PFIZER INC.

These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert.

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

PROTOCOL NO.: 3151A1-303-EU/WW (B2061069)

PROTOCOL TITLE: A 10-Month, Open-Label Evaluation of the Long-Term Safety of DVS SR in Outpatients With Major Depressive Disorder

Study Centers: One hundred seventeen (117) centers took part in the study and randomized subjects: 53 in the United States (US), 12 each in France and Poland, 11 in Finland, 9 in South Africa, 6 in Germany, 3 each in Estonia, Latvia, Lithuania, and Slovakia, and 2 in Serbia.

Study Initiation and Final Completion Dates: 05 August 2003 to 07 March 2006

Phase of Development: Phase 3

Study Objectives:

The primary objective was to evaluate the long-term safety of desvenlafaxine succinate sustained release DVS SR during open-label treatment of outpatients with major depressive disorder (MDD).

The secondary objective was to evaluate the long-term response of subjects receiving (DVS SR) for the clinical global evaluation, functionality, general well-being, pain, and absence of symptoms (Hamilton Rating Scale for Depression, 17-item [HAM-D_{17}] score ≤7).

METHODS

Study Design: This was a Phase 3, multicenter, open-label, flexible-dose, safety study in adult outpatients who had a primary diagnosis of MDD and who had completed randomized, double-blind therapy in an 8-week, Phase 3, DVS SR short-term MDD studies (A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Efficacy and Safety Study of a Flexible Dose of DVS-233 SR in Adult Outpatients With Major Depressive Disorder [NCT00063206]; A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Three Fixed Doses (100 mg, 200 g, or 400 mg) of DVS-233 SR in Adult Outpatients With Major Depressive Disorder [NCT00072774]; A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of Two Fixed Doses (200 mg, or 400 mg) of DVS-233 SR in Adult Outpatients With Major Depressive Disorder [NCT00073762]; A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Flexible-Dose

Study of DVS-233 SR and Venlafaxine ER in Adult Outpatients With Major Depressive Disorder [NCT00090649]; A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Flexible-Dose Study of DVS-233 SR and Venlafaxine ER in Adult Outpatients With Major Depressive Disorder [NCT00087737]; A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Efficacy and Safety Study of a Flexible Dose of DVS-233 SR in Adult Outpatients With Major Depressive Disorder [NCT00092911]). Following a baseline evaluation, eligible subjects were treated up to 10 months plus 2 additional weeks for tapering study drug. Subjects returned for a follow-up visit 7 days after discontinuing test article. The total duration of subject participation was approximately of 11 months. The approximate duration of the study was 25 months. The study flow chart is presented in Table 1.

Table 1. Study Flowchart

Study Day	Baseline Visit[a]	7[b]	14[b]	30[b]	45[b]	60[b]	75[b]	90[b]	105[b]	120[b]	135[b]	150[b]	165[b]	180[b]	195[b]	210[b]	225[b]	240[b]	255[b]	270[b]	285[b]	300[b, c]	304[b]	307[b, d]	311[b, d]	314[b, d]	318[b, d]	Follow-Up Day 321 Visit[b, d, e]
Obtain informed consent	X																											
Eligibility assessment	X																											
Dispense open-label medication	X[f]	X	X	X		X		X		X		X		X		X		X		X		X		X				
Telephone contact[g]					X		X		X		X		X		X		X		X		X		X		X		X	
Completion of dosage record	X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X
Recording of concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Efficacy determinations:																												
HAM-D 17-item	X	X	X	X		X		X		X		X		X		X		X		X		X						
CGI-severity	X	X	X	X		X		X		X		X		X		X		X		X		X						
CGI-improvement	X	X	X	X	X[h]	X	X[h]	X	X[h]	X	X[h]	X	X[h]	X	X[h]	X	X[h]	X	X[h]	X	X[h]	X						
MADRS	X							X						X								X						
Covi anxiety	X							X						X								X						
SDS	X							X						X								X						
VAS-PI	X							X						X								X						
WHO-5	X							X						X								X						
Safety determinations																												
Physical examination	X																					X						
Vital signs[i]	X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X
Weight	X	X	X	X		X		X		X		X		X		X		X		X		X		X		X		X
Laboratory determinations[j]	X							X						X								X						
ECG[k]	X							X						X								X						
Recording of AEs	X	X	X	X	X[h]	X	X[h]	X	X[h]	X	X[h]	X	X[h]	X	X[h]	X	X[h]	X	X[h]	X	X[h]	X	X	X	X	X	X	X

Table 1. Study Flowchart

Study Day	Baseline Visit[a]	7[b]	14[b]	30[b]	45[b]	60[b]	75[b]	90[b]	105[b]	120[b]	135[b]	150[b]	165[b]	180[b]	195[b]	210[b]	225[b]	240[b]	255[b]	270[b]	285[b]	300[b, c]	304[b]	307[b, d]	311[b, d]	314[b, d]	318[b, d]	Follow-Up Day 321 Visit[b, d, e]
AE	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CGI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG	X							X						X								X						
HAM-D_{17}	X							X						X								X						
MADRS	X							X						X								X						
SDS	X							X						X								X						
T3	X							X						X								X						
T4	X							X						X								X						
VAS-PI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
WHO-5	X							X						X								X						

AE = adverse event, CGI = Clinical Global Impressions, ECG = electrocardiogram, HAM-D_{17} = Hamilton Rating Scale for Depression, 17-item, MADRS = Montgomery-Asberg Depression Rating Scale, SDS = Sheehan Disability Scale, T3 = triiodothyronine, T4 = thyroxine, VAS-PI = Visual Analog Scale of Pain Intensity, WHO-5 = World Health Organization 5-Item Well-Being Index.

a. The Day 56 visit of short-term studies corresponded to the baseline visit for the open-label study.
b. Every effort was to be made to bring the subject back or to call the subject on the designated days; however, all office visits and telephone contacts during the maintenance phase would have a ± 3-day visit window to allow for slight variations in subject schedules. Telephone contacts designated for Study Days 304, 311, and 318 would have a ± 2-day window to allow for weekends and slight variations in subject schedules.
c. For subjects who discontinued early, the safety and efficacy determinations designated for Study Day 300 was to be obtained on the last day on which the subject took a full dose of test article (ie, before taper) or as soon as possible thereafter.
d. For those subjects who have a 1-week taper, the follow-up visit evaluations normally performed at the follow-up visit on Study Day 321 was to be performed on approximately Study Day 314. As a result, the Study Day 311 and 314 evaluations described in Table 1 would not be completed.
e. The follow-up determinations was to be obtained 7 days after study drug had been withdrawn for all subjects who had received open-label study drug regardless of duration of treatment.
f. Subjects were to begin dose administration on Study Day 1.
g. Information reported during the telephone contact and recorded on the source documents were to be recorded for the subsequent office visit.
h. Treatment tolerability and efficacy were to be assessed via telephone contacts, during which the Investigator also will obtain a CGI-improvement score.
i. Supine and standing pulse and blood pressure.
j. Hematology, blood chemistry and urinalysis will be obtained at Baseline and on Study Days 90, 180, and 300. Free T4 index including total T4 and T3-uptake were to be performed at Baseline Visit only. Serum β-HCG pregnancy tests (women of childbearing potential) were to be performed at Baseline and Study Day 300.
k. On Study Days 90, 180 and 300, only a single 12-lead ECG recording was to be made.

Number of Subjects (Planned and Analyzed): Approximately 1500 subjects were planned to be enrolled in the study; 1408 subjects entered the study (24 in Estonia, 100 in Finland, 94 in France, 43 in Germany, 13 in Latvia, 18 in Lithuania, 148 in Poland, 19 in Serbia, 5 in Slovakia, 54 in South Africa and 890 in the US), 1395 were evaluated for safety, and 1389 were evaluated for efficacy.

Diagnosis and Main Criteria for Inclusion and Exclusion: Subjects were adult outpatients who had completed double-blind therapy in a Phase 3, DVS SR short-term study for the indication of MDD. A subject was considered to have completed the short-term study if all scheduled evaluations had been done and if, in the opinion of the Investigator, the subject had no major protocol violations or adverse events (AEs) that would have precluded the subject's participation in the study.

Exclusion Criteria: Subjects with clinically important abnormalities on baseline physical examination or any unresolved clinically significant abnormalities on electrocardiograms (ECG), laboratory test results, or vital signs recorded in a previous Phase 3 DVS SR short-term study for the indication of MDD were excluded from the study.

Study Treatment: DVS SR was administered orally as 100-mg or 200-mg tablets. On Study Days 1 through 7, each subject received 1 daily tablet of DVS SR 200 mg. On Study Day 7, and at all subsequent visits, the Investigator evaluated the subject and determined whether to maintain the dosage or adjust it to improve efficacy or tolerance. If clinically indicated, the Investigator adjusted the total daily dose to 400 mg (2 x 200 mg DVS SR). Subjects who were unable to tolerate 400 mg had their dosage reduced to 200 mg DVS SR. Subjects who had received DVS SR 400 mg/day during the on-therapy period took DVS SR 200 mg/day for 7 days, then 100 mg/day for 7 days. Subjects who had received DVS SR 200 mg/day took DVS SR 100 mg/day for 7 days. Subjects who withdrew early also tapered their dosages according to this schedule. The dosage summary is provided in Table 2.

Table 2. Dosage Summary

Study Schedule	Number of Tablets (mg)	Total Daily Dose (mg)
Titration and maintenance		
Study Days 1-7	1 × 200	200
Study Days 8-300	1 or 2 × 200	200 or 400[a]
Taper		
Study Days 301-307		
From 400 mg/day	1 × 200	200
From 200 mg/day	1 × 100	100
Study Days 308-314		
From 400 mg/day	1 × 100	100
From 200 mg/day	0	0

a. Dosage could be increased to 400 mg/day from Study Day 7, if clinically indicated, and could be readjusted to the original dose, 200 mg/day.

Safety and Efficacy Endpoints:

- The primary endpoint was safety, as assessed by:

- AEs.
- Changes of potential clinical importance from Baseline on vital signs, laboratory determinations and 12-lead ECG.

