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.: 3151A2-321-WW (B2061112)

PROTOCOL TITLE: A Multicenter, Randomized, Double-Blind, Placebo- and Active-Controlled Study of DVS-233 SR for Treatment of Vasomotor Symptoms Associated With Menopause

Study Centers: Thirty-seven (37) centers took part in the study and randomized subjects; 1 each in Belgium, Croatia, Mexico and Spain; 2 each in France, Hungary and South Africa; 3 each in the Czech Republic, Finland, the Netherlands, Sweden and Ukraine; 4 each in the United Kingdom (UK), Poland and Romania.

Study Initiation and Final Completion Dates: April 2005 to January 2006

Phase of Development: Phase 3

Study Objectives:

The primary objectives were to assess the efficacy and safety of desvenlafaxine succinate sustained-release formulation (DVS SR) compared with placebo for the treatment of vasomotor symptoms (VMS) associated with menopause, and to compare the bleeding incidence of DVS SR and tibolone.

The secondary objectives were to assess the effects of DVS SR and tibolone on changes from Baseline in weight, breast pain, and health outcomes indicators (Profile of Mood States [POMS], Greene Climacteric Scale [GCS], and Satisfaction Survey).

METHODS

Study Design: This was a Phase 3, outpatient, multicenter, randomized, double-blind, placebo- and active-controlled study in postmenopausal women. After the screening period (of at least 1 week and up to 4 weeks), eligible subjects were randomized to receive DVS SR 100 mg, tibolone 2.5 mg or placebo once daily for 12 weeks. Subjects had a follow-up visit approximately 15 days after discontinuing study drug. The study flowchart is given in Table 1.

Table 1. Study Flowchart

Visit	1A Washout[a]	1B Screening[a]	2 Week 0	3 Week 4	4 Week 8	5 Week 12	6 Follow-Up[b]
Relative Week	**-12 to -1**	**-4 to -1**	**0**	**3 to 5**	**7 to 9**	**12 to 13**	**14 to 15**
Study Interval	**Screening**		**On-Therapy**				**Follow-Up**
Informed consent[c]	X						
Medical history	X						
Physical examination[d]		X				X	
Vital signs/weight (kg)		X	X	X	X	X	X
Mammography[e]		X					
12-lead electrocardiogram		X					
Laboratory safety testing[f]		X		X		X	
Cervical cytology smear		X					
FSH[g]		X					
Dispense diary[h]	X	X	X			X	
Review diary		X[i]	X	X	X	X	X
Randomization[j]			X				
Health outcomes questionnaires[k]			X	X		X	
Review adverse events		X	X	X	X	X	X
Review non study medications		X	X	X	X	X	X
Dispense test article			X				
Completion of dosage record				X	X	X	

Table 1. Study Flowchart

FSH = follicle-stimulating hormone, IEC = Independent Ethics Committee, IRB = Institutional Review Board.

a. Visits 1A and 1B could be combined for subjects who did not require a washout period.
b. Follow-up visit was to occur approximately 15 days after the last day of study drug intake to obtain information about new or persistent adverse events and concomitant medications and treatments.
c. An IRB/IEC approved written informed consent form was to be signed and dated before any screening procedures, including washout, were performed.
d. The initial physical examination included complete physical examination, breast and pelvic examination, and height (cm). The follow-up examination included physical examination at Visit 5.
e. For women whose last mammography was performed >1 year previously (provided that copies of the radiographs and report were obtained).
f. Laboratory safety testing included hematology, blood chemistry, and urine assessment by dipstick, at visits 1B, combined 1A/1B, 3, and 5.
g. For subjects with uncertain last natural menstrual period, with prior approval of the Sponsor.
h. Diaries were dispensed at Visit 1A, only for subjects requiring washout for recording medications taken and symptoms/complaints. Diaries were dispensed at Visits 1B or combined 1A/1B and at Visit 2 for recording number/severity of hot flushes, bleeding and/or spotting episodes, breast pain, medications taken, and symptoms/complaints. Diaries were dispensed at Visit 5 for recording bleeding and/or spotting episodes, medications taken and symptoms/complaints.
i. Only subjects who required a washout period were to have a diary to review at Visit 1B.
j. Randomization followed confirmation that all inclusion and no exclusion criteria were met.
k. Health Outcomes questionnaires were self-administered: Greene Climacteric Scale and Profile of Moods States at Visits 2, 3, and 5, and Satisfaction Survey at Visits 3 and 5.

Number of Subjects (Planned and Analyzed): Approximately 465 subjects (155 in each group) were planned to be enrolled in the study. A total of 485 subjects were enrolled and randomized and 476 subjects were treated; 158 received DVS SR, 166 received tibolone and 162 received placebo.

Diagnosis and Main Criteria for Inclusion: Subjects were generally healthy postmenopausal women aged 40 to 65 years with an intact uterus and whose last natural menstrual period had completed at least 12 months before screening. If that date was uncertain, a follicle-stimulating hormone level >40 mIU/mL allowed enrollment. The subject must have sought treatment for hot flushes and had a minimum of 7 moderate to severe hot flushes per day or 50 per week recorded for 7 consecutive days during screening. In addition, a subject must have had a body mass index (BMI) ≤34 kg/m^2.

Exclusion Criteria: Subjects with history, presence, or suspicion of estrogen-dependent neoplasia, malignancy, or treatment for malignancy, within the previous 2 years; active or recent arterial thromboembolic disease or history of venous thromboembolism; history of cerebrovascular accident, stroke, or transient ischemic attack; presence of major depressive disorder, bipolar disorder, psychotic disorder, or generalized anxiety disorder requiring therapy; or persistent elevated blood pressure were excluded from the study.

