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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: PD-0299685

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: Not Applicable

NATIONAL CLINICAL TRIAL NO.: NCT00739739

PROTOCOL NO.: A4291043

PROTOCOL TITLE: A Phase 2, 12 Week, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Proof of Concept Study Evaluating the Efficacy and Safety of PD-0299685 for the Treatment of Symptoms Associated With Interstitial Cystitis/Painful Bladder Syndrome.

Study Centers: The study was conducted at 36 centers (Canada 5, Denmark 1, Finland 4, France 6, Germany 2 and United States 18).

Study Initiation Date and Completion Dates: 10 September 2008 to 19 January 2010

Phase of Development: Phase 2

Study Objectives:

Primary:

- To assess the efficacy of PD-0299685 in the treatment of symptoms associated with Interstitial Cystitis (IC)/Painful Bladder Syndrome (PBS) including bladder pain, urinary urgency and frequency.

Secondary:

- To assess the safety and tolerability of PD-0299685.

METHODS

Study Design: This was a Phase 2a, randomized, double-blind, placebo-controlled, parallel-group, proof of concept study; comprising a 2-week single-blind placebo run-in, followed by a 12-week double-blind treatment phase and 10-day Follow-up visit.

After 2 weeks of single-blind placebo treatment, subjects entering the treatment phase were randomized to either placebo, PD-0299685 15 mg twice daily (BID) or PD-0299685 30 mg BID in a 1:1:1 ratio. Subjects were stratified at randomization according to the presence or absence of cystoscopic features of IC and their baseline worst daily pain score (moderate [4

to <7] or severe [≥7]). Subjects randomized to receive PD-0299685 30 mg BID received PD-0299685 15 mg BID for the first 2 weeks of their 12-week treatment phase, changing to 30 mg BID for the remaining 10 weeks.

Subjects were required to complete a series of pain, symptom and health questionnaires. Safety monitoring included adverse events (AEs), clinical laboratory monitoring, 12-lead electrocardiograms (ECG) and physical examination.

Number of Subjects (Planned and Analyzed): It was planned that a total of 147 subjects (49 per treatment group) were to be randomized to double-blind treatment in this study so that 102 subjects (34 per group) would complete the 12 week double-blind treatment phase (considering an estimated drop out rate of 30%). A total of 370 subjects were screened, and 161 subjects were randomized to treatment (Table 2): 54 subjects in the PD-0299685 15 mg BID treatment group, 55 subjects in the PD-0299685 30 mg BID treatment group and 52 subjects in the placebo treatment group. For analysis of efficacy, 1 subject, in the PD-0299685 30 mg BID treatment group, was excluded from the full analysis set (FAS) because she did not provide 4 daily pain severity scores during the 7 days prior to randomization. Subjects were excluded from the restricted analysis set (rFAS) if they did not satisfy the FAS criteria, or did not provide baseline and post-randomization data for worst daily pain score NRS (for ≥4 days) or ICSI within the pre-defined visit windows. Therefore, different numbers of subjects were included in the rFAS for each endpoint and each time point dependent on data availability. The most common reasons for exclusion from the per protocol analysis set (PPAS) were discontinuation and prohibited concomitant medication.

Diagnosis and Main Criteria for Inclusion: Male or female subjects aged ≥18 years with diagnosed IC/PBS, and evidence of cystoscopy within 2 years of Screening (Visit 1) to confirm the absence of other significant lower urinary tract pathology and the presence or absence of cystoscopic features of IC (eg, glomerulations, Hunner's ulcer). Subjects were not eligible for the study if they had a post-void residual (PVR) volume >200 mL at Screening (Visit 1), a mean voided volume (MVV) <50 mL or >350 mL measured over 3 consecutive days, or a total volume voided of >3000 mL per 24 hours. Subjects were also not eligible for the study if they had a Suicide Behaviors Questionnaire – Revised (SBQ-R) score ≥8 at Screening, a Patient Health Questionnaire – 9 (PHQ-9) total score ≥15 or a score ≥1 on Question 9, or had answered "yes" on either Question 1 or 2 of the Suicide Ideation section, or "yes" to any of the 6 questions in the Suicidal Behavior section of the Columbia-Suicide Severity Rating Scale (C-SSRS) at Screening (Visit 1) or randomization (Visit 2), or had a history, diagnosis, signs or symptoms of any clinically significant psychiatric disorder.