- The primary efficacy endpoints were:
  - Mean change from Baseline in HAM-D_{17} total score.
- The secondary efficacy endpoints were:
  - Mean change from Baseline in Clinical Global Impressions Scale-Severity (CGI-S).
  - Mean change from Baseline in Montgomery-Asberg Depression Rating Scale (MADRS).
  - Remission rate, defined as HAM-D_{17} total score ≤7.
  - Response rate, defined as subjects who had Clinical Global Impressions Scale-Improvement (CGI-I) scores of 1 (very much improved) or 2 (much improved).
  - Mean change from Baseline in Visual Analog Scale of Pain Intensity (VAS-PI).
  - Mean change from Baseline in Hamilton Rating Scale for Depression, 6-item (HAM-D_6).
  - Mean change from Baseline in Covi Anxiety Scale.

Safety Evaluations: Safety was determined using the following assessments: monitoring of AEs, withdrawal because of AEs, concomitant medication use, physical examinations, standard 12-lead ECGs, vital signs (supine and standing pulse rate and blood pressure (BP); body weight), and laboratory determinations (hematology, blood chemistry, and urinalysis; free thyroxine index, including total thyroxine and triiodothyronine uptake; and beta human chorionic gonadotropin).

Statistical Methods: The population sets used in the analysis were:

- Intent-to-Treat Population (ITT): The ITT population included all subjects who had a baseline primary efficacy evaluation, who had taken at least 1 dose of test article, and had at least 1 primary efficacy evaluation after the first dose of test article. The ITT population was the primary population for efficacy analysis.
- Safety Population: The safety population consisted of all subjects who took at least 1 dose of test article.

Statistical analyses were based on the data from all individual clinical study sites. The nominal p-value significance level (≥0.05) was used without adjustment for multiple testing.

The safety analysis, the study primary objective, was based on the safety population.

AEs, treatment-emergent AEs, and taper/poststudy-emergent AEs were listed and summarized. AEs were classified by Coding Symbols for the Thesaurus of Adverse Reaction Terms (COSTART) body system and preferred term; summaries of the number of subjects with events were provided. Summary tables were produced for vital signs (weight, supine and standing BP, and pulse rate), laboratory evaluations (hematology, blood chemistry, and urinalysis), and ECG data; these safety parameters were also listed. Changes from Baseline were summarized, and mean changes were analyzed using paired t-tests. The paired t-test was used to test for significant changes over time in the laboratory determinations. The percentages of subjects who withdrew, both overall and for specific reasons, and the incidence of study events were assessed.

The efficacy analysis was based on ITT efficacy population, ie, subjects who had a baseline primary efficacy evaluation, took at least 1 dose of open-label study medication, and had at least 1 primary efficacy evaluation after the first dose of open-label study medication. No per-protocol efficacy analysis was done.

The efficacy of open-label, long-term treatment with DVS SR was assessed by mean changes from Baseline scores in the HAM-D_{17} total, MADRS total, and CGI-S. Mean changes from Baseline scores were also tabulated for the HAM-D_6, the Covi Anxiety Scale, and the VAS-PI. The baseline scores were obtained from the final on-therapy (FOT) efficacy scores (ie, the Study Day 56 evaluation) of the respective short-term studies in which had subjects had participated before enrolling in this study.

All efficacy data were analyzed using both the last observation carried forward (LOCF) and the observed-cases techniques to handle missing data. When the LOCF approach was used, data for subjects who discontinued or who had missing evaluations were handled by carrying data forward from the last observation. Data from Baseline evaluations were not carried forward. When the observed-cases approach was used data were analyzed as observed, ie, no imputations were done. Remission was defined as an absence of symptoms, ie, HAM-D_{17} total score ≤ 7. The proportion of remitters at each time point was tabulated. A responder analysis was done using CGI-I score of 1 or 2 as the indication of response. There were 2 separate analyses of the results from the CGI-I evaluations based on whether the evaluation was obtained via the telephone or during a study visit. The baseline used for CGI-I was the subject's psychiatric condition on Study Day -1 of the short-term study.

RESULTS

Subject Disposition and Demography: A total of 1408 subjects who completed 1 of the previous short-term studies and consented to enroll in this long-term, open-label study were assigned to receive DVS SR. Thirteen (13) of these 1408 subjects were considered "no-data subjects" and were not included in the safety population. Twelve (12) of the 13 subjects were lost to follow-up and did not return the study medication. The summary of subject status is provided in Table 3.

Table 3. Summary of Subject Status

Population	DVS SR
Entered open-label	1408
No data subjects[a]	13
Safety[b]	1395
Efficacy ITT[c]	1389
Completed open-label treatment period[d]	561

DVS SR = desvenlafaxine succinate sustained release, FOT = final on-therapy, ITT = intent to treat.

a. Of the 13, 12 did not return the study medication and their study medication use is unknown. One (1) of the 13 returned the study medication unused.
b. The safety population included all randomly assigned subjects who received at least 1 dose of open-label study medication.
c. The ITT population included subjects who had a baseline primary efficacy evaluation, took at least 1 dose of open-label study medication, and had at least 1 primary efficacy evaluation after the first dose of open-label study medication.
d. Completers for exposure were subjects who had at least 297 days of exposure to the study drug and who also completed the evaluations scheduled for Study Day 300. Some subjects, although completing the visit schedule, were not considered to be completers because their FOT evaluation occurred before Study Day 297.

A total of 708 (51%) subjects withdrew prematurely from the study. Table 4 summarizes the number of subjects who discontinued treatment by primary reasons.

Table 4. Number (%) of Subjects Who Withdrew Prematurely From Study by Primary Reason

Primary Reason	DVS SR (N=1395)
Total	708 (50.8)
Adverse event	296 (21.2)
Failed to return	130 (9.3)
Other event	54 (3.9)
Protocol violation	48 (3.4)
Subject request unrelated to study	93 (6.7)
Unsatisfactory response/efficacy	87 (6.2)

DVS SR = desvenlafaxine succinate sustained release, N = total number of subjects.

Tapering was scheduled for subjects who were discontinued and for subjects who completed the Study Day 300 evaluations. The disposition of subjects with regard to the taper period is shown in Table 5. The dose taper period was electively modified for 571 subjects; the primary reason for modification is summarized in Table 6.

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

Population	DVS SR (N=1395)
Subjects in safety population	1395
Subjects whose taper status was "unknown"	2
Subjects who withdrew prematurely and were not available for a taper period	144
Subject who tapered	1249
Subjects who had elective modifications to taper period	
Taper period was omitted per Investigator	351
Taper period was shortened per Investigator[a]	74
Taper period was extended per Investigator[b]	146
Subjects who tapered according to study	678

DVS SR = desvenlafaxine succinate sustained release, N = number of subjects per treatment group.
a. Includes 1 subject whose termination record indicated the taper period was shortened, but whose medication record did not include taper data.
b. Includes 1 subject whose termination record indicated an extended taper period, but whose medication record indicated a taper dose of 0.
c. Includes all subjects who electively tapered whether they withdrew prematurely or they completed the Study Day 300 evaluations.

Table 6. Number (%) of Subjects With Elective Modifications to the Taper Period by Primary Reason

Reason	DVS SR (N=571)		
	Omitted	Extended	Shortened
Total	351	146	74
Adverse event	133 (10)	26 (2)	18 (1)
Failed to return	19 (1)	3 (<1)	3 (<1)
Other event	88 (6)	68 (5)	29 (2)
Protocol violation	21 (2)	36 (3)	7 (<1)
Subject request unrelated to treatment	68 (5)	11 (<1)	12 (<1)
Unsatisfactory response (efficacy)	22 (2)	2 (<1)	5 (<1)

DVS SR = desvenlafaxine succinate sustained release, N = number of subjects per treatment group.

The demographic characteristics for the safety and ITT populations are presented in Table 7.

Table 7. Demography, Safety and ITT Populations

Characteristic	Safety N=1395	ITT N=1389
Age (year)		
Mean ± SD	42.4±12.2	42.4±12.2
Range	18.0 to 75.0	18.0 to 75.0
Median	43.0	43.0
Sex, n (%)		
Women	907 (65)	901 (65)
Men	488 (35)	488 (35)

ITT = intent-to-treat, N = total number of subjects, n = number of subjects with specified criteria, SD = standard deviation.

Efficacy Results:

The primary objective of this study was safety.

HAM-D_{17} Total Score: Table 8 shows the mean change from Baseline (LOCF and observed cases) in HAM-D_{17} total scores at each time point. At the FOT evaluation, the mean change from Baseline (LOCF) was -3.85.

Table 8. HAM-D_{17} Total Score, Mean Change From Baseline, ITT (LOCF and Observed Cases)

Analysis	Week of Therapy	No. of Subjects	Mean Score	Mean Change From Baseline
LOCF	Baseline	1389	12.05	
	Week 1	1317	11.76	-0.22
	Week 2	1376	10.53	-1.51
	Month 1	1388	9.61	-2.45
	Month 2	1389	8.67	-3.38
	Month 3	1389	8.66	-3.39
	Month 4	1389	8.40	-3.65
	Month 5	1389	8.21	-3.84
	Month 6	1389	8.34	-3.71
	Month 7	1389	8.25	-3.80
	Month 8	1389	8.13	-3.91
	Month 9	1389	8.13	-3.92
	Month 10	1389	8.18	-3.87
	FOT	1389	8.20	-3.85
Observed cases				
	Week 1	1317	11.76	-0.22
	Week 2	1225	10.22	-1.75
	Month 1	1257	9.25	-2.72
	Month 2	1165	7.79	-4.03
	Month 3	1075	7.52	-4.26
	Month 4	968	6.85	-4.87
	Month 5	893	6.25	-5.31
	Month 6	828	6.26	-5.18
	Month 7	761	5.78	-5.45
	Month 8	738	5.45	-5.74
	Month 9	697	5.31	-5.86
	Month 10	650	5.32	-5.89

FOT = final on-therapy, HAM-D_{17} = Hamilton Rating Scale for Depression, 17-item, ITT = intent to treat, LOCF = last observation carried forward, No. = number.

