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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: PD 0299685

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: This drug is not marketed in the United States.

NCT NO.: 00314964

PROTOCOL NO.: A4291023

PROTOCOL TITLE: A Phase 2b Multicenter, Double-Blind, Placebo-Controlled, Parallel-Group, Dose-Ranging Study Evaluating the Efficacy and Safety of PD 0299685 for the Treatment of Moderate to Severe Vasomotor Symptoms Associated with Menopause

Study Centers: A total of 68 centers in 6 countries (Australia [4], Canada [5], France [4], South Africa [7], Spain [4] and the United States [44])

Study Initiation and Completion Dates: 07 August 2006 to 11 July 2007

Phase of Development: Phase 2

Study Objectives:

- To assess the efficacy of PD 0299685 in the treatment of moderate to severe vasomotor symptoms (VMS) associated with the menopause.
- To characterize the dose range and dose response relationships of PD 0299685 in the treatment of moderate to severe VMS associated with the menopause.
- To assess the safety and tolerability of PD 0299685.

METHODS

Study Design: This was a 12-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 2b study in postmenopausal women to assess the efficacy of PD 0299685 in the treatment of moderate to severe VMS associated with the menopause. A total of 527 subjects were enrolled in 58 study centers.

The study consisted of a pre-screening visit, randomization baseline visit and 6 clinic visits. The treatment phase lasted approximately 12 weeks. During the treatment phase, subjects recorded the daily frequency and severity of their VMS. Weight measurement, vital signs,

clinical breast and pelvic examinations, endometrial biopsy, transvaginal ultrasound, fasted clinical laboratory assessments, as well as patient reported outcomes (PRO) were performed according to the study schedule. Information regarding the use of concomitant medication(s) and the occurrence of adverse events (AEs) were obtained at each scheduled visit. A single blood sample for pharmacokinetic (PK) analysis was collected at Week 4 and 8 visits, for the purposes of population PK/pharmacodynamic (PD) analyses.

Number of Subjects (Planned and Analyzed): The study was designed to include approximately 455 subjects. A total of 527 subjects were randomized and subsequently treated. A total of 432/527 (82%) completed the study, 95 (18%) subjects discontinued from the study; the main reasons for discontinuation were withdrawal due to AEs and refusal to participate further.

Diagnosis and Main Criteria for Inclusion: The study enrolled postmenopausal women aged between ≥40 and ≤70 years with an average of at least 50 moderate to severe vasomotor symptoms per week during the screening period. Subjects were excluded if they were receiving estrogen or progesterone containing products or any over-the-counter products for the treatment of VMS.

Study Treatment: Subjects were randomized to 1 of the following treatments; placebo, 1, 2, 5, 10, 15 or 20 mg BID PD 0299685 in the form of 1, 5, and 10 mg tablets and matching placebo. Subjects were instructed to take their first dose in the morning with food and again at the subject's habitual bedtime without regard to food. Study treatment lasted approximately 12 weeks.

Efficacy Evaluations:

Vasomotor Symptoms: Vasomotor symptoms were defined as the combined daytime HFs and NS in a 24-hour period. The number of daytime hot flashes (HF), the severity of daytime HFs and the number of night sweats (NS) per day were collected from non-electronic (ie, paper) subject diaries. The number of VMS was collected with the HF diary for 14 days during the screening period, at least 7 of which must have been consecutive. Seven consecutive days during the screening period were used to compute the mean count of weekly VMS for the eligibility criteria (minimum 50 moderate to severe VMS per week). The HF diary also recorded efficacy data daily for the Treatment phase (baseline - Week 12).

The subject was required to adhere to the following definitions when assigning severity to each occurrence.

Mild: sensation of heat without sweating
Moderate: sensation of heat with sweating, able to continue activity
Severe: sensation of heat with sweating, causing cessation of activity

Night sweats were defined as HFs that occurred with drenching diaphoresis (ie, perspiration) during the night (sleeping hours). Hot flashes that occurred during a daytime sleep, nap, siesta, and resulted in the awakening of the subject, were to be recorded as either a mild, moderate or severe HF and not as a NS.

Patient Reported Outcomes: The following patient reported outcome (PRO) measures were included to assess the improvement in overall subject quality of life during the study and to assess treatment satisfaction:

Menopause-Specific Quality of Life

The Menopause-Specific Quality of Life (MENQoL) was a self-administered, condition-specific, health status measure, completed at baseline and Weeks 4, 8 and 12, that was used to quantify the effects of symptoms of menopause across 4 scales (vasomotor [1-3], psychosocial [4-10], physical [11-26, 30-32], and sexual [27-29]). The questionnaire was designed to be self-administered, either in person or by mail, and took about 5 minutes to complete. The questionnaire was completed as follows. For each item, the subject indicated whether or not she experienced a problem by answering "yes" or "no." If she answered "no" to a given item, she should move on to the next item. If she answered "yes," she should indicate how bothered she was by the problem by answering on a 7-point scale (0 = not at all bothered to 6 = extremely bothered).

Women's Health Questionnaire (WHQ)

The Women's Health Questionnaire (WHQ) was a self-administered; 36-item questionnaire used to assess symptom perceptions in postmenopausal women and was completed at baseline and Weeks 4, 8 and 12. It took 5-10 minutes to complete, and consisted of 9 subscales including: VMS, anxiety, attractiveness, depressed mood, memory, menstrual symptoms, sexual behavior, sleep problems and somatic symptoms (for items per domain, refer to scoring manual). Women were asked to rate each item on a 4-point scale from 'yes, definitely' to 'no, not at all' to indicate how they had been feeling over the previous 4 weeks. Higher scores indicated more dysfunction.

Treatment Satisfaction Questionnaire for Medication (TSQM)

The purpose of the Treatment Satisfaction Questionnaire for Medication (TSQM) was to quantify the subject's level of satisfaction with study medication. Subject-rated satisfaction with effectiveness (1-3), side effects (4-8), convenience (9-11), and global satisfaction (12-14) were assessed. The 14-item TSQM was designed to be self-administered and took approximately 5 minutes to complete. The questionnaire was completed as Weeks 4 and 12.

Patient Reported Treatment Impact Assessment (VS-PRTI)

The Patient Reported Treatment Impact Assessment (VS-PRTI) was a self-administered instrument, containing 4 items to assess satisfaction, previous treatment, preference and willingness to continue using the study medication. The satisfaction, preference and willingness to use questions were scored on a 5-point scale with a high score indicating greater satisfaction, preference or willingness to use the study medication. The previous treatment question was scored as a categorical variable. The questionnaire was completed as Weeks 4 and 12.

Patient Global Impression of Change (PGI-C)

The PGI-C was a subject-rated, 1-item instrument that measured change in subject's overall status on a 7-point scale ranging from 1 (very much worse) to 7 (very much improved). The questionnaire was completed as Weeks 4 and 12.

Epworth Sleepiness Scale (ESS)

The ESS was a simple 8-item, self-administered questionnaire that measured the subject's general level of daytime sleepiness, completed at baseline and Weeks 4, 8 and 12. The ESS was based on questions referring to situations that vary in their likelihood to induce a person to fall asleep. Each item (or situation, such as "sitting and reading") was rated on a 4-point Likert scale that ranged from 0 (would never doze) to 3 (high chance of dozing).

