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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Imagabalin

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: Not Applicable

NATIONAL CLINICAL TRIAL NO: NCT00658372

PROTOCOL NO: A5361018

PROTOCOL TITLE: A Phase 3, Randomized, Double-Blind, Parallel Group, 10-Week Placebo-Controlled Fixed Dose Study of PD 0332334 and Paroxetine Evaluating the Efficacy and Safety of PD 0332334 for the Treatment of Generalized Anxiety Disorder

Study Centers: This study was conducted at a total of 31 study centers: Russia (2 study centers), United States (28 study centers), and Hungary (1 center).

Study Initiation and Completion Dates: 05 May 2008 to 26 March 2009; this study was terminated prematurely due to termination of the PD 0332334 program.

Phase of Development: Phase 3

Study Objectives:

Primary Objectives:

- To assess the efficacy of PD 0332334 in the treatment of Generalized Anxiety Disorder (GAD) as measured by the change from Baseline in the Hamilton Anxiety Rating Scale (HAM-A) total score at Week 8.
- To assess the safety and tolerability of PD 0332334 in subjects with GAD.

Key Secondary Objective:

- To assess the effects of PD 0332334 on disability (as measured by the change from baseline at Week 8 in the Sheehan Disability total score [SDS]) associated with GAD.

Other Secondary Objectives:

- To assess the time course of action of PD 0332334 on the symptoms of GAD (as measured by the change from baseline HAM-A) over the 8-week double-blind treatment period.
- To assess the effect of PD 0332334 on the somatic symptoms of GAD.

- To assess the effect of PD 0332334 on the psychic symptoms of GAD.
- To assess the effect of PD 0332334 on patient reported symptom of GAD.
- To assess the Week 1 sustained response (based on the HAM-A total score) with PD 0332334 in the treatment of GAD.
- To assess the effects of PD 0332334 on sleep problems in subjects with GAD.
- To assess the effect of PD 0332334 on depressive symptoms in subjects with GAD.
- To assess the efficacy of PD 0332334 in the treatment of GAD as assessed by clinical and patient global impressions.
- To assess the effect of PD 0332334 on quality of life enjoyment and satisfaction in subjects with GAD.
- To assess the effect of PD 0332334 on sexual functioning in subjects with GAD.
- To assess the effects associated with discontinuation of PD 0332334 following short-term use in subjects with GAD.
- To compare the efficacy of PD 0332334 to paroxetine.
- To compare the efficacy of paroxetine to placebo.

METHODS

Study Design: This study was a randomized, double-blind, parallel-group, multi-site, Phase 3, placebo-controlled, fixed-dose study of PD 0332334 and paroxetine. Approximately 528 outpatients with GAD were planned for enrollment. The study consisted of 3 phases: an initial screening phase that was completed 7 to 14 days prior to randomization; an 8-week double-blind treatment phase; and a 2-week double-blind, dose-tapering follow-up phase. After obtaining written informed consent, the investigator initiated washout of prior psychotropic medications. Once the washout period was completed, the investigator ensured that the subjects were no longer taking psychotropic medication for at least 14 days prior to the randomization visit. In addition, the investigator confirmed that screening visit procedures (with the exception of obtaining informed consent) were completed within 14 days of the randomization visit. Subjects who fulfilled entry criteria were randomized to receive 1 of the following 4 treatments (132 planned subjects per treatment group) in a double-blind fashion: PD 0332334 225 mg twice daily (BID) (450 mg/day), PD 0332334 300 mg BID (600 mg/day), placebo and paroxetine 20 mg every morning (QAM) (20 mg/day). PD 0332334 was titrated up in the PD 0332334 225 mg BID and PD 0332334 300 mg BID treatment groups. The titration of PD 0332334 started at 125 mg in the beginning of the study. In addition, the PD 0332334 225 mg BID and PD 0332334 300 mg BID treatment groups were titrated down at the end of the study.

De-identified blood samples were collected from study subjects at Screening (Visit 1). Participation in this component of the study was optional for subjects. Samples may have been utilized in the future to investigate GAD genetics, expression metabonomic and protein biomarker profiles, drug-response, or other genetic or biomarker questions. This information is not included in this synopsis study report.

