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

PROTOCOL NO.: 3151A1-3360-WW (B2061004)

PROTOCOL TITLE: A Multicenter, Double-Blind, Placebo-Controlled, Randomized Withdrawal, Parallel Group Study to Evaluate the Efficacy and Safety of 50 mg/day of DVS SR in Adult Outpatients With Major Depressive Disorder

Study Center: Eighty seven (87) centers took part in the study and randomized subjects to study treatments; 11 in Canada, 3 in Chile, 7 in Colombia, 4 in Croatia, 3 in Estonia, 7 in Finland, 6 in France, 3 in Latvia, 3 in Lithuania, 6 in Poland, 6 in Romania, 6 in Slovakia, 3 in South Africa, and 19 in the United States.

Study Initiation and Final Completion Dates: 16 June 2009 to 22 March 2011

Phase of Development: Phase 3

Study Objectives:

The primary objective was to compare the long-term efficacy and safety of treatment with desvenlafaxine succinate sustained-release (DVS SR) 50 mg/day versus placebo in major depressive disorder (MDD) subjects who have responded to and been stabilized on DVS SR, using a randomized withdrawal design. This comparison was to be based on time to relapse between DVS SR and placebo treatment groups.

The secondary objective was to assess the long-term response of subjects receiving 50 mg/day of DVS SR versus placebo through clinical global assessments, remission (Hamilton Psychiatric Rating Scale for Depression, 17-item [HAM-D_{17}] ≤7) and functional and quality of life outcomes.

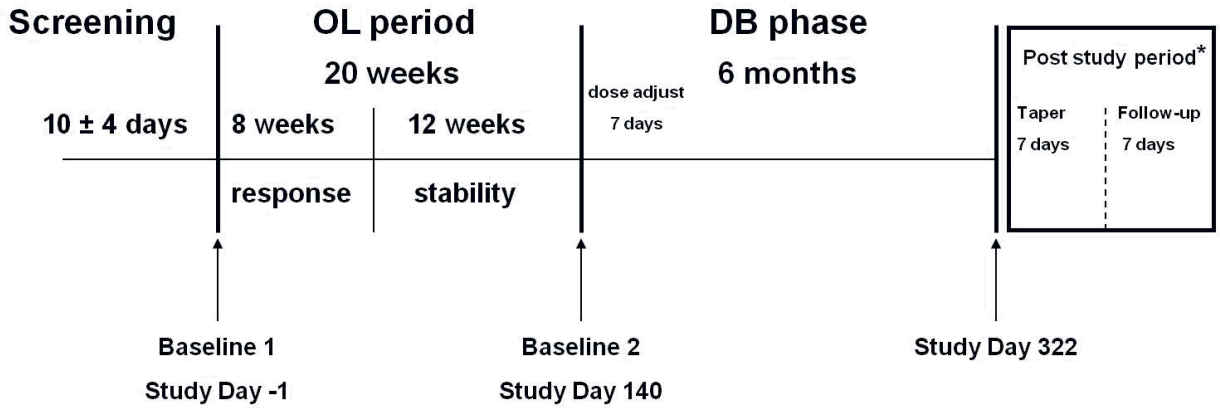
METHODS

Study Design: This was a Phase 3, multicenter, double-blind (DB), placebo-controlled, randomized withdrawal, parallel-group study in outpatients with MDD. The study consisted of a 10±4-day screening period, an open-label (OL) treatment period with 50 mg/day DVS SR (including an 8-week response phase and for responders at week 8, a 12-week stability phase), and for stable responders at Week 20, a 6-month, DB, placebo-controlled withdrawal phase, during which subjects were randomized (1:1 ratio) to treatment or treatment-withdrawal and thus received 50 mg/day of DVS SR or placebo (ie, treatment withdrawal). An overview of the study design is provided in Figure 1 and the study flowcharts for the open-label period and double

blind phase are summarized in Table 1 and Table 2, respectively. The study concluded with a 7-day taper-off and 7-day follow-up period.

Following enrollment on Day -1, subjects received 8 weeks of OL treatment with DVS SR, 50 mg/day. Subjects meeting response criteria, defined as achievement of a HAM-D_{17} total score of ≤11 and a Clinical Global Impressions – Improvement (CGI-I) score ≤2 at Week 8, could continue the OL treatment regimen for an additional 12-week stability phase. Subjects who did not demonstrate adequate response at Week 8 were discontinued from the study. At the conclusion of the stability phase, subjects who maintained a stable response (HAM-D_{17} total score of ≤11, and CGI-I score of ≤2 and did not have a HAM-D_{17} total score ≥16 or a CGI-I score ≥4 at any visit during the stability phase) were randomized to the 6-month, DB treatment phase.

Figure 1. Study Design



* Any subjects who completed the study or discontinued at anytime during the OL period or the DB phase were scheduled to enter into the taper/follow-up period.

DB = double-blind; OL = open-label.

Table 1. Study Flowchart (Open-Label Period)

Study Day	**(10±4 Days)[a]**	**-1[a]**	**7[a]**	**14[a]**	**21[a]**	**28[a]**	**42[a]**	**56[a,b]**	**84[a]**	**112[a]**	**140[a,b]**			
Study Interval			**OL Treatment**									**OL ET[c] and Follow-Up**		
	Screening	**Baseline**	**Response Phase**						**Stability Phase**			**OL ET[c]**	**OL ET Taper[d]**	**OL ET Follow-Up[d,e]**
Visit ID (for Sponsor use only)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**			
Informed consent	X													
Demographics	X													
Medical/psychiatric history[f]	X													
Prior/current substance usage[g]	X													
Modified Mini International Neuropsychiatric Interview	X													
DSM-IV-TR	X													
Eligibility assessment for open-label period	X	X												
Enroll in open-label period		X												
Open-label test article administration		X[h]	X	X	X	X	X	X	X	X				
Dosage record completion			X	X	X	X	X	X	X	X	X	X	X	
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Eligibility assessment to enter stability phase								X						
Eligibility assessment to enter double-blind phase											X			
Randomize to double-blind phase											X			

Table 1. Study Flowchart (Open-Label Period)

Study Day	**(10±4 Days)[a]**	**-1[a]**	**7[a]**	**14[a]**	**21[a]**	**28[a]**	**42[a]**	**56[a,b]**	**84[a]**	**112[a]**	**140[a,b]**			
Study Interval			**OL Treatment**									**OL ET[c] and Follow-Up**		
	Screening	**Baseline**	**Response Phase**						**Stability Phase**			**OL ET[c]**	**OL ET Taper[d]**	**OL ET Follow-Up[d,e]**
Visit ID (for Sponsor use only)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**			
Double-blind test article administration											X[i,j]			
ET taper test-article administration (if applicable)[k]								X			X	X		
Efficacy assessments:														
HAM-D_{17}	X	X	X	X	X	X	X	X	X	X	X	X		
CGI-S	X	X	X	X	X	X	X	X	X	X	X	X		
CGI-I[l]			X	X	X	X	X	X	X	X	X	X		
Health outcome assessments:														
WPAI		X						X			X	X		
WHO-5		X						X			X	X		
Safety assessments:														
Physical examination	X							X			X	X		
Vital signs/height[m]/ weight[n]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory determinations[o]	X							X		X[p]	X	X		
12-lead ECG[q]	X	X						X			X	X		
Adverse events[r]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS	X	X	X	X	X	X	X	X	X	X	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 C-SSRS = Columbia Suicide-Severity Rating Scale; DMS-IV-TR = Diagnostic and Statistical Manual of Mental Disorders, 4th Edition-Text Revision; DVS SR = desvenlafaxine succinate sustained-release; ECG = electrocardiogram; ET = Early Termination; HAM-D17 = Hamilton Psychiatric Rating Scale for Depression, 17 items; ID = identification; MINI = Mini International Neuropsychiatric Interview; OL = open-label; T_3 = triiodothyronine; T_4 = thyroxine; UDS = urine drug screen; WPAI = Work Productivity and Activity Impairment Questionnaire; WHO-5 = WHO 5-Item Well-being Index.

a. The screening period was 10±4 days from the Screening visit to the Baseline Visit. It was expected that this period was completed between 6 and 14 days;

Table 1. Study Flowchart (Open-Label Period)

however the period could be extended with approval from the Clinician or designee. Every effort was made to schedule the remaining study visits on the designated study days; however, office visits had a ± 3-day visit window to allow for slight variations in subject schedules.

b. For subjects who did not meet response criteria during assessment at the Study Day 56 Visit or stability criteria during assessment at the Study Day 140 Visit and was withdrawn, all procedures scheduled for that visit had to be completed. This served as an early termination visit for the OL period. Subjects had not been required to complete the additional OL ET visit outlined on the flowchart and was instead scheduled for the OL ET taper and OL ET follow-up visits. If for any reason a subject did not receive taper test article, the subject was still expected to complete the OL ET taper and OL ET follow-up visits.
c. For subjects who were enrolled but withdraw early, (at any point during the OL period except during the Study Day 56 or 140 Visits) the efficacy and safety determinations designated for the OL ET visit had to be obtained on the last day the subject took a full dose of test article (ie, before taper) or as soon as possible thereafter. If for any reason a subject had not received taper test article, the subject was still expected to complete the OL ET taper and OL ET follow-up visits.
d. OL ET taper and OL ET follow-up visits applied to the OL tapering and follow-up period for subjects who discontinued from the study prior to or were ineligible for randomization into the double-blind phase. Following randomization, the visit schedule for study flowchart (double-blind Phase) was followed.
e. The follow-up determinations were obtained for all subjects 7 days after the last dose of taper or the last dose of test article if taper was omitted, regardless of duration of treatment.
f. Medical history included recording method of contraception. Any changes in the method of contraception that occurred at any point after the Screening Visit had to be documented by completing a new method of contraception CRF from the unscheduled folder.
g. Prior and current substance usage records had to be completed. Prior usage was defined as use of a substance that was discontinued a year or more prior to the Screening Visit for the OL period. Current usage included any use of a substance within the past 12 months, regardless of whether or not the substance was in use at the time of Screening. Occasional use was defined as substance usage that occurred less than once a week.
h. Subjects had begun OL dose administration on Study Day 1.
i. Subjects had begun double-blind dose administration on Study Day 141.
j. Subjects randomized to receive placebo during the double-blind phase were dispensed one week of double-blind treatment with 25 mg/day of DVS SR on study Day 140 as a taper treatment. Placebo dispensation had begun on Study Day 147. Subjects randomized to receive DVS SR continued to be dispensed the 50 mg/day dose at this visit.
k. For those subjects who discontinued during the OL phase, taper test article was not dispensed if four or more consecutive doses of OL test article were missed prior to early termination, or to those who had taken test article for less than 14 days.
l. During the OL period, evaluation of improvement for the CGI-I assessment was based on comparison against Study Day -1 status.
m. Height was obtained at the Screening physical examination only.
n. Supine and standing pulse, supine and standing blood pressure.
o. Hematology, blood chemistry tests and urinalyses were done at Screening and on Study Days 56 and 140 or the OL ET Visit for the OL period. Thyroid stimulating hormone, total T4, T3 uptake and free thyroxine index, prolactin and serum β-HCG (for women of childbearing potential) were performed at the Screening Visit. Serum β-HCG (for women of childbearing potential) was also performed on Study Days 56 and 140 or the OL ET Visit. Prolactin was also performed on Study Day 140 or the OL ET Visit. A UDS for drugs of abuse was performed at screening, Day 56, Day 112, and Day 140 or the OL ET Visit. The Days 56, 112, and 140 or the OL ET Visit UDS did not contain an antidepressant screening. For subjects who continued into the 6-month double-blind phase of the study, see the double-blind phase flowchart for additional assessment time points.
p. Urine drug screen was the only laboratory assessment conducted at Study Day 112, Positive test results were discussed with the Clinician as these findings had an impact on continued participation in the study.
q. 12-lead ECG was performed at Screening, Baseline and on Study Days 56 and 140 or the OL ET Visit. For subjects who continued into the 6-month double

Table 1. Study Flowchart (Open-Label Period)

blind phase of the study, see the double-blind phase flowchart for ECG assessment time points. Procedure required that 3 separate 12-lead ECGs were recorded approximately 8 minutes apart over approximately a 15-20 minute period (only 1 ECG was recorded at Screening).

r. Adverse events were collected from the time informed consent was obtained.