Study Treatment: Subjects received study treatment supplies at each dispensing visit (bottles containing 108 capsules of PD-0299685 5 mg or 10 mg, or placebo to be taken orally). Subjects took 3 capsules in the morning and 3 capsules at bedtime starting on Day 1 (Visit 2) according to 1 of the 3 treatment groups in Table 1. Acetaminophen was issued in its approved marketed product packaging as open-label approved commercial supplies of 500 mg oral capsules.

Table 1 Study Treatments

Treatment Group	PD-0299685 15 mg BID	PD-0299685 30 mg BID	Placebo
Placebo Run-In (2 weeks)	Placebo	Placebo	Placebo
Titration Phase (2 weeks)	15 mg	15 mg	Placebo
Treatment Phase (10 weeks)	15 mg	30 mg	Placebo

BID=twice daily

Efficacy Evaluations:

Primary:

Pain Severity

A daily pain diary was used to assess severity of pain throughout the placebo run-in and treatment phases of the study, starting on the evening of the Screening visit (Visit 1) and continuing throughout the study.

Symptom Severity

The O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI) was completed at Screening, Weeks 0, 2, 6 and 12 (Visits 1 to 5/early termination).

Secondary:

Daily Symptom Diary (Urinary Variables)

A symptom diary to assess urinary symptoms and events, and the impact of these IC/PBS symptoms on sleep disturbance, and pain associated with sexual activity was completed on 3 consecutive days within the 7 days prior to attending the Week 0, 2, 6 and 12 visits (Visits 2, 3, 4, and 5/early termination).

Urinary symptom data recorded during the 3 consecutive days during the 7 days prior to the clinic visit were used to determine the following endpoints:

- Mean micturition frequency (MMF) per 24 hours,
- Mean nocturnal frequency (NF) per 24 hours,
- MVV per micturition,
- Mean incontinence episode frequency (IEF) per 24 hours,
- Mean urgency episode frequency (UEF) per 24 hours, and

- Mean IC pain severity per urinary event (toilet void, accidental urine loss, urgency episode). This was calculated as the mean of all pain severities recorded during the diary period when this was measured.

Daily Symptom Diary (Sleep Disturbance and Sexual Function)

Pain associated with sexual activity per 24 hours was recorded each morning for 3 consecutive days, within the 7 days prior to attending the Week 0, 2, 6 and 12 visits (Visits 2, 3, 4, and 5/early termination). Sleep disturbance per night was recorded at the same time each morning.

Interstitial Cystitis Problem Index

The O'Leary-Sant Interstitial Cystitis Problem Index (ICPI) was completed at Screening, and Weeks 0, 2, 6 and 12 (Visits 1 to 5/or early termination).

Pelvic Pain and Urgency/Frequency Questionnaire

Subjects completed the Pelvic Pain and Urgency/Frequency (PUF) questionnaire at Screening, and Weeks 0, 2, 6 and 12 (Visits 1 to 5/or early termination).

Global Response Assessment

The Global Response Assessment (GRA) questionnaire was completed at Weeks 2, 6 and 12 (Visits 3 to 5/or early termination).

Patient Reported Treatment Impact Assessment

Subjects completed the Patient Reported Treatment Impact Assessment (PRTI) questionnaire at Weeks 2, 6 and 12 (Visits 3 to 5/or early termination).

Exit Interview (United States sites only)

A semi-structured exit interview was conducted by the investigator (or designee) at Week 12/Visit 5 (US sites only), to elicit further information from the subject with regards to the treatment experience at the end of the treatment period.

Rescue Medication

Rescue medication (in the form of approved 500 mg/tablets/capsules) was dispensed at Visits 1, 2, 3, and 4, together with the rescue medication log. Rescue medication use, together with the log, was reviewed and collected at Visits 2, 3, 4, and 5 (or early termination).

Pharmacokinetic Evaluations: A total of 4 blood samples for assessment of PD-0299685 were collected at Week 6/Visit 4 (predose, and 30 minutes, 1 hour, and between 2 to 5 hours postdose). The exact date and time of pharmacokinetic sample collection was recorded. The

subject recorded the date and time they took their last 2 doses of study treatment in a dosing log, prior to attending Visit 4.