Study Treatment: Study drugs included 100 mg DVS SR tablets, 2.5 mg encapsulated tibolone tablets and matching placebo for each. Subjects were randomly assigned to treatment with DVS SR, tibolone, or placebo as shown in Table 2. Subjects were instructed to take 1 tablet and 1 capsule orally with food and beverage once daily for 12 weeks.

Table 2. Treatment Groups

Treatment Group	Tablet	Capsule
DVS SR 100 mg	DVS SR 100 mg	Placebo of tibolone
Tibolone 2.5 mg	Placebo of DVS SR 100 mg	Tibolone 2.5 mg
Placebo	Placebo of DVS SR 100 mg	Placebo of tibolone

DVS SR = desvenlafaxine succinate sustained release.

Efficacy and Safety Endpoints:

Primary Endpoint:

- The primary efficacy endpoints were the reduction in the average daily number of moderate and severe hot flushes and the reduction in the average daily severity of hot flushes at Weeks 4 and 12;
- The primary safety endpoint was the bleeding incidence, defined as the proportion of subjects experiencing at least one episode of bleeding or spotting during treatment.

Key Secondary Endpoints:

- Change from Baseline in the total mood disturbance score for POMS;

- Change from Baseline in the GCS total score.

Other Secondary Endpoints:

- Reduction in the number of mild, moderate, and severe hot flushes;
- Reduction in the weekly weighted severity score for moderate and severe hot flushes only, calculated for each week as follows:

  (number of moderate hot flushes) x 2 + (number of severe hot flushes) x 3
- Responder analysis, with responders defined as subjects who reached ≥50% or a ≥75% decrease in the number of hot flushes from baseline;
- Time to reach a 50% decrease in number of hot flushes from Baseline for ≥3 consecutive days;
- POMS individual factor scores (tension, depression, anger, vigor, fatigue, and confusion);
- GCS subdomain scores (psychological symptoms, anxiety, depression, somatic symptoms, vasomotor symptoms, and sexual interest).

Safety Evaluations: Safety was monitored by means of adverse events (AEs) recorded on daily diary cards, scheduled physical examinations, vital sign measurements, and clinical laboratory determinations.

Statistical Methods: Two (2) populations were defined for the primary efficacy endpoints: the intent-to-treat (ITT) population for analysis of hot flushes included all subjects who received at least 1 dose of study drug, recorded data for at least 5 days during the baseline week, and had data for at least 5 days during at least 1 week during the 12 weeks while on therapy. The per-protocol (PP) population for analysis of hot flushes included subjects from the ITT population who had ≥7 moderate to severe flushes per day or 50 per week for the baseline week, had data for at least 5 days while on therapy, and took at least 80% of assigned doses (at least 6 tablets and 6 capsules per week) for the week being evaluated, and had not taken unacceptable concomitant medications.

Analysis of covariance (ANCOVA) with treatment and study site as factors and baseline value as a covariate was used to compare the differences in reduction of the average daily number and severity of hot flushes between the DVS SR dose group and placebo. Pairwise comparisons were done using t-test based on the least square means and pooled error terms obtained from the ANCOVA. The above ANCOVA analyses for Week 1 through Week 12 were done for the ITT population based on a last-observation-carried-forward (LOCF) approach and also based on observed data. The primary analysis used the LOCF approach based on weekly data, with the last on-therapy data carried forward until Week 12. The same analyses were also done for the PP population based on observed cases only.

All safety analyses were based on the safety population; those subjects who were randomly assigned to treatment and who took at least 1 dose of study drug.

RESULTS

Subject Disposition and Demography: Of the 642 subjects screened, 485 were randomly assigned to study drug, including 9 subjects who had no on-therapy data after the baseline evaluation. Of the 476 subjects who received at least 1 dose of study drug, 158 received DVS SR, 166 received tibolone and 152 received placebo. The subject disposition is summarized in Table 3.

Table 3. Subject Disposition

Population Subset	DVS SR	Tibolone	Placebo	Total
Randomly assigned	160	167	158	485
Study drug not used	2	1	6[a]	9
Safety population[b]	158	166	152	476
Excluded from ITT for VMS[c]	21	2	2	25
ITT population for VMS	137	164	150	451
Completed study	117	144	131	392

ITT = intent to treat; VMS = vasomotor symptoms.

a. One (1) subject actually took study drug for 1 week.

b. Safety population included all randomly assigned subjects who took at least 1 dose of study drug.

c. ITT population for VMS included all randomly assigned subjects who took at least 1 dose of study drug, had at least 5 days of VMS data at the baseline week, and had at least 5 on-therapy days of VMS data per week for at least 1 week during the 12 weeks.

Overall, 84 subjects withdrew from the study during the double-blind interval: 21 (13.8%) subjects treated with placebo, 41 (25.9%) treated with DVS SR, and 22 (13.3%) treated with tibolone. Table 4 summarizes the number of subjects who discontinued by the primary reason for withdrawal of study drug in each treatment group. More subjects in the DVS SR group withdrew from the study because of AEs than in the tibolone or placebo groups ($p < 0.004$).

Table 4. Number (%) of Subjects Who Withdrew From the Study

Conclusion Status Reason	Overall p-Value[a]	DVS SR 100 mg N=158	Tibolone 2.5 mg N=166	Placebo N=152
Discontinued[b]	0.004**	41 (25.9)	22 (13.3)	21 (13.8)
Adverse event	0.002**	35 (22.2)	18 (10.8)	14 (9.2)
Protocol violation	0.605	0	1 (0.6)	1 (0.7)
Subject request	0.617	3 (1.9)	2 (1.2)	1 (0.7)
Unsatisfactory response-efficacy	0.213	3 (1.9)	1 (0.6)	5 (3.3)

Statistical significance at the 0.05, 0.01, and 0.001 levels is denoted by *, **, and ***, respectively.

