531
		DVS SR 100 mg	17 (10.8)	2.133	(0.91, 5.01)	0.082
	Week 4	Placebo	22 (13.7)	-		
		DVS SR 50 mg	28 (17.1)	1.299	(0.71, 2.39)	0.401
		DVS SR 100 mg	31 (19.6)	1.577	(0.86, 2.88)	0.138
	Week 6	Placebo	37 (23.0)	-	-	-
		DVS SR 50 mg	51 (31.1)	1.512	(0.92, 2.49)	0.105
		DVS SR 100 mg	51 (32.3)	1.639	(0.99, 2.71)	0.054
	Week 8	Placebo	45 (28.0)	-	-	-
		DVS SR 50 mg	62 (37.8)	1.576	(0.98, 2.53)	0.059
		DVS SR 100 mg	71 (44.9)	2.186	(1.36, 3.51)	0.001
Final on-therapy	Final	Placebo	46 (28.6)	-	-	-
		DVS SR 50 mg	61 (37.2)	1.488	(0.93, 2.38)	0.099
		DVS SR 100 mg	71 (44.9)	2.117	(1.32, 3.39)	0.002
Observed	Week 1	Placebo	1 (0.6)	-	-	-
		DVS SR 50 mg	1 (0.6)	0.805	(0.04, 14.41)	0.883
		DVS SR 100 mg	1 (0.6)	1.056	(0.06, 17.76)	0.970
	Week 2	Placebo	4 (2.6)	-	-	-
		DVS SR 50 mg	5 (3.2)	1.254	(0.30, 5.19)	0.755
		DVS SR 100 mg	5 (3.5)	1.709	(0.41, 7.07)	0.459
	Week 3	Placebo	9 (5.8)	-		
		DVS SR 50 mg	12 (8.1)	1.458	(0.59, 3.62)	0.416
		DVS SR 100 mg	16 (10.7)	2.035	(0.86, 4.83)	0.107
	Week 4	Placebo	22 (14.6)	-	-	-
		DVS SR 50 mg	28 (19.0)	1.378	(0.74, 2.56)	0.309
		DVS SR 100 mg	29 (20.7)	1.596	(0.86, 2.96)	0.138

Table 11. Logistic Regression Analysis of Remission From the HAM-D_{17} Score, ITT Population

Analysis	Week of Therapy	Therapy	Proportion of Remitters n (%)	Odds Ratio	Wald 95% CI Adjusted Odds Ratio	p-Value vs Placebo
	Week 6	Placebo	32 (23.4)	-	-	-
		DVS SR 50 mg	50 (34.7)	1.735	(1.02, 2.96)	0.043
		DVS SR 100 mg	46 (34.6)	1.854	(1.07, 3.20)	0.026
	Week 8	Placebo	41 (29.7)	-	-	-
		DVS SR 50 mg	61 (42.1)	1.723	(1.04, 2.84)	0.033
		DVS SR 100 mg	61 (48.4)	2.349	(1.40, 3.94)	0.001

Remission defined as HAM-D_{17} score ≤7.
CI = confidence interval; DVS SR = desvenlafaxine succinate sustained-release formulation; HAM-D_{17} = Hamilton Rating Scale for Depression, 17-item; ITT = intent-to-treat; LOCF = last observation carried forward; n = number of subject; vs = versus.

Results for the VAS-PI overall and component pain scores are not presented because of inconsistencies in the format of the translated scales and/or administration of the scale amongst sites. The results of the analyses using LOCF and observed-cases at each scheduled evaluation for HAM-D_6 total score, the Covi Anxiety Scale score, are presented in Table 12 and Table 13, respectively.

Table 12. Comparison Between Treatment Groups for the HAM-D_6, ITT Population

Analysis	Week of Therapy	Therapy Group	n	Raw Mean Score	Adjusted Change From Baseline	SE	Adjusted Mean (95% CI)	Difference in Adjusted Mean (95% CI) vs Placebo	Overall p-Value	p-Value vs DVS SR 50 mg	p-Value vs DVS SR 100 mg
LOCF	Baseline	Placebo	161	12.4	-	-	12.5 (12.5, 12.5)	-	-	-	-
		DVS SR 50 mg	164	12.4	-	-	12.5 (12.5, 12.5)	-	-	-	-
		DVS SR 100 mg	158	12.5	-	-	12.5 (12.5, 12.5)	-	-	-	-
	Week 1	Placebo	156	11.3	-1.02	0.15	11.4 (11.1, 11.7)	-	0.448	0.205	0.532
		DVS SR 50 mg	162	11.1	-1.27	0.15	11.2 (10.9, 11.5)	0.3 (-0.1, 0.6)	-	-	0.524
		DVS SR 100 mg	156	11.4	-1.15	0.15	11.3 (11.0, 11.6)	0.1 (-0.3, 0.5)	-	-	-
	Week 2	Placebo	161	9.8	-2.54	0.22	9.9 (9.5, 10.3)		0.444	0.220	0.362
		DVS SR 50 mg	164	9.5	-2.90	0.21	9.5 (9.1, 10.0)	0.4 (-0.2, 0.9)	-	-	0.759
		DVS SR 100 mg	158	9.7	-2.81	0.22	9.6 (9.2, 10.1)	0.3 (-0.3, 0.8)	-	-	-
	Week 3	Placebo	161	8.6	-3.80	0.27	8.7 (8.1, 9.2)		0.090	0.075	0.045
		DVS SR 50 mg	164	8.0	-4.44	0.26	8.0 (7.5, 8.5)	0.6 (-0.1, 1.3)	-	-	0.810
		DVS SR 100 mg	158	8.0	-4.53	0.27	7.9 (7.4, 8.4)	0.7 (0.0, 1.4)	-	-	-
	Week 4	Placebo	161	7.9	-4.47	0.28	8.0 (7.4, 8.5)		0.006	0.026	0.002
		DVS SR 50 mg	164	7.0	-5.32	0.28	7.1 (6.6, 7.7)	0.9 (0.1, 1.6)	-	-	0.368
		DVS SR 100 mg	158	6.8	-5.67	0.29	6.8 (6.2, 7.3)	1.2 (0.4, 2.0)	-	-	-
	Week 6	Placebo	161	7.3	-4.98	0.31	7.5 (6.9, 8.1)		<0.001	<0.001	<0.001
		DVS SR 50 mg	164	5.8	-6.51	0.30	5.9 (5.3, 6.5)	1.5 (0.7, 2.3)	-	-	0.976
		DVS SR 100 mg	158	5.9	-6.50	0.31	6.0 (5.4, 6.6)	1.5 (0.7, 2.3)	-	-	-
	Week 8	Placebo	161	7.1	-5.20	0.33	7.3 (6.6, 7.9)	-	<0.001	<0.001	<0.001