Safety Evaluations: AEs were recorded throughout the study from Week 0 (Visits 1 to 6). Laboratory samples were collected at Screening, and Weeks 0, 6 and 12 (Visits 1, 2, 4, and 5/or early termination), unless otherwise stated, and forwarded to a central laboratory for analysis. Blood pressure and heart rate were measured at Visits 1 to 6 (or early termination). Body weight was measured at all weeks (Visits 1 to 6). A general physical examination was performed at Screening (Visit 1) and Visit 5 (or early termination). PVR volume was measured at Screening, Weeks 0, 6 and 12 (Visits 1, 2, 4 and 5/or early termination). A 12-lead ECG was performed at Screening (Visit 1), baseline (Visit 2) and Week 12 (Visit 5/or early termination). The SBQ-R questionnaire was performed at Screening (Visit 1) and those with a score of ≥8 were excluded from the study. Subjects completed the PHQ-9 questionnaire at Screening (Visit 1) only, those with a total score ≥15 or a score of ≥1 on Question 9 (suicidality) were excluded from the study. The C-SSRS was administered at all weeks (Visits 1 to 6). The Epworth Sleepiness Scale (ESS) was completed at Weeks 0, 2, 6 and 12 (Visits 2, 3, 4 and 5/early termination).

Statistical Methods:

Primary Endpoints:

Worst Daily Pain Severity at Week 12 and Interstitial Cystitis Severity Index Score at Week 12

Change from baseline in worst daily pain severity at Week 12 was analyzed using an analysis of covariance (ANCOVA) model, with terms for baseline value of the endpoint, absence/presence of IC features, country and treatment. Change from baseline in ICSI total score at Week 12 was analyzed using ANCOVA with terms for country, absence/presence of IC features and baseline worst daily pain. The comparisons of interest were PD-0299685 dose groups versus placebo at Week 12. The differences between treatment means (least square), the standard errors associated with the differences and 90% confidence intervals (CIs) for the differences were presented. Following unblinding, it was apparent that there were very limited data in some countries. The analyses were therefore repeated using a model including a term for region where data in Europe were pooled and data in the US and Canada were pooled.

Secondary Endpoints:

Continuous Endpoints

The percentage and absolute changes from baseline at each time point during the study (Weeks 2, 6 and 12 [Visits 3 to 5/early termination]) were determined for each continuous endpoint. Unless otherwise stated below, all continuous secondary endpoints were analyzed using the same techniques as the primary endpoints. If any of the assumptions of these analysis methods were not adequately met, alternative procedures could be used. In

particular, if normality assumptions did not hold, Van Elteren's Test was to be used as a non-parametric method of analysis, which would adjust for baseline stratification groups.

Worst daily pain severity and average pain severity per 24 hours were also analyzed by response as defined by a ≥30% and a ≥50% reduction from baseline, and the proportion of responders and non-responders in each treatment group. The odds ratios with 90% two-sided CIs for the treatment contrasts were presented. The cumulative frequency distribution was presented for the percent reduction from baseline to each visit, in terms of a frequency table by categories of percentage reduction. This cumulative frequency distribution in steps of 5% was plotted for each treatment group.

Categorical Endpoints

- The GRA score was analyzed using proportional odds. Logistic regression was used for the proportion of responders (with responder defined as moderately or markedly improved in GRA at Week 12).

- PRTI were summarized by treatment. The total number of subjects, observed number of subjects in each category and observed proportions of subjects in each category were summarized by treatment for each question.

- Proportion of treatment failures was summarized using survival analyses techniques and the data presented using Kaplan-Meier curves and estimated for the median time to event and corresponding 95% CIs.

- Responder rates were assessed using cumulative distribution plots, with responders defined as subjects that did not require any rescue medication.

Plasma PD-0299685 concentrations were determined to support exposure-response analyses that was reported separately.

No formal hypothesis testing of safety data was performed. Results from the safety assessments and any AE were presented in tabular and/or graphical format adhering to current sponsor data standards.

RESULTS

Subject Disposition and Demography: Subject disposition and data sets analyzed are summarized in Table 2. Subject demography and baseline IC characteristics were similar for all treatment groups (Table 3).