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

b. Overall p-value: p-value for chi-square.

Most subjects in each treatment group were White and all subjects had natural menopause and an intact uterus. Subjects were generally healthy postmenopausal women. However, the

mean BMI was 26 kg/m^2, with 276 (58%) subjects being overweight (BMI >25 kg/m^2), and 63 (13.2%) being obese (BMI>30 kg/m^2). The subject demography is presented in Table 5.

Table 5. Demographic Characteristics, Safety Population

Characteristic	DVS SR 100 mg n=158	Tibolone 2.5 mg n=166	Placebo n=152
Age (year)			
Mean	53.97	53.42	53.60
Standard deviation	4.29	4.87	5.00
Minimum - maximum	45.00-65.00	41.00-65.00	40.00-66.00
Race			
Black or African American	1 (0.63)		
Other: Hispanic	10 (6.3)	11 (6.6)	11 (7.2)
White	147 (93.04)	155 (93.37)	141 (92.76)
Ethnic origin			
Hispanic or Latino	12 (7.59)	13 (7.83)	10 (6.58)
Non-Hispanic and non-Latino	146 (92.41)	153 (92.17)	142 (93.42)
Height (cm)			
Mean	162.45	162.56	162.75
Standard deviation	6.82	6.48	6.65
Minimum - maximum	146.00-181.50	142.80-195.00	144.00-181.00
Weight (kg)			
Mean	68.38	68.03	68.60
Standard deviation	9.77	9.95	11.02
Minimum - maximum	46.80-102.00	40.00-91.20	46.60-110.00
BMI (kg/m^2)			
Mean	25.95	25.74	25.85
Standard deviation	3.65	3.49	3.49
Minimum - maximum	17.01-34.45	15.63-34.38	18.91-33.89

BMI = body mass index, n = number of subjects per treatment group.

Efficacy Results:

Reduction in Average Daily Number of Moderate and Severe Hot Flushes: The mean change in the average daily number of moderate and severe hot flushes at Week 4 and Week 12 for the ITT LOCF analysis is shown in Table 6. All treatment groups were associated with a statistically significant reduction from Baseline in the number and severity of hot flushes. When considering the 2 time points of primary interest (Week 4 and Week 12), the decreases in the average daily number of moderate and severe hot flushes seen in the DVS SR group were not significantly greater than the decreases seen with placebo. At both time points, there was a significant difference between the placebo and the tibolone groups.

Table 6. Mean Change in the Average Daily Number of Moderate and Severe Hot Flushes at Weeks 4 and 12 for the ITT Population, LOCF

Treatment	Week	Number of Pairs	Adjusted Mean Change	SE	p-Value vs Placebo
DVS SR 100 mg	4	137	-4.63	0.34	0.558
	12	137	-5.78	0.33	0.921
Tibolone 2.5 mg	4	164	-6.16	0.31	<0.001
	12	164	-8.21	0.30	<0.001
Placebo	4	150	-4.38	0.32	
	12	150	-5.82	0.31	

DVS SR = desvenlafaxine succinate sustained release; ITT = intent-to-treat; LOCF = last observation carried forward; SE = standard error, vs = versus.

Reduction in Average Daily Severity Scores of Hot Flushes: The mean change in average daily severity scores of hot flushes in the ITT LOCF analysis at Weeks 4 and 12 is summarized in Table 7. All treatment groups had a significant decrease in the adjusted mean daily severity score from Baseline at all time points. When considering the 2 time points of primary interest (Week 4 and Week 12), the mean decreases in the average daily severity scores seen in the DVS SR group were not significantly greater than the decreases seen with placebo. At both time points, there was a significant difference between the placebo and the tibolone groups.

Table 7. Mean Change in the Average Daily Severity Score of Mild, Moderate, and Severe Hot Flushes for the ITT Population at Weeks 4 and 12, LOCF

Treatment	Week	Number of Pairs	Adjusted Mean Change	SE	p-Value vs Placebo
DVS SR 100 mg	4	137	-0.37	0.06	0.352
	12	137	-0.61	0.07	0.943
Tibolone 2.5 mg	4	164	-0.57	0.05	<0.001
	12	164	-1.14	0.07	<0.001
Placebo	4	150	-0.31	0.05	
	12	150	-0.61	0.07	

DVS SR = desvenlafaxine succinate sustained release; ITT = intent-to-treat; LOCF = last observation carried forward; SE = standard error, vs = versus.

Profile of Moods States: The mean change in total mood disturbance score at Weeks 4 and 12 in the observed data analysis is shown by treatment group in Table 8. The adjusted mean total mood disturbance scores in the DVS SR and tibolone groups and in the placebo group decreased significantly from Baseline at Weeks 4 and 12. However, these mean decreases were not significantly different from those seen with placebo. Similar results were obtained in the separate subscales (tension, depression, anger, vigor, fatigue, and confusion); mean scores improved in all treatment groups with no significant differences between treatment groups. The results for the subscales are presented in Table 9.

Table 8. Mean Changes in POMS Total Mood Disturbance Score at Weeks 4 and 12 for the ITT Population, Observed Data

Treatment	Week	Number of Pairs	Adjusted Mean Change	SE	p-Value vs Placebo	p-Value vs Tibolone
DVS SR 100 mg	4	119	-12.94	2.68	0.291	0.268
	12	107	-17.75	2.84	0.216	0.806
Tibolone 2.5 mg	4	153	-9.35	2.33	0.977	
	12	136	-16.93	2.50	0.286	
Placebo	4	138	-9.44	2.45		
	12	122	-13.51	2.60		

DVS SR = desvenlafaxine succinate sustained release; ITT = intent-to-treat; POMS = Profile of Mood States, SE = standard error, vs = versus.