Meaningful Benefit Question (MBQ)

The MBQ was a single item, self-administered instrument designed to assess subject-perceived meaningful benefit in VMS (HFs and NS) as a result of treatment. It was completed at Week 12. It was scored on a 7-point scale from 'yes, a great deal of benefit' to 'no, 'a great deal worse'. The numbers of subjects reporting a meaningful benefit at Week 12 was calculated. In addition, this item was originally intended to be used as an anchor question to help determine what a minimally important difference (MID) was on the vasomotor symptom domain of the MENQoL.

These PRO measurements were collected and evaluated in a different manner than the observed or volunteered AEs recorded during the study, and no attempt was made to reconcile the observed or volunteered AEs and the additional data collected through completion of PROs. This PRO data were presented in separate tables, figures, and data listings. AE incidence rates were not calculated from these PRO data, but rather from the information recorded on the AE pages of the data collection tool.

Safety Evaluations: At each visit the following were evaluated: reported AEs, vital signs, body weight and laboratory test results. At the baseline and Week 12 visit the following were evaluated: vital signs, 12-leas electrocardiogram (ECG), physical examination, and gynecological assessments.

Statistical Methods: The primary analyses were evaluated in the FAS using the LOCF imputation method and repeated in the PP analysis set where no LOCF imputation occurred. Frequency and severity of daily VMS were collected twice daily, in a paper diary. Average daily moderate to severe VMS frequency and severity at Week 4 were calculated from the 7 days prior to and including Day 28. At Week 12 average daily moderate to severe VMS frequency and severity were calculated from data collected in the 7 days prior to and including Day 84. The severity score was calculated by assigning a value of 2 to each moderate VMS and a value of 3 to each severe event (with NS considered a severe VMS).

Linear regression models were used to assess the trend in frequency and severity of VMS across the 7 dose groups at Weeks 4 and 12.

The dose regression coefficient and its CI were presented for each of the following 4 co-primary endpoints:

1. Change from baseline in average daily frequency of moderate to severe VMS (combined daytime HFs and NS) to Week 4.

2. Change from baseline in average daily frequency of moderate to severe VMS (combined daytime HFs and NS) to Week 12.

3. Change from baseline in average daily severity of moderate to severe VMS (combined daytime HFs and NS) to Week 4.

4. Change from baseline in average daily severity of moderate to severe VMS (combined daytime HFs and NS) to Week 12.

For each endpoint the results were displayed graphically showing the observed values, fitted regression line and its lower and upper 95% confidence bounds, at the mean observed baseline and weighted average of country effects.

For the VMS frequency endpoints the adjusted mean difference from placebo was calculated and plotted along with the 95% CIs for difference. This plot identified doses which were clinically significant ie, the 95% CI for treatment difference, PD 0299685-placebo, in the change from baseline at Weeks 4 and 12 had the upper bound less that 0 and the lower bound less than -2.

Key Secondary Analyses

The key secondary endpoints were:

1. Change from baseline in the average NS frequency at Weeks 4 and 12.

2. Change from baseline in the VMS subscale of the MENQoL at Weeks 4 and 12.

The key secondary endpoints were analyzed in an identical way to the primary endpoints and for each model the dose regression coefficient and its confidence interval were presented. For each endpoint the results were displayed graphically showing the observed values, fitted regression line and its lower and upper 95% confidence bounds, at the mean observed baseline and a weighted average of the country effects.

Other Secondary Analyses

The secondary endpoints were:

1. Change from baseline in average daily frequency of moderate to severe VMS at Weeks 1, 2, 3, 5, 6, 7, 8, 9, 10 and 11 (each week with the exception of Weeks 4 and 12 that constitute primary endpoints).

2. Proportion of subjects with ≥50%, ≥75% and 100% reduction in average daily frequency of moderate to severe VMS at Week 12.

3. Change from baseline in average daily severity of moderate to severe VMS at Weeks 1, 2, 3, 5, 6, 7, 8, 9, 10 and 11 (each week with the exception of Weeks 4 and 12 that constitute primary endpoints).

4. Change from baseline in average NS frequency at Weeks 1, 2, 3, 5, 6, 7, 8, 9, 10 and 11 (each week with the exception of Weeks 4 and 12 that constitute primary endpoints).

5. Proportion of subjects with ≥50%, ≥75% and 100% reduction in average NS frequency at Week 12.

6. Change from baseline in the quality of life subscale (psychosocial, physical and sexual) scores of the MENQoL at Weeks 4, 8 and 12.

7. Change from baseline in the vasomotor subscale at Week 8.

8. Change from baseline in the quality of life subscale (VMS, anxiety, attractiveness, depressed mood, memory, menstrual symptoms, sexual behavior, sleep problems and somatic symptoms) scores of the WHQ at Weeks 4, 8 and 12.

9. Change from baseline in ESS score at Weeks 4, 8 and 12.

10. Absolute score on sub scales (effectiveness, side effects, convenience and global treatment satisfaction) of the TSQM at Weeks 4 and 12.

11. Responder status on the subject-rated PGI-C at Weeks 4 and 12 where a responder is defined as a subject rated as very much improved or much improved.

12. Absolute score on the individual items (satisfaction, preference, willingness to use) of the VS-PRTI) at Weeks 4 and 12.

13. Response to MBQ.

For continuous secondary measures (MENQoL; ESS; WHQ; VMS frequency and severity; and NS frequency) the endpoint values and change from baseline were summarized at each week. For TSQM only absolute values were summarized. Subject VS-PRTI responses were also summarized.

Binary secondary endpoints (proportion of subjects with specified percentage reduction in average daily frequency of moderate to severe VMS at Week 12, proportion of subjects with specified percentage reduction in average NS frequency at Week 12 and percentage of responders for PGI-C at Weeks 4 and 12), were analyzed using a logistic regression model.

RESULTS

Subject Disposition and Demography:

Subject disposition is summarized in Table S1. A total of 527 postmenopausal women with at least 50 moderate to severe VMS per week during the screening period were randomized and treated. Subjects' demography is summarized in Table S2. The mean age was similar across treatment groups (range 40 and 69 years) with no ≥ 4% of the subjects being less than 45 years old. The majority of the subjects recruited into the study were White (66.6%). Less than 22% of the subjects in each treatment group were Black/Asian/other. The mean weight, body mass index (BMI), VMS frequency and severity, HF frequency and NS at baseline were all similar across the treatment groups. Of the 527 randomized subjects 520 (98.7%) were included in the FAS, 420 (79.7%) in the PP analysis set and 526 (99.8%) in the safety analysis.

Table S1. Subject Disposition

N (%)	Placebo	PD 0299685					
		1 mg BID	2 mg BID	5 mg BID	10 mg BID	15 mg BID	20 mg BID
Screened (N=1422)							
Assigned study drug (N=527)							
Randomized	76	75	80	78	71	75	72
Completed	64 (84.2)	68 (90.7)	70 (87.5)	69 (88.5)	53 (74.6)	59 (78.7)	49 (68)
Discontinued	12 (15.8)	7 (9.3)	10 (12.5)	9 (11.5)	18 (25.4)	16 (21.3)	23 (31.9)
Due to AE[a]	4 (5.3)	2 (2.7)	3 (3.8)	5 (6.4)	9 (12.7)	9 (12)	15 (20.8)
Other	2 (2.6)	1 (1.3)	2 (2.5)	1 (1.3)	2 (2.8)	3 (4)	2 (2.8)
Death	0	0	0	0	1 (1.4)	0	0
Subject defaulted[b]	6 (7.9)	4 (5.3)	5 (6.3)	3 (3.8)	6 (8.5)	4 (5.3)	6 (8.3)

BID = twice daily, AE = adverse event
[a]Subjects 10041001, 10391014, 10391060, 10881009 and 10711034 discontinued due to AEs and are not included in this table because their final status was not recorded as withdrawn due to AE, they are, however, included in the evaluation of permanent discontinuations due to AEs
[b]Subjects who discontinued due to withdrawn consent or lost to follow-up

Table S2. Demographic and Baseline Characteristics.