Table 12. Comparison Between Treatment Groups for the HAM-D_6, ITT Population

Analysis	Week of Therapy	Therapy Group	n	Raw Mean Score	Adjusted Change From Baseline	SE	Adjusted Mean (95% CI)	Difference in Adjusted Mean (95% CI) vs Placebo	Overall p-Value	p-Value vs DVS SR 50 mg	p-Value vs DVS SR 100 mg
		DVS SR 50 mg	164	5.4	-6.89	0.32	5.6 (4.9, 6.2)	1.7 (0.8, 2.6)	-	-	0.507
		DVS SR 100 mg	158	5.2	-7.19	0.33	5.3 (4.6, 5.9)	2.0 (1.1, 2.9)	-	-	-
Final on-therapy	Final	Placebo	161	7.1	-5.20	0.33	7.3 (6.6, 7.9)	-	<0.001	<0.001	<0.001
		DVS SR 50 mg	164	5.5	-6.87	0.32	5.6 (4.9, 6.2)	1.7 (0.8, 2.5)	-	-	0.448
		DVS SR 100 mg	158	5.2	-7.21	0.33	5.2 (4.6, 5.9)	2.0 (1.1, 2.9)	-	-	-
Observed	Baseline	Placebo	161	12.4	-	-	12.5 (12.5, 12.5)	-	-	-	-
		DVS SR 50 mg	164	12.4	-	-	12.5 (12.5, 12.5)	-	-	-	-
		DVS SR 100 mg	158	12.5	-	-	12.5 (12.5, 12.5)	-	-	-	-
	Week 1	Placebo	156	11.3	-1.02	0.15	11.4 (11.1, 11.7)	-	0.448	0.205	0.532
		DVS SR 50 mg	162	11.1	-1.27	0.15	11.2 (10.9, 11.5)	0.3 (-0.1, 0.6)	-	-	0.524
		DVS SR 100 mg	156	11.4	-1.15	0.15	11.3 (11.0, 11.6)	0.1 (-0.3, 0.5)	-	-	-
	Week 2	Placebo	155	9.8	-2.63	0.22	9.8 (9.4, 10.3)		0.299	0.159	0.206
		DVS SR 50 mg	155	9.4	-3.05	0.22	9.4 (9.0, 9.8)	0.4 (-0.2, 1.0)	-	-	0.908
		DVS SR 100 mg	144	9.5	-3.02	0.23	9.4 (9.0, 9.9)	0.4 (-0.2, 1.0)	-	-	-
	Week 3	Placebo	154	8.6	-3.80	0.27	8.7 (8.2, 9.2)	-	0.014	0.009	0.015
		DVS SR 50 mg	148	7.8	-4.77	0.28	7.7 (7.2, 8.3)	1.0 (0.2, 1.7)	-	-	0.860
		DVS SR 100 mg	149	7.9	-4.70	0.28	7.8 (7.3, 8.3)	0.9 (0.2, 1.6)	-	-	-
	Week 4	Placebo	151	7.8	-4.66	0.28	7.9 (7.3, 8.4)	-	<0.001	<0.001	<0.001

Table 12. Comparison Between Treatment Groups for the HAM-D_6, ITT Population

Analysis	Week of Therapy	Therapy Group	n	Raw Mean Score	Adjusted Change From Baseline	SE	Adjusted Mean (95% CI)	Difference in Adjusted Mean (95% CI) vs Placebo	Overall p-Value	p-Value vs DVS SR 50 mg	p-Value vs DVS SR 100 mg
		DVS SR 50 mg	147	6.6	-5.93	0.29	6.6 (6.0, 7.1)	1.3 (0.5, 2.0)	-	-	0.805
		DVS SR 100 mg	140	6.6	-6.02	0.29	6.5 (5.9, 7.1)	1.4 (0.6, 2.1)	-	-	-
	Week 6	Placebo	137	7.1	-5.34	0.32	7.1 (6.5, 7.7)	-	<0.001	<0.001	<0.001
		DVS SR 50 mg	144	5.3	-7.25	0.31	5.2 (4.6, 5.8)	1.9 (1.1, 2.7)	-	-	0.871
		DVS SR 100 mg	133	5.4	-7.18	0.32	5.3 (4.6, 5.9)	1.8 (1.0, 2.7)	-	-	-
	Week 8	Placebo	138	6.8	-5.64	0.34	6.9 (6.2, 7.5)	-	<0.001	<0.001	<0.001
		DVS SR 50 mg	145	4.9	-7.63	0.33	4.9 (4.2, 5.5)	2.0 (1.1, 2.9)	-	-	0.497
		DVS SR 100 mg	126	4.6	-7.94	0.35	4.6 (3.9, 5.2)	2.3 (1.4, 3.2)	-	-	-
	Week >8	Placebo	10	5.7	-	-	-	-	-	-	-
		DVS SR 50 mg	5	7.0	-	-	-	-	-	-	-
		DVS SR 100 mg	5	4.6	-	-	-	-	-	-	-

CI = confidence interval; DVS SR = desvenlafaxine succinate sustained-release formulation; HAM-D_6 = Hamilton Rating Scale for Depression, 6-item; ITT = intent-to-treat; LOCF = last observation carried forward; n = number of subject; SE = standard error; vs = versus.