Table 9. Mean Changes in POMS Subscale Scores at Weeks 4 and 12 for the ITT Population, Observed Data

Treatment	Week	Number of Pairs	Adjusted Mean Change	SE	p-Value vs Placebo	p-Value vs Tibolone
Anger hostility						
DVS SR 100 mg	4	119	-3.14	0.64	0.314	0.157
	12	110	-3.89	0.67	0.731	0.765
Tibolone 2.5 mg	4	154	-2.04	0.55	0.684	
	12	136	-3.65	0.60	0.956	
Placebo	4	140	-2.34	0.58		
	12	122	-3.61	0.63		
Confusion bewilderment						
DVS SR 100 mg	4	120	-1.27	0.38	0.218	0.833
	12	110	-1.71	0.38	0.254	0.689
Tibolone 2.5 mg	4	155	-1.37	0.33	0.125	
	12	136	-1.90	0.34	0.106	
Placebo	4	141	-0.69	0.34		
	12	123	-1.17	0.36		
Depression dejection						
DVS SR 100 mg	4	120	-2.84	0.79	0.504	0.637
	12	111	-3.92	0.83	0.630	0.722
Tibolone 2.5 mg	4	155	-2.38	0.69	0.826	
	12	136	-4.28	0.76	0.382	
Placebo	4	141	-2.18	0.72		
	12	123	-3.42	0.79		
Fatigue inertia						
DVS SR 100 mg	4	120	-2.77	0.54	0.334	0.103
	12	111	-3.97	0.55	0.113	0.361
Tibolone 2.5 mg	4	155	-1.69	0.47	0.498	
	12	136	-3.37	0.50	0.465	
Placebo	4	141	-2.12	0.49		
	12	123	-2.89	0.52		
Tension anxiety						
DVS SR 100 mg	4	120	-3.09	0.56	0.215	0.245
	12	111	-4.65	0.58	0.104	0.493
Tibolone 2.5 mg	4	155	-2.30	0.49	0.915	
	12	136	-4.16	0.52	0.313	
Placebo	4	141	-2.23	0.51		
	12	123	-3.48	0.55		
Vigor activity						
DVS SR 100 mg	4	120	0.18	0.50	0.455	0.360
	12	109	0.77	0.55	0.085	0.498
Tibolone 2.5 mg	4	154	-0.38	0.44	0.873	
	12	136	0.33	0.49	0.261	
Placebo	4	140	-0.28	0.46		
	12	123	-0.39	0.51		

DVS SR = desvenlafaxine succinate sustained release; ITT = intent-to-treat; POMS = Profile of Mood States, SE = standard error, vs = versus.

Greene Climacteric Scale: The mean changes in total GCS score in the observed data analysis at Weeks 4 and 12 are shown by treatment group in Table 10. There was a significant decrease from baseline in all groups in the GCS total score at Weeks 4 and 12.

There was no significant difference between the DVS SR group and the placebo group at any time point. The decrease in the GCS total score observed in the tibolone group was significantly greater than in the placebo group at Week 12.

Mean scores improved in all treatment groups for each subscale (psychological symptoms, anxiety, depression, somatic symptoms, vasomotor symptoms, and sexual interest), with no significant difference between the DVS SR and placebo groups. The summary statistics for GCS subscale scores are provided in Table 11. The improvements in VMS and sexual interest subscales seen in the tibolone group were significantly greater than in the placebo group.

Table 10. Adjusted Mean Change in GCS Total Score for the ITT Population, Observed Data

Treatment	Week	Number of Pairs	Adjusted Mean Change	SE	p-Value vs Placebo	p-Value vs Tibolone
DVS SR 100 mg	4	119	-5.70	0.79	0.715	0.915
	12	110	-8.03	0.80	0.255	0.169
Tibolone 2.5 mg	4	157	-5.80	0.68	0.615	
	12	138	-9.37	0.72	0.009	
Placebo	4	139	-5.34	0.72		
	12	122	-6.90	0.75		

DVS SR = desvenlafaxine succinate sustained release; GCS = Greene Climacteric Scale; ITT = intent-to-treat; SE = standard error, vs = versus.

Table 11. Adjusted Mean Change in GCS Subscale Scores for the ITT Population, Observed Data

Treatment	Week	Number of Pairs	Adjusted Mean Change	SE	p-Value vs Placebo	p-Value vs Tibolone
Anxiety scale						
DVS SR 100 mg	4	119	-1.67	0.28	0.862	0.992
	12	110	-2.16	0.29	0.414	0.632
Tibolone 2.5 mg	4	157	-1.66	0.24	0.860	
	12	138	-2.33	0.26	0.175	
Placebo	4	139	-1.61	0.26		
	12	122	-1.87	0.27		
Depression scale						
DVS SR 100 mg	4	119	-1.18	0.25	0.644	0.472
	12	110	-1.83	0.27	0.675	0.728
Tibolone 2.5 mg	4	157	-0.96	0.22	0.212	
	12	138	-1.71	0.24	0.931	
Placebo	4	139	-1.33	0.23		
	12	122	-1.68	0.26		
Psychological scale						
DVS SR 100 mg	4	119	-2.85	0.48	0.887	0.701
	12	110	-3.99	0.50	0.489	0.931
Tibolone 2.5 mg	4	157	-2.62	0.42	0.580	
	12	138	-4.04	0.45	0.411	
Placebo	4	139	-2.93	0.44		
	12	122	-3.55	0.47		
Sexual interest scale						
DVS SR 100 mg	4	119	-0.24	0.08	0.884	0.406
	12	110	-0.40	0.10	0.175	0.423
Tibolone 2.5 mg	4	157	-0.32	0.07	0.305	
	12	138	-0.49	0.09	0.024	
Placebo	4	139	-0.22	0.08		
	12	121	-0.23	0.09		
Somatic scale						
DVS SR 100 mg	4	119	-0.94	0.28	0.778	0.589
	12	110	-1.37	0.29	0.767	0.238
Tibolone 2.5 mg	4	157	-0.76	0.24	0.793	
	12	138	-1.78	0.26	0.126	
Placebo	4	139	-0.84	0.25		
	12	122	-1.26	0.27		
Vasomotor scale						
DVS SR 100 mg	4	119	-1.67	0.17	0.114	0.037
	12	110	-2.26	0.18	0.053	<0.001
Tibolone 2.5 mg	4	157	-2.09	0.14	<0.001	
	12	138	-3.03	0.17	<0.001	
Placebo	4	139	-1.34	0.15		
	12	122	-1.82	0.17		