Table 2 Subject Disposition

Number of Subjects		PD-0299685 15 mg BID	PD-0299685 30 mg BID	Placebo
Screened	370			
Assigned to study treatment	161	54	55	52
Treated		54	55	52
Completed		40 (74.1)	31 (56.4)	41 (78.8)
Discontinued		14 (25.9)	24 (43.6)	11 (21.2)
Related to study treatment		9 (16.7)	14 (25.5)	7 (13.5)
Adverse event		8 (14.8)	13 (23.6)	3 (5.8)
Lack of efficacy		1 (1.9)	1 (1.8)	4 (7.7)
Not related to study treatment		5 (9.3)	10 (18.2)	4 (7.7)
Adverse event		1 (1.9)	2 (3.6)	2 (3.8)
Other[a]		3 (5.6)	7 (12.7)	2 (3.8)
Subject no longer willing to participate in study		1 (1.9)	1 (1.8)	0
Analyzed for efficacy				
FAS		54 (100.0)	54 (98.2)	52 (100.0)
rFAS[b]		54 (100.0)	54 (98.2)	52 (100.0)
PPAS		37 (68.5)	30 (54.5)	33 (63.5)
Analyzed for pharmacokinetics		42 (77.8)	35 (63.6)	NA
Analyzed for safety				
Adverse events		54 (100.0)	55 (100.0)	52 (100.0)
Laboratory data		52 (96.3)	51 (92.7)	52 (100.0)
Safety analysis set		54 (100.0)	55 (100.0)	52 (100.0)

BID=twice daily; FAS=full analysis set; rFAS = restricted full analysis set; PPAS=per protocol analysis set
[a] Other = protocol deviations

Table 3 Demographic and Baseline Characteristics

	PD-0299685 15 mg BID	PD-0299685 30 mg BID	Placebo
Number of subjects	54	55	52
Gender			
Female (%)	49 (90.7)	51 (92.7)	47 (90.4)
Male (%)	5 (9.3)	4 (7.3)	5 (9.6)
Age (years)			
Mean (SD)	49.9 (13.6)	49.6 (14.6)	52.1 (14.0)
Range	19-76	21-80	22-79
Race			
White (%)	49 (90.7))	54 (98.2)	46 (88.5)
Black (%)	3 (5.6)	1 (1.8)	3 (5.8)
Other (%)	2[a] (3.7)	0	3[b] (5.8)
Weight (kg)			
Mean (SD)	69.5 (14.7)	72.3 (15.3)	76.5 (18.8)
Range	46.8-122.5	44.0-117.0	36.0-129.4
Interstitial cystitis characteristics			
Mean duration since symptom onset, years (range)	9.1 (0.6-31.3)	9.3 (0.6-54.3)	10.2 (0.7-49.4)
Mean duration since diagnosis, years (range)	5.2 (0.1-28.9)	3.9 (0.1-17.3)	5.0 (0.1-28.4)
Daily worst pain severity, mean (SD)	6.24 (1.42)	6.60 (1.30)	6.28 (1.42)
Interstitial cystitis system index, mean (SD)	14.17 (3.62)	13.74 (3.80)	14.73 (3.95)
Daily average pain severity, mean (SD)	4.82 (1.64)	5.06 (1.70)	4.81 (1.62)
Micturition frequency/24 hours (SD)	15.83 (7.37)	15.83 (6.22)	15.88 (6.80)
Mean voided volume, mL (SD)	128.19 (61.92)	127.22 (60.83)	125.96 (55.27)
Urgency frequency episode/24 hours (SD)	11.33 (8.38)	10.03 (8.00)	11.19 (7.73)
Interstitial cystitis pain index/micturition, mean (SD)	4.40 (1.96)	4.80 (2.03)	4.90 (2.00)

BID=twice daily; SD=standard deviation
[a] Other = Magrehb (*sic.*) and Middle Eastern.
[b] Other = Canadian Indian, Portuguese and Middle Eastern.

Efficacy Results: For the primary endpoints of worst daily pain severity and O'Leary-Sant ICSI at Week 12, improvements were observed for all treatment groups including the placebo treatment group. The improvements were greater for the PD-0299685 30 mg BID treatment group compared to the placebo treatment group. Improvements observed in the PD-0299685 15 mg BID treatment group were similar to those observed for the placebo treatment group. The improvements for the PD-0299685 30 mg BID treatment group in worst daily pain severity increased throughout the study, while those for the O'Leary-Sant ICSI, compared to placebo, were largely constant over time. Analysis of responder rates (where a responder was defined as both a ≥30% and ≥50% reduction from baseline worst daily pain severity) showed that, generally the odds of being a responder were greater in the PD-0299685 30 mg BID treatment group than in the placebo treatment group with the best odds being at Week 2.