Table 13. Comparison Between Treatment Groups for the Covi Anxiety Scale, ITT Population

Analysis	Week of Therapy	Therapy Group	n	Raw Mean Score	Adjusted Change From Baseline	SE	Adjusted Mean (95% CI)	Difference in Adjusted Mean (95% CI) vs Placebo	Overall p-Value	p-Value vs DVS SR 50 mg	p-Value vs DVS SR 100 mg
LOCF	Baseline	Placebo	161	6.2	-	-	6.4 (6.4, 6.4)	-	-	-	-
		DVS SR 50 mg	164	6.5	-	-	6.4 (6.4, 6.4)	-	-	-	-
		DVS SR 100 mg	158	6.4	-	-	6.4 (6.4, 6.4)	-	-	-	-
	Week 2	Placebo	154	5.7	-0.62	0.11	5.8 (5.5, 6.0)	-	0.488	0.848	0.355
		DVS SR 50 mg	160	5.8	-0.65	0.11	5.7 (5.5, 6.0)	0.0 (-0.3, 0.3)	-	-	0.260
		DVS SR 100 mg	150	6.0	-0.48	0.11	5.9 (5.7, 6.1)	-0.1 (-0.4, 0.2)	-	-	-
	Week 4	Placebo	161	5.3	-0.95	0.12	5.4 (5.2, 5.7)	-	0.144	0.172	0.056
		DVS SR 50 mg	164	5.2	-1.17	0.12	5.2 (5.0, 5.4)	0.2 (-0.1, 0.5)	-	-	0.572
		DVS SR 100 mg	157	5.1	-1.26	0.12	5.1 (4.9, 5.3)	0.3 (-0.0, 0.6)	-	-	-
	Week 8	Placebo	161	5.3	-1.11	0.13	5.3 (5.0, 5.5)	-	0.002	0.001	0.003
		DVS SR 50 mg	164	4.8	-1.70	0.13	4.7 (4.4, 4.9)	0.6 (0.2, 0.9)	-	-	0.772
		DVS SR 100 mg	157	4.8	-1.65	0.13	4.7 (4.5, 5.0)	0.5 (0.2, 0.9)	-	-	-
Final on-therapy	Final	Placebo	161	5.3	-1.10	0.13	5.3 (5.0, 5.5)	-	0.002	0.001	0.004
		DVS SR 50 mg	164	4.8	-1.69	0.13	4.7 (4.4, 4.9)	0.6 (0.2, 0.9)	-	-	0.742
		DVS SR 100 mg	157	4.8	-1.63	0.13	4.8 (4.5, 5.0)	0.5 (0.2, 0.9)	-	-	-
Observed	Baseline	Placebo	161	6.2	-	-	6.4 (6.4, 6.4)	-	-	-	-
		DVS SR 50 mg	164	6.5	-	-	6.4 (6.4, 6.4)	-	-	-	-
		DVS SR 100 mg	158	6.4	-	-	6.4 (6.4, 6.4)	-	-	-	-
	Week 2	Placebo	153	5.7	-0.64	0.11	5.7 (5.5, 6.0)	-	0.442	0.902	0.296
		DVS SR 50 mg	154	5.8	-0.66	0.11	5.7 (5.5, 6.0)	0.0 (-0.3, 0.3)	-	-	0.242
		DVS SR 100 mg	142	6.0	-0.48	0.12	5.9 (5.7, 6.1)	-0.2 (-0.5, 0.1)	-	-	-
	Week 4	Placebo	143	5.3	-1.04	0.13	5.4 (5.1, 5.6)	-	0.048	0.031	0.036
		DVS SR 50 mg	140	5.0	-1.41	0.13	5.0 (4.8, 5.3)	0.4 (0.0, 0.7)	-	-	0.961

Table 13. Comparison Between Treatment Groups for the Covi Anxiety Scale, ITT Population

Analysis	Week of Therapy	Therapy Group	n	Raw Mean Score	Adjusted Change From Baseline	SE	Adjusted Mean (95% CI)	Difference in Adjusted Mean (95% CI) vs Placebo	Overall p-Value	p-Value vs DVS SR 50 mg	p-Value vs DVS SR 100 mg
		DVS SR 100 mg	137	5.1	-1.40	0.13	5.0 (4.8, 5.3)	0.4 (0.0, 0.7)	-	-	-
	Week 8	Placebo	138	5.2	-1.24	0.14	5.2 (4.9, 5.5)	-	<0.001	<0.001	0.003
		DVS SR 50 mg	144	4.5	-1.97	0.14	4.5 (4.2, 4.8)	0.7 (0.4, 1.1)	-	-	0.466
		DVS SR 100 mg	126	4.7	-1.83	0.15	4.6 (4.3, 4.9)	0.6 (0.2, 1.0)	-	-	-

CI = confidence interval; DVS SR = desvenlafaxine succinate sustained-release formulation; ITT = intent-to-treat; LOCF = last observation carried forward; n = number of subject; SE = standard error; vs = versus.

The results of the ANCOVA using LOCF of the SDS at Baseline, at Weeks 2, 4, and 8, and at the Final On-therapy evaluation for the SDS total score and the subscales of work, social life and leisure activities, family life and home responsibilities, and work and social disability are shown in Table 14. At the final on-therapy evaluation, the adjusted mean change from Baseline in the SDS total score was significantly greater for subjects in the DVS SR 50-mg ($p=0.003$) and 100-mg ($p<0.001$) treatment groups compared with the placebo group. At the final on-therapy evaluation, the adjusted mean change from Baseline in the SDS total score was -10.3 in the DVS SR 50 mg group and -11.1 in the DVS SR 100-mg group compared with -7.58 in the placebo group. Significant differences on the SDS subscale scores were similar to those on the SDS total scores.