DVS SR = desvenlafaxine succinate sustained release; GCS = Greene Climacteric Scale, ITT = intent-to-treat; SE = standard error, vs = versus.

Reduction in Average Daily Number of Mild, Moderate, and Severe Hot Flushes:

The average daily numbers of mild, moderate, and severe hot flushes for the ITT LOCF analyses at all-time points over 12 weeks of therapy are presented in Table 12. There was a

significant difference between the DVS SR and the placebo group at Weeks 1 and 2. The tibolone group was significantly different from the placebo group from Week 3 onwards.

Table 12. Average Daily Number of Mild, Moderate, and Severe Hot Flushes: ITT LOCF Population

Treatment	Time Slot	Number of Pairs	Baseline		Observed		Change From Baseline		% Change From Baseline	
			Mean	SD	Mean	SD	Mean	SD	Mean	SD
DVS SR 100 mg	Screening /Baseline	137	12.0	4.9	-	-	-	-	-	-
	Week 1	137	12.0	4.9	9.4	4.8	-2.6	4.0	-21.0	29.8
	Week 2	137	12.0	4.9	8.1	5.4	-3.9	5.5	-31.3	37.9
	Week 3	137	12.0	4.9	7.6	5.6	-4.4	5.8	-35.9	42.7
	Week 4	137	12.0	4.9	7.3	5.7	-4.7	5.9	-38.9	43.7
	Week 5	137	12.0	4.9	6.6	5.3	-5.4	5.9	-44.0	41.6
	Week 6	137	12.0	4.9	6.2	5.7	-5.8	6.4	-46.9	50.6
	Week 7	137	12.0	4.9	6.3	6.3	-5.7	7.0	-46.7	61.6
	Week 8	137	12.0	4.9	6.0	5.6	-6.0	6.4	-48.9	50.3
	Week 9	137	12.0	4.9	5.8	5.6	-6.2	6.4	-50.8	51.2
	Week 10	137	12.0	4.9	5.7	5.3	-6.3	6.1	-52.0	44.0
	Week 11	137	12.0	4.9	5.6	5.3	-6.4	6.1	-52.7	45.0
	Week 12	137	12.0	4.9	5.8	5.7	-6.2	6.5	-51.2	51.3
Tibolone	Screening /Baseline	164	11.8	4.7	-	-	-	-	-	-
	Week 1	164	11.8	4.7	9.7	5.4	-2.1	3.1	-18.9	27.8
	Week 2	164	11.8	4.7	8.1	5.7	-3.7	3.5	-33.9	31.4
	Week 3	164	11.8	4.7	6.6	5.6	-5.2	3.7	-47.0	30.6
	Week 4	164	11.8	4.7	5.6	5.3	-6.2	4.0	-55.1	30.5
	Week 5	164	11.8	4.7	5.0	5.2	-6.9	4.0	-61.2	30.4
	Week 6	164	11.8	4.7	4.5	4.9	-7.4	3.9	-65.5	29.5
	Week 7	164	11.8	4.7	4.2	4.6	-7.7	3.9	-67.4	29.2
	Week 8	164	11.8	4.7	3.9	4.6	-7.9	3.9	-69.9	28.5
	Week 9	164	11.8	4.7	3.5	4.4	-8.3	4.0	-73.1	27.8
	Week 10	164	11.8	4.7	3.2	4.3	-8.6	4.1	-75.0	27.8
	Week 11	164	11.8	4.7	3.1	4.1	-8.7	4.0	-76.1	27.0
	Week 12	164	11.8	4.7	3.0	3.9	-8.8	4.5	-76.0	27.8
Placebo	Screening /Baseline	150	11.5	3.5	-	-	-	-	-	-
	Week 1	150	11.5	3.5	9.8	4.5	-1.7	3.3	-15.0	27.8
	Week 2	150	11.5	3.5	8.8	4.7	-2.7	3.8	-24.6	31.3
	Week 3	150	11.5	3.5	8.1	5.1	-3.4	4.2	-30.6	33.8
	Week 4	150	11.5	3.5	7.4	4.9	-4.1	4.3	-36.9	34.8
	Week 5	150	11.5	3.5	6.8	4.8	-4.7	4.3	-42.2	34.6
	Week 6	150	11.5	3.5	6.5	4.9	-5.0	4.3	-44.6	35.5
	Week 7	150	11.5	3.5	6.4	4.8	-5.2	4.5	-45.5	36.2
	Week 8	150	11.5	3.5	6.2	5.1	-5.4	4.8	-47.4	38.8
	Week 9	150	11.5	3.5	5.8	4.9	-5.7	4.5	-50.6	36.6
	Week 10	150	11.5	3.5	5.8	5.0	-5.7	4.5	-51.2	36.9
	Week 11	150	11.5	3.5	5.9	5.1	-5.6	4.6	-50.6	37.8
	Week 12	150	11.5	3.5	5.6	4.8	-5.9	4.5	-52.3	36.7

DVS SR = desvenlafaxine succinate sustained-release formulation, ITT = intent-to-treat, LOCF = last observation carried forward, SD = standard deviation.