Mean CGI-S Scores: Mean CGI-S scores decreased from Baseline until Study Day 150 (-0.73) and were sustained through the FOT (-0.72) evaluation. Table 9 shows the LOCF and observed-cases scores at all-time points. Mean scores for the observed-cases analysis decreased throughout the study by -1.11 at Study Day 300.

Table 9. Means Over Time – CGI-S LOCF and Observed Cases, ITT Population

Analysis	Week of Therapy	No. of Subjects	Mean Score	Mean Change From Baseline
LOCF	Baseline	1389	2.78	
	Study Day 7	1316	2.72	-0.05
	Study Day 14	1380	2.53	-0.25
	Study Day 30	1387	2.34	-0.44
	Study Day 60	1388	2.16	-0.62
	Study Day 90	1388	2.13	-0.65
	Study Day 120	1388	2.10	-0.68
	Study Day 150	1388	2.06	-0.73
	Study Day 180	1388	2.08	-0.70
	Study Day 210	1388	2.06	-0.73
	Study Day 240	1388	2.05	-0.73
	Study Day 270	1388	2.04	-0.74
	Study Day 300	1388	2.06	-0.72
	FOT	1388	2.06	-0.72
Observed cases				
	Baseline	1389	2.78	
	Study Day 7	1316	2.72	-0.05
	Study Day 14	1278	2.49	-0.27
	Study Day 30	1242	2.27	-0.49
	Study Day 60	1104	1.97	-0.77
	Study Day 90	968	1.93	-0.80
	Study Day 120	770	1.82	-0.90
	Study Day 150	707	1.73	-1.00
	Study Day 180	687	1.72	-0.98
	Study Day 210	654	1.62	-1.05
	Study Day 240	636	1.58	-1.09
	Study Day 270	620	1.54	-1.13
	Study Day 300	601	1.58	-1.11
	>Study Day 300	26	1.81	-0.58

CGI- S = Clinical Global Impressions Scale-Severity, FOT = final on-therapy, ITT = intent to treat, LOCF = last observation carried forward, No. = number.

Mean MADRS Total Scores: Mean scores (LOCF) decreased throughout the study by -5.16 at the FOT evaluation. Mean scores (observed cases) had decreased at Month 10 by -7.70. Table 10 presents the results of the LOCF and observed-cases analysis for mean MADRS total scores at all-time points.

Table 10. Means Over Time – MADRS Total - LOCF and Observed Cases, ITT Population

Analysis	Week of Therapy	No. of Subjects	Mean Score	Mean Change From Baseline
LOCF	Baseline	1389	15.09	
	Month 3	1290	10.22	-4.78
	Month 6	1297	10.10	-4.91
	Month 10	1297	9.85	-5.16
	FOT	1297	9.85	-5.16
Observed cases	Baseline	1389	15.09	
	Month 3	1075	8.83	-5.78
	Month 6	819	7.40	-6.69
	Month 10	647	6.11	-7.70
	>Month 10	9	7.00	-6.22

FOT = final on-therapy, ITT = intent to treat, LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale, No. = number.

Mean CGI-I Scores: Mean CGI-I scores for all-time points, including telephone contact data, are presented in Table 11. For the LOCF analysis, mean scores decreased for the first 60 days to 1.75. These decreases were sustained through the FOT evaluation (1.74). For the observed-cases analysis, mean scores generally decreased throughout the study to 1.29 at Study Day 300. Mean CGI-I scores showed decreases that were similar to the scores that included telephone contact data. The mean score was 1.74 (LOCF) at the FOT evaluation and 1.30 (observed cases) at Study Day 300.

Table 11. Means Over Time – CGI-I (Including Telephone Data) – LOCF and Observed Cases, ITT Population

Analysis	Therapy	Week of Therapy	n	Mean Score
LOCF	DVS SR	Study Day 7	1317	2.17
		Study Day 14	1380	2.00
		Study Day 30	1387	1.85
		Study Day 45	1388	1.85
		Study Day 60	1388	1.75
		Study Day 75	1388	1.76
		Study Day 90	1388	1.75
		Study Day 105	1388	1.75
		Study Day 120	1388	1.73
		Study Day 135	1388	1.74
		Study Day 150	1388	1.71
		Study Day 165	1388	1.72
		Study Day 180	1388	1.73
		Study Day 195	1388	1.74
		Study Day 210	1388	1.72
		Study Day 225	1388	1.74
		Study Day 240	1388	1.72
		Study Day 255	1388	1.73
		Study Day 270	1388	1.72
		Study Day 285	1388	1.73
		Study Day 300	1388	1.73
		FOT	1388	1.74
Observed	DVS SR	Study Day 7	1317	2.17
		Study Day 14	1278	1.96
		Study Day 30	1243	1.77
		Study Day 45	1102	1.73
		Study Day 60	1126	1.57
		Study Day 75	1020	1.57
		Study Day 90	1021	1.53
		Study Day 105	929	1.50
		Study Day 120	902	1.44
		Study Day 135	843	1.42
		Study Day 150	821	1.39
		Study Day 165	791	1.37
		Study Day 180	784	1.39
		Study Day 195	722	1.37
		Study Day 210	735	1.32
		Study Day 225	698	1.35
		Study Day 240	702	1.28
		Study Day 255	676	1.29
		Study Day 270	678	1.27
		Study Day 285	647	1.28
		Study Day 300	609	1.29
		>Study Day 300	26	1.58

CGI-I = Clinical Global Impressions Scale-Improvement, DVS SR = desvenlafaxine succinate sustained release, FOT = final on-therapy, ITT = intent to treat, LOCF = last observation carried forward, n = number of subjects in specified criteria.

HAM-D_{17} Remission Rates: For the LOCF analysis, the proportion of subjects in remission increased throughout the study from 32% at Week 1 to 59% by Month 10. For the

observed-cases analysis, the proportion of subjects in remission also increased throughout the study to 77% by Month 10 (Table 12).

Table 12. Proportion of HAM-D_{17} Remitters, ITT Population

Day of Therapy	Proportion (%) of Remitters (N=1389[a])	
	LOCF	Observed Cases
Week 1	416/1317 (32)	416/1317 (32)
Week 2	520/1376 (38)	478/1225 (39)
Month 1	611/1388 (44)	571/1257 (45)
Month 2	716/1389 (52)	654/1165 (56)
Month 3	728/1389 (52)	629/1075 (59)
Month 4	750/1389 (54)	598/968 (62)
Month 5	775/1389 (56)	596/893 (67)
Month 6	763/1389 (55)	549/828 (66)
Month 7	789/1389 (57)	543/761 (71)
Month 8	799/1389 (58)	540/738 (73)
Month 9	805/1389 (58)	521/697 (75)
Month 10	813/1389 (59)	499/650 (77)
FOT	812/1389 (58)	812/1389 (58)

FOT = final on-therapy, HAM-D_{17} = Hamilton Rating Scale for Depression, 17-item, ITT = intent-to-treat, LOCF = last observation carried forward, N = total number of subjects.

a. Remission data are presented for the on-therapy period beginning with the Week 1 evaluation.

CGI-I Response Rates: Response rates (LOCF and observed cases) are presented in Table 13. The proportion of CGI-I responders (LOCF) increased from 64% at Study Day 7 to 80% by Study Day 60. Similar rates were sustained (between 78% and 80%) for the remainder of the study. The trend for the observed-cases analysis was similar, although response rates continued to increase to 94% by Study Day 165 with rates ranging between 92% and 95% for the remainder of the study. CGI-I response rates were similar for the analysis that excluded telephone contact data.

Table 13. Proportion of CGI-I Responders (Including Telephone Contact Data), ITT Population

	Proportion of Responders (N=1388[a, b])	
Day of Therapy	**LOCF**	**Observed Cases**
7	843/1317 (64)	843/1317 (64)
14	970/1380 (70)	921/1278 (72)
30	1062/1387 (77)	989/1243 (80)
45	1068/1388 (77)	906/1102 (82)
60	1110/1388 (80)	973/1126 (86)
75	1102/1388 (79)	886/1020 (87)
90	1102/1388 (79)	896/1021 (88)
105	1107/1388 (80)	830/929 (89)
120	1111/1388 (80)	817/902 (91)
135	1105/1388 (80)	772/843 (92)
150	1107/1388 (80)	754/821 (92)
165	1112/1388 (80)	740/791 (94)
180	1097/1388 (79)	722/784 (92)
195	1090/1388 (79)	663/722 (92)
210	1097/1388 (79)	687/735 (93)
225	1095/1388 (79)	654/698 (94)
240	1093/1388 (79)	660/702 (94)
255	1093/1388 (79)	641/676 (95)
270	1094/1388 (79)	639/678 (94)
285	1095/1388 (79)	615/647 (95)
300	1086/1388 (78)	568/609 (93)
FOT	1083/1388 (78)	1083/1388 (78)

CGI-I = Clinical Global Impressions Scale-Improvement, FOT = final on-therapy, ITT = intent-to-treat, LOCF = last observation carried forward, N = number of subjects.

a. Remission data are presented for the on-therapy period beginning with the Week 1 evaluation of this study.
b. One (1) subject was included in ITT population because she had a post-baseline Hamilton Rating Scale for Depression, 17 item, evaluation, but did not have a post-baseline CGI-I evaluation and so was not included in the denominator of subjects who responded.

VAS-PI Overall Pain Score and Component Scores: The results of the LOCF and observed-cases analyses at each scheduled time point for the VAS-PI overall score is provided in Table 14. For the LOCF analysis, the mean decrease in the overall pain score was -0.02 at the FOT evaluation. The results for the component scores, ie stomach pain, back pain and chest pain are provided in Table 15, Table 16 and Table 17 respectively. For the component scores, there were very slight decreases compared with baseline for stomach pain and chest pain, but no decreases for back pain or arms/legs/joints pain as shown in Table 18.