Table 2. Study Flowchart (Double-Blind Phase)

Study Day	**147**[a]	**154**[a]	**161**[a]	**168**[a]	**182**[a]	**210**[a]	**238**[a]	**266**[a]	**294**[a]	**322**[a,b] / **ET**	**329**[a]	**336**[a]
Study Interval	**Double-Blind Treatment Phase**										**Taper**	**Follow-Up**[c]
Visit ID (for Sponsor use only)	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**[d]	**23**[d]
Dosage record completion	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Double-blind test article administration[e]	X	X	X	X	X	X	X	X	X			
Taper test article administration[f]										X		
Efficacy assessments**:**												
HAM-D_{17}	X	X	X	X	X	X	X	X	X	X		
CGI-S	X	X	X	X	X	X	X	X	X	X		
CGI-I[g]	X	X	X	X	X	X	X	X	X	X		
Health outcomes assessments:												
WPAI							X			X		
WHO-5							X			X		
Safety assessments:												
Physical examination							X			X		
Vital signs/weight[h]	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory determinations[i]							X			X		
12-lead ECG[j]							X			X		
Adverse events[k]	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X

Table 2. Study Flowchart (Double-Blind Phase)

β-HCG = beta-human chorionic gonadotropin; CGI-I = Clinical Global Impressions Scale-Improvement; CGI-S = Clinical Global Impressions Scale-Severity of Illness; C-SSRS = Columbia Suicide-Severity Rating Scale; ECG = electrocardiogram; ET = early termination; HAM-D17 = Hamilton Psychiatric Rating Scale for Depression, 17 items; MINI = Mini International Neuropsychiatric Interview; WPAI = Work Productivity and Activity Impairment Questionnaire; WHO-5 = WHO 5-Item Well-being Index.

a. Every effort was made to bring the subject back in the office on the designated study days; however, office visits had a ± 3-day visit window to allow for slight variations in subject schedules. The office visit window was extended to ± 7 days from Study Day 210 to Study Day 322.
b. For subjects who had withdrawn early, the efficacy and safety determinations designated for Day 322 was obtained on the last day the subject took a full dose of the test article (ie, before taper) or as soon as possible thereafter.
c. The follow-up determinations was obtained for all subjects 7 days after the last dose of taper or the last dose of test article if taper was omitted, regardless of duration of treatment.
d. Visit ID numbers 22 and 23 applied to the double-blind tapering and follow-up period for subjects who had completed the study or who had discontinued from the double-blind phase prior to completion.
e. Subjects had begun double-blind dose administration on Study Day 141.
f. For those subjects who discontinued during the double-blind phase, taper test article was not dispensed if four or more consecutive doses of double-blind test article were missed prior to early termination.
g. During the double-blind phase, evaluation of improvement for the CGI-I assessment was based on comparison against status at randomization to double-blind treatment (Study Day 140).
h. Supine and standing pulse, supine and standing blood pressure.
i. Hematology, blood chemistry tests and urinalyses were done on Study Day 238 and Day 322 or early termination including serum β-HCG (for women of childbearing potential) and prolactin. Subjects who had withdrawn prior to completion of the double-blind phase had laboratory assessments performed as indicated for Day 322.
j. A 12-lead ECG was performed on Study Days 238 and 322. Procedure required that 3 separate 12-lead ECG were recorded approximately 8 minutes apart over approximately a 15-20 minute period.
k. Adverse events were collected from the time informed consent was obtained.

Number of Subjects (Planned and Analyzed): It was planned to enroll approximately 850 subjects in this study at approximately 75 centers, to reach the sample size of 340 subjects (170 subjects per treatment arm). A total of 874 subjects were enrolled into the OL response phase of the study, 659 subjects entered the OL stability phase, and 548 subjects were randomized into the DB phase.

Diagnosis and Main Criteria for Inclusion: Male and female outpatients, 18 years or older with a primary diagnosis of MDD based on the criteria in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition, single or recurrent episode, without psychotic features. If other allowable psychiatric diagnoses were present, MDD must have been the predominant psychiatric disorder present. Other main criteria for inclusion included depressive symptoms for at least 30 days before the screening visit, a HAM-D_{17} total score ≥20 at the Screening and Baseline Visits, a score ≥2 on item 1 (depressed mood) of the HAM-D_{17} at the Screening and Baseline Visits, and a score ≥4 on the Clinical Global Impressions Scale-Severity (CGI-S) at the screening and Baseline visits. In addition, subjects could not be at significant risk of suicide based on clinical judgment including common suicidal thoughts, and suicide being considered as a possible solution, even without specific plans or intention. Subjects who had past treatment with DVS SR were also excluded from the study.

Main Criteria for Entry in Open Label Stability Phase: Response to treatment, as defined as a HAM-D_{17} total score of ≤11 at the conclusion of the 8-week OL response phase and a CGI-I score ≤2 at the conclusion of the 8-week OL response phase with continued consent to participate in the study.

Main Criteria for Entry in Double Blind Phase: Maintenance of stability, as defined as a HAM-D_{17} total score of ≤11 at the conclusion of the 12-week stability phase and CGI-I score ≤2 at the conclusion of the 12-week stability phase and absence of an assessed HAM-D_{17} total score of ≥16 or CGI-I score of ≥4 at any visit during the stability phase with continued consent to participate in the study.

Study Treatment: The study drug was supplied as 25 or 50 mg DVS SR tablets and matching placebo tablets. During the OL treatment phases (Day 1 to Day 140), 50 mg DVS SR was dispensed to all subjects in the form of 1 tablet/day. Subjects who discontinued from the study before or at the end of the OL period received 7 days of unblinded taper treatment with DVS SR 25 mg, 1 tablet/day. Taper study drug was not dispensed to subjects who received <14 days of OL study drug or if 4 or more consecutive doses of OL study drug were missed before completion or early termination. On Study Day 140, subjects were randomized to the DB period; subjects were assigned to either continue receiving 50 mg/day of DVS SR, or to receive a matching placebo for the remainder of the study (until study completion at 6 months, or until relapse). Subjects randomized to receive placebo during the DB phase were dispensed one week of DB treatment with 25 mg/day of DVS SR on Study Day 140 as a taper from OL treatment of DVS SR 50 mg. Placebo administration began on study Day 147. Subjects randomized to DVS SR continued to be dispensed the 50 mg/day dose. Subjects dispensed DVS SR 50 mg/day at any phase of the study who concluded or discontinued participation were dispensed DVS SR 25 mg tablets for a 7-day period of taper. The approximate duration of study was 29 months.

Efficacy Endpoints:

Primary Endpoint: Time to relapse following randomization to the DB phase. Criteria for relapse were defined as the occurrence of one or more of the following at any time during the DB phase: HAM-D_{17} total score ≥16, discontinuation for unsatisfactory response, including need for additional/alternate treatment for depression, investigator decision to remove from the study for efficacy reasons, failure to return if investigator determined it was related to efficacy, hospitalization for depression; suicide attempt, or suicide.

Secondary Endpoints: CGI-I as assessed from baseline of the DB phase through conclusion of subject participation, HAM-D_{17} total score, HAM-D_{17} remission assessment (defined as a total score ≤7), Hamilton Psychiatric Rating Scale for Depression, 6-item (HAM-D_6), and CGI-S.

Safety Evaluations: At specified time points, the following safety evaluations were done: monitoring of adverse events (AEs) and withdrawals due to AEs, concomitant medications, physical examinations, vital signs (supine and standing blood pressure [BP], supine and standing pulse rate, and body weight), laboratory determinations (hematology, blood chemistry, lipid profile, and urinalysis), beta-human chorionic gonadotropin , urine drug screen, 12-lead electrocardiograms (ECGs), and the Columbia Suicide-Severity Rating Scale (C-SSRS).

Other Assessment Methods: Self-administered health outcomes endpoints and health economics measures included the Work Productivity and Activity Impairment Questionnaire (WPAI) and the World Health Organization-5-Item Well-being Index (WHO-5).

Statistical Methods: The following populations were defined for analysis:

All-Enrolled Population: All subjects who were eligible to enter the OL period of the study after baseline evaluation and had been assigned treatment.

All-Randomized Population: All subjects randomly assigned to the DB treatment phase of the study.

Per-Protocol (PP) Population: All randomly assigned subjects in the DB treatment phase without a major protocol violation.

Efficacy Analysis:

The all-enrolled population was used for efficacy analyses in the OL period and the All-randomized population was used for efficacy analyses in the DB phase. A listing of subjects who met criteria for major protocol violations was documented in a PP violation memo before unblinding the data.

Summary descriptive statistics were provided for efficacy variables for both the OL period and the DB phase of the study, but hypothesis testing was performed for the DB phase only and was conducted at a 2-sided 5% level. The same analysis method used in the primary analysis was also applied to the PP population.

The primary analysis compared time to relapse in the DVS SR 50-mg treatment arm with that in the placebo treatment arm during the DB phase of the study using the log-rank test. Relapses that occurred after Study Day 325 (DB Day 185) were considered censored on DB Day 185. The Kaplan-Meier survival curve was provided as a graphic tool to display time to relapse in each arm. Two additional (sensitivity) analyses were conducted on the following variation of the primary endpoint using similar methods as in the primary analysis: one excluding the first 4 weeks of DB treatment and the other excluding the first 2 weeks of DB treatment. This was done to avoid potential confounding between drug taper (discontinuation) symptoms and relapse symptoms. As a sensitivity analysis, similar analyses to the primary analysis with respect to the relapse criterion based on HAM-D_{17} total score ≥16 alone were also performed.

The following secondary efficacy variables were analyzed during the DB phase using a mixed-effects model for repeated measures (MMRM): HAM-D_{17} total score, HAM-D_6, and CGI-S. The change from the DB Baseline in each of these variables was modeled with treatment, visit, treatment-by-visit interaction, and site as factors and the corresponding DB baseline score as a covariate. The remission status at each DB study visit (last observation carried forward [LOCF]) was analyzed using a logistic model with treatment and sites as factors and baseline HAM-D_{17} total score as covariate. CGI-I was descriptively summarized for all DB study visits by treatment arm.

The numbers and percentages of the subjects who completed the response phase of the OL period were summarized. The numbers and percentages (with respect to both the population rolling over from the response phase and the All-Enrolled population since Day –1) of the subjects who completed the stability phase was provided.

Cox regression model was applied as sensitivity analyses to determine which factors assisted in predicting relapse. The hazard function for relapse was modeled with treatment, treatment remission status (HAM-D_{17} total score ≤7) at the end of the OL period, and the interaction between these 2 factors. The model with main effects only was also fit in a post-hoc fashion. An additional Cox regression model with treatment, HAM-D_{17} total score at DB Baseline, age, sex, number of prior MDD episodes, and duration of current episode as the explanatory variables were investigated.

Safety Analysis:

Safety analyses were conducted on the all-enrolled population for the OL period and on the All-randomized population for the DB phase. All safety analyses on the All-randomized population were performed by treatment arm with respect to both the baseline of Day –1 and the DB baseline defined as the measurement at the Day 140 visit with the following exceptions:

- 12-lead ECG recordings: the average of the 3 separate recordings at each Baseline Visit (Day 1 for OL, and Day 140 for DB, respectively) were used as the baseline ECG value.
- The baseline assessment for BP for the OL period was the average of the second measurements per position of the screening period and at the visit on Day -1 and the baseline of BP for the DB phase was the second measurement per position at the visit on Day 140.

- The baseline assessment for supine pulse for the OL period was the average of the measurements of the screening period and at the visit on Day -1 and the baseline of supine pulse for the DB was the measurement at the visit on Day 140.

- The baseline form of C-SSRS was completed at the screening visit and the since last visit form was completed throughout the study (Day 140 was not a new baseline).

AEs recorded throughout the study were coded using the Medical Dictionary for Regulatory Activities (version 14.0). The number and percentage of subjects experiencing at least 1 AE were summarized overall and by system organ class and preferred term. In any given category, a subject was counted only once.

Treatment-emergent adverse events (TEAEs) were summarized for the OL and DB treatment periods. In the DB period, listings and summary tables were presented by treatment arms with respect to OL and DB Baseline. Taper/post-study emergent adverse events (TPEAEs) for the OL treatment period were presented. TPEAEs for the DB treatment phase were summarized by treatment arms.

Baselines for vital signs, laboratory parameters, and electrocardiograms were defined in the statistical analysis plan. With the exception of baseline values, if multiple observations fell in the same data analysis interval, the mean of the evaluations were used for the purposes of analysis, with the exception of BP, which used the second or the last measure instead of the mean of the evaluations. Orthostatic BP or pulse change was measured as the difference between the last supine and the first standing BP or pulse observations.

Listings and summary tables of descriptive statistics were produced for vital signs (supine and standing blood pressure, supine and standing pulse rate, and weight), laboratory evaluations, and 12-lead ECGs. Descriptive statistics were presented for the actual and change from Baseline to each time point. To test for significant changes over time of descriptive statistics, changes from Baseline to each time point were summarized and mean changes were analyzed using a paired t-test. The nominal 5% significance level without adjustment for multiple testing was used. Statistical comparisons were performed between treatment groups for the DB phase.

For each laboratory, vital sign, and ECG parameter, the proportion of subjects with at least 1 value of potential clinical importance (PCI) over the whole treatment period were summarized.

Listings for C-SSRS were produced. Summary tables were produced by treatment group and overall. Only summary statistics were provided without statistical comparisons since suicidal events were rare and a single study is not expected to provide sufficient number of events for meaningful statistical analysis, and for this study the common treatment in the OL period further confounded data interpretation.

Health Outcome Assessments:

Health-related assessments included the WHO-5 and the WPAI. The WPAI-derived scores and the WHO-5 total scores were analyzed in the same way as secondary continuous efficacy variables.

The WPAI measured the impact of disease on productivity and other activities. Six questions were used to derive 4 scores. Statistical analyses were performed for four derived scores: Absenteeism (work time missed); Presenteeism (impairment at work/reduced on-the-job effectiveness); Work productivity loss (overall work impairment/absenteeism plus presenteeism); and Activity impairment.

WPAI outcomes were expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, ie, worse outcomes.

The WHO-5 is a 5-item, self-administered questionnaire that assesses positive mood, vitality, and general interests during the past 2 weeks. Each item had a score ranging from 0 to 5. Response values were obtained by summing up all 5 individual scores (0 to 25), with higher scores indicating better well-being/quality of life.