Table 14. Comparison Between Treatment Groups for the Sheehan Disability Scale (ANCOVA), ITT Population, LOCF Analysis

Week of Therapy	Treatment	n	Raw Mean Score	Adjusted Change From Baseline	SE	Adjusted Mean (95% CI)	Difference in Adjusted Mean (95% CI) vs Placebo	Overall p-Value	p-Value vs DVS SR 50 mg	p-Value vs DVS SR 100 mg
Total										
Baseline	Placebo	159	24.0	-	-	23.7 (23.7, 23.7)	-	-	-	-
	DVS SR 50 mg	164	23.6	-	-	23.7 (23.7, 23.7)	-	-	-	-
	DVS SR 100 mg	158	23.7	-	-	23.7 (23.7, 23.7)	-	-	-	-
Week 2	Placebo	152	20.1	-3.89	0.50	19.8 (18.8, 20.8)	-	0.824	0.581	0.975
	DVS SR 50 mg	159	19.2	-4.26	0.49	19.5 (18.5, 20.4)	0.4 (-0.9, 1.7)	-	-	0.604
	DVS SR 100 mg	150	19.7	-3.91	0.50	19.8 (18.8, 20.8)	0.0 (-1.3, 1.4)	-	-	-
Week 4	Placebo	159	17.6	-6.36	0.59	17.4 (16.2, 18.5)		0.104	0.126	0.041
	DVS SR 50 mg	163	16.1	-7.57	0.58	16.2 (15.0, 17.3)	1.2 (-0.3, 2.8)	-	-	0.591
	DVS SR 100 mg	157	15.7	-8.00	0.59	15.7 (14.6, 16.9)	1.6 (0.1, 3.2)	-	-	-
Week 8	Placebo	159	16.2	-7.33	0.68	16.4 (15.1, 17.7)		<0.001	0.001	<0.001
	DVS SR 50 mg	163	13.1	-10.3	0.67	13.4 (12.1, 14.7)	3.0 (1.2, 4.8)	-	-	0.415
	DVS SR 100 mg	157	12.4	-11.1	0.68	12.6 (11.3, 14.0)	3.7 (1.9, 5.6)	-	-	-
Final on-therapy	Placebo	159	15.9	-7.58	0.68	16.1 (14.8, 17.5)	-	<0.001	0.003	<0.001
	DVS SR 50 mg	163	13.0	-10.3	0.67	13.4 (12.1, 14.7)	2.8 (1.0, 4.6)	-	-	0.416
	DVS SR 100 mg	157	12.3	-11.1	0.68	12.6 (11.3, 14.0)	3.5 (1.7, 5.3)	-	-	-
Work										
Baseline	Placebo	149	6.6	-	-	6.5 (6.5, 6.5)	-	-	-	-
	DVS SR 50 mg	157	6.4	-	-	6.5 (6.5, 6.5)	-	-	-	-
	DVS SR 100 mg	151	6.4	-	-	6.5 (6.5, 6.5)	-	-	-	-
Week 2	Placebo	141	5.7	-0.93	0.17	5.5 (5.2, 5.9)	-	0.651	0.359	0.563
	DVS SR 50 mg	152	5.2	-1.14	0.17	5.3 (5.0, 5.7)	0.2 (-0.2, 0.7)	-	-	0.741
	DVS SR 100 mg	142	5.4	-1.06	0.17	5.4 (5.1, 5.7)	0.1 (-0.3, 0.6)	-	-	-
Week 4	Placebo	148	4.6	-1.93	0.20	4.5 (4.1, 4.9)	-	0.420	0.408	0.193
	DVS SR 50 mg	156	4.3	-2.15	0.19	4.3 (3.9, 4.7)	0.2 (-0.3, 0.7)	-	-	0.623
	DVS SR 100 mg	149	4.1	-2.27	0.19	4.2 (3.8, 4.6)	0.3 (-0.2, 0.9)	-	-	
Week 8	Placebo	148	4.3	-2.09	0.22	4.4 (3.9, 4.8)	-	<0.001	0.005	<0.001
	DVS SR 50 mg	156	3.4	-2.91	0.21	3.5 (3.1, 4.0)	0.8 (0.3, 1.4)	-	-	0.385
	DVS SR 100 mg	149	3.2	-3.17	0.21	3.3 (2.9, 3.7)	1.1 (0.5, 1.7)	-	-	-

Table 14. Comparison Between Treatment Groups for the Sheehan Disability Scale (ANCOVA), ITT Population, LOCF Analysis

Week of Therapy	Treatment	n	Raw Mean Score	Adjusted Change From Baseline	SE	Adjusted Mean (95% CI)	Difference in Adjusted Mean (95% CI) vs Placebo	Overall p-Value	p-Value vs DVS SR 50 mg	p-Value vs DVS SR 100 mg
Final on-therapy	Placebo	148	4.2	-2.16	0.22	4.3 (3.9, 4.7)	-	0.002	0.010	<0.001
	DVS SR 50 mg	156	3.4	-2.91	0.21	3.5 (3.1, 4.0)	0.8 (0.2, 1.3)	-	-	-
	DVS SR 100 mg	149	3.2	-3.19	0.22	3.3 (2.8, 3.7)	1.0 (0.5, 1.6)	-	-	0.339
Social Life and Leisure Activities										
Baseline	Placebo	160	6.9	-	-	6.8 (6.8, 6.8)	-	-	-	-
	DVS SR 50 mg	164	6.6	-	-	6.8 (6.8, 6.8)	-	-	-	-
	DVS SR 100 mg	158	6.8	-	-	6.8 (6.8, 6.8)	-	-	-	-
Week 2	Placebo	153	5.6	-1.31	0.16	5.4 (5.1, 5.8)	-	0.790	0.903	0.519
	DVS SR 50 mg	159	5.4	-1.28	0.16	5.5 (5.2, 5.8)	-0.0 (-0.5, 0.4)	-	-	0.597
	DVS SR 100 mg	150	5.6	-1.16	0.16	5.6 (5.3, 5.9)	-0.1 (-0.6, 0.3)	-	-	-
Week 4	Placebo	160	4.9	-1.88	0.19	4.9 (4.5, 5.2)		0.121	0.110	0.055
	DVS SR 50 mg	163	4.3	-2.30	0.19	4.5 (4.1, 4.8)	0.4 (-0.1, 0.9)	-	-	0.734
	DVS SR 100 mg	157	4.3	-2.38	0.19	4.4 (4.0, 4.7)	0.5 (-0.0, 1.0)	-	-	-
Week 8	Placebo	160	4.4	-2.27	0.21	4.5 (4.1, 4.9)		<0.001	0.002	<0.001
	DVS SR 50 mg	163	3.4	-3.17	0.21	3.6 (3.2, 4.0)	0.9 (0.3, 1.5)	-	-	0.518
	DVS SR 100 mg	157	3.3	-3.35	0.21	3.4 (3.0, 3.8)	1.1 (0.5, 1.7)	-	-	-
Final on-therapy	Placebo	160	4.4	-2.32	0.21	4.4 (4.0, 4.8)	-	<0.001	0.003	<0.001
	DVS SR 50 mg	163	3.4	-3.18	0.21	3.6 (3.2, 4.0)	0.9 (0.3, 1.4)	-	-	0.516
	DVS SR 100 mg	157	3.3	-3.36	0.21	3.4 (3.0, 3.8)	1.0 (0.5, 1.6)	-	-	-
Family Life and Home Responsibilities										
Baseline	Placebo	160	6.4	-	-	6.5 (6.5, 6.5)	-	-	-	-
	DVS SR 50 mg	164	6.5	-	-	6.5 (6.5, 6.5)	-	-	-	-
	DVS SR 100 mg	158	6.6	-	-	6.5 (6.5, 6.5)	-	-	-	-
Week 2	Placebo	153	5.3	-1.07	0.17	5.4 (5.1, 5.7)	-	0.492	0.236	0.625
	DVS SR 50 mg	159	5.1	-1.35	0.17	5.1 (4.8, 5.5)	0.3 (-0.2, 0.7)	-	-	0.493
	DVS SR 100 mg	150	5.3	-1.19	0.17	5.3 (5.0, 5.6)	0.1 (-0.3, 0.6)	-	-	-
Week 4	Placebo	160	4.7	-1.78	0.19	4.7 (4.3, 5.1)	-	0.042	0.046	0.020
	DVS SR 50 mg	163	4.2	-2.30	0.19	4.2 (3.8, 4.6)	0.5 (0.0, 1.0)	-	-	0.719