		PD 0299685					
	Placebo	1 mg BID	2 mg BID	5 mg BID	10 mg BID	15 mg BID	20 mg BID
N	76	75	80	78	71	75	72
Race (n/%)							
White	57 (75)	56 (74.7)	67 (83.8)	56 (71.8)	58 (81.7)	51 (68)	62 (86.1)
Black	12 (15.8)	11 (14.7)	9 (11.3)	17 (21.8)	8 (11.3)	16 (21.3)	6 (8.3)
Asian	2 (2.6)	5 (6.7)	2 (2.5)	3 (3.8)	3 (4.2)	4 (5.3)	3 (4.2)
Other	5 (6.6)	3 (4)	2 (2.5)	2 (2.6)	2 (2.8)	4 (5.3)	1 (1.4)
Age							
Mean (SD)	53.4 (5.4)	52.6 (5.2)	53.7 (5.8)	55.2 (5.4)	55.1 (6.0)	53.4 (5.1)	53.6 (5)
Range	42-66	41-68	40-68	43-69	42-69	42-65	41-65
Age Category (n/%)							
18-44	2 (2.6)	2 (2.7)	3 (3.8)	3 (3.8)	2 (2.8)	3 (4.0)	2 (2.8)
45-64	73 (96.1)	71 (94.7)	73 (91.3)	71 (91)	65 (91.5)	70 (93.3)	69 (95.8)
≥ 65	1 (1.3)	2 (2.7)	4 (5.0)	4 (5.1)	4 (5.6)	2 (2.7)	1 (1.4)
Weight (kg)							
Mean (SD)	72.1 (14.3)	70.3 (12.1)	74.4 (15.1)	73.7 (14)	70.5 (11.4)	72 (11.5)	74.7 (14.2)
Range	50.5-120.6	46.3-101	51.7-126.1	46.8-118.9	49.2-97.1	53.1-110.1	49.5-115
BMI[a]							
Mean (SD)	27.3 (5.0)	26.5 (4.1)	27.8 (5.2)	27.8 (4.8)	26.7 (4.2)	27.6 (4.5)	28.5 (6.0)
Range	20-41.8	19-37.1	18.8-45.8	19.9-41.2	19.5-37.8	18.4-42.7	18.3-48.3
Baseline Daily VMS Frequency							
Mean (SD)	10.80 (3.5)	11.51 (6.38)	11.74 (4.67)	12.81 (6.78)	11.15 (7.62)	12.40 (6.33)	11.36 (5.45)
Median	10	10	10.8	10.6	9.1	10.3	10.3
(Range)	(4.4, 26)	(2.1, 53.6)	(6.2, 27.3)	(5.6, 45.6)	(4.7, 65.1)	(5.4, 41.1)	(5.6, 33.6)
Baseline Daily VMS Severity							
Mean (SD)	2.58 (0.20)	2.56 (0.22)	2.57 (0.21)	2.60 (0.20)	2.61 (0.23)	2.59 (0.23)	2.62 (0.19)
Median	2.6	2.6	2.6	2.6	2.6	2.6	2.6
(Range)	(2.1, 3)	(2.1, 3)	(2.1, 3)	(2, 3)	(1.9, 3)	(2.1, 3)	(2.2, 3)
Weekly NS Frequency							
Mean (SD)	3.42 (1.36)	3.42 (2.06)	3.58 (1.68)	4.24 (3.75)	3.36 (3.55)	3.97 (1.70)	3.85 (2.76)
Median	3.3	3.3	3.5	3.5	2.9	3.7	3.0
(Range)	(0.6, 6.9)	(0,14.9)	(0, 8.4)	(0,27.9)	(0.6, 29.7)	(0.3, 8.9)	(0.9, 20.6)
Weekly HF Frequency							
Mean (SD)	10.81 (3.68)	11.81 (6.64)	11.89 (4.89)	12.94 (7.12)	11.29 (8.36)	12.70 (6.85)	11.64 (6.03)
Median	10.1	10.1	10.7	10.4	10.1	10.4	10
(Range)	(4.4, 26)	(5, 53.6)	(6.2, 27.3)	(5.6, 45.6)	(4.7, 65.1)	(5.9, 41.1)	(6.7, 33.6)

N = number of subjects, n = number of subjects in subgroup, BID = twice daily, BMI = body mass index, HF= daytime hot flash, SD = standard deviation, NS = night sweat, VMS = vasomotor symptom,
[a]BMI was calculated as weight/(height)

Efficacy Results: ***Primary Endpoints: Daily VMS Frequency- Week 4 and Week 12.*** Overall, there was a statistically significant negative trend in average daily VMS frequency at Week 4 and Week 12 across the dose range (Table S3 and Table S4). The adjusted mean difference from placebo in change from baseline in average daily VMS frequency at Week 4 and Week 12 (Figures S1 and Figures S2) shows that PD 0299685 10, 15 and 20 mg BID treatment groups met the criteria for clinical relevance (defined as treatment difference [PD 0299685-placebo] in VMS frequency per day with a 95% CI [<-2, <0]).

Table S3. Summary Statistics for Daily Vasomotor Symptom Frequency at Baseline, Week 4 and Week 12 (FAS)

	Placebo	PD 0299685					
		1 mg BID	2 mg BID	5 mg BID	10 mg BID	15 mg BID	20 mg BID
N	76	75	80	78	71	75	72
Baseline[a]							
Mean (SD)	10.8 (3.5)	11.51 (6.4)	11.74 (4.7)	12.81 (6.8)	11.15 (7.6)	12.4 (6.3)	11.36 (5.4)
Median	10.0	10.0	10.8	10.6	9.1	10.3	10.3
(range)	(4.4, 26.0)	(2.1, 53.6)	(6.2, 27.3)	(5.6, 45.6)	(4.7, 65.1)	(5.4, 41.1)	(5.6, 33.6)
Week 4							
Mean (SD)	6.6 (3.6)	7.2 (4.5)	7.4 (5.9)	7.2 (4.6)	4.9 (6.3)	5.3 (4.5)	4.3 (4.1)
Mean[b] Change From Baseline	-4.23	-4.31	-4.35	-5.59	-6.18	-7.12	-7.06
Median	-3.7	-3.3	-4.2	-4.8	-5.8	-6.4	-7.1
(range)	(-14.1, 1.4)	(-49.3, 4.0)	(-18.9, 16.4)	(-30.6, 13.9)	(-19.7, 1.6)	(-32.7, 4.3)	(-22.1, 0.0)
Week 12							
Mean (SD)	5.9 (4.5)	6.14 (4.85)	6.8 (6.5)	5.6 (5.0)	4.1 (3.4)	5.3 (4.3)	4.1 (4.1)
Mean[b] Change From Baseline	-4.92	-5.37	-4.97	-7.18	-7.03	-7.13	-7.22
Median	-5.0	-5.1	-5.4	-6.8	-5.6	-6.6	-6.8
(range)	(-15.7, 5.0)	(-41.1, 6.4)	(-16.9, 21.6)	(-36.0, 19.3)	(-60.3, 1.6)	(-35.6, 1.9)	(-22.7, 0.2)

BID = twice daily, SD = standard deviation, FAS = full analysis set
[a]Baseline was defined as average of VMS recorded over the last 7 consecutive days of the screening period
[b]Unadjusted mean