Reduction in Weekly Weighted Severity Score: The results of the ITT LOCF analysis for the mean changes from Baseline in weekly weighted severity scores at Weeks 4 and 12 are shown in Table 13.

Table 13. Reduction in Weekly Weighted Score of Moderate and Severe Hot Flushes for the ITT Population, LOCF

Treatment	Week	Number of Pairs	Adjusted Mean Change	SE	p-Value vs Placebo
DVS SR 100 mg	4	137	-84.08	5.99	0.316
	12	137	-111.6	4.98	0.952
Tibolone 25 mg	4	164	-109.6	5.42	<0.001
	12	164	-149.4	4.50	<0.001
Placebo	4	150	-76.47	5.65	
	12	150	-111.2	4.70	

DVS SR = desvenlafaxine succinate sustained-release formulation, ITT = intent-to-treat; LOCF = last observation carried forward; SE = standard error, vs = versus.

For the ITT LOCF analysis at Weeks 4 and 12, there were significant decreases from Baseline in weekly weighted score of moderate and severe hot flushes in all treatment groups. However, there was no significant difference between the DVS SR group and the placebo group at any time point. The decreases observed in the tibolone group were significantly greater than those seen in the placebo group.

Subjects With ≥75% Decrease in Average Daily Number of Hot Flushes: The numbers (%) of subjects with a mean decrease from Baseline of at least 75% in the average daily number of moderate and severe hot flushes at Weeks 4 and 12 are shown in Table 14 for the ITT LOCF analysis.

Table 14. Number (%) of Subjects With ≥75% Decrease in Average Daily Number of Moderate and Severe Hot Flushes for the ITT Population, LOCF

Treatment	Week	No. of Pairs	No.	Percent	Relative ratio vs Placebo	95% CI		p-value vs Placebo
						Lower CI	Upper CI	
DVS SR 100 mg	4	137	39	28.47	1.43	0.82	2.51	0.211
	12	137	55	40.15	1.05	0.63	1.73	0.863
Tibolone 2.5 mg	4	164	66	40.24	2.67	1.58	4.52	<0.001
	12	164	117	71.34	4.87	2.93	8.10	<0.001
Placebo	4	150	33	22.00	-	-	-	
	12	150	57	38.00	-	-	-	

CI = confidence interval, DVS SR = desvenlafaxine succinate sustained-release formulation, ITT = intent-to-treat, LOCF = last observation carried forward, No. = number, vs = versus.

The number (%) of subjects with a decrease of at least 75% in the average daily number of moderate and severe hot flushes was not significantly greater in the DVS SR group than in the placebo group.

Subjects With ≥50% Decrease in Average Daily Number of Hot Flushes: The numbers (%) of subjects with decreases of at least 50% in the average daily number of moderate and severe hot flushes at Weeks 4 and 12 are shown in Table 15 for the ITT LOCF analysis.

Table 15. Number (%) of Subjects With ≥50% Decrease in Average Daily Number of Moderate and Severe Hot Flushes for the ITT Population, LOCF

Treatment	Week	No. of Pairs	No.	Percent	Relative ratio vs Placebo	95% CI		p-Value vs Placebo
						Lower CI	Upper CI	
DVS SR 100 mg	4	137	67	48.91	1.16	0.70	1.91	0.559
	12	137	90	65.69	1.17	0.70	1.95	0.544
Tibolone 2.5 mg	4	164	114	69.51	3.35	2.03	5.52	<0.001
	12	164	146	89.02	5.79	3.14	10.70	<0.001
Placebo	4	150	67	44.67	-	-	-	
	12	150	92	61.33	-	-	-	

CI = confidence interval, DVS SR = desvenlafaxine succinate sustained-release formulation, ITT = intent-to-treat, LOCF = last observation carried forward, No. = number, vs = versus.

The number (%) of subjects with a decrease of at least 50% in the average daily number of moderate and severe hot flushes was not significantly greater in the DVS SR group than in the placebo group.

Time to Consecutive Days of 50% Decrease in Hot Flushes: The results of the observed-data analysis for the time to reach at least 3 consecutive days of a ≥50% from Baseline in the daily number of moderate and severe hot flushes are given in Table 16. The median time to achieve a 50% reduction in hot flushes for at least 3 consecutive days with DVS SR treatment was 13 days, significantly sooner ($p < 0.006$) than the 26 days required with placebo.

Table 16. Median Time to the First Day of 3 Consecutive Days of ≥50% Reduction in Moderate and Severe Hot Flushes for the ITT Population, Observed Data

Treatment	Median Days to 50% Reduction	Lower Limit	Upper Limit	Log-Rank p-Value vs Placebo
DVS SR 100 mg	13.0	11.0	23.0	0.006
Tibolone 2.5 mg	16.0	13.0	18.0	<0.001
Placebo	26.0	22.0	33.0	

DVS SR = desvenlafaxine succinate sustained release, ITT = intention to treat, vs = versus.

Overall, the results for the primary and secondary efficacy endpoints from the PP population were consistent with the results obtained in the ITT population.

Safety Results:

Adverse Events: The treatment-emergent AEs reported by ≥5% of subjects in any treatment group are provided in Table 17.