Table 14. Comparison Between Treatment Groups for the Sheehan Disability Scale (ANCOVA), ITT Population, LOCF Analysis

Week of Therapy	Treatment	n	Raw Mean Score	Adjusted Change From Baseline	SE	Adjusted Mean (95% CI)	Difference in Adjusted Mean (95% CI) vs Placebo	Overall p-Value	p-Value vs DVS SR 50 mg	p-Value vs DVS SR 100 mg
	DVS SR 100 mg	157	4.2	-2.39	0.19	4.1 (3.7, 4.5)	0.6 (0.1, 1.1)	-	-	-
Week 8	Placebo	160	4.4	-2.02	0.21	4.5 (4.1, 4.9)	-	<0.001	<0.001	<0.001
	DVS SR 50 mg	163	3.4	-3.00	0.21	3.5 (3.1, 3.9)	1.0 (0.4, 1.5)	-	-	0.420
	DVS SR 100 mg	157	3.2	-3.23	0.21	3.3 (2.9, 3.7)	1.2 (0.6, 1.8)	-	-	-
Final on-therapy	Placebo	160	4.2	-2.16	0.21	4.4 (3.9, 4.8)	-	<0.001	0.002	<0.001
	DVS SR 50 mg	163	3.4	-3.02	0.21	3.5 (3.1, 3.9)	0.9 (0.3, 1.4)	-	-	0.487
	DVS SR 100 mg	157	3.2	-3.22	0.21	3.3 (2.9, 3.7)	1.1 (0.5, 1.6)	-	-	
Work and Social Disability										
Baseline	Placebo	159	4.0	-	-	4.0 (4.0, 4.0)	-	-	-	-
	DVS SR 50 mg	161	4.0	-	-	4.0 (4.0, 4.0)	-	-	-	-
	DVS SR 100 mg	158	3.9	-	-	4.0 (4.0, 4.0)	-	-	-	-
Week 2	Placebo	152	3.6	-0.41	0.07	3.6 (3.4, 3.7)	-	0.578	0.328	0.868
	DVS SR 50 mg	154	3.5	-0.50	0.07	3.5 (3.3, 3.6)	0.1 (-0.1, 0.3)	-	-	0.419
	DVS SR 100 mg	150	3.5	-0.43	0.07	3.5 (3.4, 3.7)	0.0 (-0.2, 0.2)	-	-	-
Week 4	Placebo	159	3.3	-0.65	0.08	3.3 (3.2, 3.5)		0.041	0.065	0.016
	DVS SR 50 mg	159	3.2	-0.85	0.08	3.1 (3.0, 3.3)	0.2 (-0.0, 0.4)	-	-	0.562
	DVS SR 100 mg	157	3.0	-0.91	0.08	3.1 (2.9, 3.2)	0.3 (0.0, 0.5)	-	-	-
Week 8	Placebo	159	3.1	-0.88	0.09	3.1 (2.9, 3.3)		0.001	0.004	<0.001
	DVS SR 50 mg	159	2.7	-1.25	0.09	2.7 (2.5, 2.9)	0.4 (0.1, 0.6)	-	-	0.631
	DVS SR 100 mg	157	2.6	-1.31	0.09	2.7 (2.5, 2.8)	0.4 (0.2, 0.7)	-	-	-
Final on-therapy	Placebo	159	3.1	-0.87	0.09	3.1 (2.9, 3.3)		0.001	0.003	<0.001
	DVS SR 50 mg	159	2.7	-1.24	0.09	2.7 (2.5, 2.9)	0.4 (0.1, 0.6)	-	-	0.597
	DVS SR 100 mg	157	2.6	-1.31	0.09	2.7 (2.5, 2.8)	0.4 (0.2, 0.7)	-	-	-

ANCOVA = analysis of covariance; CI = confidence interval; DVS SR = desvenlafaxine sustained release; ITT = intent-to-treat; LOCF = last observation carried forward; n = number of subjects; SE = standard error; vs = versus.

The results of the ANCOVA using LOCF of the WHO-5 at Baseline, Weeks 2, 4, and 8, and at the final on-therapy evaluation are shown in Table 15. The adjusted mean change from Baseline in the WHO-5 scale was significantly greater than that for placebo for both DVS SR treatment groups at the final on-therapy evaluation; for the WHO-5 scale an increase in score indicates improvement. At the final on-therapy evaluation, the adjusted mean change from Baseline in the WHO-5 score was significantly greater for subjects in the DVS SR 50-mg ($p=0.006$) and 100-mg ($p<0.001$) treatment groups compared with the placebo group. At the final on-therapy evaluation, the adjusted mean changes from Baseline in the WHO-5 score was 7.54 in the DVS SR 50-mg group and 8.46 in the DVS SR 100-mg group compared with 5.75 in the placebo group.