Table S4. Linear Regression Analysis for Change From Baseline in the Daily Vasomotor Symptom Frequency at Week 4 and Week 12 (FAS)

Endpoint	Slope of regression line	95% CI of slope	p-value
Frequency at Week 4	-0.15	(-0.20, -0.10)	<0.0001
Frequency at Week 12	-0.11	(-0.16, -0.05)	<0.0001

Models included terms for baseline severity and country
FAS = full analysis set, CI = confidence interval

Figure S1. Adjusted Mean Difference From Placebo in Change From Baseline in Vasomotor Symptoms Frequency at Week 4 (FAS)

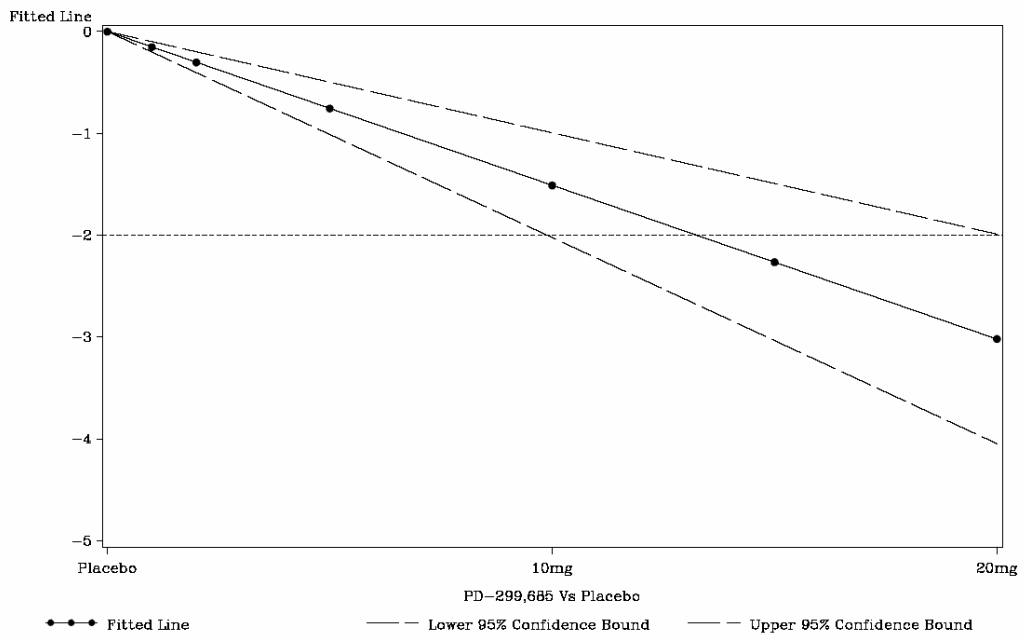
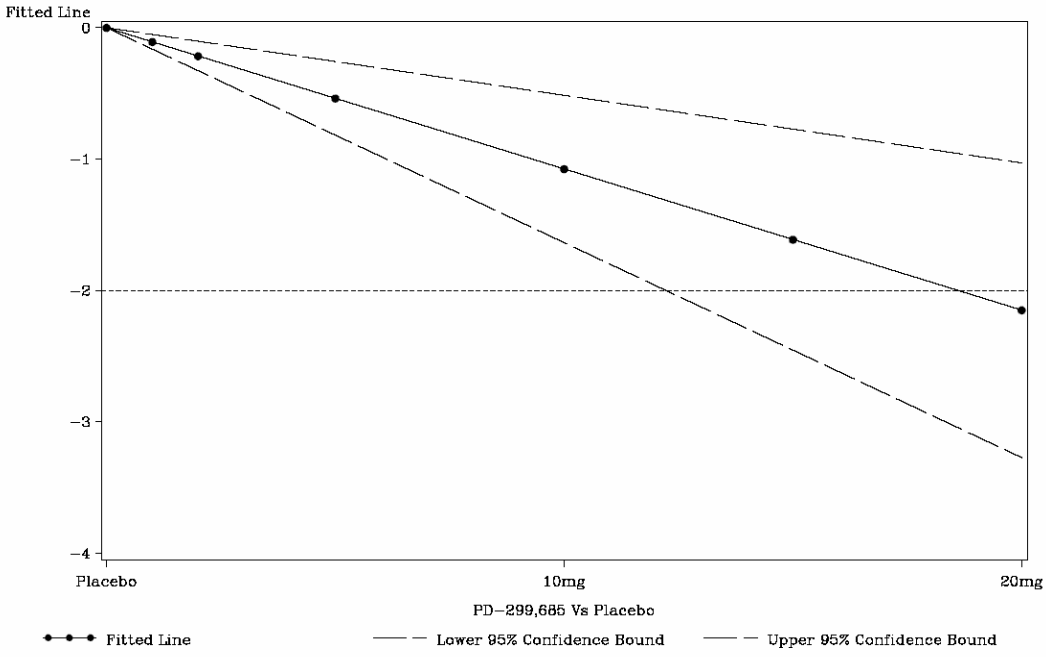


Figure S2. Adjusted Mean Difference From Placebo in Change From Baseline in Vasomotor Symptoms Frequency at Week 12 (FAS)



VMS Daily Severity Week 4 and Week 12: The mean daily VMS severity at baseline for Weeks 4 and 12 are shown Table S5 and statistical regression summary in Table S6. Overall, there was a statistically significant negative trend in average daily VMS severity at Week 4 and Week 12 across the dose range.

Table S5. Summary Statistics for Daily Vasomotor Symptom Severity at Baseline, Week 4 and Week 12 (FAS)

		PD 0299685					
	Placebo	1 mg BID	2 mg BID	5 mg BID	10 mg BID	15 mg BID	20 mg BID
N	76	75	80	78	71	75	72
Baseline[a]							
Mean (SD)	2.6 (0.2)	2.6 (0.2)	2.6 (0.2)	2.6 (0.2)	2.6(0.2)	2.6 (0.2)	2.6 (0.2)
Median	2.6	2.6	2.6	2.6	2.6	2.6	2.6
(range)	(2.1, 3.0)	(2.1, 3.0)	(2.1, 3.0)	(2.0, 3.0)	(1.9, 3.0)	(2.1, 3.0)	(2.2, 3.0)
Week 4							
Mean (SD)	2.4 (0.5)	2.4 (0.5)	2.4 (0.6)	2.5 (0.4)	2.2 (0.8)	2.2 (0.7)	2.0 (0.8)
Mean[b] Change From Baseline	-0.14	-0.14	-0.22	-0.11	-0.44	-0.41	-0.54
Median	-0.0	-0.0	-0.0	-0.1	-0.1	-0.2	-0.3
(range)	(-2.4, 0.3)	(-2.2, 0.9)	(-3.0, 0.5)	(-1.4, 1.0)	(-2.7, 0.7)	(-2.6, 0.5)	(-2.6, 0.3)
Week 12							
Mean (SD)	2.3 (0.7)	2.2(0.8)	2.2 (0.7)	2.3 (0.7)	1.9 (0.9)	2.2 (0.7)	2.0 (0.8)
Mean[b] Change From Baseline	-0.29	-.0.35	-0.35	-0.27	-0.64	-0.45	-0.57
Median	-0.0	-0.0	-0.1	-0.1	-0.2	-0.2	-0.3
(range)	(-2.7, 0.4)	(-3.0, 0.6)	(-2.5, 0.2)	(-3.0, 1.0)	(-2.7, 0.3)	(-2.8, 0.5)	(-2.7, 0.6)