Number of Subjects (Planned and Analyzed): A total of 528 subjects were planned to be enrolled in this study. A total of 532 subjects were screened for entry into this study, of which 93 subjects were assigned to paroxetine 20 mg with 44 completing treatment and 178 subjects were assigned to PD 0332334 with 90 completing treatment. There were 89 subjects assigned to placebo with 50 subjects completing treatment.

Diagnosis and Main Criteria for Inclusion: Subjects were healthy males and females between 18 and 65 years of age, inclusive. Subjects were required to have a diagnosis of GAD according to the Diagnostic and Statistical Manual-IV (DSM-IV), 300.02. Subjects were required to have a HAM-A total score ≥20 at the Screening (Visit 1) and Randomization (Visit 2) visits. Subjects were also required to have a Covi Anxiety Scale score ≥9 and a Raskin Depression Scale score ≤7 at the Screening (Visit 1) visit to ensure predominance of anxiety symptoms over depression symptoms. Otherwise healthy men or nonpregnant, nonlactating women (women must have been using a hormonal or barrier method of contraception or must have been postmenopausal or surgically sterilized). Healthy was defined as no other clinically relevant abnormalities identified by a detailed medical history, full physical examination (including sitting blood pressure [BP] and heart rate measurement), 12-lead electrocardiogram (ECG), and clinical laboratory tests. All women were required to have a negative pregnancy test at the Screening (Visit 1) and Randomization (Visit 2) visits.

Study Treatment: The study drugs consisted of blinded oral capsules containing PD 0332334 25 mg, PD 0332334 100 mg, placebo, paroxetine 10 mg, or paroxetine 20 mg. Study drug was administered to each subject in a BID regimen for PD 0332334 and placebo, and a once daily (QD) dose regimen for paroxetine and placebo. Subjects randomized to receive PD 0332334 225 mg BID, or PD 0332334 300 mg BID began dosing with 125 mg at bedtime (HS) on study Day 1 (day of randomization to double-blind treatment). Subjects were titrated up to their full treatment dose over the first week of treatment according to the schedule in Table 1.

Table 1. Titration Schedule for PD 0332334 Treatment Groups

Day	PD 0332334 225 mg BID	PD 0332334 300 mg BID
1	125 mg HS	125 mg HS
2	125 mg BID	125 mg BID
3	125 mg BID	125 mg BID
4	125 mg BID	225 mg BID
5	225 mg BID	225 mg BID
6	225 mg BID	300 mg BID
7	225 mg BID	300 mg BID

Abbreviations: BID = twice daily, HS = at bedtime

Subjects self-administered study drug as outpatients in this study. Study drug was administered with or without food.

Following titration, subjects in both PD 0332334 treatment groups received the full treatment dose for the remainder of the 8-week double-blind treatment phase. Subjects randomized to placebo received placebo BID for the duration of the 8-week treatment phase. Subjects randomized to paroxetine received treatment with 20 mg QD on Day 1 and 20 mg QAM (every morning) for the remainder of the 8-week treatment phase, with no titration period.

From Day 1 until completion of the double-blind treatment phase, subjects took 1 capsule of paroxetine 20 mg or matching placebo in the morning, or 4 capsules of PD 0332334 or matching placebo in the morning and evening, approximately 12 hours apart (PD 0332334 or matching placebo were taken in the evening only on Day 1). Study drug was taken with 6 to 8 ounces of water and without regard to food intake. Subjects swallowed the study drug intact.

During the 2-week double-blind dose-tapering follow-up phase, study treatments were discontinued according to the schedule in Table 2. All subjects received placebo BID on study Days 65 to 71.