RESULTS:

Subject Disposition and Demography: A total of 1072 subjects were screened for participation in the study. Among these, 195 subjects who had signed an ICF did not meet 1 or more eligibility requirements (screen failure subjects), and 3 subjects who met all eligibility requirements withdrew before enrollment. A total of 874 subjects were enrolled into the initial OL treatment period, 659 subjects entered the OL stability phase, and 548 subjects were randomized into the DB phase. A total of 386 subjects completed the DB period of the study. A summary of subject status is provided by treatment group and study phase in Table 3. Two (2) subjects were randomized in error and the randomization system would not allow them to be deleted.

Table 3. Summary of Subject Status: Number of Subjects by Population Subset

Population Category	DVS SR 50 mg OL	Placebo	DVS SR 50 mg DB	Total
Screening phase				
Signed the ICF				1072
Screen failures				195
Eligible but withdrawn[a]				3
OL phase				
Entered open-label[b]	874	NA	NA	874
Took at least one dose	866	NA	NA	866
No dose taken	8	NA	NA	8
Completed response phase	752	NA	NA	752
Entered the stability phase	659	NA	NA	659
Completed the stability phase	576	NA	NA	576
DB phase				
Randomized to DB[c]	NA	276	272	548
Took at least one dose	NA	272	270	542
No dose taken	NA	4	2	6
Efficacy PP population	NA	188	182	370
Completed DB	NA	176	210	386

DB = double-blind; DVS SR = desvenlafaxine succinate sustained-release; ICF = informed consent form; OL = open-label; PP = per protocol.

a. One (1) subject was withdrawn and re-screened when her screening period extended beyond 14 days, 1 subject was withdrawn after site was unable to obtain screening labs, and 1 subject was withdrawn when site met enrollment goal prior to subject enrolling.
b. This population was referred to as all-enrolled population and was a basis for the efficacy and safety analysis during the OL phase.
c. This population was referred to as all-randomized population and was a basis for the efficacy and safety analysis during the DB phase.

There were several discontinuations in this study. Table 4 summarizes number (%) of subjects who discontinued response phase of OL treatment - all-enrolled population.

Table 4. Number (%) of Subjects Who Discontinued Response Phase of Open-Label Treatment - All-Enrolled Population

Conclusion Status Reason[a]	Treatment
	DVS SR 50 mg OL N=874
Discontinued	122 (14.0)
Adverse event	46 (5.3)
Failed to return	6 (0.7)
Lack of efficacy	26 (3.0)
Lost to follow-up	16 (1.8)
Other	1 (0.1)
Protocol violation	12 (1.4)
Withdrawal by subject	15 (1.7)

DVS SR = desvenlafaxine succinate sustained-release; N = total number of subjects in treatment group; OL = open-label.

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

Table 5 summarizes number (%) of subjects who discontinued stability phase of OL treatment-all-enrolled population.

Table 5. Number (%) of Subjects Who Discontinued Stability Phase of Open-Label Treatment - All-Enrolled Population

	DVS SR 50 mg OL
Entered OL phase	874
Completed response phase	752
Entered stability phase	659 (100)
Total discontinued	83 (12.6)
Adverse event	22 (3.3)
Failed to return	3 (0.5)
Lack of efficacy	16 (2.4)
Lost to follow-up	9 (1.4)
Other	1 (0.2)
Protocol violation	13 (2.0)
Withdrawal by subject	19 (2.9)

DVS SR = desvenlafaxine succinate sustained-release; OL = open-label.

Table 6 summarizes number (%) of subjects who discontinued OL early termination taper-all-enrolled population.

Table 6. Number (%) of Subjects Who Discontinued Open-Label Early Termination Taper - All-Enrolled Population

	DVS SR 50 mg OL
Entered OL phase	874
Randomized to DB	548
Did not enter DB phase	326
Did not enter OL taper phase	21
Entered OL taper phase	307 (100)
Completed OL taper phase as planned	163 (53.1)
Discontinued OL taper phase	144 (46.9)
Adverse event	28 (9.1)
Failed to return	17 (5.5)
Investigator request	10 (3.3)
Lost to follow-up	8 (2.6)
Other	30 (9.8)
Protocol violation	3 (1.0)
Withdrawal by subject	48 (15.6)

Two subject were randomized in error and immediately entered the OL taper phase on the date of randomization. Therefore, these subjects are counted both in randomized to DB row and entered the OL taper phase.
DB = double-blind; DVS SR = desvenlafaxine succinate sustained-release; OL = open-label.

Table 7 summarizes the number of subjects who discontinued DB treatment by the reasons for withdrawal in each treatment group.

Table 7. Number (%) of Subjects Who Discontinued Double-Blind Treatment – All-Randomized Population

Conclusion Status Reason[a]	Treatment		
	Placebo n=276	DVS SR 50 mg DB n=272	Total N=548
Discontinued	100 (36.2)	62 (22.8)	162 (29.6)
Adverse event	7 (2.5)	2 (0.7)	9 (1.6)
Failed to return	2 (0.7)	2 (0.7)	4 (0.7)
Lack of efficacy	67 (24.3)	33 (12.1)	100 (18.2)
Lost to follow-up	8 (2.9)	8 (2.9)	16 (2.9)
Other	2 (0.7)	0	2 (0.4)
Protocol violation	8 (2.9)	5 (1.8)	13 (2.4)
Withdrawal by subject	6 (2.2)	12 (4.4)	18 (3.3)

DB = double-blind; DVS SR = desvenlafaxine succinate sustained-release; N = total number of subjects; n = number of subjects in the treatment group.
a. Total discontinued was the sum of individual reasons since they were mutually exclusive by subject.

Subjects who discontinued the DB taper/post-study period are shown in Table 8. This table does not address whether or not subjects took the full course of taper medication.

Table 8 Number (%) of Subjects Who Discontinued Taper/Post-Study After Double-Blind Treatment - All-Randomized Population

	Placebo (n=276)	DVS SR 50 mg DB (n=272)	Total (N=548)
Randomized to DB	276	272	548
Did not enter taper phase	9	7	16
Entered taper phase	267 (100)	265 (100)	532 (100)
Completed taper phase as planned	226 (84.6)	235 (88.7)	461 (86.7)
Discontinued taper phase	41 (15.4)	30 (11.3)	71 (13.3)
Adverse event	5 (1.9)	0	5 (0.9)
Failed to return	5 (1.9)	4 (1.5)	9 (1.7)
Investigator request	6 (2.2)	0	6 (1.1)
Lost to follow-up	2 (0.7)	2 (0.8)	4 (0.8)
Other	11 (4.1)	12 (4.5)	23 (4.3)
Protocol violation	4 (1.5)	1 (0.4)	5 (0.9)
Withdrawal by subject	8 (3.0)	11 (4.2)	19 (3.6)

DB=double-blind; DVS SR = desvenlafaxine succinate sustained-release; N = total number of subjects; n = number of subjects in each treatment group.

A total of 874 subjects enrolled in the OL response period of the study. The all-enrolled population was 69.6% female, 83.4% White, and the mean age of 44.98 years. The mean duration of the current depressive episode was 12.36 months (median 4.60 months). The mean HAM-D_{17} total score at Baseline was 24.21, and the CGI-S score at Baseline indicated that 56.8% of subjects were moderately ill, 38.7% were markedly ill, and 4.6% were severely ill (Table 9). Of the 874 subjects who entered the OL response phase, 659 subjects continued in the OL stability phase of the study. The OL stability phase subgroup of the all-enrolled population was 70.3% female, 85.7% White, and had a mean age of 45.59 years (Table 10). The mean baseline severity of MDD based on the HAM-D_{17} total score at OL Baseline was 24.32 for the placebo group and 23.93 for the DVS SR group (Table 11). At DB Baseline, the mean HAM-D_{17} total score had decreased to 4.58 in the placebo group and 4.69 in the DVS SR group, and

CGI-I ratings for the placebo group and DVS SR groups, respectively were very much improved 86.6% and 82.0%, and much improved 13.0% and 18.0%. The remission rate at DB Baseline was 83.3% in the placebo group and 80.9% in the DVS SR group (Table 11). The demographic and baseline characteristics in the PP population were well balanced across treatment groups.

Table 9. Demographic and Baseline Characteristics, Response Phase of Open-Label Period - All-Enrolled Population

Characteristic	Treatment
	DVS SR 50 mg OL N=874
Age (year)	
N	874
Mean (SD)	44.98 (13.25)
Min, max	18.00, 87.00
Median	46.00
Age group, n (%)	
18-64	811 (92.8)
≥65	63 (7.2)
Sex, n (%)	
Female	608 (69.6)
Male	266 (30.4)
Race, n (%)	
Asian	9 (1.0)
Black or African American	55 (6.3)
Other	81 (9.3)
White	729 (83.4)
Ethnic origin, n (%)	
Hispanic or Latino	143 (16.4)
Non-Hispanic and Non-Latino	731 (83.6)
Baseline height (cm)	
N	874
Mean (SD)	166.76 (9.45)
Min, max	139.70, 195.60
Median	165.10
Baseline weight (kg)	
N	874
Mean (SD)	77.23 (19.51)
Min, max	38.50, 178.40
Median	74.95
Body mass index (kg/m^2)	
N	874
Mean (SD)	27.74 (6.55)
Min, max	16.34, 56.49
Median	26.48
Duration of current episode (months)	
N	874
Mean (SD)	12.36 (30.17)
Min, max	1.00, 369.60
Median	4.60
Duration of current episode (months)	
<6	516 (59.0)
6-<12	167 (19.1)
12-<24	95 (10.9)
24-<60	62 (7.1)
60-<120	24 (2.7)
≥120	10 (1.1)

Table 9. Demographic and Baseline Characteristics, Response Phase of Open-Label Period - All-Enrolled Population

Characteristic	Treatment
	DVS SR 50 mg OL N=874
Number of previous episodes	
N	874
Mean (SD)	2.18 (4.39)
Min, max	0.00, 90.00
Median	1.00
HAM-D_{17} total score at OL Baseline	
N	874
Mean (SD)	24.21 (2.82)
Min, max	19.00, 35.00
Median	24.00
CGI-S, n (%) at OL Baseline	
(4) Moderately ill	496 (56.8)
(5) Markedly ill	338 (38.7)
(6) Severely ill	40 (4.6)

CGI-S = Clinical Global Impressions Scale-Severity of Illness; DVS SR = desvenlafaxine succinate sustained-release; HAM-D_{17} = Hamilton Rating Scale for Depression, 17-item; max = maximum; min = minimum; n = number of subjects with specified criteria; N = total number of subjects; OL = open-label; SD = standard deviation.

Table 10. Demographic and Baseline Characteristics, Stability Phase of Open-Label Period - All-Enrolled Population

Characteristic	Treatment
	DVS SR 50 mg OL N=659
Age (year)	
N	659
Mean (SD)	45.59 (13.20)
Min, max	18.00, 79.00
Median	47.00
Age group, n (%)	
18-64	607 (92.1)
≥65	52 (7.9)
Sex, n (%)	
Female	463 (70.3)
Male	196 (29.7)
Race, n (%)	
Asian	6 (0.9)
Black or African American	32 (4.9)
Other	56 (8.5)
White	565 (85.7)
Ethnic origin, n (%)	
Hispanic or Latino	109 (16.5)
Non-Hispanic and Non-Latino	550 (83.5)
Baseline height (cm)	
N	659
Mean (SD)	166.70 (9.40)
Min, max	139.70, 195.60
Median	166.00
Baseline weight (kg)	
N	659
Mean (SD)	77.20 (19.29)
Min, max	38.50, 178.40
Median	75.00
Body mass index (kg/m^2)	
N	659
Mean (SD)	27.74 (6.38)
Min, max,	16.34, 56.49
Median	26.57
Duration of current episode (months)	
N	659
Mean (SD)	11.95 (29.84)
Min, max	1.00, 367.70
Median	4.30
Duration of current episode (months)	
<6	402 (61.0)
6-<12	121 (18.4)
12-<24	69 (10.5)
24-<60	42 (6.4)
60-<120	17 (2.6)
≥120	8 (1.2)

Table 10. Demographic and Baseline Characteristics, Stability Phase of Open-Label Period - All-Enrolled Population

Characteristic	Treatment
	DVS SR 50 mg OL N=659
Number of previous episodes	
N	659
Mean (SD)	2.18 (4.66)
Min, max	0.00, 90.00
Median	1.00
HAM-D_{17} total score at OL Baseline	
N	659
Mean (SD)	24.16 (2.77)
Min, max	19.00, 33.00
Median	24.00
CGI-S, n (%) at OL Baseline	
(4) Moderately ill	371 (56.3)
(5) Markedly ill	253 (38.4)
(6) Severely ill	35 (5.3)

CGI-S = Clinical Global Impressions Scale-Severity of Illness; DVS SR = desvenlafaxine succinate sustained-release; HAM-D_{17} = Hamilton Rating Scale for Depression, 17-item; max = maximum; min = minimum; n = number of subjects with specified criteria; N = total number of subjects; OL = open-label; SD = standard deviation.