SD= standard deviation, BID = twice daily, FAS = full analysis set
[a]Baseline was defined as average of VMS recorded over the last 7 consecutive days of the screening period
[b]Unadjusted mean

Table S6. Linear Regression Analysis Change From Baseline in the Severity of Vasomotor Symptoms at Week 4 and Week 12 (FAS)

Endpoint	Slope of regression line	95% CI of slope	p-value
Severity at Week 4	-0.02	(-0.03, 0.01)	<0.0001
Severity at Week 12	-0.01	(-0.02, 0.00)	0.0067

Models included terms for baseline severity and country
FAS = full analysis set, CI = confidence interval

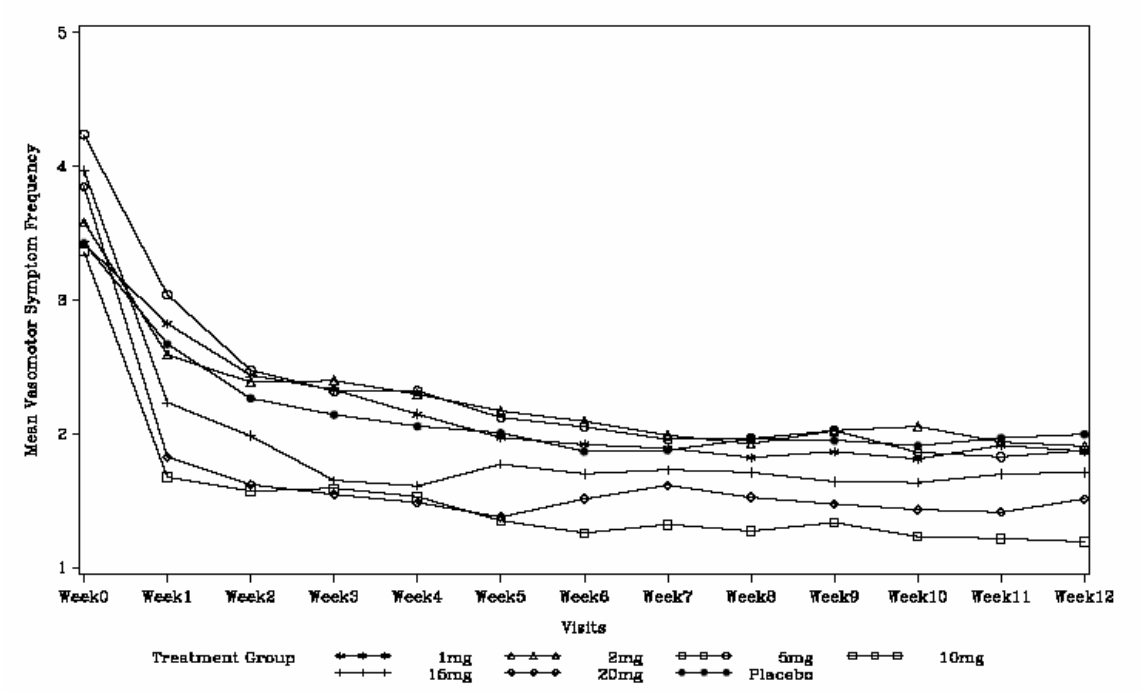
Key Secondary Endpoints: *Daily Average NS Frequency at Week 4 and Week 12*: Overall, there was a statistically significant negative trend in average daily NS frequency at Week 4 and Week 12 across the dose range (Table S7). Unadjusted means are summarised in Figure S3.

Table S7. Summary Statistics for Daily Night Sweat Frequency at Baseline, Week 4 and Week 12 (FAS)

	Placebo	PD 0299685					
		1 mg BID	2 mg BID	5 mg BID	10 mg BID	15 mg BID	20 mg BID
N	76	75	80	78	71	75	72
Baseline[a]							
Mean (SD)	3.4 (1.4)	3.4 (2.1)	3.6 (1.7)	4.2 (3.7)	3.4 (3.5)	3.9 (1.7)	3.8 (2.8)
Median	3.3	3.3	3.5	3.6	2.9	3.7	3.0
(range)	(0.6, 6.9)	(0.0,14.9)	(0.0, 8.4)	(0.0, 27.9)	(0.6, 29.7)	(0.3, 8.9)	(0.9, 20.6)
Week 4							
Mean (SD)	2.0 (1.5)	2.1 (1.4)	2.3 (1.7)	2.3 (1.9)	1.5 (2.4)	1.6 (1.3)	1.5 (1.9)
Mean[b] Change From Baseline	-1.37	-1.27	-1.29	-1.96	-1.87	-2.35	-2.41
Median	-1.3	-0.9	-1.3	-1.2	-1.7	-2.2	-2.3
(range)	(-6.3 1.4)	(-13.6, 1.0)	(-5.4, 2.0)	(-23.1, 4.9)	(-11.5, 1.1)	(-7.7, 1.1)	(-9.9, 0.5)
Week 12							
Mean (SD)	2.0 (1.7)	1.9 (1.5)	1.9 (1.7)	1.9 (2.0)	1.2 (1.3)	1.7 (1.6)	1.5 (2.0)
Mean[b] Change From Baseline	-1.43	-1.55	-1.67	-2.41	-2.17	-2.25	-2.38
Median	-1.5	-1.1	-1.4	-2	-1.7	-2.1	-2.3
(range)	(-6.3,2.7)	(-14.9,1.1)	(-5.6, 2.9)	(-23.6, 5.3)	(-27.5, 0.8)	(-8.7, 0.9)	(-7.1, 0.5)

SD= standard deviation, BID = twice daily, FAS = full analysis set
[a]Baseline was defined as average of VMS recorded over the last 7 consecutive days of the screening period
[b]Unadjusted mean

Figure S3. Mean Night Sweat Frequency at Each Week by Dose (FAS)



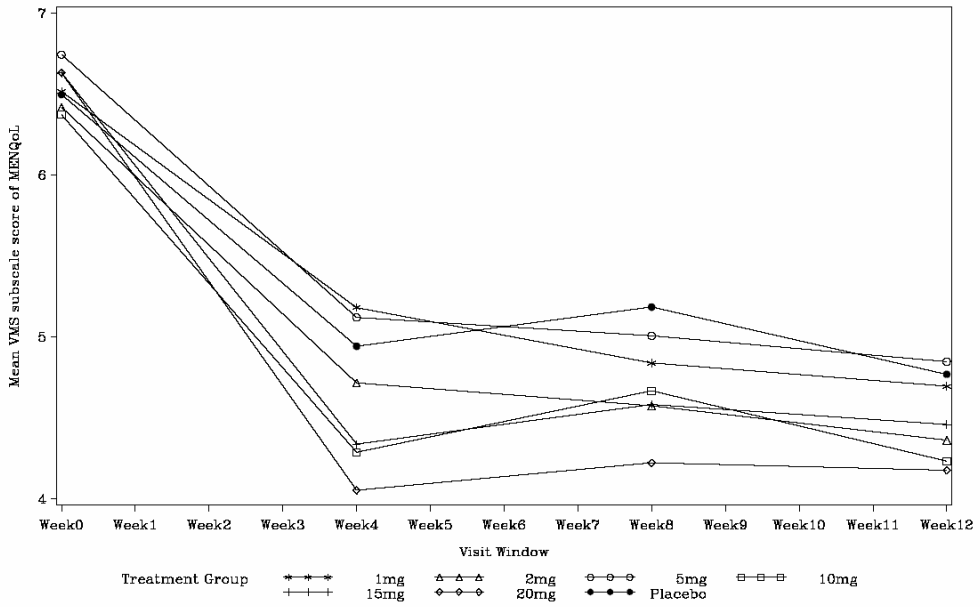
MENQoL: Linear regression analysis of the change from baseline of the VMS subscale score at Weeks 4 and 12 showed that there was a statistically significant trend over the dose range at Weeks 4 and Week 12 (Table S8 and Figure S4).