Table 14. Means Over Time VAS-PI Overall Pain Score – LOCF and Observed Cases, ITT Population

Analysis	Therapy	Week of Therapy	n	Mean Score	Mean Change From Baseline
LOCF	DVS SR	Baseline	1388	15.84	
		Month 3	1283	16.17	0.30
		Month 6	1292	16.38	0.55
		Month 10	1292	15.79	-0.04
		FOT	1292	15.81	-0.02
Observed cases	DVS SR	Baseline	1388	15.84	
		Month 3	1071	15.38	-0.41
		Month 6	817	14.46	-0.97
		Month 10	645	13.00	-2.49
		>Month 10	9	14.89	-0.89

DVS SR = desvenlafaxine succinate sustained-release formulation, FOT = final on-therapy, ITT = intent-to-treat, LOCF = last observation carried forward, n = number of subjects with prespecified criteria, VAS-PI = Visual Analog Scale of Pain Intensity.

Table 15. Means Over Time VAS-PI Stomach Pain Score – LOCF and Observed Cases, ITT Population

Analysis	Therapy	Week of Therapy	n	Mean Score	Mean Change From Baseline
LOCF	DVS SR	Baseline	1388	9.44	
		Month 3	1283	9.22	-0.37
		Month 6	1292	9.44	-0.12
		Month 10	1292	8.75	-0.82
		FOT	1292	8.84	-0.73
Observed cases	DVS SR	Baseline	1388	9.44	
		Month 3	1071	8.26	-1.45
		Month 6	818	8.02	-1.34
		Month 10	646	6.66	-2.61
		>Month 10	9	17.11	6.44

DVS SR = desvenlafaxine succinate sustained-release formulation, FOT = final on-therapy, ITT = intent-to-treat, LOCF = last observation carried forward, n = number of subjects with prespecified criteria, VAS-PI = Visual Analog Scale of Pain Intensity.

Table 16. Means Over Time VAS-PI Back Pain Score – LOCF and Observed Cases, ITT Population

Analysis	Therapy	Week of Therapy	n	Mean Score	Mean Change From Baseline
LOCF	DVS SR	Baseline	1388	15.26	
		Month 3	1283	15.11	-0.18
		Month 6	1292	15.17	-0.05
		Month 10	1292	15.26	0.07
		FOT	1292	15.29	0.10
Observed cases	DVS SR	Baseline	1388	15.26	
		Month 3	1071	14.69	-0.51
		Month 6	817	14.07	-0.75
		Month 10	646	13.54	-1.37
		>Month 10	9	18.11	0.78

DVS SR = desvenlafaxine succinate sustained-release formulation, FOT = final on-therapy, ITT = intent-to-treat, LOCF = last observation carried forward, n = number of subjects with prespecified criteria, VAS-PI = Visual Analog Scale of Pain Intensity.

Table 17. Means Over Time VAS-PI Chest Pain Score – LOCF and Observed Cases, ITT Population

Analysis	Therapy	Week of Therapy	n	Mean Score	Mean Change From Baseline
LOCF	DVS SR	Baseline	1388	7.71	
		Month 3	1283	6.71	-1.15
		Month 6	1292	6.53	-1.27
		Month 10	1292	6.41	-1.41
		FOT	1292	6.49	-1.33
Observed cases	DVS SR	Baseline	1388	7.71	
		Month 3	1071	6.18	-1.81
		Month 6	818	5.83	-1.88
		Month 10	646	5.43	-2.61
		>Month 10	9	13.78	11.56

DVS SR = desvenlafaxine succinate sustained-release formulation, FOT = final on-therapy, ITT = intent-to-treat, LOCF = last observation carried forward, n = number of subjects with prespecified criteria, VAS-PI = Visual Analog Scale of Pain Intensity.

Table 18. Means Over Time VAS-PI Arms/Leg/Joint Pain Score – LOCF and Observed Cases, ITT Population

Analysis	Therapy	Week of Therapy	n	Mean Score	Mean Change From Baseline
LOCF	DVS SR	Baseline	1388	15.47	
		Month 3	1283	15.51	0.01
		Month 6	1292	16.41	0.98
		Month 10	1292	16.26	0.85
		FOT	1292	16.23	0.82
Observed cases	DVS SR	Baseline	1388	15.47	
		Month 3	1071	15.12	-0.27
		Month 6	817	15.50	0.12
		Month 10	646	15.07	-0.52
		>Month 10	9	15.11	-0.22

DVS SR = desvenlafaxine succinate sustained-release formulation, FOT = final on-therapy, ITT = intent-to-treat, LOCF = last observation carried forward, n = number of subjects with prespecified criteria, VAS-PI = Visual Analog Scale of Pain Intensity.

HAM-D_6 (Bech Version: HAM-D_{17} Items 1, 2, 7, 8, 10, and 13): The results of the LOCF and observed-cases analyses at each time point for the HAM-D_6 are shown in Table 19. For the LOCF analysis, mean scores had decreased by -2.18 from Baseline to the FOT evaluation. For the observed-cases analysis, mean scores had decreased by -3.14 from Baseline to Month 10.

Table 19. Means Over Time – HAM-D_6 Total – LOCF and Observed Cases, ITT Population

Analysis	Therapy	Week of Therapy	n	Mean Score	Mean Change From Baseline
LOCF	DVS SR	Baseline	1389	6.28	
		Week 1	1317	5.95	-0.30
		Week 2	1376	5.31	-0.96
		Month 1	1388	4.78	-1.50
		Month 2	1389	4.31	-1.97
		Month 3	1389	4.30	-1.98
		Month 4	1389	4.17	-2.11
		Month 5	1389	4.11	-2.17
		Month 6	1389	4.19	-2.09
		Month 7	1389	4.14	-2.14
		Month 8	1389	4.05	-2.23
		Month 9	1389	4.05	-2.23
		Month 10	1389	4.09	-2.19
		FOT	1389	4.10	-2.18
Observed cases	DVS SR	Baseline	1389	6.28	
		Week 1	1317	5.95	-0.30
		Week 2	1225	5.18	-1.06
		Month 1	1257	4.61	-1.61
		Month 2	1165	3.87	-2.28
		Month 3	1075	3.71	-2.39
		Month 4	968	3.35	-2.70
		Month 5	893	3.09	-2.88
		Month 6	828	3.10	-2.81
		Month 7	761	2.86	-2.92
		Month 8	738	2.62	-3.13
		Month 9	697	2.57	-3.17
		Month 10	650	2.62	-3.14
		>Month 10	9	3.33	-2.44

DVS SR = desvenlafaxine succinate sustained-release formulation, FOT = final on-therapy, HAM-D_6 = Hamilton Rating Scale for Depression, 6-item, ITT = intent-to-treat, LOCF = last observation carried forward, n = number of subjects with prespecified criteria.

Covi Anxiety Scale: Mean scores had decreased by -0.24 from Baseline to the FOT evaluation and for the observed-cases analysis, mean scores had decreased by -0.58 from Baseline to Month 10. The results are summarized in Table 20.

Table 20. Means Over Time – Covi Anxiety Scale – LOCF and Observed Cases, ITT Population

Analysis	Therapy	Week of Therapy	n	Mean Score	Mean Change From Baseline
LOCF	DVS SR	Baseline	1389	4.75	
		Month 3	1288	4.50	-0.25
		Month 6	1296	4.50	-0.25
		Month 10	1296	4.51	-0.24
		FOT	1296	4.51	-0.24
Observed	DVS SR	Baseline	1389	4.75	
		Month 3	1074	4.31	-0.41
		Month 6	817	4.15	-0.50
		Month 10	647	4.02	-0.58
		>Month 10	9	4.11	-0.44

DVS SR = desvenlafaxine succinate sustained-release formulation, FOT = final on-therapy,
ITT = intent-to-treat, n = number of subjects in pre-specified criteria, LOCF = last observation carried forward.

Safety Results:

The primary objective of the study was safety.

Serious adverse events (SAEs) and noteworthy AEs were reported by 65 of the 1395 subjects (<5%) in the safety population. Of these 65 subjects, 50 (<4% of the safety population) had AEs during the on-therapy period, and 16 (1% of the safety population) had AEs during the poststudy period (including subject who was counted in each period because he had 2 SAEs, 1 during the on-therapy period and 1 during the poststudy period). Most of the noteworthy AEs were unintended pregnancies. No patterns were observed in the type or frequency of occurrence for SAEs or noteworthy AEs during the course of the study. Subjects who had serious or other noteworthy AEs during on-therapy period and poststudy period are provided in Table 21 and Table 22 respectively.

Table 21. Subjects Who Had Serious or Other Noteworthy Adverse Events, On-Therapy Period

Body System Subject Serial Number	Age[a] (Years)/Sex	Days From Start of Therapy to Onset[b]	AE COSTART Term (Verbatim Term)[c]	Drug Relationship[d]	SAE	Withdrawal Because of Identified AE
Body as a Whole						
1	41/F	121	Chest pain (pulmonary chest pain)	Definitely not	X	No
2	45/M	188	Cellulitis (cellulitis, right leg)	Definitely not	X	No
3	24/F	60	Intentional overdose (intentional overdose of study medication)	Definitely not		No
4	47/F	166	Intentional overdose (intentional overdose)	Definitely not		No
5	34/F	189, 192	Intentional overdose (intentional overdose)	Definitely not		No
6[e]	43/F	119	Cellulitis (cellulitis left hand)	Definitely not	X	No
7	50/M	248	Accidental injury (intertrochanteric fracture left hip)	Definitely not	X	No
8	46/M	102	Hernia (hernia)	Definitely not	X	No
9	50	113	Cyst (sebaceous cyst)	Definitely not	X	No
10	55/M	355	Chest pain substernal (precardial pain)	Probably not	X	No
11[e,f]	53/F	10	Pain (finger pain)	Definitely not	X	No
		67	Infection (finger infection)	Definitely not	X	No
12[g]	43/M	134	Withdrawal syndrome (acute alcohol withdrawal)	Definitely not	X	Yes
		240	Withdrawal syndrome (hypomanic secondary to alcohol)	Possibly	X	No
13[e, g]	47/M	217	Headache (headache)	Probably not	X	Yes
14	44/M	160	Accidental injury (accidental injury: laceration of fifth digit left hand; right hand fifth digit fracture; right leg bone fracture; right leg fracture; right thigh laceration)	Definitely not	X	No
15	73/M	201	Abdominal syndrome, acute (appendicitis)	Definitely not	X	No
16[e, g]	31/F	132	Intentional overdose (intentional overdose); Suicide attempt (suicidal attempt)	Possibly	X	Yes
17[g]	58/F	62	Asthenia (weakness)	Probably	X	Yes
18	48/F	100	Intentional overdose (intentional overdose)	Definitely	X	No
Cardiovascular						
1[g]	45/F	156	Cerebrovascular accident (stroke)	Probably not	X	Yes
2[e, g]	47/M	217	Cerebral ischemia (transient ischemic attack)	Definitely not	X	Yes
Digestive						
1[g]	42/F	108	Colitis (diverticulitis)	Possibly	X	No
2[g,h]	46/F	125	Rectal disorder (rectal prolapse)	Probably	X	Yes
Hemic and lymphatic						
1[e]	43/F	120	Neutropenia (neutropenia)	Probably not	X	Yes
2[e]	22/F	63	Anemia (anemia)	Definitely not	X	Yes
Musculoskeletal						
1[e, g]	38/M	96	Rhabdomyolysis (rhabdomyolysis)	Possibly	X	Yes