Table 11. Demographic and Baseline Characteristics, Double-Blind Period-All-Randomized Population

Characteristic	Treatment		
	Placebo N=276	DVS SR 50 mg DB N=272	Total N=548
Age (year)			
N	276	272	548
Mean (SD)	45.34 (12.98)	46.55 (12.99)	45.94 (12.99)
Min, max	18.00, 77.00	19.00, 73.00	18.00, 77.00
Median	45.00	48.00	47.00
Age group, n (%)			
18-64	255 (92.4)	248 (91.2)	503 (91.8)
≥65	21 (7.6)	24 (8.8)	45 (8.2)
Sex, n (%)			
Female	198 (71.7)	193 (71.0)	391 (71.4)
Male	78 (28.3)	79 (29.0)	157 (28.6)
Race, n (%)			
Asian	4 (1.4)	0	4 (0.7)
Black or African American	15 (5.4)	12 (4.4)	27 (4.9)
Other	27 (9.8)	20 (7.4)	47 (8.6)
White	230 (83.3)	240 (88.2)	470 (85.8)
Ethnic origin, n (%)			
Hispanic or Latino	42 (15.2)	48 (17.6)	90 (16.4)
Non-Hispanic and Non-Latino	234 (84.8)	224 (82.4)	458 (83.6)
Baseline height (cm)			
N	276	272	548
Mean (SD)	166.76 (9.77)	166.73 (9.02)	166.74 (9.40)
Min, max	143.00, 195.60	139.70, 190.50	139.70, 195.60
Median	165.00	167.00	166.00
Baseline weight (kg)			
N	276	272	548
Mean (SD)	78.27 (21.42)	76.02 (16.50)	77.15 (19.15)
Min, max	38.50, 178.40	45.00, 139.60	38.50, 178.40
Median	75.20	74.05	75.00
Body mass index (kg/m^2)			
N	276	272	548
Mean (SD)	28.08 (7.05)	27.33 (5.48)	27.70 (6.33)
Min, max	16.34, 56.49	17.06, 53.13	16.34, 56.49
Median	26.76	26.59	26.74
Duration of current episode (months)			
N	276	272	548
Mean (SD)	12.22 (34.87)	11.13 (26.54)	11.68 (30.99)
Min, max	1.00, 367.70	1.00, 356.30	1.00, 367.70
Median	4.05	4.05	4.05
Duration of current episode (months)			
<6	174 (63.0)	170 (62.5)	344 (62.8)
6-<12	49 (17.8)	45 (16.5)	94 (17.2)
12-<24	29 (10.5)	29 (10.7)	58 (10.6)
24-<60	13 (4.7)	20 (7.4)	33 (6.0)
60-<120	7 (2.5)	6 (2.2)	13 (2.4)
≥120	4 (1.4)	2 (0.7)	6 (1.1)

Table 11. Demographic and Baseline Characteristics, Double-Blind Period-All-Randomized Population

Characteristic	Treatment		
	Placebo N=276	DVS SR 50 mg DB N=272	Total N=548
Number of previous episodes			
N	276	272	548
Mean (SD)	1.95 (2.75)	2.30 (6.07)	2.12 (4.70)
Min, max	0.00, 20.00	0.00, 90.00	0.00, 90.00
Median	1.00	1.00	1.00
HAM-D_{17} total score at OL Baseline			
N	276	272	548
Mean (SD)	24.32 (2.79)	23.93 (2.63)	24.12 (2.71)
Min, max	20.00, 33.00	20.00, 32.00	20.00, 33.00
Median	24.00	23.00	24.00
CGI-S, n (%) at OL Baseline			
(4) Moderately ill	148 (53.6)	161 (59.2)	309 (56.4)
(5) Markedly ill	116 (42.0)	96 (35.3)	212 (38.7)
(6) Severely ill	12 (4.3)	15 (5.5)	27 (4.9)
HAM-D_{17} total score at DB Baseline			
N	276	272	548
Mean (SD)	4.58 (3.02)	4.69 (2.97)	4.64 (2.99)
Min, max	0.00, 20.00	0.00, 12.00	0.00, 20.00
Median	4.00	4.00	4.00
Remission at DB Baseline (HAM-D_{17} ≤7)			
No	46 (16.7)	52 (19.1)	98 (17.9)
Yes	230 (83.3)	220 (80.9)	450 (82.1)
CGI-I, n (%) at DB Baseline			
(1) Very much improved	239 (86.6)	223 (82.0)	462 (84.3)
(2) Much improved	36 (13.0)	49 (18.0)	85 (15.5)
(3) Minimally improved	1 (0.4)	0	1 (0.2)

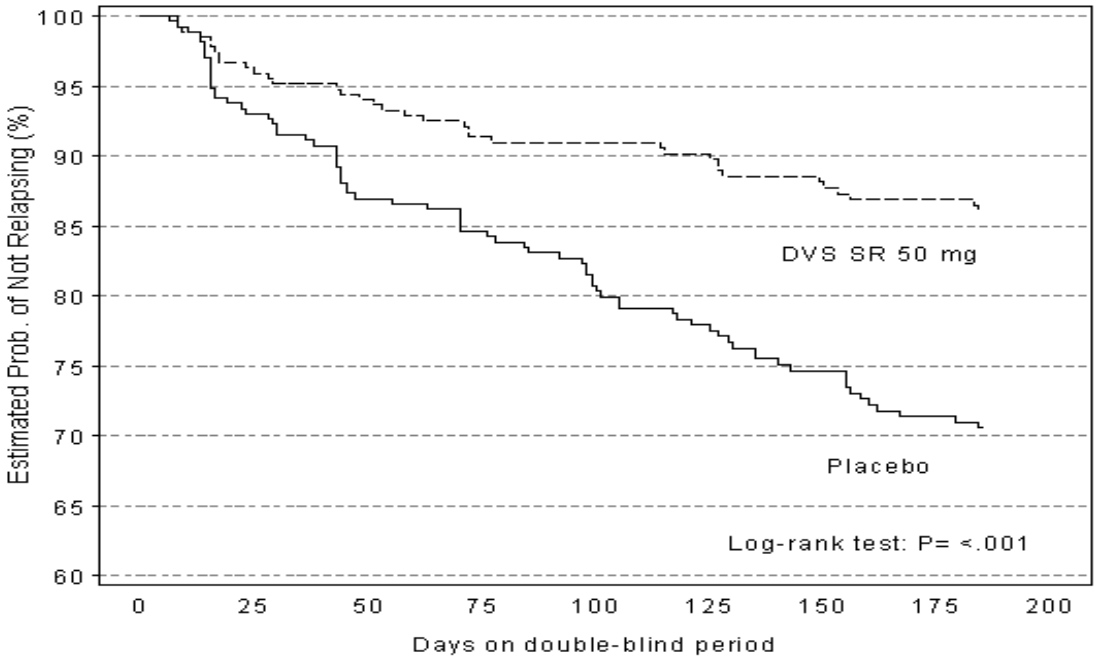
CGI-I = Clinical Global Impressions Scale-Improvement; CGI-S = Clinical Global Impressions Scale-Severity of Illness; DVS SR = desvenlafaxine succinate sustained-release; DB = double-blind; HAM-D_{17} = Hamilton Rating Scale for Depression, 17-item; max = maximum; min = minimum; n = number of subjects with specified criteria; N = total number of subjects; OL= open-label; SD = standard deviation.

Efficacy Results:

Primary Endpoints:

The primary efficacy endpoint was the time to relapse following randomization to the DB phase for subjects in the all-randomized population. In the primary analysis, subjects who received DVS SR treatment showed a significantly longer time to relapse compared to those who received placebo, (p-value of <0.001). The Kaplan-Meier survival curve by treatment group is shown in Figure 2. The survival curves started to separate at approximately Day 15, and the difference steadily increased until the end of DB treatment. The estimated probability of relapse at the end of 6 months of DB treatment was 14.3% for the DVS SR 50-mg group, compared with 30.2% for the placebo group (Table 12).

Figure 2. Kaplan-Meier Survival Curve for Relapse



No. at Risk

DVS SR 50 mg	272	247	233	214
Placebo	276	229	203	183

Subjects who relapsed after double-blind day 185 or completed the double-blind therapy without relapse were considered as censored on double-blind day 185.

Table 12. Survival Analysis of Time to Relapse as Days From Randomization - All-Randomized Population

	Placebo	DVS SR 50 mg DB	p-Value[a]
Total	276	272	
Number (%) of subjects relapsed	78 (28.3)	37 (13.6)	<0.001
Estimated probability (%) of relapse on Day 185	30.2	14.3	

Subjects who relapsed after double-blind Day 185 or completed the double-blind therapy without relapse were considered as censored on DB Day 185.
DB = double-blind; DVS SR = desvenlafaxine succinate sustained-release.
a. p-Value obtained from the log-rank test.

The reasons for relapse during the DB period are provided in Table 13. All relapses during the DB phase were due to the HAM-D_{17} total score ≥16 and/or discontinuation of treatment due to unsatisfactory efficacy, except for 1 case of hospitalization for depression in the placebo group.

Table 13. Criteria for Relapse, First Events per Subject - All-Randomized Population

	Placebo	DVS SR 50 mg DB
Total	276	272
All Relapsed	78 (28.3)	37 (13.6)
HAM-D_{17} total ≥16	60 (21.7)	34 (12.5)
Discontinuation for unsatisfactory efficacy	66 (23.9)	33 (12.1)
Hospitalization for depression	1 (0.4)	0
Suicide attempt	0	0
Suicide	0	0

Subjects may have more than 1 first event (reason for relapse), eg, HAM-D17 total ≥16 and discontinuation due to unsatisfactory efficacy if they occurred on the same day.
DB = double-blind; DVS SR = desvenlafaxine succinate sustained-release; HAM-D_{17} = Hamilton Rating Scale for Depression, 17-item.

Two sensitivity analyses were performed to avoid potential confounding between drug taper (discontinuation) and relapse symptoms via excluding the first 4 weeks and first 2 weeks of DB treatment. After eliminating the potential for confounding, treatment with DVS SR was still found to be superior to placebo with relapse rates approximately half of that of placebo across both analyses. The analysis based on HAM-D_{17} criteria alone showed similar results. The results of all sensitivity analyses were consistent with the primary analysis (Table 14).

Table 14. Analysis of Time to Relapse as Days From Randomization - All-Randomized Population

	Placebo	DVS SR 50 mg DB	p-Value[a]
Excluding first 4 weeks of DB treatment			
Total	246	255	
Number (%) relapsed	58 (23.6)	25 (9.8)	<0.001
Estimated probability (%) of relapse on Day 185	24.7	10.4	
Excluding first 2 weeks of DB treatment			
Total	265	266	
Number (%) relapsed	70 (26.4)	33 (12.4)	<0.001
Estimated probability (%) of relapse on Day 185	28.1	13.1	
Relapse criterion of HAM-D17 total ≥16 alone[b]			
Total	276	272	
Number (%) relapsed	60 (21.7)	34 (12.5)	0.0019
Estimated probability (%) of relapse on Day 185	24.2	13.3	

Subjects who had on-therapy evaluation after day 185 or completed the double-blind therapy were considered as censored on Day 185 - duration of exclusion, if applicable.
DB = double-blind; DVS SR = desvenlafaxine succinate sustained-release; HAM-D_{17}; = Hamilton Rating Scale for Depression, 17-item.
a. p-Value was obtained from the log-rank test.
b. Subjects who relapsed due to other criteria were considered as censored on the day of relapse.

Several Cox regression models were applied as sensitivity analyses to determine which factors assist in predicting relapse. The results are shown in Table 15.

Table 15. Analysis of Relapse Using Cox Regression - All-Randomized Population

Model/Effect	Interpretation	Log HR Estimate (SE)	p-Value	Estimated HR
Model 1				
Treatment	DVS SR/Placebo	-0.410 (0.374)	0.2725	0.664
Remission status[a]	Yes/No	-0.356 (0.281)	0.2050	0.701
Treatment by remission status interaction	DVS SR and Remission	-0.604 (0.444)	0.1739	0.547
Model 1A				
Treatment	DVS SR/Placebo	-0.846 (0.200)	<0.001	0.429
Remission status[a]	Yes/No	-0.578 (0.215)	0.0072	0.561
Model 2				
Treatment	DVS SR/Placebo	-0.859 (0.201)	<0.001	0.424
HAM-D_{17} total at DB Baseline	Per 1 unit increase	0.080 (0.032)	0.0136	1.083
Age	Per 10 year increase	-0.007 (0.073)	0.9286	0.993
Sex	Female/Male	-0.092 (0.207)	0.6562	0.912
No. of prior MDD episodes	Per 1 unit increase	0.061 (0.014)	<0.001	1.062
Duration of current episodes	Per log (months) increase	0.040 (0.087)	0.6435	1.041

DB = double-blind; DVS SR = desvenlafaxine succinate sustained-release; HAM-D_{17} = Hamilton Rating Scale for Depression, 17-item; HR = hazard ratio; MDD = major depressive disorder; OL = open-label; SE = standard error.

a. Defined as HAM-D_{17} Total ≤7 at the end of OL period (DB baseline).

Time to relapse for subjects in the PP population (all randomly assigned subjects in the DB phase without a major protocol violation) is shown in Table 16. As in the all-randomized population, subjects in the PP population who received DVS SR showed a significantly longer time to relapse compared to those who received placebo (p-value of 0.0108).

Table 16. Survival Analysis of Time to Relapse as Days From Randomization - Per-Protocol Population

	Placebo	DVS SR 50 mg DB	p-Value[a]
Total	188	182	
Number (%) of subjects relapsed	47 (25.0)	26 (14.3)	0.0108
Estimated probability (%) of relapse on Day 185	25.8	14.7	

Subjects who relapsed after double-blind Day 185 or completed the double-blind therapy without relapse were considered as censored on double-blind Day 185.
DB = double-blind; DVS SR = desvenlafaxine succinate sustained-release.

a. p-Value is obtained from the log-rank test.