Table 15. Comparison Between Treatment Groups for the WHO-5 Scale (ANCOVA), ITT Population, LOCF Analysis

Time Point	Treatment	n	Raw Mean Score	Adjusted Change From Baseline	SE	Adjusted Mean (95% CI)	Difference in Adjusted Mean (95% CI) vs Placebo	Overall p-Value	p-Value vs DVS SR 50 mg	p-Value vs DVS SR 100 mg
Baseline	Placebo	159	6.0	-	-	5.9 (5.9, 5.9)	-	-	-	-
	DVS SR 50 mg	164	6.1	-	-	5.9 (5.9, 5.9)	-	-	-	-
	DVS SR 100 mg	158	5.6	-	-	5.9 (5.9, 5.9)	-	-	-	-
Week 2	Placebo	152	9.1	3.16	0.37	9.1 (8.4, 9.8)	-	0.945	0.755	0.791
	DVS SR 50 mg	159	9.3	3.31	0.36	9.2 (8.5, 10.0)	-0.2 (-1.1, 0.8)	-	-	0.966
	DVS SR 100 mg	150	8.9	3.29	0.37	9.2 (8.5, 10.0)	-0.1 (-1.1, 0.9)	-	-	
Week 4	Placebo	159	10.6	4.79	0.42	10.7 (9.9, 11.5)	-	0.050	0.071	0.019
	DVS SR 50 mg	163	11.6	5.82	0.42	11.7 (10.9, 12.5)	-1.0 (-2.1, 0.1)	-	-	0.572
	DVS SR 100 mg	157	11.8	6.14	0.42	12.0 (11.2, 12.9)	-1.4 (-2.5, -0.2)	-	-	-
Week 8	Placebo	159	11.9	5.78	0.48	11.7 (10.8, 12.6)		<0.001	0.007	<0.001
	DVS SR 50 mg	163	13.5	7.52	0.47	13.4 (12.5, 14.4)	-1.7 (-3.0, -0.5)	-	-	0.169
	DVS SR 100 mg	157	14.3	8.42	0.48	14.3 (13.4, 15.3)	-2.6 (-3.9, -1.4)	-	-	-
Final on-therapy	Placebo	159	11.8	5.75	0.48	11.7 (10.7, 12.6)	-	<0.001	0.006	<0.001
	DVS SR 50 mg	163	13.5	7.54	0.48	13.4 (12.5, 14.4)	-1.8 (-3.1, -0.5)	-	-	0.158
	DVS SR 100 mg	157	14.3	8.46	0.48	14.4 (13.4, 15.3)	-2.7 (-4.0, -1.4)	-	-	-

ANCOVA = analysis of covariance; CI = confidence interval; DVS SR = desvenlafaxine sustained release; ITT = intent-to-treat; LOCF=last observation carried forward; n = number of subjects; SE=standard error; vs = versus; WHO-5 = World Health Organization 5-Item Well-Being Index. .

Safety Results: A total of 3 subjects had serious AEs (SAEs) as presented in Table 16. None of the SAEs was found to be related to study drug.

During the on-therapy period, treatment-emergent adverse events (TEAEs) were reported by 99 (61.5%) subjects in the placebo group, 129 (77.7%) subjects in the DVS SR 50-mg group, and 122 (77.2%) subjects in the DVS SR 100-mg group. The most common (incidence ≥5% in any treatment group) TEAEs (coded in Coding Symbols for the Thesaurus of Adverse Reaction Terms [COSTART]) during the on-therapy period are shown in Table 17. Taper/Poststudy-emergent adverse events (TPAEs) were reported by 33 (20.5%) subjects in the placebo group, 74 (44.6%) subjects in the DVS SR 50-mg group, and 64 (40.5%) subjects in the DVS SR 100-mg group. The most common (incidence ≥5% in any treatment group) TPAEs are shown in Table 18 and the most common (incidence ≥5% in any treatment group) related to study drug is provided in Table 19.

Table 16. Subjects Who Had Serious Adverse Events

Subject Serial number	Treatment Body system	Age[a] (Y)/Sex	Mean Daily Dose[b] (mg)	Days From Start of Therapy to Onset of SAE	AE COSTART Preferred Term	Drug Relationship[c]	SAE	Discontinued Because of Identified AE
	Placebo							
1	Body as whole[d]	42/F	0.0	60 (Poststudy)	Infection (Womb infection)	No	Yes	No
2	Digestive	46/M	0.0	-7 (Prestudy)	Intestinal obstruction (Stercoral mass [Fecal obstruction])	No	Yes	No
					Abdominal pain (abdominal pain)	No	Yes	No
	DVS SR 100 mg							
3	Body as whole	48/F	95.5	64 (Poststudy)[d]	Accidental injury (Left L4 L5 discal hernia)[e]	No	Yes	No

AE = adverse event; COSTART = Coding Symbols for the Thesaurus of Adverse Reaction Terms; DVS SR = desvenlafaxine succinate sustained release; F = female; M = male; MedDRA = Medical Dictionary of Regulatory Activities; SAE = serious adverse event.

a. Age at study entry.
b. Included missed doses.
c. Relationship to study drug is based on the Investigator's assessment. When an event was reported more than once for a subject, the most conservative assessment of relationship was listed.
d. Event occurred during the poststudy period.
e. COSTART preferred term is identical to the MedDRA term for each subject except this subject for whom the MedDRA term is "intervetebral disc protrusion".