Average daily pain severity, O'Leary-Sant ICPI, IC pain severity per urinary event, nightly sleep disturbance, MF, NF and UEF showed improvements for the PD-0299685 30 mg BID treatment group compared to placebo. Improvements were also observed in the PD-0299685 15 mg BID treatment group compared to placebo for average daily pain severity, the

O'Leary-Sant ICPI, IC pain severity per urinary event, MF, NF and UEF at Weeks 2 and 6 (with the exception of Week 6 for average daily pain severity). At Weeks 2 and 6, for MF and UEF, there were large improvements for the PD-0299685 15 mg BID and 30 mg BID treatment groups compared to placebo. However, by Week 12 for MF, NF and UEF, no improvements compared to placebo were observable in either the PD-0299685 15 mg BID or 30 mg BID treatment groups.

Analysis of responder rates (where a responder was defined as both a ≥30% and ≥50% reduction from baseline average daily pain severity) showed that generally the odds of being a responder were greater in the PD-0299685 30 mg BID group than in placebo group, with the largest odds being at Week 2. The odds of being a responder in the 15 mg group were only better than placebo at Week 2.

The reductions from baseline in IEF scores were similar both for the PD-0299685 15 mg BID and 30 mg BID treatment groups compared to the placebo treatment group.

Improvements were observed in average daily pain associated with sexual activity for both the PD-0299685 15 mg BID and 30 mg BID treatment groups compared to the placebo treatment group; the improvements increased throughout the study.

Improvements were observed in MVV per urinary event for both the PD-0299685 15 mg BID and 30 mg BID treatment groups compared to the placebo treatment group. Improvements were greater at Weeks 2 and 6 compared to Week 12.

At Weeks 2, 6 and 12, the PUF scores were reduced compared to baseline for all treatment groups (PD-0299685 15 mg BID and 30 mg BID and placebo), and the reductions increased throughout the study.

At Week 12, when a responder was defined with a GRA category of moderately or markedly improved, results indicated increased odds of being a responder in the PD-0299685 30 mg BID treatment group.

For the PRTI, there were improvements compared to placebo for the PD-0299685 15 mg BID and 30 mg BID treatment groups.

The proportions of subjects requiring rescue medication were lower in the PD-0299685 15 mg BID and 30 mg BID treatment groups than the placebo treatment group.

Safety Results: The proportion of subjects with treatment-emergent AEs was greater in the PD-0299685 15 mg BID and 30 mg BID treatment groups compared to the placebo treatment group: 81.5% and 89.1% compared to 75.0%, respectively. Similarly and more markedly, the proportion of subjects with AEs considered treatment-related was greater in the PD-0299685 15 mg BID and 30 mg BID treatment groups compared to the placebo treatment group: 64.8% and 80.0% compared to 38.5%, respectively. Furthermore, AEs were reported by a greater proportion of subjects in the PD-0299685 30 mg BID treatment group. The proportion of subjects with severe AEs was greater in the PD-0299685 15 mg BID and 30 mg BID treatment groups compared to the placebo treatment group: 13.0% and 21.8% compared to 7.7%, respectively. Severe AEs were reported by a greater proportion of subjects in the

PD-0299685 30 mg BID treatment group. The severe AEs which occurred in more than 1 subject in any treatment group were abdominal pain reported by 2 subjects (3.7%) in the PD-0299685 15 mg BID treatment group, and somnolence (2 subjects [3.6%]), IC (2 subjects [3.6%]) and dizziness (3 subjects [5.5%]) reported in the PD-0299685 30 mg BID treatment group. The most frequently reported AEs are summarized in Table 4.

The number of subjects who discontinued due to a treatment-emergent AE was greater in the PD-0299685 15 mg BID and 30 mg BID treatment groups compared to the placebo treatment group: 8 subjects (14.8%) in the PD-0299685 15 mg BID treatment group and 15 subjects (27.3%) in the PD-0299685 30 mg BID treatment group, compared to 5 subjects (9.6%) in the placebo treatment group (Table 5). Four subjects had temporary discontinuations due to AEs: 1 subject in the PD-0299685 15 mg BID treatment group and 3 subjects in the PD-0299685 30 mg BID treatment group.