Table 21. Subjects Who Had Serious or Other Noteworthy Adverse Events, On-Therapy Period

Body System Subject Serial Number	Age[a] (Years)/Sex	Days From Start of Therapy to Onset[b]	AE COSTART Term (Verbatim Term)[c]	Drug Relationship[d]	SAE	Withdrawal Because of Identified AE
2[e, f]	53/F	161	Tenosynovitis (trigger finger syndrome)	Definitely not	X	No
Nervous						
1[e, g]	38/M	96	Agitation (agitation due to manic event); manic reaction (agitation due to manic event)	Possibly	X	Yes
			Manic depressive reaction (bipolar disorder)	Probably	X	Yes
2[g]	26/M	66	Convulsion (seizure)	Possibly	X	Yes
3	27/F	91	Suicidal ideation (suicidal ideation)	Definitely not	X	No
4[g]	32/F	128	Suicidal ideation (suicidal ideation)	Possibly	X	Yes
5	31/F	314	Depression (relapse of depression)	Probably not	X	Yes
6[g]	70/F	98	Depression (anxio-depressive syndrome)	Probably	X	Yes
7	28/M	106	Suicidal ideation (suicidal ideation)	Probably not	X	Yes
8	55/M	139	Depression (worsening of depression); Suicidal ideation (suicidal ideation)	Probably not	X	Yes
9[e, g]	31/F	132	Depression (worsening of depression)	Possibly	X	Yes
10[g]	53/F	236	Suicidal ideation (suicidal thoughts)	Definitely not	X	Yes
11	41/F	133	Suicidal ideation (suicidal ideations)	Definitely not	X	Yes
12	30/M	300	Suicidal ideation (suicidal ideation)	Definitely not	X	No
13	44/F	69	Anxiety (panic attack)	Definitely not	X	No
Skin and Appendages						
1	45/F	219	Skin carcinoma (basal cell carcinoma, lesion right side)	Definitely not	X	No
2	54/F	104	Skin carcinoma (basal cell carcinoma)	Definitely not	X	No
3	70/F	125	Skin carcinoma (basal cell carcinoma)	Probably not	X	No
Urogenital						
1	32/F	88	Unintended pregnancy (pregnancy)	Definitely not		Yes
2	29/F	89	Unintended pregnancy (pregnancy)	Definitely not		Yes
3	20/F	74	Unintended pregnancy (pregnancy)	Definitely not		Yes
4	42/F	232	Unintended pregnancy (pregnancy)	Definitely not		No
5	32/F	66	Unintended pregnancy (pregnancy)	Definitely not		Yes
6	33/F	153	Unintended pregnancy (pregnancy)	Definitely not		Yes
7	29/F	179	Unintended pregnancy (pregnancy)	Definitely not		Yes
8	51/M	262	Testis disorder (hydrocele of left testis)	Probably not	X	No
9	26/F	91	Ovarian cyst (ovarian rupture follicular cyst)	Probably not	X	No
10	36/M	144	Urinary tract disorder (urethral stenosis)	Probably not	X	No

Table 21. Subjects Who Had Serious or Other Noteworthy Adverse Events, On-Therapy Period

Body System Subject Serial Number	Age[a] (Years)/Sex	Days From Start of Therapy to Onset[b]	AE COSTART Term (Verbatim Term)[c]	Drug Relationship[d]	SAE	Withdrawal Because of Identified AE
11[e]	22/F	64	Endometrial disorder (endometriosis); uterine fibroids enlarged (fibroid tumors); uterine hemorrhage (abnormal uterine bleeding)	Definitely not	X	No
12	29/F	291	Unintended pregnancy (unintended pregnancy)	Definitely not		Yes
13	23/F	56	Unintended pregnancy (unintended pregnancy)	Definitely not		No
14	53/F	100	Cervix carcinoma (cervical carcinoma)	Definitely not	X	Yes

Note: The subject serial number is consecutive per system organ class.
AE = adverse event, COSTART = Coding Symbols for the Thesaurus of Adverse Reaction Terms, F = female, IND = investigational new drug, M = male, SAE = serious adverse event.

a. Age at study entry.
b. Days from the start of treatment to the onset of the AE (including exposure in the short-term study).
c. COSTART terms are presented; verbatim terms are included in parentheses to add information to COSTART terms.
d. Relationship to study drug was based on Investigator's assessment. When an event was reported more than once for a subject, the most conservative assessment of relationship was listed.
e. This subject has AEs listed under >1 body system.
f. This subject had the SAE of finger pain during the previous short-term study (NCT00073762) and the SAE of infection (finger infection) during this study for which 2 surgeries were done. The subject also had the SAE tenosynovitis (trigger finger syndrome) during this study.
g. An IND Safety Report was filed with the United States Food and Drug Administration for these subjects.
h. This subject also had an SAE during the poststudy period.

Table 22. Subjects Who Had Serious or Other Noteworthy Adverse Events, Poststudy Period

Body System Subject Serial Number	Age[a] (Years)/Sex	Days From Start of Therapy to Onset[b]	AE COSTART Term (Verbatim Term)[c]	Drug Relationship[d]	SAE	Withdrawal Because of Identified AE
Body as a Whole						
1[e,f]	42/M	NA	Sarcoidosis	Probably not		NA
2	42/F	88	Cellulitis (cellulitis)	Probably not	X	No
3	41/F	185	Back pain (back pain)	Definitely not	X	No
Cardiovascular						
1	33/M	91	Pulmonary embolus (pulmonary embolism)	Definitely not	X	No
2	59/F	222	Myocardial infarct (heart attack)	Definitely not	X	No
3[f]	41/F	140	QT interval prolonged (prolonged QTc interval)	Possibly		No
Digestive						
1[g]	46/F	179	Intestinal obstruction (small bowel obstruction)	Definitely not	X	No
Endocrine						
1[h]	56/F	92	Hyperthyroidism (hyperthyroidism)	Possibly	X	No
Hemic and lymphatic						
1[e,f]	42/M	NA	Chronic lymphocytic leukemia	Possibly		NA
Nervous						
1[h]	31/F	229	Convulsion (seizure disorder)	Possibly	X	Yes
2	40/M	133	Addiction (cocaine dependence)	Definitely not		Yes
3	32/M	215	Homicidal ideation (homicidal ideation); suicidal ideation (suicidal ideation)	Probably not	X	Yes
4[f,h]	41/F	140	Convulsion (seizure)	Possibly	X	No
5[f,h]	51/M	95	Ataxia (ataxia); speech disorder (speech impairment)	Probably not	X	No
6	31/F	331	Depression (depression, relapse); suicidal ideation (suicidal ideation)	Definitely not	X	Yes
7	53/M	127	Depression (worsening of major depression); suicidal ideation (suicidal ideation)	Definitely not	X	No
8	25/F	104	Suicidal ideation (suicidal ideation)	Definitely not	X	No
Special senses						
1[f, h]	51/M	95	Abnormal vision (blurred vision)	Probably not	X	No
Urogenital						
1	33/F	175	Unintended pregnancy (pregnancy)	Definitely not		Yes

Table 22. Subjects Who Had Serious or Other Noteworthy Adverse Events, Poststudy Period

Body System Subject Serial Number	Age[a] (Years)/Sex	Days From Start of Therapy to Onset[b]	AE COSTART Term (Verbatim Term)[c]	Drug Relationship[d]	SAE	Withdrawal Because of Identified AE

Note: The subject serial number is consecutive per system organ class.
AE = adverse event, CLL = chronic lymphyocytic leukemia, COSTART = Coding Symbols for the Thesaurus of Adverse Reaction Terms, F = female, IND = investigational new drug, M = male, NA = not available, SAE = serious adverse event, QTc = corrected QT interval.

a. Age at study entry.
b. Days from the start of treatment to the onset of the AE (including exposure in the short-term study).
c. COSTART terms are presented; verbatim terms are included in parentheses to add information to COSTART terms.
d. Relationship to study drug was based on Investigator's assessment. When an event was reported more than once for a subject, the most conservative assessment of relationship was listed.
e. On the database, the AE of sarcoidosis was the reason for the initial filing of an IND Safety Report, which was submitted 29 April 2005. CLL was also reported by the Investigator, not as a SAE but as an event possibly related to use of study medication. In the follow-up 15-day report (13 May 2005), CLL was removed as a diagnosis and the assessment for sarcoidosis was changed to not related to study medication use, but rather probably related to a pre-existing condition. On the database, sarcoidosis was listed as a SAE probably not related to study medication use.
f. This subject has AEs listed under >1 body system.
g. This subject also had an SAE during the on-therapy period.
h. An IND Safety Report was filed with the United States Food and Drug Administration for these subjects.

Treatment-emergent AEs were reported by 1238 (89%) of 1395 subjects taking DVS SR during the on-therapy period. This number includes subjects who had reported AEs during the previous short-term study (on-therapy and/or taper/poststudy period) that were ongoing at the time the subject entered this study. Table 23 and Table 24 presents the most common (incidence ≥5%) treatment-emergent AEs (all-causality) and treatment-related.