Table S8. Summary Statistics for Vasomotor Symptom Subscale Score of Menopause-Specific Quality of Life Questionnaire Subscale at Baseline, Week 4 and Week 12

		PD 0299685					
N	Placebo	1 mg BID	2 mg BID	5 mg BID	10 mg BID	15 mg BID	20 mg BID
Baseline[a]							
Mean (SD)	6.5 (1.2)	6.5 (1.2)	6.4 (1.1)	6.7 (1.0)	6.4 (1.2)	6.6 (1.1)	6.6 (1.0)
Median	6.7	6.7	6.3	6.7	6.7	6.7	6.7
(range)	(3.3, 8.0)	(2.3, 8.0)	(3.3, 8.0)	(4.0, 8.0)	(2.3, 8.0)	(3.7, 8.0)	(3.7, 8.0)
Week 4							
Mean (SD)	5.0 (1.7)	5.2 (2.0)	4.7 (1.7)	5.0 (1.6)	4.3 (1.6)	4.3 (1.9)	4.0 (1.7)
Mean[b] change from baseline	-1.6 (2.0)	-1.3 (1.6)	-1.7 (1.8)	-1.8 (1.6)	-2.0 (1.8)	-2.3 (1.9)	-2.6 (1.6)
Median	-1	-1	-1.5	-1.7	-2.0	-2.5	-2.3
(range)	(-6.0, 2.3)	(-5.0, 2.0)	(-6.7, 1.7)	(-5.3, 1.0)	(-6.0, 3.0)	(-6.3, 2.0)	(-6.3, 1.0)
Week 12							
Mean (SD)	4.8 (2.0)	4.7 (2.2)	4.4 (2.0)	4.9 (1.8)	4.2 (2.0)	4.5 (2.0)	4.2 (2.0)
Mean[b] change from baseline	-7 (2.0)	-1.8 (1.9)	-2.0 (2.0)	-1.9 (1.9)	-2.0 (2.3)	-2.2 (1.9)	-2.5 (2.2)
Median	-1.7	-1.5	-2.0	-2.0	-2.3	-2.3	-2.3
(range)	(-6.0, 2.3)	(-5.7, 1.7)	(-6.3, 2.3)	(-5.7, 3.0)	(-6.3, 3.0)	(-6.3, 2.0)	(-7.0, 1.3)

BID = twice daily, SD = standard deviation
[a]Baseline was defined as average of VMS recorded over the last 7 consecutive days of the screening period
[b]Unadjusted mean

Figure S4. Mean Daily Vasomotor Symptom Subscale Score of Menopause-Specific QoL Questionnaire at Each Week by Dose (FAS)



Secondary Endpoints: *Daily VMS Frequency and Severity:* In the FAS the unadjusted mean changes from baseline to Weeks 1, 2, 3, 5, 6, 7, 8, 9, 10 and 11 in the daily frequency and severity of average daily VMS generally increased with time and dose. Decreases in frequency and severity of average daily VMS were apparent as early as Week 1 in the 10, 15 and 20 mg PD 0299685 treatment groups.

Proportion of subjects with ≥50%, ≥75% and 100% reductions in VMS frequency: The proportion of subjects with ≥50% reductions from baseline in average daily VMS frequency by Week 12 ranged from 49.33% to 74.29% for the PD 0299685 treatment groups compared with 52.7% in the placebo group. The proportion of subjects with ≥75% reductions from baseline in average daily VMS frequency by Week 12 ranged from 26.67% to 45.71% for the PD 0299685 treatment groups compared with 31.08% in the placebo group. The proportion of subjects with 100% reductions from baseline in average daily VMS frequency by Week 12 ranged from 2.5% to 8.8% for the PD 0299685 treatment groups compared with 4.05% in the placebo group. For 5, 10, 15 and 20 mg BID PD 0299685 treated subjects a total of 117 subjects (45.3%) had achieved ≥75% (39.5%) reductions in their average daily VMS frequency by Week 12.

Logistic regression analysis of the proportion of subjects with a ≥50% reduction in average daily VMS at Week 12 showed no general increase in odds ratio with increasing dose. However, subjects were 2.5 times more likely to have a ≥50% reduction in average daily VMS at Week 12 with 20 mg BID PD 0299685 compared to placebo. The same analysis of the proportion of subjects with a ≥75% reduction in average daily VMS at Week 12 showed that there was a general trend for odds ratios to increase with increasing dose, but no treatment group was statistically significantly different from placebo.

Daily NS frequency: In the FAS the unadjusted mean changes from baseline to Weeks 1, 2, 3, 5, 6, 7, 8, 9, 10 and 11 in the daily frequency of NS generally increased with dose up to Week 6 for the PD 0299685 treatment groups and were larger for the 15, 10 and 20 mg BID PD 0299685 treatment groups.

Proportion of subjects with ≥50%, ≥75% and 100% reductions in NS frequency: The proportion of subjects with ≥50% reductions from baseline in average NS frequency by Week 12 ranged from 49.33% to 66.18% for the PD 0299685 treatment groups compared with 51.35% in the placebo group. The proportion of subjects with ≥75% reductions from baseline in average daily NS frequency by Week 12 ranged from 28% to 51.47% for the PD 0299685 treatment groups compared with 29.73% in the placebo group. The proportion of subjects with 100% reductions from baseline in average NS frequency by Week 12 ranged from 12.5% to 25% for the PD 0299685 treatment groups compared with 10.81% in the placebo treatment group. For 5, 10, 15 and 20 mg BID PD 0299685 treated subjects a total of 127 subjects (43.0%) had achieved ≥75% reduction in their average NS frequency by Week 12.

Logistic regression analysis showed that the odds of achieving a ≥50% reduction in NS was only statistically significantly greater than placebo for the 10 mg PD 0299685 group where subjects were 1.9 times more likely to achieve this result. Odds ratio showed that the subjects were approximately twice as likely to achieve a reduction of ≥75% in average NS frequency in the 10, 15 and 20 mg BID PD 0299685 treatment groups.

MENQoL: The psychosocial, physical and sexual subscales did not show any trends towards improvement over time in any of the PD 0299685 groups.

Linear regression showed that there was a statistically significant negative trend across the doses studied in the change from baseline in VMS subscale score at Week 8.

WHQ: Only the VMS and sleep problems domains showed a trend towards improvement from baseline. No trend towards improvement was evident in the anxiety, attractiveness, depressed mood, memory, menstrual symptoms, sexual behavior, and somatic symptoms domains. There was no trend towards improvement across the dose range.

ESS: No impact on daytime sleepiness was observed for all PD 0299685 treatment groups; the scores ranged from 7.17 to 8.53 for Week 4, 6.68 to 8.16 for Week 8 and 7.01 to 7.91 for Week 12.

TSQM: The Satisfaction with Effectiveness subscale demonstrated a trend towards increasing satisfaction with increasing dose. Higher absolute effectiveness scores were observed for the PD 0299685 5, 10, 15 and 20 mg BID treatment groups compared with placebo at Weeks 4 and 12. Satisfaction with effectiveness slightly decreased from Week 4 to Week 12 in the treatment groups and slightly increased in the placebo group.