There were 2 subjects with serious AEs (deep vein thrombosis and attempted suicide), both in the PD-0299685 15 mg BID treatment group (Table 6). There were no deaths during the study.

There were no safety concerns for laboratory test results, vital signs, physical examinations, PVR results, ECG results, C-SSRS scores or ESS scores.

Table 4 Summary of Most Commonly Reported Treatment-Emergent Adverse Events (Occurring in ≥5% of Subjects in any Treatment Group) - All Causality and Treatment-Related, and Inclusive of Follow-up Period (After Withdrawal from Study Treatment)

Number of Subjects with MedDRA v12.0 Preferred Term	PD-0299685 15 mg BID (N=54)		PD-0299685 30 mg BID (N=55)		Placebo (N=52)	
	AC	TR	AC	TR	AC	TR
Number (%) of subjects with AEs	44 (81.5)	35 (64.8)	49 (89.1)	44 (80.0)	39 (75.0)	20 (38.5)
Number (%) of subjects with:						
Dizziness	14 (25.9)	14 (25.9)	21 (38.2)	19 (34.5)	1 (1.9)	1 (1.9)
Somnolence	13 (24.1)	11 (20.4)	18 (32.7)	18 (32.7)	4 (7.7)	4 (7.7)
Nausea[a]	9 (16.7)	7 (13.0)	13 (23.6)	10 (18.2)	2 (3.8)	2 (3.8)
Headache	8 (14.8)	1 (1.9)	12 (21.8)	6 (10.9)	11 (21.2)	4 (7.7)
Euphoric mood	5 (9.3)	5 (9.3)	5 (9.1)	4 (7.3)	0	0
Urinary tract infection	4 (7.4)	2 (3.7)	7 (12.7)	0	4 (7.7)	2 (3.8)
Weight increased	4 (7.4)	4 (7.4)	6 (10.9)	6 (10.9)	1 (1.9)	1 (1.9)
Fatigue	4 (7.4)	4 (7.4)	3 (5.5)	1 (1.8)	3 (5.8)	0
Arthralgia	4 (7.4)	3 (5.6)	2 (3.6)	0	0	0
Abdominal pain	4 (7.4)	1 (1.9)	2 (3.6)	1 (1.8)	0	0
Insomnia[a]	3 (5.6)	2 (3.7)	9 (16.4)	7 (12.7)	1 (1.9)	0
Edema peripheral	3 (5.6)	2 (3.7)	4 (7.3)	4 (7.3)	0	0
Vomiting[a]	3 (5.6)	3 (5.6)	4 (7.3)	1 (1.8)	0	0
Back pain	3 (5.6)	1 (1.9)	3 (5.5)	1 (1.8)	2 (3.8)	0
Anxiety[a]	3 (5.6)	2 (3.7)	3 (5.5)	2 (3.6)	0	0
Gait disturbance	3 (5.6)	3 (5.6)	3 (5.5)	3 (5.5)	0	0
Dry mouth	3 (5.6)	3 (5.6)	1 (1.8)	1 (1.8)	0	0
Migraine	3 (5.6)	1 (1.9)	1 (1.8)	0	0	0
Tooth infection	3 (5.6)	0	0	0	1 (1.9)	0
Upper respiratory tract infection	3 (5.6)	1 (1.9)	0	0	0	0
Diarrhea[a]	2 (3.7)	2 (3.7)	11 (20.0)	7 (12.7)	1 (1.9)	1 (1.9)
Constipation	2 (3.7)	2 (3.7)	7 (12.7)	5 (5.5)	2 (3.8)	2 (3.8)
Chills[a]	2 (3.7)	2 (3.7)	6 (10.9)	5 (5.5)	1 (1.9)	1 (1.9)
Depression	1 (1.9)	1 (1.9)	4 (7.3)	3 (5.5)	0	0
Hot flush[a]	0	0	3 (5.5)	3 (5.5)	0	0