Table 23. Number (%) of Subjects Reporting Treatment-Emergent Adverse Events (Incidence ≥5%), On-Therapy Period

Body System Adverse Event	DVS SR (N=1395) n (%)[a]
Body as a whole	
Abdominal pain	79 (6)
Accidental injury	119 (9)
Asthenia	166 (12)
Back pain	109 (8)
Flu syndrome	90 (6)
Headache	441 (32)
Infection	192 (14)
Pain	76 (5)
Cardiovascular	
Hypertension	127 (9)
Digestive	
Anorexia	84 (6)
Constipation	123 (9)
Diarrhea	96 (7)
Dry mouth	174 (12)
Dyspepsia	71 (5)
Nausea	337 (24)
Vomiting	80 (6)
Metabolic and nutritional	
Weight gain	70 (5)
Nervous	
Abnormal dreams	70 (5)
Dizziness	213 (15)
Insomnia	216 (15)
Somnolence	147 (11)
Respiratory	
Upper respiratory infection	163 (12)
Skin and appendages	
Sweating	223 (16)
Urogenital	
Abnormal ejaculation[b]	36 (7)
Impotence[b]	32 (7)

Non SAE and SAE results are not separated out.
N = number of subjects per treatment group, n = number of subjects in pre-specified criteria, SAE = serious adverse event.
a. Incidence evaluated before rounding.
b. Based on the number of men in the safety population, n=488.

Table 24. Number (%) of Subjects Reporting Treatment-Emergent Adverse Events Related to Study Drug (Incidence ≥5%), On-Therapy Period

Body System[a] Adverse Event	DVS SR (N=1395) n (%)
Any adverse event	878 (62.9)
Body as a whole	337 (24.2)
Asthenia	131 (9.4)
Headache	236 (16.9)
Cardiovascular system	214 (15.3)
Hypertension	108 (7.7)
Digestive system	557 (39.9)
Anorexia	80 (5.7)
Constipation	109 (7.8)
Dry mouth	171 (12.3)
Nausea	302 (21.6)
Nervous system	608 (43.6)
Dizziness	185 (13.3)
Insomnia	176 (12.6)
Somnolence	134 (9.6)
Skin and appendages	256 (18.4)
Sweating	212 (15.2)
Urogenital system	148 (10.6)
Impotence	31 (6.4)

Non SAE and SAE results are not separated out.
N = number of subjects per treatment group, n = number of subjects in pre-specified criteria, SAE = serious adverse event.
a. Body system totals are not necessarily the sum of the individual adverse events since a subject might have reported ≥2 different adverse events in the same body system.

Table 25 presents AEs with ≥2% incidence that were taper/poststudy emergent by body system, therapy and drug relationship. The most common (incidence ≥5%) taper/poststudy-emergent AEs were dizziness (12%), nausea (9%), headache (8%), and withdrawal syndrome (5%).

Table 25. Adverse Events With ≥2% Incidence by Therapy and Drug Relationship That Were Taper/Poststudy Emergent

Body System[a] Adverse Event	Desvenlafaxine SR (N=1395)
Any adverse event	582 (42)
Body as a whole	252 (18)
Asthenia	22 (2)
Headache	117 (8)
Withdrawal syndrome	72 (5)
Digestive system	180 (13)
Diarrhea	31 (2)
Nausea	124 (9)
Vomiting	34 (2)
Nervous system	345 (25)
Abnormal dreams	25 (2)
Anxiety	27 (2)
Depression	29 (2)
Dizziness	172 (12)
Emotional lability	22 (2)
Hostility	43 (3)
Insomnia	51 (4)
Paresthesia	40 (3)
Vertigo	34 (2)
Skin and appendages	37 (3)
Sweating	22 (2)

Non SAE and SAE results are not separated out.
N = total number of subjects, SAE = serious adverse events, SR = sustained release.
a. Body system totals are not necessarily the sum of the individual adverse events since a subject might have reported ≥2 different adverse events in the same body system.

Table 26 provides a summary of all AEs that led to withdrawal from study during the on-therapy period.

Table 26. Number (%) of Subjects Reporting Adverse Events That Caused Withdrawal From Study, Safety Population (On-Therapy)

Body System[a] Adverse Event	Desvenlafaxine SR N=1395
Any adverse event	306 (22)
Body as a whole	43 (3)
Abdominal pain	7 (<1)
Accidental injury	1 (<1)
Asthenia	17 (1)
Chills	3 (<1)
Flu syndrome	1 (<1)
Generalized edema	1 (<1)
Headache	10 (<1)
Hormone level altered	1 (<1)
Infection	1 (<1)
Intentional overdose	1 (<1)
Pain	1 (<1)
Suicide attempt	1 (<1)
Withdrawal syndrome	1 (<1)
Cardiovascular system	58 (4)
Cerebral ischemia	1 (<1)
Cerebrovascular accident	1 (<1)
Embolus	1 (<1)
Hypertension	36 (3)
Hypotension	1 (<1)
Migraine	2 (<1)
Pallor	1 (<1)
Palpitation	10 (<1)
Postural hypotension	1 (<1)
QT interval prolonged	1 (<1)
Sinus bradycardia	1 (<1)
Syncope	2 (<1)
Tachycardia	1 (<1)
Vasodilatation	1 (<1)
Digestive system	93 (7)
Anorexia	7 (<1)
Constipation	6 (<1)
Diarrhea	6 (<1)
Dry mouth	9 (<1)
Dyspepsia	1 (<1)
Flatulence	1 (<1)
Gamma glutamyl transpeptidase increased	9 (<1)
Ileitis	1 (<1)
Increased appetite	1 (<1)
Liver function tests abnormal	10 (<1)
Nausea	49 (4)
Rectal disorder	1 (<1)
Vomiting	11 (<1)
Endocrine system	3 (<1)
Diabetes mellitus	1 (<1)
Hypothyroidism	1 (<1)
Prolactin increased	1 (<1)
Hemic and lymphatic system	3 (<1)
Anemia	1 (<1)

Table 26. Number (%) of Subjects Reporting Adverse Events That Caused Withdrawal From Study, Safety Population (On-Therapy)

Body System[a] Adverse Event	Desvenlafaxine SR N=1395
Neutropenia	2 (<1)
Metabolic and nutritional	25 (2)
Alkaline phosphatase increased	1 (<1)
Edema	1 (<1)
Hemochromatosis	1 (<1)
Hypercholesteremia	4 (<1)
Hyperglycemia	2 (<1)
Hyperlipemia	7 (<1)
Peripheral edema	1 (<1)
SGOT increased	5 (<1)
SGPT increased	5 (<1)
Weight gain	6 (<1)
Musculoskeletal system	8 (<1)
Intervertebral disc protrusion	1 (<1)
Muscle spasms	1 (<1)
Musculoskeletal stiffness	5 (<1)
Rhabdomyolysis	1 (<1)
Nervous system	133 (10)
Abnormal dreams	1 (<1)
Addiction	1 (<1)
Agitation	6 (<1)
Alcoholism	1 (<1)
Anxiety	10 (<1)
Apathy	1 (<1)
Ataxia	1 (<1)
Confusion	3 (<1)
Convulsion	2 (<1)
Depersonalization	1 (<1)
Depression	8 (<1)
Dizziness	35 (3)
Energy increased	1 (<1)
Euphoria	1 (<1)
Homicidal ideation	1 (<1)
Hostility	5 (<1)
Hypesthesia	1 (<1)
Incoordination	2 (<1)
Insomnia	22 (2)
Libido decreased	10 (<1)
Manic depressive reaction	1 (<1)
Manic reaction	3 (<1)
Memory impairment	1 (<1)
Myoclonus	1 (<1)
Nervousness	7 (<1)
Paresthesia	5 (<1)
Restless legs syndrome	2 (<1)
Sleep disorder	5 (<1)
Somnolence	18 (1)
Suicidal ideation	8 (<1)
Thinking abnormal	8 (<1)
Tremor	10 (<1)

Table 26. Number (%) of Subjects Reporting Adverse Events That Caused Withdrawal From Study, Safety Population (On-Therapy)

Body System[a] Adverse Event	Desvenlafaxine SR N=1395
Trismus	5 (<1)
Twitching	1 (<1)
Vertigo	6 (<1)
Respiratory system	8 (<1)
Dyspnea	2 (<1)
Epistaxis	1 (<1)
Pleural disorder	1 (<1)
Upper respiratory infection	1 (<1)
Yawn	3 (<1)
Skin and appendages	33 (2)
Acne	1 (<1)
Eczema	1 (<1)
Night sweats	1 (<1)
Rash	5 (<1)
Skin disorder	2 (<1)
Sweating	19 (1)
Urticaria	4 (<1)
Special senses	17 (1)
Abnormal vision	8 (<1)
Mydriasis	6 (<1)
Photophobia	1 (<1)
Taste loss	1 (<1)
Taste perversion	1 (<1)
Tinnitus	3 (<1)
Vestibular disorder	1 (<1)
Urogenital system	43 (3)
Abnormal ejaculation/orgasm	6 (<1)
Amenorrhea	1 (<1)
Anorgasmia	6 (<1)
Cervix carcinoma	1 (<1)
Dysuria	2 (<1)
Galactorrhea	1 (<1)
Impotence	7 (1)
Metrorrhagia	2 (<1)
Ovarian cyst	1 (<1)
Sexual function abnormal	1 (<1)
Unintended pregnancy	8 (<1)
Urinary frequency	2 (<1)
Urinary hesitation	4 (<1)
Urination impaired	1 (<1)
Uterine hemorrhage	1 (<1)
Terms not classifiable	1 (<1)
Reaction unevaluable	1 (<1)

N = total number of subjects, SR = sustained release.

a. Body system totals are not necessarily the sum of the individual adverse events since subject might have reported ≥2 different adverse events in the same body system.