Secondary Endpoints:

Results of the HAM-D_{17} total scores among the all-enrolled population during the OL response phase are provided in Table 17. At Week 8 the LOCF analysis showed an improvement from Baseline in depression symptoms with a mean score of 9.29 compared to a baseline score of 24.21.

Table 17. Descriptive Summary of HAM-D_{17} Total Score, Response Phase, Open-Label Period - All-Enrolled Population

Week of Therapy	N	Mean (SD)	Change From Baseline Mean (SD)
LOCF			
Baseline OL	874	24.21 (2.82)	
Week 1 OL	851	20.63 (4.73)	-3.59 (4.16)
Week 2 OL	864	16.95 (5.70)	-7.26 (5.53)
Week 3 OL	866	14.31 (6.07)	-9.90 (6.10)
Week 4 OL	866	12.44 (6.27)	-11.77 (6.38)
Week 6 OL	866	10.58 (6.29)	-13.63 (6.59)
Week 8 OL	866	9.29 (6.42)	-14.92 (6.68)
Observed cases			
Baseline OL	874	24.21 (2.82)	
Week 1 OL	851	20.63 (4.73)	-3.59 (4.16)
Week 2 OL	824	16.79 (5.70)	-7.43 (5.53)
Week 3 OL	817	14.05 (5.94)	-10.19 (5.93)
Week 4 OL	806	11.85 (5.88)	-12.33 (6.04)
Week 6 OL	786	9.66 (5.47)	-14.55 (5.86)
Week 8 OL	753	7.88 (4.99)	-16.33 (5.38)

HAM-D_{17} = Hamilton Rating Scale for Depression, 17-item; LOCF = last observation carried forward; OL = open-label; SD = standard deviation.

Results of the HAM-D_{17} total score among the all-enrolled population who entered the OL stability phase are provided in Table 18. During the stability phase, the mean HAM-D_{17} total scores (LOCF) maintained the effect achieved in the response phase, ranging from 5.6 to 6.5.

Table 18. Descriptive Summary of HAM-D_{17} Total Score, Stability Phase Open-Label Period - All-Enrolled Population

Week of Therapy	N	Mean (SD)	Change From Baseline Mean (SD)
LOCF			
Baseline OL[a]	659	24.16 (2.77)	
Week 8 OL[b]	659	6.49 (3.01)	-17.68 (3.84)
Week 12 OL	659	5.93 (3.83)	-18.23 (4.58)
Week 16 OL	659	5.62 (4.12)	-18.55 (4.68)
Week 20 OL	659	5.60 (4.46)	-18.56 (5.03)
Observed cases			
Baseline OL[a]	659	24.16 (2.77)	
Week 8 OL[b]	659	6.49 (3.01)	-17.68 (3.84)
Week 12 OL	647	5.90 (3.81)	-18.27 (4.56)
Week 16 OL	611	5.27 (3.69)	-18.88 (4.37)
Week 20 OL	584	4.96 (3.65)	-19.22 (4.38)

HAM-D_{17} = Hamilton Rating Scale for Depression, 17-item; LOCF = last observation carried forward; OL = open-label; SD = standard deviation.
a. Baseline of open-label period, Study Day -1.
b. End of response phase/ start of stability phase.

Table 19 presents the Week 26 HAM-D_{17} results for the all-randomized population. The adjusted mean change from DB Baseline in the HAM-D_{17} total score was 3.12 in the placebo group and 0.77 in the DVS SR 50-mg group. The resulting adjusted mean difference (95%

confidence interval [CI]) versus placebo was 2.35 (1.39, 3.32). The adjusted difference between the DVS SR 50-mg group and placebo was statistically significant (p<0.001).

Table 19. Comparison of Changes From Baseline for HAM-D_{17} Total Score Using MMRM at Double-Blind Week 26 Double-Blind Period - All-Randomized Population

Week of Therapy	Therapy Group	N	Raw Mean	Adj. Mean[a]	Adj. Mean Change (SE)	Adj. Difference From Placebo Mean (95% CI)	p-Value[b]
Baseline at Randomization	Placebo	276	4.58				
	DVS SR 50 mg DB	272	4.69				
Week 26 DB	Placebo	174	5.21	7.66	3.12 (0.36)		
	DVS SR 50 mg DB	210	4.24	5.31	0.77 (0.34)	2.35 (1.39, 3.32)	<0.001

Adj. = adjusted; CI = confidence interval; DB = double-blind; DVS SR = desvenlafaxine succinate sustained-release; HAM-D_{17} = Hamilton Rating Scale for Depression, 17-item; MMRM = mixed-effects model for repeated measures; SE = standard error.
a. Adjusted mean = the adjusted mean change + overall baseline mean.
b. p-Value obtained from mixed model: change from Baseline = baseline + site + treatment + visit + treatment × visit with 'Unstructured' covariance structure.

Subjects with a HAM-D_{17} score ≤7 were considered to be in remission. A summary of remission rates during the OL response phase in the all-enrolled population is provided in Table 20. At the end of the OL response phase, 46.8% of subjects (LOCF) were considered to be in remission.

Table 20. Descriptive Summary of HAM-D_{17} Remissions Rates Response Phase Open-Label Period All-Enrolled Population

Week of Therapy	Proportions of Remissions
LOCF	
Week 1 OL	5/851 (0.6%)
Week 2 OL	62/864 (7.2%)
Week 3 OL	123/866 (14.2%)
Week 4 OL	204/866 (23.6%)
Week 6 OL	301/866 (34.8%)
Week 8 OL	405/866 (46.8%)
Observed cases	
Week 1 OL	5/851 (0.6%)
Week 2 OL	62/824 (7.5%)
Week 3 OL	119/817 (14.6%)
Week 4 OL	202/806 (25.1%)
Week 6 OL	296/786 (37.7%)
Week 8 OL	397/753 (52.7%)

Remission on HAM-D_{17} was defined as a HAM-D_{17} score ≤7.
HAM-D_{17} = Hamilton Rating Scale for Depression, 17-item; LOCF = last observation carried forward; OL = open-label.

Remission rates during the OL stability phase among the all-enrolled population who entered the stability phase are provided in Table 21. By the end of the OL stability phase, HAM-D_{17}

remission rates had increased from 59.6% at Week 8 to 75.9% at Week 20 of treatment with DVS SR (LOCF).

Table 21. Descriptive Summary of HAM-D_{17} Remissions Rates Stability Phase Open-Label Period - All-Enrolled Population

Week of Therapy	Proportions of Remissions
LOCF	
Week 8 OL[a]	393/659 (59.6%)
Week 12 OL	470/659 (71.3%)
Week 16 OL	498/659 (75.6%)
Week 20 OL	500/659 (75.9%)
Observed cases	
Week 8 OL[a]	393/659 (59.6%)
Week 12 OL	464/647 (71.7%)
Week 16 OL	478/611 (78.2%)
Week 20 OL	466/584 (79.8%)

HAM-D_{17} = Hamilton Rating Scale for Depression 17-item; LOC F= last observation carried forward; OL = open-label.
a. End of response phase/start of stability phase.

The results of the logistic regression analysis of HAM-D_{17} remission rates among the all-randomized population using LOCF and OC data at DB Week 26 are shown in Table 22. At the end of the DB period (LOCF), the proportion of subjects in remission was 74.4% for the DVS SR 50-mg group and 54.2% for the placebo group ($p<0.0001$), showing rates of remission comparable with DB baseline for the DVS SR group, but lower rates for subjects who switched to placebo.

Table 22. Analysis of HAM-D_{17} Remissions Rates at Double-Blind Week 26 – All-Randomized Population

Week of Therapy	Therapy Group	Proportions of Remissions	Adj. Odds Ratio	Wald 95% CI for Adj Odds Ratio	p-Value[a]
LOCF					
Week 26 DB	Placebo	148/273 (54.2%)			
	DVS SR 50 mg DB	201/270 (74.4%)	2.85	(1.93, 4.20)	<0.0001
Observed cases					
Week 26 DB	Placebo	127/174 (73.0%)			
	DVS SR 50 mg DB	174/210 (82.9%)	2.00	(1.17, 3.45)	0.0120

Remission on HAM-D_{17} is defined as a HAM-D_{17} score ≤7.
Adj = adjusted; CI = confidence interval; DB = double-blind; DVS SR = desvenlafaxine succinate sustained-release; HAM-D_{17} = Hamilton Rating Scale for Depression, 17-item; LOCF = last observation carried forward.
a. Obtained from logistic regression analysis using Remission (Y/N) at each time point as a response variable, and treatment and country as factors, and the baseline HAM-D_{17} score as a covariate.

HAM-D_6 scores for the all-enrolled population using LOCF and OC data at each scheduled evaluation in the OL response phase are provided in Table 23. Mean HAM-D_6 scores decreased in both LOCF and OC at each visit through Week 8. Mean scores decreased from a baseline score of 12.83 to a score of 4.77 at Week 8 (change from baseline: -8.06) (LOCF).

Table 23. Descriptive Summary of HAM-D_6 Total Score Response Phase Open-Label Period – All-Enrolled Population

Week of Therapy	N	Mean Score (SD)	Change From Baseline Mean (SD)
LOCF			
Baseline OL	874	12.83 (1.63)	
Week 1 OL	851	10.85 (2.72)	-1.98 (2.45)
Week 2 OL	864	8.96 (3.35)	-3.86 (3.29)
Week 3 OL	866	7.56 (3.54)	-5.27 (3.55)
Week 4 OL	866	6.52 (3.58)	-6.31 (3.64)
Week 6 OL	866	5.53 (3.63)	-7.30 (3.79)
Week 8 OL	866	4.77 (3.64)	-8.06 (3.81)
Observed cases			
Baseline OL	874	12.83 (1.63)	
Week 1 OL	851	10.85 (2.72)	-1.98 (2.45)
Week 2 OL	824	8.87 (3.34)	-3.96 (3.29)
Week 3 OL	817	7.43 (3.47)	-5.41 (3.45)
Week 4 OL	806	6.23 (3.43)	-6.60 (3.49)
Week 6 OL	786	5.04 (3.26)	-7.78 (3.46)
Week 8 OL	753	4.03 (2.95)	-8.79 (3.17)

HAM-D_6 = Hamilton Rating Scale for Depression, 6-item; LOCF = last observation carried forward; OL = open-label; SD = standard deviation.

Results of the HAM-D_6 scores among the all-enrolled population who entered the OL stability phase are provided in Table 24. During the OL stability phase, the mean HAM-D_6 total scores maintained the effect achieved in the response phase, ranging from 3.29 at Week 8 to 2.85 at Week 20 (LOCF).

Table 24. Descriptive Summary of HAM-D_6 Total Score Stability Phase Open-Label Period - All-Enrolled Population

Week of Therapy	N	Mean Score (SD)	Change From Baseline Mean (SD)
LOCF			
Baseline OL[a]	659	12.80 (1.62)	
Week 8 OL[b]	659	3.29 (2.03)	-9.51 (2.45)
Week 12 OL	659	3.04 (2.40)	-9.76 (2.72)
Week 16 OL	659	2.83 (2.59)	-9.97 (2.91)
Week 20 OL	659	2.85 (2.70)	-9.95 (2.97)
Observed cases			
Baseline OL[a]	659	12.80 (1.62)	
Week 8 OL[b]	659	3.29 (2.03)	-9.51 (2.45)
Week 12 OL	647	3.02 (2.38)	-9.78 (2.71)
Week 16 OL	611	2.65 (2.38)	-10.12 (2.72)
Week 20 OL	584	2.52 (2.25)	-10.28 (2.58)

HAM-D_6 = Hamilton Rating Scale for Depression, 6-item; LOCF = last observation carried forward; OL = open-label; SD = standard deviation.
a. Baseline of open-label period, Study Day -1.
b. End of response phase/ start of stability phase.

A comparison of changes from DB Baseline in HAM-D_6 total score at Week 26 using MMRM is shown in Table 25. The adjusted mean change from DB Baseline in the HAM-D_6 total score at Week 26 by MMRM was 1.53 in the placebo group and 0.26 in the DVS SR 50-mg group. The resulting adjusted mean difference (95% CI) versus placebo was 1.27 (0.75, 1.79; p<0.001).

Table 25. Comparison of Changes From Baseline for HAM-D_6 Total Score Using MMRM at Double-Blind Week 26 Double-Blind Period - All-Randomized Population

						Adj. Difference From Placebo	
Week of Therapy	Therapy Group	N	Raw Mean	Adj. Mean[a]	Adj Mean Change (SE)	Mean (95% CI)	p-Value[b]
Baseline at Randomization	Placebo	276	2.24				
	DVS SR 50 mg DB	272	2.46				
Week 26 DB	Placebo	174	2.60	3.79	1.53 (0.20)		
	DVS SR 50 mg DB	210	2.09	2.52	0.26 (0.19)	1.27(0.75, 1.79)	<0.001

Adj. = adjusted; CI = confidence interval; DB = double-blind; DVS SR = desvenlafaxine succinate sustained-release; HAM-D_6 = Hamilton Rating Scale for Depression, 6-item; MMRM = mixed-effects model for repeated measures; SE = standard error.
a. Adjusted mean = the adjusted mean change + overall baseline mean.
b. p-value obtained from mixed model: change from Baseline = baseline + site + treatment + visit + treatment × visit with 'Unstructured' covariance structure.

A descriptive summary of CGI-I scores at each scheduled evaluation during the OL response phase are provided in Table 26.