The Satisfaction with Side effects subscale demonstrated a trend towards decreasing satisfaction with increasing dose. Satisfaction with side effects also decreased over time for the PD 0299685 treatment groups, but increased for the placebo treatment group. At

Week 12, the 5, 10, 15 and 20 mg BID PD 0299685 treatment groups had lower absolute scores than the placebo group. Satisfaction with convenience was similar among the treatment and placebo groups, although the scores suggest a decrease in satisfaction with convenience over time for all groups.

Global satisfaction takes into account all aspects of treatment satisfaction, including satisfaction with effectiveness, side effects and convenience, providing an overall net evaluation of patient satisfaction. Absolute scores for the global satisfaction for TSQM suggest a trend towards higher global satisfaction over placebo for the 10, 15 and 20 mg BID PD 0299685 treatment groups at Week 4 (Appendix B4.2.5). However, this difference disappeared by Week 12 when scores were similar between the PD 0299685 treatment groups and placebo.

PGI-C: Logistic regression of the change from baseline in PGI-C subscale scores at Week 4 showed that the odds of being a responder increased with increasing dose compared to placebo. Subjects receiving 20 mg BID PD 0299685 were 3.1 times more likely to be a responder than those on placebo at Week 4. These odds were not maintained to Week 12 where there were slightly increased odds compared to placebo in the 2, 5, 10 and 20 mg BID PD 0299685 treatment groups. It is likely that this was due to the continuing improvement in the placebo treated subjects

VS-PRTI: Scores for satisfaction, willingness to use and preference subscales were similar across all treatment groups and did not change much with time.

MBQ: Of those subjects who completed the study, two-hundred and seventy-six (79%) subjects in the PD 0299685 treatment group, (70.3%, 79.1%, 90.6%, 79% and 89% in the 2, 5, 10, 15 and 20 mg BID PD 0299685 treatment groups respectively) reported a meaningful benefit with study drug compared with 43 (72%) in the placebo group

Safety Results: *AEs:* One death resulting from cerebrovascular accident and 7 SAEs in 4 subjects occurred subsequent to their randomization into this study (Table S9). A total of 51 (9.7%) subjects discontinued due to AEs, 47 (10.4%) PD 0299685 treated subjects and 4 (5.3%) placebo treated subjects. Discontinuations increased with increasing doses of PD 0299685 ranging from 2 (2.7%) at 1 mg BID to 17 (23.6%) at 20 mg BID. The most frequently reported AEs leading to discontinuation in the PD 0299685 treatment groups were somnolence (9/47 [19%]) and dizziness (9/47 [19.0%]) all of which were considered to be related to study drug by the investigators. One placebo treated subject discontinued due to dizziness. A total of 75 (14.2%) subjects experienced 108 discontinuation emergent signs and symptoms (DESS) AEs during the study. The incidence of DESS AEs in the placebo treated subjects (7 [9.2%]) was lower compared with the PD 0299685 (68 [15%]) treated subjects, of these subjects 43 (63.0%) were receiving 10 (12 [16.9%)], 15 (13 [17.3%]) and 20 (18 [25.0%]) mg BID PD 0299685.

A total of 380 subjects (72.1%) experienced 1088 treatment emergent signs and symptoms (TESS) AEs during the study and 576 (52.9%) of these were considered to be related to study drug (Table S10). The most frequently reported AEs in the PD 0299685 treatment groups were dizziness (64 [14.2%]), somnolence and headache (both 46 [10.2%]) and nausea (26

[5.8%]). The highest incidence of dizziness and nausea occurred in the PD 0299685 20 mg BID treatment group and somnolence in the 15 mg BID PD 0299685 treatment group. The most frequently reported TESS AEs in the placebo group were headache (13 [17.1%]), upper respiratory tract infection (5 [6.6%]), dizziness, nausea and dry mouth (all 4 [5.3%]). The most frequently reported TESS AEs by ≥3% of subjects are summarized in Table S2. The majority of TESS AEs reported during the study were mild or moderate in severity. No severe TESS AEs were reported in ≥1 placebo treated subject. The most common severe TESS AEs reported for PD 0299685 treated subjects were headache (5 [1.1%]), somnolence (5 [1.1%]), vomiting and dizziness (both 3 [0.6%]).

Table S9. Serious Adverse Events

Subject	SAE[a]	Treatment	Onset Day[b]	Relationship to study drug[c]	Outcome
10411001	Abdominal Discomfort	20 mg BID PD 0299685	1	Yes[d]	Recovered
11111027	Pneumonia, Cerbrovascular accident	10 mg BID PD 0299685	14	No[d]	Death
10401017	Radius Fracture	10 mg BID PD 0299685	48	No	Recovered
	Constipation	10 mg BID PD 0299685	60	Yes	Recovered
10451002	Intussusception, Cholecystitis	20 mg BID PD 0299685	88	No	Recovered

[a] MedDRA (v10)
[b] Relative to start of study drug (Day 1)
[c] As assessed by the investigator
[d] Permanently discontinued

Table S10. Most frequent TESS AEs (≥3%) Listed by Decreasing Frequency and Treatment Group (all Causalities)