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

Of the 1395 subjects in the safety population, 1195 subjects were tested for a particular laboratory assessment at least once during the on-therapy period and received at least 1 dose of study drug during the data analysis interval in which they were tested. Of these 1195 subjects, 524 (44%) had laboratory values of potential clinical importance during the on-therapy period. Table 27 summarizes the number of subjects with values of potential clinical importance during the on-therapy period for this study, grouped by laboratory assessment.

Table 27. Number (%) of Subjects With Laboratory Test Results of Potential Clinical Importance/Number of Subjects Tested (On-Therapy Period)

Category Test Criterion	n/N (%)[a]
Blood Chemistry	
Bicarbonate, mmol/L	
Increase from Baseline of ≥4 mmol/L and ONR	51/1186 (4)
Decrease from Baseline of ≥4 mmol/L and ONR	3/1186 (<1)
Calcium, mmol/L	
<2.046 mmol/L	4/1189 (<1)
Chloride, mmol/L	
<90 mmol/L	2/1189 (<1)
Creatinine, mcmol/L	
≥1.5 x ULN	2/1189 (<1)
Glucose, mmol/L fasting	9/1082 (<1)
≥11.10 mmol/L	
AST/SGOT, U/L	
≥3 x ULN	6/1183 (<1)
ALT/SGPT, U/L	
≥3 x ULN	12/1186 (1)
Total bilirubin, mcmol/L	
≥1.5 x ULN	7/1188 (<1)
Total protein, g/L	
<45 g/L	1/1189 (<1)
Uric acid, mmol/L	
>0.4758 mmol/L (women)	8/771 (1)
>0.5948 mmol/L (men)	5/418 (1)
Hematology	
Hematocrit	
>0.50 (women)	1/764 (<1)
<0.32 (women)	10/764 (1)
>0.55 (men)	4/414 (<1)
<0.37 (men)	1/414 (<1)
Hemoglobin	
>165 g/L (women)	2/764 (<1)
<95 g/L (women)	11/764 (1)
>185 g/L (men)	1/414 (<1)
<115 g/L (men)	1/414 (<1)
WBC	
>16 x 10^9/L	2/1178 (<1)
<2.8 x 10^9/L	9/1178 (<1)
Lipid Profile	
Total cholesterol/lipid, mmol/L fasting	
Increase ≥1.29 mmol/L and value ≥6.75 mmol/L (Sponsor)	55/1081 (5)
Cholesterol, mmol/L	
≥7.758 mmol/L (FDA)	65/1081 (6)
HDL, mmol/L fasting	
Decrease >0.21 mmol/L and value <0.96 mmol/L	21/1079 (2)
LDL, mmol/L fasting	
Increase ≥1.29 mmol/L and value ≥4.91 mmol/L	25/1064 (2)

Table 27. Number (%) of Subjects With Laboratory Test Results of Potential Clinical Importance/Number of Subjects Tested (On-Therapy Period)

Category Test Criterion	n/N (%)[a]
Triglycerides/lipid, mmol/L fasting ≥3.7 mmol/L	86/1081 (8)
Urinalysis	
Specific gravity >1.035	33/1175 (3)
Urine hemoglobin/blood Positive value	207/1175 (18)
Urine protein/albumin Positive value	91/1175 (8)
Urine ketones/acetone Positive value	50/1175 (4)
Urine sugar/glucose Positive value	30/1175 (3)
Urine pH ≤4	1/1175 (<1)
≥9	1/1175 (<1)

AST/SGOT = aspartate aminotransferase/serum glutamic oxaloacetic transaminase, ALT/SGPT = alanine aminotransferase/serum glutamic pyruvic transaminase, FDA = US Food and Drug Administration; HDL = high density lipoprotein, LDL = low-density lipoprotein, N = total number of subjects, n = number of subjects in pre-specified criteria, pH = hydrogen ion concentration, ONR = outside normal range, ULN = upper limit of normal, WBC = white blood count.

a. Denominators are comprised of subjects in the safety population who were tested for a particular laboratory assessment at least once during the on-therapy period and who received at least 1 dose of study drug during the data analysis interval in which they were tested.

The Medical Monitor determined that 42 subjects (3% of 1395) had clinically important changes in laboratory tests. Table 28 presents a summary tabulation of these clinically important laboratory test results.

Table 28. Summary Tabulation of Individual Clinically Important Laboratory Test Results

Clinically Important Laboratory Test Result	N=42
Elevated total cholesterol	17
Elevated LFT	9
Anemia	6
Elevated triglycerides	3
Hematuria	3
Elevated thyroid function	1
Elevated serum glucose	1
WBC decreased	1
Howell Jolly bodies	1

LFT = liver function test, N = total number of subjects, WBC = white blood cell count.

Changes from Baseline values in laboratory tests were evaluated for statistical significance. The baseline data for this study was the Study Day 56 data of the short-term studies. Mean

differences from Baseline in laboratory evaluations that were statistically significant are presented in Table 29 for selected laboratory tests.

Table 29. Baseline Mean and Mean Change From Baseline for Selected Laboratory Tests

Test (Units) Time Period	N	Baseline Mean[a]	Mean Change From Baseline[b]
Creatinine (mcmol/L)			
Month 3	1023	70.788	-0.133
Month 6	788	70.381	-0.227
Month 10	617	70.622	1.018*
FOT	1188	71.064	-0.098
Alkaline phosphatase (mU/mL)			
Month 3	1022	75.5	3.0†
Month 6	786	75.1	1.4*
Month 10	617	73.8	2.4†
FOT	1185	75.6	1.6†
GGT (mU/mL)			
Month 3	1021	29.0	6.1†
Month 6	786	28.5	6.5†
Month 10	617	28.1	5.5†
FOT	1185	29.4	6.0†
ALT/SGPT (mU/mL)			
Month 3	1021	24.2	1.0*
Month 6	783	23.8	0.7
Month 10	616	23.6	1.3
FOT	1185	24.6	0.7
AST/SGOT (mU/mL)			
Month 3	1015	22.7	0.6‡
Month 6	778	22.5	0.8
Month 10	611	22.3	0.8
FOT	1182	22.9	0.5
Total bilirubin (mcmol/L)			
Month 3	1022	8.038	-0.744†
Month 6	788	8.017	-0.672†
Month 10	616	7.988	-0.749†
FOT	1187	8.121	-0.721†
Total cholesterol/lipid, fasting (mmol/L)			
Month 3	872	5.464	0.176†
Month 6	690	5.503	0.137†
Month 10	564	5.512	0.126†
FOT	979	5.478	0.127†
HDL cholesterol, fasting (mmol/L)			
Month 3	871	1.40279	0.04153†
Month 6	688	1.42780	0.05703†
Month 10	563	1.43872	0.05772†
FOT	977	1.40670	0.05049†
LDL cholesterol, fasting (mmol/L)			
Month 3	848	3.36799	0.08394†
Month 6	672	3.40011	0.00668

Table 29. Baseline Mean and Mean Change From Baseline for Selected Laboratory Tests

Test (Units) Time Period	N	Baseline Mean[a]	Mean Change From Baseline[b]
Month 10	549	3.40415	-0.00509
FOT	966	3.38320	0.01707
Triglycerides/fasting (mmol/L)			
Month 3	872	1.51171	0.10351†
Month 6	690	1.46897	0.16599†
Month 10	564	1.46672	0.15244†
FOT	979	1.51936	0.11844†

AST/SGOT = aspartate aminotransferase/serum glutamic oxaloacetic transaminase, ALT/SGPT = alanine aminotransferase/serum glutamic pyruvic transaminase, FOT = final on-therapy; GGT = gamma-glutamyltransferase, HDL = high-density lipoprotein, LDL = low-density lipoprotein, N = number of subjects.

a. The baseline used for comparison was the last value at the Study Day 56 evaluation (or final evaluation) of the short-term study.

b. All statistics are evaluated using data with non-missing baseline values. n: the number of matched non-missing pairs. Statistical significance at the 0.05, 0.01, and 0.001 levels is denoted by ‡,*, and, † respectively.

Of the 1395 subjects in the safety population, 1353 subjects had a weight measurement or were tested for a particular vital sign measurement at least once during the on-therapy period and also received at least 1 dose of study drug during the data analysis interval in which they were measured or tested. Of the 1353 subjects, 456 (34%) had vital sign measurements of potential clinical importance during the on-therapy period as shown in Table 30.

Table 30. Number (%) of Subjects With Changes in Vital Signs of Potential Clinical Importance by Criterion (On-Therapy Period)

Test Criterion[a]	n/N (%)[b]
Supine pulse rate (beats/min)	
Increase ≥15 and ≥120	2/1353 (<1)
Decrease ≥15 and ≤50	5/1353 (<1)
Postural blood pressure change, diastolic (mm Hg)	
Decrease ≥15 last supine to first standing	56/1353 (4)
Postural blood pressure change, systolic (mm Hg)	
Decrease ≥30 systolic last supine to first standing	28/1353 (2)
Diastolic blood pressure, standing (mm Hg) [c]	
Increase ≥15 and value ≥105	73/1353 (5)
Decrease ≥15 and value ≤50	6/1353 (<1)
Systolic blood pressure, standing (mm Hg) [c]	
Increase ≥20 and value ≥180	8/1353 (<1)
Decrease ≥20 and value ≤90	20/1353 (1)
Diastolic blood pressure supine (mm Hg) [c]	
Increase ≥15 and value ≥105	35/1353 (3)
Decrease ≥15 and value ≤50	8/1353 (<1)
Systolic blood pressure supine (mm Hg) [c]	
Increase ≥20 and value ≥180	7/1353 (<1)
Decrease ≥20 and value ≤90	15/1353 (1)
Weight (kg)	
Increase ≥7%	221/1353 (16)
Decrease ≥7%	82/1353 (6)

N = total number of subjects, n = number of subjects in treatment group.

a. For this study, the Baseline used for comparison of pulse rate and blood pressure measurements was the average of all values at the Study Day 56 evaluation (or final evaluation) of the short-term study. The Baseline used for comparison of weight was the last value at the Study Day 56 evaluation (or final evaluation) of the short term study.

b. Denominators are comprised of subjects in the safety population who were tested for a particular vital sign measurement or who had a weight measurement at least once during the on-therapy period and who received at least 1 dose of study drug during the data analysis interval in which they were measured or tested.

c. An average for a visit was used in calculating on-therapy values.