Table 26. Descriptive Summary of CGI-I Scores Response Phase Open-Label Period - All-Enrolled Population

Week of Therapy	Total	1 n (%)	2 n (%)	3 n (%)	4 n (%)	5 n (%)	6 n (%)	7 n (%)
LOCF								
Week 1 OL	849	15 (1.8)	90 (10.6)	302 (35.6)	428 (50.4)	13 (1.5)	1 (0.1)	0
Week 2 OL	864	78 (9.0)	221 (25.6)	349 (40.4)	204 (23.6)	12 (1.4)	0	0
Week 3 OL	866	163 (18.8)	327 (37.8)	248 (28.6)	114 (13.2)	10 (1.2)	4 (0.5)	0
Week 4 OL	866	251 (29.0)	351 (40.5)	167 (19.3)	79 (9.1)	14 (1.6)	4 (0.5)	0
Week 6 OL	866	347 (40.1)	328 (37.9)	111 (12.8)	61 (7.0)	15 (1.7)	4 (0.5)	0
Week 8 OL	866	476 (55.0)	240 (27.7)	73 (8.4)	55 (6.4)	16 (1.8)	6 (0.7)	0
Observed cases								
Week 1 OL	849	15 (1.8)	90 (10.6)	302 (35.6)	428 (50.4)	13 (1.5)	1 (0.1)	0
Week 2 OL	824	77 (9.3)	217 (26.3)	337 (40.9)	183 (22.2)	10 (1.2)	0	0
Week 3 OL	817	158 (19.3)	321 (39.3)	238 (29.1)	91 (11.1)	5 (0.6)	4 (0.5)	0
Week 4 OL	806	247 (30.6)	344 (42.7)	152 (18.9)	56 (6.9)	6 (0.7)	1 (0.1)	0
Week 6 OL	786	341 (43.4)	315 (40.1)	93 (11.8)	30 (3.8)	6 (0.8)	1 (0.1)	0
Week 8 OL	753	465 (61.8)	220 (29.2)	43 (5.7)	19 (2.5)	3 (0.4)	3 (0.4)	0

CGI-I Scoring: 1= Very much improved; 2= Much improved; 3= Minimally improved; 4= No change; 5= Minimally worse; 6= Much worse; 7= Very much worse.
CGI-I = Clinical Global Impressions Scale-Improvement; LOCF = last observation carried forward; OL = open-label.

A descriptive summary of CGI-I scores among the all-enrolled population at each scheduled evaluation during the OL stability phase are provided in Table 27.

Table 27. Descriptive Summary of CGI-I Scores Stability Phase Open-Label Period - All-Enrolled Population

Week of Therapy	Total	1 n (%)	2 n (%)	3 n (%)	4 n (%)	5 n (%)	6 n (%)	7 n (%)
LOCF								
Week 8 OL[a]	659	460 (69.8)	198 (30.0)	0	1 (0.2)	0	0	0
Week 12 OL	659	503 (76.3)	132 (20.0)	23 (3.5)	1 (0.2)	0	0	0
Week 16 OL	659	514 (78.0)	115 (17.5)	25 (3.8)	4 (0.6)	1 (0.2)	0	0
Week 20 OL	659	511 (77.5)	106 (16.1)	33 (5.0)	8 (1.2)	1 (0.2)	0	0
Observed Cases								
Week 8 OL[a]	659	460 (69.8)	198 (30.0)	0	1 (0.2)	0	0	0
Week 12 OL	647	495 (76.5)	129 (19.9)	23 (3.6)	0	0	0	0
Week 16 OL	611	491 (80.4)	103 (16.9)	13 (2.1)	3 (0.5)	1 (0.2)	0	0
Week 20 OL	584	478 (81.8)	90 (15.4)	12 (2.1)	4 (0.7)	0	0	0

CGI-I Scoring: 1=Very much improved; 2=Much improved; 3=Minimally improved; 4=No change; 5=Minimally worse; 6=Much worse; 7=Very much worse.
CGI-I = Clinical Global Impressions Scale-Improvement; LOCF = last observation carried forward; OL = open-label.
a. End of response phase/start of stability phase, CGI-I measured against the OL baseline.

A descriptive summary of CGI-I scores at Week 26 among the all-randomized population during the DB period is provided in Table 28

Table 28. Descriptive Summary of CGI-I Scores at Double-Blind Week 26 - All-Randomized Population

			CGI-S Score						
Week of Therapy	**Therapy Group**	**Total**	**1 n (%)**	**2 n (%)**	**3 n (%)**	**4 n (%)**	**5 n (%)**	**6 n (%)**	**7 n (%)**
LOCF									
Week 26 DB	Placebo	273	8 (2.9)	8 (2.9)	17 (6.2)	123 (45.1)	43 (15.8)	70 (25.6)	4 (1.5)
	DVS SR 50 mg DB	270	11 (4.1)	12 (4.4)	31 (11.5)	157 (58.1)	27 (10.0)	29 (10.7)	3 (1.1)
Observed cases									
Week 26 DB	Placebo	174	7 (4.0)	7 (4.0)	13 (7.5)	105 (60.3)	31 (17.8)	10 (5.7)	1 (0.6)
	DVS SR 50 mg DB	210	9 (4.3)	10 (4.8)	29 (13.8)	135 (64.3)	22 (10.5)	5 (2.4)	0

CGI-I Scoring: 1= Very much improved; 2= Much improved; 3= Minimally improved; 4= No change; 5= Minimally worse; 6= Much worse; 7= Very much worse.

During the double-blind phase, evaluation of improvement for the CGI-I was based on comparison against status at Randomization to double-blind treatment.

CGI-I = Clinical Global Impressions Scale-Improvement; DB = double-blind; DVS SR = desvenlafaxine succinate sustained-release; LOCF = last observation carried forward.

A descriptive summary of CGI-S scores for the all-enrolled population at each scheduled evaluation during the OL response phase is provided in Table 29. At Week 8 (LOCF) the mean CGI-S score was 2.26 (classified as borderline mental illness), compared to a baseline score of 4.48 (classified as moderate illness).

Table 29. Descriptive Summary of CGI-S Score Response Phase Open-Label Period – All-Enrolled Population

Week of Therapy	N	Mean (SD)	Change From Baseline Mean (SD)
LOCF			
Baseline OL	874	4.48 (0.58)	
Week 1 OL	851	4.11 (0.71)	-0.37 (0.65)
Week 2 OL	864	3.62 (0.88)	-0.86 (0.91)
Week 3 OL	866	3.19 (0.99)	-1.29 (1.05)
Week 4 OL	866	2.86 (1.07)	-1.62 (1.17)
Week 6 OL	866	2.53 (1.08)	-1.95 (1.21)
Week 8 OL	866	2.26 (1.11)	-2.22 (1.24)
Observed cases			
Baseline OL	874	4.48 (0.58)	
Week 1 OL	851	4.11 (0.71)	-0.37 (0.65)
Week 2 OL	824	3.60 (0.89)	-0.88 (0.92)
Week 3 OL	817	3.16 (0.97)	-1.33 (1.04)
Week 4 OL	806	2.78 (1.03)	-1.70 (1.15)
Week 6 OL	786	2.40 (0.99)	-2.08 (1.14)
Week 8 OL	753	2.04 (0.93)	-2.44 (1.09)

CGI-S = Clinical Global Impressions Scale-Severity of Illness; LOCF = last observation carried forward; OL = open-label.

A descriptive summary of CGI-S scores for the all-enrolled population who entered the OL stability phase at each scheduled evaluation during the OL stability phase is provided in Table 30.

Table 30. Descriptive Summary of CGI-S Score Stability Phase Open-Label Period-All-Enrolled Population

Week of Therapy	N	Mean (SD)	Change From Baseline Mean (SD)
LOCF			
Baseline OL[a]	659	4.49 (0.60)	
Week 8 OL[b]	659	1.81 (0.70)	-2.68 (0.90)
Week 12 OL	659	1.71 (0.77)	-2.78 (0.95)
Week 16 OL	659	1.68 (0.82)	-2.81 (0.97)
Week 20 OL	659	1.68 (0.87)	-2.81 (0.99)
Observed cases			
Baseline OL[a]	659	4.49 (0.60)	
Week 8 OL[b]	659	1.81 (0.70)	-2.68 (0.90)
Week 12 OL	647	1.71 (0.76)	-2.79 (0.94)
Week 16 OL	611	1.61 (0.74)	-2.88 (0.93)
Week 20 OL	584	1.57 (0.74)	-2.93 (0.89)

CGI-S = Clinical Global Impressions Scale-Severity of Illness; LOCF = last observation carried forward; OL = open-label.
a. Baseline of OL period, Study Day -1.
b. End of response phase/start of stability phase.

A comparison of changes from DB Baseline in CGI-S total score at Week 26 for the all-randomized population using an MMRM is shown in Table 31.

Table 31. Comparison of Changes From Baseline for CGI-S Score Using MMRM at Double-Blind Week 26 - All-Randomized Population

						Adj. Difference From Placebo	
Week of Therapy	Therapy Group	N	Raw Mean	Adj. Mean[a]	Adj. Mean Change (SE)	Mean(95% CI)	p-Value[b]
Baseline at Randomization	Placebo	276	1.46				
	DVS SR 50 mg DB	272	1.53				
Week 26 DB	Placebo	174	1.62	2.01	0.53 (0.06)		
	DVS SR 50 mg DB	210	1.43	1.57	0.09 (0.06)	0.44 (0.28, 0.61)	<0.001

Adj. = adjusted; CI = confidence interval; CGI-S = Clinical Global Impressions Scale-Severity of Illness; DB = double-blind; DVS SR = desvenlafaxine succinate sustained-release; MMRM = mixed-effects model for repeated measures; SE = standard error.
a. Adjusted mean = the adjusted mean change + overall baseline mean.
b. p-Value obtained from mixed model: change from Baseline = baseline + site + treatment + visit + treatment × visit with 'Unstructured' covariance structure.

Safety Results: Non-serious AEs that occurred during the OL response phase in the All-enrolled population with an incidence ≥5% are summarized in Table 32.

Table 32. Number (%) of Subjects Reporting Non-Serious Adverse Events With Incidence ≥ 5%, Response Phase, Open-Label Period – All-Enrolled Population

System Organ Class[a] Preferred Term	Treatment DVS SR 50 mg OL n=874
Any adverse event	609 (69.7)
Gastrointestinal disorders	368 (42.1)
Constipation	51 (5.8)
Diarrhoea	44 (5.0)
Dry mouth	104 (11.9)
Nausea	184 (21.1)
Nervous system disorders	277 (31.7)
Dizziness	62 (7.1)
Headache	160 (18.3)
Somnolence	45 (5.1)
Psychiatric disorders	117 (13.4)
Insomnia	44 (5.0)
Skin and subcutaneous tissue disorders	78 (8.9)
Hyperhidrosis	50 (5.7)

Classifications of AEs were based on the Medical Dictionary for Regulatory Activities.
DVS SR = desvenlafaxine succinate sustained-release; n = number of subjects in treatment group; OL = open-label.
a. Totals for the number of subjects at a higher level were not necessarily the sum of those at the lower levels since a subject may have reported 2 or more different AEs within the higher level category.

Non-serious AEs that occurred during the OL stability phase in the all-enrolled population among those who entered the stability phase with an incidence ≥5% are summarized in Table 33.

Table 33. Number (%) of Subjects Reporting Non-Serious Adverse Events With Incidence ≥5% Stability Phase, Open-Label Period – All-Enrolled Population

System Organ Class[a] Preferred Term	Treatment DVS SR 50 mg OL n=659
Any adverse event	275 (41.7)
Nervous system disorders	63 (9.6)
Headache	37 (5.6)

Classifications of AEs were based on the Medical Dictionary for Regulatory Activities.
AE = adverse event; DVS SR = desvenlafaxine succinate sustained-release; n = number of subjects in treatment group; OL = open-label.
a. Totals for the number of subjects at a higher level were not necessarily the sum of those at the lower levels since a subject may have reported 2 or more different AEs within the higher level category.

Table 34 summarizes TPEAEs that occurred after the OL period with an incidence ≥5% in the all-enrolled population excluding randomized subjects.

Table 34. Number (%) of Subjects Reporting Adverse Events With Incidence ≥5% Open−Label Taper/Poststudy Period – All-Enrolled Population Excluding Randomized Subjects

System Organ Class[a] Preferred Term	Treatment
	DVS SR 50 mg OL n=326
Any adverse event	193 (59.2)
Gastrointestinal disorders	66 (20.2)
Dry mouth	24 (7.4)
Nausea	28 (8.6)
Nervous system disorders	67 (20.6)
Headache	28 (8.6)
Psychiatric disorders	52 (16.0)
Insomnia	21 (6.4)

Two subjects were randomized in error and immediately entered the OL taper phase on the date of randomization.
Classifications of AEs were based on the Medical Dictionary for Regulatory Activities.
AE = adverse event; DVS SR = desvenlafaxine succinate sustained-release; n = number of subjects in treatment group; OL = open-label.
a. Totals for the number of subjects at a higher level were not necessarily the sum of those at the lower levels since a subject may have reported 2 or more different AEs within the higher level category.

Non-serious adverse events that occurred in ≥5% of subjects during the DB period in the all-randomized population using OL baseline (Baseline 1), are summarized in Table 35.