Table 17. Number (%) of Subjects Who Reported Treatment-Emergent Adverse Events (Incidence ≥5% of Subjects in Any Treatment Group), On-Therapy Period (Excluding Taper), Safety Population

Body System Adverse Event	Placebo n=161	DVS SR 50 mg n=166	DVS SR 100 mg n=158
Any adverse event	99 (61.5)	129 (77.7)	122 (77.2)
Body as a whole			
Abdominal pain	10 (6.2)	11 (6.6)	12 (7.6)
Asthenia	8 (5.0)	15 (9.0)	16 (10.1)
Back pain	10 (6.2)	6 (3.6)	6 (3.8)
Headache	28 (17.4)	35 (21.1)	39 (24.7)
Infection	9 (5.6)	5 (3.0)	10 (6.3)
Digestive			
Anorexia	2 (1.2)	9 (5.4)	9 (5.7)
Constipation	7 (4.3)	13 (7.8)	8 (5.1)
Diarrhea	12 (7.5)	11 (6.6)	8 (5.1)
Dry mouth	15 (9.3)	21 (12.7)	27 (17.1)
Nausea	17 (10.6)	44 (26.5)	48 (30.4)
Nervous			
Anxiety	5 (3.1)	4 (2.4)	11 (7.0)
Dizziness	6 (3.7)	17 (10.2)	11 (7.0)
Insomnia	8 (5.0)	16 (9.6)	16 (10.1)
Somnolence	5 (3.1)	8 (4.8)	13 (8.2)
Skin and appendages			
Sweating	11 (6.8)	20 (12.0)	21 (13.3)
Urogenital			
Abnormal ejaculation/orgasm[a]	0	0	4 (8.7)

Non SAE and SAE results are not separated out.
DVS SR = desvenlafaxine sustained release; n = number of subjects; SAE = serious adverse event.
a. Percentage based on the number of men in each treatment group: placebo (n=52); DVS SR 50 mg (n=50); and DVS SR 100 mg (n=46).

Table 18. Number (%) of Subjects Who Reported Taper/Poststudy-Emergent Adverse Events (Incidence ≥5% of Subjects in Any Treatment Group), Safety Population

Body System Adverse Event	Placebo n=161	DVS SR 50 mg n=166	DVS SR 100 mg n=158
Any adverse event	33 (20.5)	74 (44.6)	64 (40.5)
Body as a whole			
Headache	10 (6.2)	11 (6.6)	11 (7.0)
Digestive			
Nausea	4 (2.5)	19 (11.4)	15 (9.5)
Nervous			
Depression	1 (0.6)	5 (3.0)	8 (5.1)
Dizziness	4 (2.5)	22 (13.3)	15 (9.5)
Insomnia	3 (1.9)	10 (6.0)	7 (4.4)
Vertigo	0	4 (2.4)	8 (5.1)

Non SAE and SAE results are not separated out.
DVS SR = desvenlafaxine sustained release; n = number of subjects; SAE = serious adverse event.

Table 19. Number (%) of Subjects Reporting Treatment-Related Treatment-Emergent Adverse Events (Incidence ≥5% of Subjects in Any Treatment Group), On-Therapy Period (Excluding Taper), Safety Population

Body System[a] Adverse Event	Placebo n=161	DVS SR 50 mg n=166	DVS SR 100 mg n=158
Any adverse event	57 (35.4)	99 (59.6)	100 (63.3)
Body as a whole	25 (15.5)	32 (19.3)	36 (22.8)
Asthenia	5 (3.1)	10 (6.0)	12 (7.6)
Headache	15 (9.3)	22 (13.3)	25 (15.8)
Digestive system	32 (19.9)	69 (41.6)	76 (48.1)
Anorexia	2 (1.2)	7 (4.2)	9 (5.7)
Constipation	4 (2.5)	13 (7.8)	7 (4.4)
Dry mouth	15 (9.3)	21 (12.7)	27 (17.1)
Nausea	14 (8.7)	43 (25.9)	42 (26.6)
Nervous system	23 (14.3)	52 (31.3)	54 (34.2)
Anxiety	2 (1.2)	3 (1.8)	9 (5.7)
Dizziness	6 (3.7)	16 (9.6)	10 (6.3)
Insomnia	5 (3.1)	14 (8.4)	14 (8.9)
Somnolence	4 (2.5)	8 (4.8)	13 (8.2)
Skin and appendages	15 (9.3)	20 (12.0)	24 (15.2)
Sweating	9 (5.6)	18 (10.8)	19 (12.0)

Non SAE and SAE results are not separated out.
DVS SR = desvenlafaxine sustained release; n = number of subjects; SAE = serious adverse event.
a. Body system totals are not necessarily the sum of the individual adverse events since a subject may have reported ≥2 different adverse events in the same body system.

AEs of clinical importance were reported by 35 subjects (7% of the safety population) during the on-therapy or poststudy periods: 10 in the placebo group, 15 in the DVS SR 50-mg group, and 10 in the DVS SR 100-mg group. The majority of these events were changes in blood pressure or episodes of irritability-like AEs that occurred during the taper and poststudy periods. One (1) subject in the DVS SR 100-mg group was withdrawn from the study due to an AE of clinical importance (uncontrolled mouth/tongue movements [abnormal/changed behavior]).

AEs led to discontinuation of treatment for 24 (4.9%) of the 485 subjects in the safety population. Table 20 summarizes the AEs that led to discontinuation of treatment during the on-therapy period.

Table 20. Number (%) of Subjects Reporting Adverse Events That Caused Discontinuation During the On-Therapy Period