Table 2. Dose-Tapering Follow-up Phase Schedule

Day	PD 0332334 225 mg BID Treatment Group	PD 0332334 300 mg BID Treatment Group	Placebo BID Treatment Group	Paroxetine 20 mg QAM Treatment Group
57	225 mg BID	300 mg BID	Placebo BID	20 mg QAM
58	125 mg BID	225 mg BID	Placebo BID	10 mg QAM
59	125 mg BID	225 mg BID	Placebo BID	10 mg QAM
60	125 mg BID	125 mg BID	Placebo BID	10 mg QAM
61	125 mg BID	125 mg BID	Placebo BID	10 mg QAM
62	125 mg BID	125 mg BID	Placebo BID	10 mg QAM
63	Placebo BID	Placebo BID	Placebo BID	Placebo QAM
64	Placebo BID	Placebo BID	Placebo BID	Placebo QAM

Abbreviations: BID = twice daily, QAM = every morning

Efficacy Evaluations: The HAM-A, Hamilton Rating Scale for Depression (HAM-D), Daily Diary (DD), Clinical Global Impression of Improvement (CGI-I), Patient Global Impression of Change (PGI-C), Clinical Global Impression of Severity (CGI-S), SDS, Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), and Medical Outcomes Study (MOS) Sleep Scale data were collected for the evaluation of efficacy. Only HAM-A data were analyzed due to termination of the development of PD 0332334.

Other Evaluations: Other evaluations included the Mini International Neuropsychiatric Interview (MINI), Covi Anxiety Scale, Raskin Depression Scale, Clinical Trial and Site Scale (CTSS), and Health Care Utilization (HCU), which were collected at Screening or randomization only.

Safety Evaluations: Safety endpoints for this study included the nature, incidence, and severity of adverse events (AEs); discontinuation due to AEs; AEs that occurred during and after study drug discontinuation; and body weight, clinical safety laboratory tests, 12-lead

ECGs, physical examinations, vital signs measurements; and Changes in Sexual Functioning Questionnaire (CSFQ). Suicidal ideation and suicidal behavior were evaluated using the Columbia-Suicide Severity Scale (C-SSRS).

Statistical Methods: Safety, demographics, and HAM-A data were summarized using data tabulations and descriptive statistics. Due to termination of the development of PD 0332334, only the primary endpoint was analyzed. Change from baseline in the HAM-A total score was analyzed using an analysis of covariance (ANCOVA) model with baseline HAM-A total score and investigator site as covariates for both the Full Analysis Set (FAS) and the Per Protocol Analysis Set (PPAS) The PPAS was a subset of the Full Analysis Set (ie, all randomized and treated subjects) and excluded all subjects who discontinued on or after termination of the PD 0332334 development program (on or after 23 February 2009) unless the subject discontinued on or after 23 February 2009 due to an AE.

RESULTS

Subject Disposition and Datasets Analyzed: Table 3 provides a summary of subject disposition. A total of 532 subjects were screened for entry into this study, of which 93 subjects were assigned to paroxetine 20 mg with 44 completing treatment, and 178 subjects were assigned to PD 0332334 with 90 completing treatment. There were 89 subjects assigned to placebo with 50 subjects completing treatment.

Table 3. Subject Disposition and Subjects Analyzed

No. of Subjects	PD 0332334 225 mg BID	PD 0332334 300 mg BID	Paroxetine 20 mg	Placebo
Planned: N=528				
Screened: N=532				
Assigned to Treatment (n)	86	92	93	89
Treated (n)	86	92	93	89
Completed (n)	45	45	44	50
Discontinued (n)	41	47	49	39
Analyzed for Safety				
Adverse events (n)	86	92	93	89
Laboratory data (n)	76	82	85	79

Abbreviation: BID = twice daily

Subject discontinuations from Day 1 to Week 10 overall were similar between the placebo, paroxetine 20 mg, PD 0332334 225 mg BID, and PD 0332334 300 mg BID treatment groups; the lowest overall number of discontinuations occurred in the placebo group.

Table 4 summarizes subject discontinuations that occurred from Day 1 to Week 10 of the study.

Table 4. Subject Discontinuations From Study (Day 1 to Week 10)