The Medical Monitor determined that 46 subjects (3% of 1395) had clinically important changes in vital signs and Table 31 presents a summary tabulation of these clinically important vital signs results. Changes in mean values for vital signs were evaluated for statistically significant differences from Baseline. The means and statistical significance from Baseline for supine diastolic BP, supine pulse rate, supine systolic BP, and weight are presented in Table 32.

Table 31. Summary Tabulation of Individual Clinically Important Vital Sign Results

Clinically Important Vital Sign Results	N=46
Hypertension	6
Hypotension	2
Postural hypotension	2
Weight gain	30
Weight loss	6

N = total number of subjects.

Table 32. Baseline Mean and Mean Change From Baseline for Selected Vital Signs

Test (Units) Time Period	N	Baseline Mean[a]	Mean Change From Baseline[b]
Systolic BP, supine (mm Hg)			
Week 1	1289	121.58	1.57*
Week 2	1203	121.69	1.55*
Month 1	1237	121.89	1.90*
Month 2	1142	121.89	2.03*
Month 3	1051	121.90	2.02*
Month 4	949	122.15	2.45*
Month 5	885	122.23	2.24*
Month 6	815	122.26	1.70*
Month 7	749	122.04	2.33*
Month 8	728	122.08	2.23*
Month 9	688	121.85	2.59*
Month 10	639	121.98	1.70*
Poststudy	1158	121.76	1.39*
FOT	1353	121.60	2.58*
Diastolic BP, supine (mm Hg)			
Week 1	1289	77.46	0.61†
Week 2	1203	77.49	0.38
Month 1	1237	77.69	0.70†
Month 2	1142	77.64	0.91*
Month 3	1051	77.62	1.41*
Month 4	949	77.70	0.97*
Month 5	885	77.69	1.03*
Month 6	815	77.74	1.28*
Month 7	749	77.67	0.65‡
Month 8	728	77.62	0.50
Month 9	688	77.49	0.86‡
Month 10	639	77.44	1.13*
Poststudy	1158	77.49	0.24
FOT	1353	77.54	1.20*
Pulse rate, supine (beats/min)			
Week 1	1289	70.52	2.55*
Week 2	1203	70.50	3.43*
Month 1	1236	70.76	3.87*
Month 2	1142	70.68	3.89*
Month 3	1051	70.78	2.99*
Month 4	949	70.72	4.67*
Month 5	885	70.65	4.51*
Month 6	815	70.63	3.32*
Month 7	749	70.39	5.29*
Month 8	728	70.45	5.04*
Month 9	688	70.42	4.30*
Month 10	639	70.53	3.29*
Poststudy	1158	70.53	3.84*
FOT	1353	70.53	3.26*
Weight (kg)			
Week 1	1288	79.65	-0.07‡
Week 2	1205	79.81	-0.08
Month 1	1235	79.69	-0.07

Table 32. Baseline Mean and Mean Change From Baseline for Selected Vital Signs

Test (Units) Time Period	N	Baseline Mean[a]	Mean Change From Baseline[b]
Month 2	1141	79.43	0.17‡
Month 3	1047	79.14	0.29†
Month 4	949	79.17	0.66*
Month 5	884	79.02	0.78*
Month 6	816	78.91	0.97*
Month 7	749	78.53	1.40*
Month 8	728	78.26	1.60*
Month 9	688	77.96	1.90*
Month 10	638	77.80	1.85*
Poststudy	1156	79.30	1.76*
FOT	1353	79.69	1.25*

BP = blood pressure, FOT = final on-therapy, N = number of subjects.

a. For this study, the baseline used for comparison of pulse rate and blood pressure measurements was the average of all values at the Study Day 56 evaluation (or final evaluation) of the short-term studies. The baseline used for comparison of weight was the last value at the Study Day 56 evaluation (or final evaluation) of the short-term studies.

b. All statistics are evaluated using data with non-missing baseline values. n: the number of matched non-missing pairs. Statistical significance at the 0.05, 0.01, and 0.001 levels is denoted by ‡, †, and *, respectively.

Of the 1395 subjects in the safety population, 1161 subjects had an ECG recording at least once during the on-therapy period and received at least 1 dose of study drug during the data analysis interval in which they had the ECG. Of those 1161 subjects, 238 (21%) had changes of potential clinical importance as summarized in Table 33.

Table 33. Number (%) of Subjects With Electrocardiogram Results of Potential Clinical Importance/Number Tested (On-Therapy Period)

Test Criterion[a]	n/N (%)[b]
Heart rate	
Decrease ≥15 bpm and value ≤50 bpm	2/1161 (<1)
Overall evaluation	
Not normal	178/1161 (15)
PR Interval	
≥200 ms	29/1161 (3)
QRS interval	
≥120 ms	12/1161 (1)
QT interval	
≥480 ms	1/1161 (<1)
Rhythm	
Not sinus	58/1161 (5)
QTcN interval (men)	
>450 ms or increase of ≥60 ms	5/406 (1)
QTcF interval (women)	
>470 ms or increase of ≥60 ms	1/755 (<1)
QTcF interval (men)	
>450 ms or increase of ≥60 ms	6/406 (2)
QTcB interval (women)	
>470 ms or increase of ≥60 ms	15/755 (2)
QTcB interval (men)	
>450 ms or increase of ≥60 ms	19/406 (5)

n = number of subjects in treatment group, N = total number of subjects, PR = pulse rate, QTcB = QT interval based on the Bazett correction, QTcF = QT interval based on the Fridericia correction, QTcN = population-corrected QT interval.

a. For this study, the baseline used for comparison was the average of all values at the Study Day 56 evaluation (or final evaluation) of the short-term study.

b. Denominators are comprised of subjects in the safety population who had an electrocardiogram at least once during the on-therapy period and who received at least 1 dose of study drug during the data analysis interval in which they were tested.

The Medical Monitor determined that 4 subjects (<1%) had clinically important ECG results as presented in Table 34.

Table 34. Subjects Who Had Clinically Important Changes in Electrocardiogram Results

Subject	Age/Sex	Finding
1	35/F	QRS prolongation
2	54/M	Left anterior hemiblock
3	56/M	QRS prolongation
4	56/M	Increased QTcF, QTcB

F = female, M = male, QTcB = QT correction using the Bazett formula; QTcF = QT correction using the Fridericia formula.

Mean changes in ECG results were evaluated for statistically significant differences from Baseline. Significant changes from Baseline were noted for each measurement at the FOT

evaluation, and most measurements showed significant changes from Baseline throughout the study as well (Table 35).

Table 35. Baseline Mean and Mean Change From Baseline for Quantitative Electrocardiogram Measurements

Test (Units) Time Period	N	Baseline Mean[a]	Mean Change From Baseline[b]
Heart rate, 12-lead (beats/min)			
Month 3	1023	70.51	3.49*
Month 6	793	70.42	3.64*
Month 10	617	70.28	3.59*
FOT	1161	70.40	3.47*
PR interval, 12-lead (ms)			
Month 3	1023	156.03	-2.89*
Month 6	793	156.21	-2.80*
Month 10	617	155.71	-2.62*
FOT	1161	156.04	-3.17*
QRS interval, 12-lead (ms)			
Month 3	1023	85.17	0.28
Month 6	793	84.92	0.75†
Month 10	617	85.08	0.74†
FOT	1161	85.19	0.78*
QT interval, 12-lead (ms)			
Month 3	1023	380.54	-6.63*
Month 6	793	380.84	-5.64*
Month 10	617	380.93	-5.08*
FOT	1161	380.76	-5.17*
QTcB interval 12-lead (ms)			
Month 3	1023	409.68	2.77*
Month 6	793	409.72	4.28*
Month 10	617	409.45	4.70*
FOT	1161	409.60	4.24*
QTcF interval, 12-lead (ms)[c]			
Month 3	1023	399.47	-0.52
Month 6	793	399.60	0.77
Month 10	617	399.45	1.26
FOT	1161	399.49	0.97‡
QTcN interval, 12-lead (ms)			
Month 3	1023	400.34	-7.93*
Month 6	793	400.58	-6.77*
Month 10	617	400.65	-6.44*
FOT	1161	400.31	-6.43*
RR interval, 12-lead (ms)			
Month 3	1023	870.64	-41.18*
Month 6	793	871.73	-43.29*
Month 10	617	872.77	-42.07*
FOT	1161	872.09	-40.57*

Table 35. Baseline Mean and Mean Change From Baseline for Quantitative Electrocardiogram Measurements

FOT = final on-therapy, N = number of subjects, QTcB = QT correction using the Bazett formula, QTcF = QT correction using the Fridericia formula, QTcN = QT correction based on the population correction factor.

a. For this study, the baseline used for comparison was the average of all values at the Study Day 56 evaluation (or final evaluation) of the short-term study.
b. All statistics are evaluated using data with non-missing baseline values. n: the number of matched non-missing pairs. Statistical significance at the 0.05, 0.01, and 0.001 levels is denoted by ‡, †, and *, respectively.
c. QTcF (Fridericia) intervals were calculated by vendor.

CONCLUSIONS:

The overall results of this long-term, open-label study indicate that DVS SR has a safety profile similar to that observed in short-term (up to 8 weeks) DVS SR MDD studies and to that observed in the long-term DVS SR MDD studies (A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group Study to Evaluate the Efficacy and Safety of DVS-233 SR for Prevention of Depressive Relapse in Adult Outpatients With Major Depressive Disorder [NCT00075257], A 6 Month, Open-Label Evaluation of the Long-Term Safety of DVS-233 SR in Elderly Outpatients With Major Depressive Disorder (MDD) [NCT00242229] and A 12-Month Open-Label Evaluation of the Long-Term Safety of DVS-233 SR in Outpatients With Major Depressive Disorder [NCT00452595], (from 6 months up to 12 months). DVS SR can be safely administered for up to 12 months. Long-term (6-month) treatment with DVS SR also improved symptoms of depression based on HAM-D_{17} total scores that decreased over time and were sustained through the FOT evaluation.