Table 17. Number (%) of Subjects With Treatment-Emergent Adverse Events Reported by ≥5% of Subjects in any Treatment Group

Body System Adverse Event	DVS SR 100 mg N=158	Tibolone 2.5 mg N=166	Placebo N=152
Any adverse event	116 (73.4)	107 (64.5)	85 (55.9)
Body as a whole			
Abdominal pain	10 (6.3)	17 (10.2)	10 (6.6)
Asthenia	14 (8.9)	5 (3.0)	3 (2.0)
Back pain	4 (2.5)	7 (4.2)	11 (7.2)
Flu syndrome	4 (2.5)	9 (5.4)	6 (3.9)
Headache	34 (21.5)	36 (21.7)	31 (20.4)
Infection	10 (6.3)	8 (4.8)	10 (6.6)
Cardiovascular system			
Palpitation	7 (4.4)	4 (2.4)	8 (5.3)
Digestive system			
Constipation	17 (10.8)	3 (1.8)	4 (2.6)
Dry mouth	16 (10.1)	5 (3.0)	4 (2.6)
Nausea	49 (31.0)	14 (8.4)	7 (4.6)
Musculoskeletal system			
Arthralgia	6 (3.8)	18 (10.8)	1 (0.7)
Nervous system			
Dizziness	17 (10.8)	11 (6.6)	6 (3.9)
Insomnia	11 (7.0)	3 (1.8)	5 (3.3)
Somnolence	11 (7.0)	4 (2.4)	2 (1.3)
Special senses			
Abnormal vision	9 (5.7)	1 (0.6)	0
Urogenital system			
Breast pain	4 (2.5)	7 (4.2)	8 (5.3)
Leukorrhea	1 (0.6)	10 (6.0)	1 (0.7)

Non serious AEs and SAEs are not separated out.
AE = adverse event, DVS SR = desvenlafaxine succinate sustained-release formulation, N = number of subjects per treatment group, SAE = serious adverse event.

The treatment-emergent treatment-related AEs reported by ≥5% of subjects in any treatment group are provided in Table 18.

Table 18. Number (%) of Subjects With Treatment-Emergent Treatment-Related Adverse Events Reported by ≥5% of Subjects in any Treatment Group

Body System Adverse Event	DVS SR 100 mg N=158	Tibolone 2.5 mg N=166	Placebo N=152
Any adverse event	80 (50.6)	57 (34.3)	41 (27.0)
Body as a whole	32 (20.3)	28 (16.9)	21 (13.8)
Abdominal pain	4 (2.5)	10 (6.0)	7 (4.6)
Asthenia	11 (7.0)	2 (1.2)	3 (2.0)
Headache	22 (13.9)	17 (10.2)	14 (9.2)
Digestive system	49 (31.0)	18 (10.8)	12 (7.9)
Constipation	11 (7.0)	3 (1.8)	2 (1.3)
Dry mouth	10 (6.3)	5 (3.0)	4 (2.6)
Nausea	36 (22.8)	10 (6.0)	4 (2.6)
Nervous system	48 (30.4)	25 (15.1)	15 (9.9)
Dizziness	16 (10.1)	8 (4.8)	5 (3.3)
Insomnia	8 (5.1)	1 (0.6)	3 (2.0)
Somnolence	10 (6.3)	3 (1.8)	2 (1.3)
Special senses	16 (10.1)	2 (1.2)	1 (0.7)
Abnormal vision	9 (5.7)	1 (0.6)	0
Urogenital system	11 (7.0)	28 (16.9)	9 (5.9)
Breast pain	4 (2.5)	7 (4.2)	8 (5.3)
Leukorrhea	1 (0.6)	9 (5.4)	0

Non serious AEs and SAEs are not separated out.
AE = adverse event, DVS SR = desvenlafaxine succinate sustained-release formulation, N = number of subjects per treatment group, SAE = serious adverse event.

Serious Adverse Events: A total of 7 subjects reported serious adverse events (SAEs): 4 of the subjects who received placebo, 2 of the subjects who received DVS SR and 1 of the subjects who received tibolone. All events were considered to be not related to study drug by the Investigator.

One (1) subject in the DVS SR group reported an event of dizziness which was considered by the Sponsor to be possibly related to the study drug. Table 19 presents the SAEs reported in the study.

Table 19. Subjects With Serious Adverse Events

Serial No.	Body System Preferred Term[a]	Treatment	Relationship to Study Drug	Discontinued Because of Identified Adverse Event(s)[b]
	Gastrointestinal disorders			
1	Intestinal obstruction	DVS SR 100 mg	DNOT	Yes
2	Gastrointestinal infection[c]	Placebo	DNOT	No
	Metabolism and nutrition disorders			
3	Elevated GGT	Placebo	PNOT	Yes
	Neoplasms			
4	Non-Hodgkin's lymphoma, renal cell carcinoma	Placebo	DNOT	Yes
5	Endometrial cancer	Tibolone 2.5 mg	PNOT	No
	Nervous system disorders			
6	Dizziness	DVS SR 100 mg	PNOT	No
7	Head injury, loss of consciousness[c]	Placebo	DNOT	No

DNOT = definitely not; GGT = gamma-glutamyl transferase; No. = number, PNOT = probably/possibly not.
a. Medical Dictionary for Regulatory Activity (MedDRA) terms. The adverse events listed occurred during the on-therapy or follow-up intervals.
b. Listed adverse event was a primary or secondary reason for discontinuation from the study.
c. The event occurred after the last dose of study drug during the follow-up period.

Adverse Events Leading to Discontinuation: AEs led to withdrawal from the study for 35 subjects (22.2%) in the DVS SR group, 18 subjects (10.8%) in the tibolone group, and 14 subjects (9.2%) in the placebo group. The incidence of discontinuations due to AEs was significantly higher in the DVS SR group than in the placebo group during the first week of therapy ($p<0.001$). After the first week of therapy, there was no difference between groups in safety-related discontinuations. Nausea was the most frequent cause for discontinuation of treatment in DVS SR treated subjects; significantly more than in the placebo group ($p<0.001$). Table 20 summarizes the number of subjects reporting AEs resulting in withdrawal from the study.