No. (%) of Subjects	PD 0332334 225 mg BID N=86	PD 0332334 300 mg BID N=92	Paroxetine 20 mg N=93	Placebo N=89
Discontinuations related to study drug	21 (24.4)	23 (25.0)	27 (29.0)	27 (30.3)
AE related to study drug	4 (4.7)	5 (5.4)	9 (9.7)	5 (5.6)
Lack of efficacy	2 (2.3)	4 (4.3)	1 (1.1)	5 (5.6)
Study terminated by sponsor	15 (17.4)	14 (15.2)	17 (18.3)	17 (19.1)
Discontinuations not related to study drug	20 (23.3)	24 (26.1)	22 (23.7)	12 (13.5)
AE not related to study drug	1 (1.2)	4 (4.3)	2 (2.2)	0
Lost to follow-up	6 (7.0)	8 (8.7)	5 (5.4)	6 (6.7)
Other	6 (7.0)	3 (3.3)	7 (7.5)	2 (2.2)
Protocol Violation	3 (3.5)	6 (6.5)	3 (3.2)	3 (3.4)
Subject no longer willing to participate in the study	4 (4.7)	3 (3.3)	5 (5.4)	1 (1.1)
Total Discontinuations	41 (47.7)	47 (51.1)	49 (52.7)	39 (43.8)

Abbreviations: AE = adverse event, BID = twice daily

Demography: Subject demographics are summarized in Table 5. Overall, 242 of the subjects were female and 118 subjects were male. The mean age of females enrolled in the study was between 38.9 to 40.9 years. The mean age of males enrolled in the study was between 40.3 to 44.5 years. The majority of subjects (288/360 [80.0%]) enrolled in the study were white.

Table 5. Demographic Characteristics

Demographic Characteristics Parameters	PD 0332334 225 mg BID N=86		PD 0332334 300 mg BID N=92		Paroxetine 20 mg N=93		Placebo N=89	
	M	F	M	F	M	F	M	F
No. (%) of Subjects	26	60	28	64	31	62	33	56
Age (years)								
18-44	15 (57.7)	35 (58.3)	17 (60.7)	44 (68.8)	21 (67.7)	37 (59.7)	12 (36.4)	29 (51.8)
45-65	11 (42.3)	25 (41.7)	11 (39.3)	20 (31.3)	10 (32.3)	25 (40.3)	21 (63.6)	27 (48.2)
Mean	41.5	40.8	40.3	38.9	41.0	39.7	44.5	40.9
SD	11.0	12.1	10.2	11.5	12.0	12.3	12.1	13.4
Range	22-63	19-65	20-62	18-63	20-62	18-64	18-62	18-65
Race								
White	24 (92.3)	47 (78.3)	25 (89.3)	48 (75.0)	28 (90.3)	45 (72.6)	28 (84.8)	43 (76.8)
Black	2 (7.7)	8 (13.3)	3 (10.7)	14 (21.9)	2 (6.5)	16 (25.8)	3 (9.1)	11 (19.6)
Asian	0	0	0	1 (1.6)	1 (3.2)	1 (1.6)	1 (3.0)	1 (1.8)
Other	0	5 (8.3)	0	1 (1.6)	0	0	1 (3.0)	1 (1.8)
Ethnicity								
Hispanic/Latino	1 (3.8)	10 (16.7)	2 (7.1)	6 (9.4)	1 (3.2)	4 (6.5)	2 (6.1)	3 (5.4)
Not Hispanic/Latino	25 (96.2)	50 (83.3)	26 (92.9)	58 (90.6)	30 (96.8)	58 (93.5)	31 (93.9)	53 (94.6)
Height (cm)								
Mean	176.3	163.7	177.1	164.2	178.3	164.5	175.2	164.4
SD	9.0	7.2	6.5	7.3	7.8	7.5	7.1	5.2
Range	145.0-187.9	147.3-180.3	165.0-193.0	147.3-180.4	159.4-195.0	144.8-180.3	164.0-193.0	152.4-175.3
N	26 (100.0)	60 (100.0)	28 (100.0)	64 (100.0)	31 (100.0)	62 (100.0)	33 (100.0)	56 (100.0)

Abbreviations: BID=twice daily, F = female, M = male, SD = standard deviation

Primary Objective Findings: The primary objective of the study was to assess the efficacy of PD 0332334 in the treatment of GAD as measured by the change from Baseline in the HAM-A total score at Week 8. Table 6 provides a summary of change in the HAM-A total score from Baseline to Week 8 (using last-observation-carried forward [LOCF] for missing Week-8 data). Change from Baseline in HAM-A total score at Week 8 was similar across treatment groups (Table 6).