Body System[a] Adverse Event	Placebo n=161	DVS SR 50 mg n=166	DVS SR 100 mg n=158
Any adverse event	5 (3.1)	8 (4.8)	11 (7.0)
Body as a whole			
Abdominal pain	1 (0.6)	1 (0.6)	0
Asthenia	0	0	2 (1.3)
Back pain	1 (0.6)	0	0
Headache	1 (0.6)	1 (0.6)	2 (1.3)
Pain	1 (0.6)	0	0
Cardiovascular			
Bradycardia	0	1 (0.6)	0
Hypertension	1 (0.6)	0	1 (0.6)
Palpitation	1 (0.6)	0	0
Digestive			
Anorexia	0	1 (0.6)	0
Constipation	0	1 (0.6)	0
Diarrhea	0	1 (0.6)	0
Dyspepsia	1 (0.6)	0	0
Gastritis	0	1 (0.6)	0
Nausea	1 (0.6)	2 (1.2)	6 (3.8)
Nausea and vomiting	0	0	1 (0.6)
Vomiting	0	2 (1.2)	1 (0.6)
Musculoskeletal			
Muscle cramp	0	1 (0.6)	0
Musculoskeletal stiffness	0	0	1 (0.6)
Nervous			
Abnormal/changed behavior	0	0	1 (0.6)
Anxiety	0	0	1 (0.6)
Depersonalization	0	0	1 (0.6)
Dizziness	0	1 (0.6)	1 (0.6)
Hostility	0	1 (0.6)	0
Insomnia	0	0	1 (0.6)
Nervousness	0	1 (0.6)	0
Neuropathy	1 (0.6)	0	0
Paresthesia	0	0	1 (0.6)
Somnolence	0	1 (0.6)	1 (0.6)
Suicidal ideation	0	1 (0.6)	0
Vertigo	0	0	1 (0.6)
Skin and appendages			
Sweating	0	2 (1.2)	1 (0.6)
Special senses			
Ear pain	1 (0.6)	0	0
Urogenital			
Anorgasmia[b]	0	0	1 (2.1)
Oliguria	0	1 (0.6)	0

DVS SR = desvenlafaxine sustained release; n = number of subjects.

a. The number of subjects who discontinued for "any adverse event" does not equal the number of adverse events listed because some subjects had multiple adverse events listed as reasons for discontinuation.

b. Percentage based on the number of men in each treatment group: placebo (n=52); DVS SR 50 mg (n=50); and DVS SR 100 mg (n=46).

No deaths occurred during this study and none were reported to Sponsor subsequently.

The DESS checklist was used to evaluate symptoms that first occurred, or that worsened, during the taper period (the 7-day period after the end of the double-blind treatment period). During the taper period, doses of DVS SR were tapered to 50 mg for subjects in the DVS SR 100-mg group, and to 0 for subjects in the DVS SR 50-mg group. Subjects did not receive study medication after the 7-day taper period. The results of the DESS analysis for completers are shown in Table 21. The DESS checklist was administered to 420 of the 423 subjects who had completed at least 53 days of on-therapy DVS SR treatment: 146 (99%) completers in the DVS SR 50-mg group, 128 (100%) completers in the DVS SR 100-mg group, and 146 (99%) completers in the placebo group.

Table 21. DESS Total Score - Comparison Between Treatment Groups (t-Test With Data From Completers)

Final On-Therapy DVS SR Dose, mg	Week	n	DESS Mean Score	Standard Deviation	p-Value vs Placebo[a]
0	End DB	146	0.63	1.67	
	Post-DB Week 1	142	0.86	2.01	
	Post-DB Week 2	135	0.62	1.41	
	Post-DB Week 3	8	1.00	1.69	
	Post-DB Week >3	1	0.00	.	
50	End DB	146	0.47	1.70	0.722
	Post-DB Week 1	145	2.14	3.64	0.001
	Post-DB Week 2	141	0.87	2.48	0.316
	Post-DB Week 3	10	0.70	0.95	0.663
100	End DB	128	0.56	1.47	0.722
	Post-DB Week 1	126	1.09	2.05	0.360
	Post-DB Week 2	118	1.36	2.72	0.017
	Post-DB Week 3	7	0.14	0.38	0.403

The definition of a completer for the DESS analysis is a subject who had ≥53 days of on-therapy study drug.
DB = double-blind (on-therapy); DESS = discontinuation-emergent signs and symptoms;
DVS SR = desvenlafaxine succinate sustained release; n = number of subjects; vs = versus.
a. False discovery rate adjusted p-value (from t-test).

Few subjects had blood chemistry, hematology, or lipid values that met the criteria for potential clinical importance.

Liver function test results considered of clinical importance by the medical monitor occurred in <1% of the 485 subjects in the safety population (1 subject in the placebo group and 1 subject in the DVS SR 50-mg group had elevated aspartate aminotransferase/serum glutamic oxaloacetic transaminase levels, and another subject in the DVS SR 50-mg group had elevated alanine aminotransferase/serum glutamic pyruvic transaminase levels). There were no cases of liver failure. Elevated lipid/triglyceride values considered of clinical importance by the medical monitor also occurred in <1% of the 485 subjects in the safety population (1 subject in the DVS SR 50-mg group had increased total cholesterol levels). Although 8.8% of the 432 subjects tested for urine protein had values of potential clinical importance, the medical monitor did not identify any subject with proteinuria of clinical importance.

Clinically important vital sign results considered of clinical importance by the medical monitor occurred in 4% of the 485 subjects in the safety population. Among DVS SR-treated subjects, 6 had elevations in supine systolic or diastolic BP, 6 had sustained hypertension,

2 had postural hypertension, 1 had weight loss, and 2 had weight gain. None of the subjects had changes in supine pulse rate considered clinically important by the medical monitor.

Significant ($p \leq 0.05$) mean increases from Baseline at the FOT evaluation were seen in the DVS SR 100-mg group significant ($p \leq 0.05$) mean increases from Baseline at the FOT evaluation were seen for supine systolic BP. For weight, both DVS SR groups showed significant ($p \leq 0.05$) mean decreases from Baseline throughout the study and at the FOT evaluation in comparison with a mean decreases for the placebo group.

Comparisons between treatment groups showed significant ($p \leq 0.05$) mean differences at the FOT evaluation between the DVS SR 50-mg group and the placebo group for weight. For the DVS SR 100-mg group in comparison with the placebo group, there were significant ($p \leq 0.05$) mean differences at the FOT evaluation for supine systolic BP and weight. There were no significant differences between treatment groups at the FOT evaluation for supine diastolic BP.

None of the subjects had ECGs findings considered clinically important by the medical monitor, and none of the subjects had AEs of clinical importance related to ECG results.

CONCLUSIONS:

The results of these analyses demonstrated the efficacy of DVS SR 50-mg and 100-mg doses for the treatment of MDD. The safety profile for DVS SR 50 mg/day and 100 mg/day was similar to that observed in short-term (up to 8 weeks) and long-term (from 6 months up to 12 months) DVS SR studies in which doses ranged up to 400 mg/day. No new safety findings were observed.