Table 20. Number (%) of Subjects Reporting Adverse Events Resulting in Withdrawal From the Study

Body System Adverse Event	DVS SR 100 mg N=158 n (%)	Tibolone 2.5 mg N=166 n (%)	Placebo N=152 n (%)
Any adverse event	35 (22.2)	18 (10.8)	14 (9.2)
Body as a whole			
Abdomen enlarged	1 (0.6)	0	0
Abdominal pain	2 (1.3)	1 (0.6)	1 (0.7)
Asthenia	2 (1.3)	0	0
Headache	6 (3.8)	2 (1.2)	2 (1.3)
Malaise	0	1 (0.6)	0
Neoplasm	0	0	1 (0.7)
Pain	1 (0.6)	0	1 (0.7)
Cardiovascular system			
Hypertension	1 (0.6)	2 (1.2)	1 (0.7)
Hypotension	0	0	1 (0.7)
Migraine	0	0	1 (0.7)
Palpitation	4 (2.5)	2 (1.2)	3 (2.0)
Digestive system			
Constipation	1 (0.6)	0	0
Diarrhea	0	0	1 (0.7)
Dyspepsia	0	0	1 (0.7)
Gamma-glutamyl transpeptidase increased	0	0	1 (0.7)
Intestinal obstruction	1 (0.6)	0	0
Nausea	14 (8.9)	2 (1.2)	1 (0.7)
Vomiting	3 (1.9)	0	0
Hemic and lymphatic system			
Lymphoma	0	0	1 (0.7)
Metabolic and nutritional			
Peripheral edema	0	1 (0.6)	0
Weight gain	0	2 (1.2)	0
Musculoskeletal system			
Arthralgia	0	1 (0.6)	0
Nervous system			
Anxiety	1 (0.6)	2 (1.2)	0
Confusion	1 (0.6)	0	0
Depression	3 (1.9)	2 (1.2)	1 (0.7)
Dizziness	7 (4.4)	1 (0.6)	2 (1.3)
Feeling drunk	1 (0.6)	0	0
Insomnia	1 (0.6)	0	1 (0.7)
Nervousness	0	1 (0.6)	0
Paresthesia	0	1 (0.6)	0
Somnolence	2 (1.3)	0	0
Speech disorder	2 (1.3)	0	0
Tremor	4 (2.5)	0	0
Trismus	1 (0.6)	0	0
Respiratory system			
Dyspnea	0	0	1 (0.7)
Skin and appendages			
Alopecia	0	1 (0.6)	0
Pruritus	0	1 (0.6)	0
Special senses			

Table 20. Number (%) of Subjects Reporting Adverse Events Resulting in Withdrawal From the Study

Body System Adverse Event	DVS SR 100 mg N=158 n (%)	Tibolone 2.5 mg N=166 n (%)	Placebo N=152 n (%)
Abnormal vision	2 (1.3)	0	0
Mydriasis	1 (0.6)	0	0
Tinnitus	1 (0.6)	0	0
Urogenital system			
Breast enlargement	0	1 (0.6)	0
Breast pain	0	1 (0.6)	0
Metrorrhagia	0	0	1 (0.7)
Urinary incontinence	0	0	1 (0.7)

DVS SR = desvenlafaxine succinate sustained release, N = total number of subjects, n = number of subjects with adverse event.

Deaths: No deaths occurred during the study.

Clinical Laboratory Test Results: DVS SR treatment was associated with clinically important changes from baseline in laboratory test results in few subjects. For subjects in the DVS SR group, there were statistically significant increases from baseline laboratory values in adjusted mean alkaline phosphatase, total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol concentrations; there were significant decreases from baseline in adjusted mean bilirubin concentration. For other laboratory values, no pattern was observed in the few data points with statistically significant changes from baseline. None of the mean changes in laboratory values appeared to be clinically important.

Vital Signs: Mean pulse rate and blood pressure values remained stable or increased very slightly in the DVS SR group, and tended to decrease slightly in the placebo and tibolone groups; all changes were of very limited magnitude.

CONCLUSIONS:

All treatment groups were associated with a statistically significant reduction from Baseline in the number and severity of hot flushes. The number of moderate and severe hot flushes decreased by 57% in the DVS SR group at Week 12 as compared with an 81% decrease in the tibolone group. In the ITT population, for the primary efficacy endpoints (reduction in the number of moderate and severe hot flushes and reduction in the severity score of hot flushes), both the LOCF and observed data analyses showed no significant differences between placebo and DVS SR at any of the 2 time points of primary interest (Week 4 and Week 12). In the observed-data analysis, DVS SR was statistically different from placebo for the number of moderate and severe hot flushes at Weeks 2 and 3. For key secondary endpoints (total mood disturbance score and total GCS score), there was no significant difference between DVS SR and placebo at Weeks 4 and 12. There were no significant differences between DVS SR and placebo for other secondary endpoints. Results in the PP population were similar to those in the ITT population.

The absence of statistically significant differences from baseline in the pairwise comparisons for DVS SR versus placebo may be explained by a particularly high response rate in the placebo group (up to 57% reduction in the number of moderate and severe hot flushes at Week 12). However, tibolone, with a drug effect of greater magnitude compared with DVS SR, achieved statistically significant differences from placebo for the primary efficacy endpoints and most secondary endpoints.

There were no unexpected safety findings or deaths in this study.

In conclusion, DVS SR was associated with a significant decrease from baseline in the number and severity of hot flushes. However, these decreases were not statistically different from those observed in the placebo group.