Table 35. Number (%) of Subjects Reporting Non-Serious Adverse Events With Incidence ≥5% in Either Group Double-Blind Period All-Randomized Population

System Organ Class[a] Preferred Term	Treatment		
	Placebo n=276	DVS SR 50 mg DB n=272	Total N=548
Any adverse event	158 (57.2)	149 (54.8)	307 (56.0)
Nervous system disorders	65 (23.6)	54 (19.9)	119 (21.7)
Dizziness	29 (10.5)	13 (4.8)	42 (7.7)
Headache	35 (12.7)	34 (12.5)	69 (12.6)
Psychiatric disorders	38 (13.8)	27 (9.9)	65 (11.9)
Depression	17 (6.2)	8 (2.9)	25 (4.6)

Classifications of AE were based on the Medical Dictionary for Regulatory Activities.
AE = adverse event; DB = double-blind; DVS SR = desvenlafaxine succinate sustained-release; N = total number of subjects; n = number of subjects in each treatment group.
a. Totals for the number of subjects at a higher level were not necessarily the sum of those at the lower levels since a subject may have reported 2 or more different AEs within the higher level category.

The most frequently reported TEAEs in the all-randomized population using the DB baseline (Baseline 2) are summarized in Table 36.

Table 36. Number (%) of Subjects Reporting Treatment-Emergent Adverse Events With Incidence ≥5% in Either Group Double-Blind On-Therapy Period Using Baseline 2 - All-Randomized Population

System Organ Class[a] Preferred Term	Treatment		
	Placebo n=276	DVS SR 50 mg DB n=272	Total N=548
Any adverse event	158 (57.2)	148 (54.4)	306 (55.8)
Nervous system disorders	59 (21.4)	54 (19.9)	113 (20.6)
Dizziness	28 (10.1)	13 (4.8)	41 (7.5)
Headache	32 (11.6)	34 (12.5)	66 (12.0)
Psychiatric disorders	39 (14.1)	27 (9.9)	66 (12.0)
Depression	18 (6.5)	8 (2.9)	26 (4.7)

Classifications of AEs were based on the Medical Dictionary for Regulatory Activities.
AE = adverse event; DB = double-blind; DVS SR = desvenlafaxine succinate sustained-release; N = total number of subjects; n = number of subjects in each treatment group.
a. Totals for the number of subjects at a higher level were not necessarily the sum of those at the lower levels since a subject may have reported 2 or more different AEs within the higher level category.

Table 37 summarizes TPEAEs that occurred after the DB period in the all-randomized population.

Table 37. Number (%) of Subjects Reporting Adverse Events Double-Blind Taper/Poststudy Period With Incidence ≥5% All-Randomized Population

System Organ Class[a] Preferred Term	Treatment		
	Placebo n=276	DVS SR 50 mg DB n=272	Total N=548
Any adverse event	126 (45.7)	120 (44.1)	246 (44.9)
Investigations	27 (9.8)	21 (7.7)	48 (8.8)
Weight increased	15 (5.4)	7 (2.6)	22 (4.0)
Nervous system disorders	21 (7.6)	30 (11.0)	51 (9.3)
Dizziness	9 (3.3)	14 (5.1)	23 (4.2)
Psychiatric disorders	43 (15.6)	28 (10.3)	71 (13.0)
Depression	22 (8.0)	9 (3.3)	31 (5.7)

Excludes 2 subjects who were randomized in error and immediately entered the OL taper phase.
Classifications of AEs were based on the Medical Dictionary for Regulatory Activities.
AE = adverse event; DB = double-blind; DVS SR = desvenlafaxine succinate sustained-release; N = total number of subjects; n = number of subjects in each treatment group.
a. Totals for the number of subjects at a higher level were not necessarily the sum of those at the lower levels since a subject may have reported 2 or more different AEs within the higher level category.

Treatment-related AEs that occurred during the OL response phase in the all-enrolled population with an incidence ≥5% are summarized in Table 38.

Table 38. Number (%) of Subjects Reporting Adverse Events by Drug Relationship Response Phase, Open-Label Period With Incidence ≥5% All-Enrolled Population

System Organ Class[a] Preferred Term	Treatment DVS SR 50 mg OL n=874
Any adverse event	424 (48.5)
Gastrointestinal disorders	318 (36.4)
Constipation	50 (5.7)
Dry mouth	103 (11.8)
Nausea	169 (19.3)
Nervous system disorders	220 (25.2)
Dizziness	51 (5.8)
Headache	116 (13.3)
Skin and subcutaneous tissue disorders	65 (7.4)
Hyperhidrosis	47 (5.4)

Classifications of AEs were based on the Medical Dictionary for Regulatory Activities.
AE = adverse event; DVS SR = desvenlafaxine succinate sustained-release; n = number of subjects in treatment group;
OL = open-label.
a. Totals for the number of subjects at a higher level were not necessarily the sum of those at the lower levels since a subject may have reported 2 or more different AEs within the higher level category.

Treatment-related AEs that occurred during the OL stability phase in the all-enrolled population with an incidence ≥5% are summarized in Table 39.

Table 39. Number (%) of Subjects Reporting Adverse Events by Drug Relationship Stability Phase, Open−Label Period With Incidence ≥5% in Subjects Who Entered the Stability Phase, All-Enrolled Population

System Organ Class[a] Preferred Term	Treatment DVS SR 50 mg OL n=659
Any adverse event	196 (29.7)
Gastrointestinal disorders	72 (10.9)
Dry mouth	36 (5.5)

Classifications of AEs were based on the Medical Dictionary for Regulatory Activities.
AE = adverse event; DVS SR = desvenlafaxine succinate sustained-release; n = number of subjects in treatment group; OL = open-label.
a. Totals for the number of subjects at a higher level were not necessarily the sum of those at the lower levels since a subject may have reported 2 or more different AEs within the higher level category.

Treatment related AEs that occurred in ≥5% of subjects during the DB period in the all-randomized population are summarized in Table 40.

Table 40. Number (%) of Subjects Reporting Adverse Events by Drug Relationship Double−Blind On−Therapy Period With Incidence ≥5% All-Randomized Population

System Organ Class[a] Preferred Term	Treatment		
	Placebo n=276	DVS SR 50 mg DB n=272	Total N=548
Any adverse event	102 (37.0)	85 (31.3)	187 (34.1)
Investigations	26 (9.4)	20 (7.4)	46 (8.4)
Weight increased	14 (5.1)	10 (3.7)	24 (4.4)
Nervous system disorders	54 (19.6)	29 (10.7)	83 (15.1)
Dizziness	27 (9.8)	10 (3.7)	37 (6.8)
Headache	25 (9.1)	15 (5.5)	40 (7.3)
Psychiatric disorders	38 (13.8)	25 (9.2)	63 (11.5)
Depression	15 (5.4)	6 (2.2)	21 (3.8)

Classifications of AEs were based on the Medical Dictionary for Regulatory Activities.
AE = adverse event; DB = double-blind; DVS SR = desvenlafaxine succinate sustained-release; N = total number of subjects; n = number of subjects in each treatment group.

a. Totals for the number of subjects at a higher level were not necessarily the sum of those at the lower levels since a subject may have reported 2 or more different AEs within the higher level category.

Serious Adverse Events (SAEs): A summary tabulation of SAEs that occurred during the OL response phase in the all-enrolled population is provided in Table 41. SAEs were reported regardless of causal relationship to study drug.

Table 41. Number (%) of Subjects Reporting Serious Adverse Events Response Phase, Open-Label Period - All-Enrolled Population

System Organ Class[a] Preferred Term	Treatment DVS SR 50 mg OL n=874
Any adverse event	9 (1.0)
Cardiac disorders	1 (0.1)
Atrioventricular block second degree	1 (0.1)
Infections and infestations	1 (0.1)
Subcutaneous abscess	1 (0.1)
Injury, poisoning and procedural complications	2 (0.2)
Intentional overdose	2 (0.2)
Psychiatric disorders	6 (0.7)
Abnormal behaviour	1 (0.1)
Aggression	1 (0.1)
Depressive symptom	1 (0.1)
Suicidal ideation	2 (0.2)
Suicide attempt	2 (0.2)
Skin and subcutaneous tissue disorders	1 (0.1)
Angioedema	1 (0.1)

Classifications of AEs were based on the Medical Dictionary for Regulatory Activities.
AE = adverse event; DVS SR = desvenlafaxine succinate sustained-release; n = number of subjects in treatment group; OL = open-label.
a. Totals for the number of subjects at a higher level were not necessarily the sum of those at the lower levels since a subject may have reported 2 or more different AEs within the higher level category.

A summary tabulation of SAEs that occurred during the OL stability phase in the all-enrolled population who entered the OL stability phase is provided in Table 42.

Table 42. Number (%) of Subjects Reporting Serious Adverse Events Stability Phase, Open−Label Period, Subjects Who Entered the Stability Phase All-Enrolled Population

System Organ Class[a] Preferred Term	Treatment DVS SR 50 mg OL n=659
Any adverse event	6 (0.9)
Cardiac disorders	1 (0.2)
Tachycardia	1 (0.2)
Infections and infestations	1 (0.2)
Viral infection	1 (0.2)
Injury, poisoning and procedural complications	2 (0.3)
Ankle fracture	1 (0.2)
Concussion	1 (0.2)
Fall	1 (0.2)
Subdural haematoma	1 (0.2)
Metabolism and nutrition disorders	1 (0.2)
Dehydration	1 (0.2)
Nervous system disorders	2 (0.3)
Intracranial aneurysm	1 (0.2)
Loss of consciousness	1 (0.2)
Psychiatric disorders	2 (0.3)
Depression	1 (0.2)
Self-injurious behaviour	1 (0.2)
Suicidal ideation	2 (0.3)

Classifications of AEs were based on the Medical Dictionary for Regulatory Activities.
AE = adverse event; DVS SR = desvenlafaxine succinate sustained-release; n = number of subjects in treatment group; OL = open-label.
a. Totals for the number of subjects at a higher level were not necessarily the sum of those at the lower levels since a subject may have reported 2 or more different AEs within the higher level category.

A summary tabulation of SAEs that occurred in the all-enrolled population excluding randomized subjects during the OL taper/post-study period is provided in Table 43.

Table 43. Number (%) of Subjects Reporting Serious Adverse Events Open-Label Taper/Post-Study Period - All-Enrolled Population Excluding Randomized Subjects

System Organ Class[a] Preferred Term	Treatment DVS SR 50 mg OL n=326
Any adverse event	4 (1.2)
Pregnancy, puerperium and perinatal conditions	2 (0.6)
Abortion spontaneous	1 (0.3)
Intra-uterine death	1 (0.3)
Psychiatric disorders	2 (0.6)
Alcohol abuse	1 (0.3)
Depression	1 (0.3)
Suicidal ideation	1 (0.3)

Classifications of AEs were based on the Medical Dictionary for Regulatory Activities.
AE = adverse events; DVS SR = desvenlafaxine succinate sustained-release; n = number of subjects in treatment group; OL = open-label.
a. Totals for the number of subjects at a higher level were not necessarily the sum of those at the lower levels since a subject may have reported 2 or more different AEs within the higher level category.

A summary tabulation of SAEs that occurred during the DB period in the all-randomized population is provided in Table 44.

Table 44. Number (%) of Subjects Reporting Serious Adverse Events Double-Blind On-Therapy Period - All-Randomized Population

System Organ Class[a] Preferred Term	Treatment		
	Placebo n=276	DVS SR 50 mg DB n=272	Total N=548
Any adverse event	7 (2.5)	8 (2.9)	15 (2.7)
Blood and lymphatic system disorders	0	1 (0.4)	1 (0.2)
Anaemia	0	1 (0.4)	1 (0.2)
Cardiac disorders	2 (0.7)	0	2 (0.4)
Atrial fibrillation	1 (0.4)	0	1 (0.2)
Myocardial infarction	1 (0.4)	0	1 (0.2)
General disorders and administration site conditions	2 (0.7)	0	2 (0.4)
Non-cardiac chest pain	1 (0.4)	0	1 (0.2)
Pyrexia	1 (0.4)	0	1 (0.2)
Infections and infestations	1 (0.4)	2 (0.7)	3 (0.5)
Genital infection bacterial	1 (0.4)	0	1 (0.2)
Pelvic inflammatory disease	0	1 (0.4)	1 (0.2)
Pyelonephritis acute	0	1 (0.4)	1 (0.2)
Injury, poisoning and procedural complications	1 (0.4)	3 (1.1)	4 (0.7)
Rib fracture	1 (0.4)	1 (0.4)	2 (0.4)
Subdural haematoma	0	1 (0.4)	1 (0.2)
Tibia fracture	0	1 (0.4)	1 (0.2)
Musculoskeletal and connective tissue disorders	0	1 (0.4)	1 (0.2)
Cervical spinal stenosis	0	1 (0.4)	1 (0.2)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (0.4)	2 (0.7)	3 (0.5)
Bladder cancer	1 (0.4)	0	1 (0.2)
Breast cancer	0	1 (0.4)	1 (0.2)
Colon cancer	0	1 (0.4)	1 (0.2)
Nervous system disorders	0	1 (0.4)	1 (0.2)
Partial seizures	0	1 (0.4)	1 (0.2)
Psychiatric disorders	1 (0.4)	0	1 (0.2)
Depression	1 (0.4)	0	1 (0.2)
Renal and urinary disorders	1 (0.4)	0	1 (0.2)
Haematuria	1 (0.4)	0	1 (0.2)
Reproductive system and breast disorders	1 (0.4)	0	1 (0.2)
Benign prostatic hyperplasia	1 (0.4)	0	1 (0.2)

Classifications of AEs were based on the Medical Dictionary for Regulatory Activities.
AE = adverse event; DB = double-blind; DVS SR = desvenlafaxine succinate sustained-release; N = total number of subjects; n = number of subjects in each treatment group.
a. Totals for the number of subjects at a higher level were not necessarily the sum of those at the lower levels since a subject may have reported 2 or more different AEs within the higher level category.