Preferred Term[a]		PD 0299685					
	Placebo	1 mg BID	2 mg BID	5 mg BID	10 mg BID	15 mg BID	20 mg BID
N	76	75	80	78	71	75	72
Number of (%) subjects with AEs[b]	53 (69.7)	46 (61.3)	53 (66.3)	55 (70.5)	54 (76.1)	58 (77.3)	61 (84.7)
Dizziness	4 (5.3)	2 (2.7)	1 (1.3)	6 (7.7)	16 (22.5)	17 (22.7)	22 (30.6)
Somnolence	0	2 (2.7)	0	5 (6.4)	8 (11.3)	17 (22.7)	14 (19.4)
Nausea	4 (5.3)	1 (1.3)	5 (6.3)	1 (1.3)	1 (1.4)	6 (8.0)	12 (16.7)
Headache	13 (17.1)	7 (9.3)	9 (11.3)	7 (9.0)	10 (14.1)	6 (8.0)	7 (9.7)
Vomiting	2 (2.6)	1 (1.3)	1(1.3)	1 (1.3)	0	3 (4.0)	6 (8.3)
Diarrhea	2 (2.6)	2 (2.7)	2 (2.5)	3 (3.8)	1 (1.4)	3 (4.0)	4 (5.6)
Vertigo	0	0	0	1 (1.3)	2 (2.8)	3 (4.0)	5 (6.9)
Fatigue	2 (2.6)	1 (1.3)	2 (2.5)	3 (3.8)	0	7 (9.3)	3 (4.2)
Arthralgia	1 (1.3)	2 (2.7)	2 (2.5)	7 (9.0)	1 (1.4)	3 (4.0)	3 (4.2)
Weight Increased	2 (2.6)	1 (1.3)	1 (1.3)	3 (3.8)	1 (1.4)	6 (8.0)	3 (4.2)
Euphoric Mood	0	0	1 (1.3)	2 (2.6)	5 (7.0)	0	3 (4.2)
Upper Respiratory Tract Infection	5 (6.6)	5 (6.7)	3 (3.8)	4 (5.1)	1 (1.4)	3 (4.0)	3 (4.2)
Constipation	3 (3.9)	3 (4.0)	0	1 (1.3)	4 (5.6)	3 (4.0)	3 (4.2)
Flatulence	0	0	4 (5.0)	4 (5.1)	3 (4.2)	2 (2.7)	3 (4.2)
Insomnia	3 (3.9)	2 (2.7)	0	1 (1.3)	2 (2.8)	3 (4.0)	3 (4.2)
Coordination Abnormal	0	0	0	1 (1.3)	1 (1.4)	1 (1.3)	3 (4.2)
Back Pain	1 (1.3)	6 (8.0)	5 (6.3)	4 (5.1)	2 (2.8)	2 (2.7)	2 (2.8)
Nasopharyngitis	6 (7.9)	3 (4.0)	4 (5.0)	2 (2.6)	3 (4.2)	1 (1.3)	2 (2.8)
Urinary Tract Infection	0	2 (2.7)	1 (1.3)	4 (5.1)	1 (1.4)	4 (5.3)	2 (2.8)
Disturbance in Attention	0	0	0	0	2 (2.8)	4 (5.3)	2 (2.8)
Paraesthesia	3 (3.9)	0	2 (2.5)	1 (1.3)	2 (2.8)	1 (1.3)	2 (2.8)
Hot Flush	3 (3.9)	1 (1.3)	3 (3.8)	0	1 (1.4)	0	2 (2.8)
Pain in Extremity	0	0	1 (1.3)	2 (2.6)	0	3 (4.0)	2 (2.8)
Sinusitis	0	4 (5.3)	1 (1.3)	1 (1.3)	1 (1.4)	2 (2.7)	1 (1.4)
Neck Pain	0	2 (2.7)	0	1 (1.3)	1 (1.4)	4 (5.3)	1 (1.4)
Dry Mouth	4 (5.3)	3 (4.0)	2 (2.5)	1 (1.3)	7 (9.9)	5 (6.7)	1 (1.4)
Abdominal Distension	3 (3.9)	4 (5.3)	0	5 (6.4)	2 (2.8)	1 (1.3)	1 (1.4)
Muscle Spasm	1 (1.3)	2 (2.7)	4 (5.0)	2 (2.6)	0	1 (1.3)	1(1.4)
Anxiety	1 (1.3)	0	2 (2.5)	3 (3.8)	1 (1.4)	1 (1.3)	1 (1.4)
Depression	1 (1.3)	0	2 (2.5)	3 (3.8)	2 (2.8)	2 (2.7)	1 (1.4)
Dyspepsia	0	4 (5.3)	1 (1.3)	2 (2.6)	0	1 (1.3)	0
Myalgia	1 (1.3)	0	1 (1.3)	4 (5.1)	3 (4.2)	1 (1.3)	0
Influenza	1 (1.3)	2 (2.7)	2 (2.5)	2 (2.6)	3 (4.2)	2 (2.7)	0
Edema Peripheral	0	3 (4.0)	2 (2.5)	2 (2.6)	0	2 (2.7)	0
Hypoaesthesia	0	3 (4.0)	1 (1.3)	1 (1.3)	1 (1.4)	0	0
Vaginal Hemorrhage	1 (1.3)	2 (2.7)	1 (1.3)	0	0	0)	0

BID = twice daily, AE = adverse event
[a]Table includes AEs with at least 3% of subjects in 1 or more treatment group. Sorted in decreasing frequency by the PD 0299685 20 mg BID treatment group.
[b]Subjects with multiple AEs were counted once.

Body Weight Analysis: At Week 12 the mean change from baseline in weight for the placebo group was 0.74 kg compared with 0.38, 0.67, 0.62, 1.06, 1.85 and 1.55 kg, respectively for the PD 0299685 1, 2, 5, 10, 15 and 20 mg BID treatment groups. Analysis of the change from baseline showed statistically significant weight increases for the PD 0299865 15 mg BID treatment group at Week 12 compared to placebo. However, there was no statistically

significant difference recorded at follow-up. A total of 24 (4.6%) subjects experienced a ≥7% change in body weight during the course of the study, 2 (8%), 3 (13%), 3 (13%), 5 (21%) and 6 (25%) in the PD 0299685 1, 2, 10, 15 and 20 mg BID treatment groups compared to 5 (21%) subjects in the placebo group. The highest percent change in body weight at Week 12 occurred in the PD 0299685 15 and 20 mg BID treatment groups.

ECG Findings: Clinically significant ECG changes included QRS percent changes ≥25/50% (2 [0.5%]) and QTc changes of ≥30 to ≤60 msec reported by QTcB (18 [4.2%]) and QTcF (10 [2.3%]). There were no clinically significant ECG changes in placebo treated subjects; there were 0 clinically significant ECG changes in placebo treated subjects. No subject in any treatment group had a post baseline QT, QTcB or QTcF interval of ≥ 500 msec or an increase from baseline QTcB or QTcF interval of ≥60 msec.

Gynecological Examinations: No overall change in endometrial thickness was seen in the PD 0299685 treated subjects. At Week 12 the change from baseline in endometrial thickness for the placebo group was -0.07 mm compared with -0.08, 0.14, 0.18, -0.35, -0.1 and 0.22 mm for the PD 0299865 1, 2, 5, 10, 15 and 20 mg treatment groups. Endometrial biopsy results for Week 12 show that the majority of subjects had no change, evidenced by insufficient tissue and atrophic endometrium, with active proliferative, weakly proliferatvie, and atrophic polyps reported in a greater proportion of subjects in the placebo and lower dose groups than in the higher dose groups of PD 0299685.

CONCLUSIONS: The objectives of the study were successfully met based on the results of the analysis of the 4 co-primary endpoints. The primary analysis showed that a statistically significant negative trend was observed for the linear regression slopes for all of the 4 co-primary endpoints. In addition, PD 0299685 doses 15 and 20 mg BID achieved the clinical relevance criteria (defined as treatment difference [PD 0299685-placebo] in VMS frequency per day with a 95% CI [<-2, <0]). The PRO results suggest an overall trend towards treatment satisfaction (TSQM) and quality of life (MENQoL, WHQ, MBQ, PGIC) with increasing dose to Week 4; however, these improvements were not maintained at Week 12 when the difference between the PD 0299685 treatment groups and the placebo treatment group was less apparent.

Adverse events typical for this class of compound were reported for PD 0299685, with 1, 2, and 5 mg BID doses being well tolerated and equivalent to placebo. PD 0299685 10, 15 and 20 mg BID doses resulted in a higher incidence of AEs and AEs leading to discontinuations. Endometrial biopsy results for Week 12 show that the majority of subjects had no change; active proliferative, weakly proliferatvie, and atrophic polyps were reported in a greater proportion placebo and lower PD 0299685 dose treated subjects compared with the higher PD 099685 doses. The mean weight change from baseline was highest in the 10, 15 and 20 mg BID PD 0299685 treatment groups. A statistically significant weight change occurred in the 15 mg BID PD 0299685 treatment group at Week 12. A total of 24 (4.6%) subjects experienced a ≥7% change in body weight during the study with 12 subjects continuing to experience this weight change at follow-up. The largest percent changes in body weight at Week 12 occurred in the PD 0299685 15 and 20 mg BID treatment groups. There was no apparent dose related effect on vital signs or laboratory parameters.

In general, the PD 0299685 1, 2, and 5 mg BID groups showed similar tolerability profiles and efficacy to that observed with placebo. The higher dose groups achieved the clinical relevance criteria and led to an earlier reduction in daily VMS frequency and severity. However, the PD 0299685 10 mg and 15 mg BID groups had the highest incidence of dizziness and somnolence, with the 20 mg dose group reporting the highest drop out rate and total incidence of AEs.