AEs listed in descending frequency for PD-0299685 15 mg treatment group
If the same subject in a given treatment had more than 1 occurrence in the same preferred term event category, only the most severe occurrence was taken.
Subjects were counted only once per treatment in each row.
Includes data up to 30 days after last dose of study drug.
MedDRA v12.1 coding dictionary applied.
MedDRA=Medical Dictionary for Regulatory Activities; BID=twice daily; N=total number of subjects; AC=all causality; TR=treatment related
[a] Predominantly DESS AEs

Table 5 Subjects Discontinued from Study Treatment due to Adverse Events

Subject Sex/ Age [years]	Adverse Event	Start Day	Stop Day	Severity	Outcome	Causality
PD-0299685 15 mg BID (N=54)						
F/65	Cognitive disorder[a]	0	16	Moderate	Resolved	ST
F/57	Urinary tract infection	44	65	Mild	Resolved	ST
F/75	Asthenia	19	34	Mild	Resolved	ST
F/66	Deep vein thrombosis[b]	3	107	Severe	Resolved	ST
F/44	Somnolence	5	21	Mild	Resolved	ST
F/54	Somnolence	18	54	Mild	Resolved	ST
M/44	Suicide attempt[b]	80	99	Severe	Resolved	Other illness
F/31	Migraine	38	>59	Moderate	Still present	ST
F/47	Fatigue	2	7	Moderate	Resolved	ST
PD-0299685 30 mg BID (N=55)[c]						
F/72	Urinary tract infection	14	>19	Moderate	Still present	Other illness
F/56	Lethargy	1	1	Severe	Resolved	ST
F/59	Constipation	15	>21	Severe	Still present	ST
F/35	White blood cell count decreased	38	63	Moderate	Resolved	ST
F/30	Somnolence	2	4	Moderate	Resolved	ST
F/58	Euphoric mood	2	36	Moderate	Resolved	ST
F/40	Dizziness	2	3	Moderate	Resolved	ST
F/43	Vomiting	73	81	Moderate	Resolved	Other illness
F/23	Somnolence[d]	-11	16	Severe	Resolved	ST
F/54	Depression	35	>42	Moderate	Still present	ST
F/54	Depression	42	46	Moderate	Resolved	ST
F/59	Diplopia	16	43	Mild	Resolved	ST
F/64	Somnolence	15	22	Severe	Resolved	ST
F/36	Somnolence	2	6	Severe	Resolved	ST
F/32	Blood pressure increased	17	33	Moderate	Resolved	ST
Placebo (N = 52)						
F/79	Urinary tract infection	46	>59	Mild	Still present	ST
F/67	Urinary tract infection	1	19	Mild	Resolved	Disease under study
F/48	Cystitis interstitial	19	36	Severe	Resolved	Disease under study
F/66	Mood altered	22	44	Moderate	Resolved	ST
F/47	Constipation	5	15	Moderate	Resolved	ST

BID=twice daily; N=total number of subjects; M=male; F=female; ST=study treatment; AE=adverse event
[a]Onset of AE was before administration of study treatment during the double-blind treatment phase, therefore the AE was not recorded as treatment-emergent.
[b] Serious adverse event
[c] An additional subject was discontinued on Day 53 due to an AE (urinary tract infection); however, the reason for discontinuation was recorded as protocol deviation.
[d] Onset of AE was before administration of study treatment during the double-blind treatment phase; therefore, the AE was not recorded as treatment-emergent.

Table 6 Serious Adverse Events

Subject Sex/Age (years)	Adverse Event	Start Day	Stop Day	Severity	Outcome	Causality
PD-0299685 15 mg BID (N=54)						
F/66	Deep vein thrombosis	3	107	Severe	Resolved	Study drug
M/44	Suicide attempt[a]	80	99	Severe	Resolved	Other illness

BID=twice daily; N=total number of subjects; F=female; M=male
[a] Adverse event led to discontinuation

CONCLUSIONS:

- Efficacy for worst pain was demonstrated at the higher dose of 30 mg BID, but not at 15 mg BID, and effects on urinary endpoints were mixed and non-sustained. Therefore, PD-0299685 has a narrow therapeutic index in this indication.

- Tolerability was poor, with a dose response for neuropsychiatric AEs. There were no other significant safety concerns.

- The overall benefit risk assessment is negative for PD-0299685 in the treatment of the symptoms of IC/PBS.