A summary tabulation of SAEs that occurred during the DB taper/post-study period in the All-randomized population is provided in Table 45.

Table 45. Number (%) of Subjects Reporting Serious Adverse Events Double-Blind Taper/Post-Study Period - All-Randomized Population

System Organ Class[a] Preferred Term	Treatment		
	Placebo	DVS SR 50 mg DB	Total
	n=276	n=272	N=548
Any adverse event	1 (0.4)	1 (0.4)	2 (0.4)
Infections and infestations	1 (0.4)	0	1 (0.2)
Diverticulitis	1 (0.4)	0	1 (0.2)
Injury, poisoning and procedural complications	0	1 (0.4)	1 (0.2)
Road traffic accident	0	1 (0.4)	1 (0.2)

Classifications of AEs we based on the Medical Dictionary for Regulatory Activities.
AE = adverse event; DB = double-blind; DVS SR = desvenlafaxine succinate sustained-release; N = total number of subjects; n = number of subjects in each treatment group.
a. Totals for the number of subjects at a higher level were not necessarily the sum of those at the lower levels since a subject may have reported 2 or more different AEs within the higher level category.

Discontinuations: Only 1 dose of study drug was used during the study (50 mg/day), and dose reduction was not allowed.

During the OL response phase, AEs led to discontinuation of treatment for 51 (5.8%) DVS SR treated subjects of the 874 subjects in the All-enrolled population (Table 46).

Table 46. Number (%) of Subjects Reporting Adverse Events Causing Withdrawal From the Response Phase, Open-Label Period - All-Enrolled Population

System Organ Class[a] Preferred Term	Treatment DVS SR 50 mg OL n=874
Any adverse event	51 (5.8)
Cardiac disorders	
Palpitations	2 (0.2)
Tachycardia	1 (0.1)
Gastrointestinal disorders	
Abdominal discomfort	1 (0.1)
Abdominal pain upper	1 (0.1)
Dry mouth	2 (0.2)
Flatulence	1 (0.1)
Gastritis	1 (0.1)
Nausea	9 (1.0)
Vomiting	2 (0.2)
General disorders and administration site conditions	
Asthenia	1 (0.1)
Fatigue	2 (0.2)
Feeling jittery	1 (0.1)
Immune system disorders	1 (0.1)
Drug hypersensitivity	1 (0.1)
Injury, poisoning and procedural complications	
Intentional overdose	2 (0.2)
Investigations	
Pulse pressure increased	1 (0.1)
Quality of life decreased	1 (0.1)
Weight increased	1 (0.1)
Metabolism and nutrition disorders	
Decreased appetite	1 (0.1)
Musculoskeletal and connective tissue disorders	
Myalgia	1 (0.1)
Nervous system disorders	
Disturbance in attention	2 (0.2)
Dizziness	1 (0.1)
Dysgeusia	1 (0.1)
Headache	5 (0.6)
Hypersomnia	1 (0.1)
Migraine	2 (0.2)
Paraesthesia	1 (0.1)
Restless legs syndrome	1 (0.1)
Somnolence	5 (0.6)
Tremor	2 (0.2)
Pregnancy, puerperium and perinatal conditions	
Pregnancy[b]	2 (0.2)
Psychiatric disorders	
Depression	4 (0.5)
Depressive symptom	1 (0.1)
Euphoric mood	1 (0.1)
Insomnia	5 (0.6)
Suicidal ideation	3 (0.3)
Suicide attempt	2 (0.2)
Skin and subcutaneous tissue disorders	

Table 46. Number (%) of Subjects Reporting Adverse Events Causing Withdrawal From the Response Phase, Open-Label Period - All-Enrolled Population

System Organ Class[a] Preferred Term	Treatment DVS SR 50 mg OL n=874
Angioedema	1 (0.1)
Hyperhidrosis	2 (0.2)
Rash generalised	1 (0.1)
Vascular disorders	
Hypertension	2 (0.2)
Orthostatic hypotension	1 (0.1)

Classifications of AEs were based on the Medical Dictionary for Regulatory Activities.
AE = adverse event; DVS SR = desvenlafaxine succinate sustained-release; HCG = human chorionic gonadotropin; n = number of subjects in treatment group; OL = open-label.

a. Totals for the number of subjects at a higher level were not necessarily the sum of those at the lower levels since a subject may have reported 2 or more different AEs within the higher level category.
b. One (1) additional pregnancy was diagnosed by a positive β-HCG test 2 days after the last dose in the OL response phase.

AEs led to discontinuation of treatment for 25 (3.8%) of 659 subjects who entered the stability phase among the all-enrolled population (Table 47).

Table 47. Number (%) of Subjects Reporting Adverse Events Causing Withdrawal From the Stability Phase Open-Label Period - All-Enrolled Population

System Organ Class[a] Preferred Term	Treatment DVS SR 50 mg OL n=659
Any adverse event	25 (3.8)
Cardiac disorders	
Palpitations	1 (0.2)
Tachycardia	1 (0.2)
Ear and labyrinth disorders	
Vertigo	1 (0.2)
Gastrointestinal disorders	
Abdominal pain upper	1 (0.2)
Dyspepsia	1 (0.2)
Gastrooesophageal reflux disease	1 (0.2)
Nausea	1 (0.2)
Vomiting	1 (0.2)
General disorders and administration site conditions	
Chest discomfort	1 (0.2)
Irritability	1 (0.2)
Infections and infestations	
Gastroenteritis	1 (0.2)
Investigations	
Electrocardiogram QT prolonged	1 (0.2)
Weight increased	1 (0.2)
White blood cell count decreased	1 (0.2)
Metabolism and nutrition disorders	
Type 1 diabetes mellitus	1 (0.2)
Musculoskeletal and connective tissue disorders	
Sensation of heaviness	1 (0.2)
Nervous system disorders	
Headache	1 (0.2)
Intracranial aneurysm	1 (0.2)
Paraesthesia	1 (0.2)
Syncope	1 (0.2)
Pregnancy, puerperium and perinatal conditions	
Pregnancy	3 (0.5)
Psychiatric disorders	
Anorgasmia	1 (0.2)
Depression	1 (0.2)
Insomnia	2 (0.3)
Self-injurious behaviour	1 (0.2)
Sleep disorder	1 (0.2)
Suicidal ideation	2 (0.3)
Respiratory, thoracic and mediastinal disorders	
Epistaxis	1 (0.2)
Skin and subcutaneous tissue disorders	
Rash	1 (0.2)

Table 47. Number (%) of Subjects Reporting Adverse Events Causing Withdrawal From the Stability Phase Open-Label Period - All-Enrolled Population

System Organ Class[a] Preferred Term	Treatment
	DVS SR 50 mg OL n=659
Vascular disorders	
Hypertension	1 (0.2)

Classifications of AEs were based on the Medical Dictionary for Regulatory Activities.
AE = adverse event; DVS SR = desvenlafaxine succinate sustained-release; n = number of subjects in treatment group; OL = open-label.
a. Totals for the number of subjects at a higher level were not necessarily the sum of those at the lower levels since a subject may have reported 2 or more different AEs within the higher level category.

During the DB period, AEs in the all-randomized population led to discontinuation of treatment for 23 (8.3%) of 276 subjects in the placebo group and 10 (3.7%) of 272 subjects in the DVS SR-group (Table 48).

Table 48. Number (%) of Subjects Reporting Adverse Events Causing Withdrawal From the Double-Blind Period - All-Randomized Population

System Organ Class[a] Preferred Term	Treatment		
	Placebo n=276	DVS SR 50 mg DB n=272	Total N=548
Any adverse event	23 (8.3)	10 (3.7)	33 (6.0)
Endocrine disorders			
Hyperthyroidism	1 (0.4)	0	1 (0.2)
General disorders and administration site conditions			
Non-cardiac chest pain	1 (0.4)	0	1 (0.2)
Pain	1 (0.4)	0	1 (0.2)
Injury, poisoning and procedural complications			
Rib fracture	1 (0.4)	0	1 (0.2)
Subdural haematoma	0	1 (0.4)	1 (0.2)
Investigations			
Blood pressure increased	1 (0.4)	0	1 (0.2)
Musculoskeletal and connective tissue disorders			
Back pain	0	1 (0.4)	1 (0.2)
Pain in extremity	0	1 (0.4)	1 (0.2)
Nervous system disorders			
Dizziness	1 (0.4)	1 (0.4)	2 (0.4)
Headache	0	1 (0.4)	1 (0.2)
Tremor	0	1 (0.4)	1 (0.2)
Psychiatric disorders			
Depression	14 (5.1)	6 (2.2)	20 (3.6)
Depressive symptom	0	1 (0.4)	1 (0.2)
Insomnia	1 (0.4)	0	1 (0.2)
Major depression	1 (0.4)	0	1 (0.2)
Suicidal ideation	1 (0.4)	1 (0.4)	2 (0.4)

Classifications of AEs were based on the Medical Dictionary for Regulatory Activities.
AE = adverse event; DB = double-blind; DVS SR = desvenlafaxine succinate sustained-release; N = total number of subjects; n = number of subjects in each treatment group.
a. Totals for the number of subjects at a higher level were not necessarily the sum of those at the lower levels since a subject may have reported 2 or more different AEs within the higher level category.

Death: One death occurred during the study. A 68-year-old female subject was withdrawn on Week 2 of the DB phase due to lack of efficacy. Thirty-five (35) days after the last dose of study medication (DVS SR), the subject died as the result of an automobile accident, which was assessed as unrelated to study medication.

Laboratory values of PCI were reported in 296 (38.5%) of 769 subjects in the OL response phase, 237 (38.5%) of 616 subjects in the OL stability phase, and in the DB period, in 120 (46.5%) of 258 subjects in the placebo group, and 127 (49.2%) of 258 subjects in the DVS SR group. The most common PCI laboratory test result (triglycerides/lipids ≥2.258 mmol/L) occurred in 86 (14.2%) subjects pre study, 72 (14.6%) subjects in the OL response phase, 57 (14.1%) subjects in the OL stability phase, and in 40 (20.8%) placebo treated subjects, and 39 (20.0%) of DVS SR treated subjects in the DB period.

Changes in vital signs of PCI were reported in 309 (36.2%) of 853 subjects in the OL response phase, 179 (27.8%) of 644 subjects in the OL stability phase, and in the DB period, in 121 (44.5%) of 272 subjects in the placebo group, and 143 (53.0%) of 270 subjects in the

DVS SR group. The most common PCI vital sign result, pulse orthostatic change increase ≥20 beats/ minute supine to standing, occurred in 128 (14.6%) subjects pre study, 195 (22.9%) subjects in the OL response phase, 88 (13.7%) subjects in the OL stability phase, and in 51 (18.8%) placebo treated subjects, and 62 (23.0%) of DVS SR treated subjects in the DB period.

ECG results of PCI were reported in 200 (25.6%) of 782 subjects in the OL response phase, 187 (30.9%) of 605 subjects in the OL stability phase, and in the DB period, in 106 (41.7%) of 254 subjects in the placebo group, and 119 (46.5%) of 256 subjects in the DVS SR group. The most frequent PCI ECG result was a ≥30 increase in corrected QT interval, (Bazett's correction), seen in 86 (11.0%) subjects in the OL response phase, 93 (15.4%) subjects in the OL stability phase, and in 51 (20.1%) placebo treated subjects, and 72 (28.1%) DVS SR treated subjects in the DB period.

Health Outcomes Assessments: In the OL response phase, mean scores for all parameters of the WPAI decreased from Baseline to Week 8, with the greatest improvement seen in activity impairment (mean change -31.0) (LOCF). The mean change in WHO-5 total score was 8.35. In the OL stability phase, mean scores for all parameters of the WPAI decreased from OL Week 8 to Week 20, with the greatest improvement seen in activity impairment (mean change -39.9) (LOCF). The mean change in WHO-5 total score was 10.65. In the DB period, a significant difference from placebo was seen in favor of DVS SR at Week 14 and Week 26 in WPAI parameters "presenteeism," "work productivity loss," and "activity impairment." A significant difference in WHO-5 total score between treatment groups in favor of DVS SR was seen at Week 14 and Week 26 ($p \leq 0.001$).

Conclusions:

- This study presents evidence to demonstrate that DVS SR can maintain long term efficacy for the treatment of MDD in adults at the dose of 50 mg/day. DVS SR at a dose of 50 mg/day is effective in the prevention of relapse of MDD in adults stabilized after 20 weeks of OL treatment.

- Superiority of the DVS SR 50 mg group over placebo in the analysis of time to relapse was demonstrated via statistically significant p-value of <0.001.

- Long-term response of subjects receiving 50 mg/day of DVS SR versus placebo measured through clinical global assessments, remission ($HAM\text{-}D_{17}$ score ≤7), $HAM\text{-}D_{17}$, $HAM\text{-}D_6$, and functional and quality-of-life outcomes was demonstrated via statistically significant differences between treatment groups.

- There were no new safety signals, and DVS SR 50 mg/day benefit risk profile is unchanged and remains favor.