Table 6. HAM-A Total Score Change From Baseline to Week 8; Full Analysis Set

Parameters	PD 0332334		Paroxetine 20 mg	Placebo
	225 mg BID	300 mg BID		
Baseline				
Number of Subjects	86	92	93	89
Mean (SD)	24.6 (4.2)	24.6 (4.0)	25.1 (4.6)	25.1 (4.7)
Change from Baseline at Week 8 (LOCF)[a]				
N	80	84	82	84
LS mean (SE)	-10.9 (0.8)	-11.0 (0.8)	-9.3 (0.8)	-10.2 (0.8)
95% CI	-12.4, -9.3	-12.5, -9.4	-10.8, -7.7	-11.7, -8.6

Abbreviations: ANCOVA = analysis of covariance, BID=twice daily, CI = confidence interval, HAM-A = Hamilton Anxiety Rating Scale, LOCF = last observation carried forward, LS = least squares, SD = standard deviation, SE = standard error

[a] ANCOVA model of change from Baseline in HAM-A total score, with Baseline HAM-A total score and study site as covariates.

Safety Results: There were no deaths in the study. None of the AEs that occurred in this study were coded by investigators as serious. Table 7 summarizes the AEs for each treatment group. The incidence of AEs was similar across the PD 0332334 225 mg BID, 300 mg BID treatment group, and the paroxetine 20 mg treatment group. AEs were slightly less in the placebo group.

Table 7. Treatment-Emergent Adverse Events

No. (%) of Subjects	PD 0332334		Paroxetine 20 mg	Placebo
	225 mg BID	300 mg BID		
All Causality				
Subjects evaluable for AEs	86	92	93	89
Number of AEs	214	215	185	135
Subjects with AEs	68 (79.1)	67 (72.8)	73 (78.5)	62 (69.7)
Subjects with serious AEs	0	0	0	0
Subjects with severe AEs	5 (5.8)	8 (8.7)	7 (7.5)	3 (3.4)
Subjects discontinued due to AEs	5 (5.8)	9 (9.8)	11 (11.8)	5 (5.6)
Subjects with dose reduced or temporary discontinuation due to AEs	1 (1.2)	0	1 (1.1)	0
Treatment-Related				
Subjects evaluable for AEs	86	92	93	89
Number of AEs	131	147	110	59
Subjects with AEs	55 (64.0)	56 (60.9)	53 (57.0)	36 (40.4)
Subjects with serious AEs	0	0	0	0
Subjects with severe AEs	3 (3.5)	6 (6.5)	2 (2.2)	1 (1.1)
Subjects discontinued due to AEs	4 (4.7)	5 (5.4)	9 (9.7)	5 (5.6)
Subjects with dose reduced or temporary discontinuation due to AEs	1 (1.2)	0	0	0

Abbreviations: AEs = adverse events, BID = twice daily, MedDRA = Medical Dictionary for Regulatory Activities
Except for the number of AEs, subjects were counted only once per treatment in each row. Serious Adverse Events were according to the investigator's assessment.
MedDRA (v12.0) coding dictionary applied.

The most common treatment-related AEs reported in this study (Medical Dictionary for Regulatory Activities [MedDRA], Version 12.0) by system organ class were gastrointestinal disorders, nervous system disorders, psychiatric disorders, and general disorders and administration site conditions. Table 8 provides a summary of AEs by preferred term (all causality) from Day 1 through Week 10 in >4% of subjects in any treatment group.

Table 8. Summary of Treatment-Emergent Adverse Events (All Causality) From Day 1 through Week 10 in >4% of Subjects in Any Treatment Group – Safety Analysis Set

No. (%) of Subjects	PD 0332334 225 mg BID N=86	PD 0332334 300 mg BID N=92	Paroxetine 20 mg N=93	Placebo N=89
System Organ Class[a] Preferred Term[a]				
Eye Disorders	1 (1.2)	5 (5.4)	2 (2.2)	1 (1.1)
Vision blurred	1 (1.2)	5 (5.4)	1 (1.1)	0
Gastrointestinal Disorders	34 (39.5)	29 (31.5)	34 (36.6)	26 (29.2)
Constipation	5 (5.8)	2 (2.2)	3 (3.2)	5 (5.6)
Diarrhea	3 (3.5)	1 (1.1)	7 (7.5)	3 (3.4)
Dry mouth	11 (12.8)	11 (12.0)	8 (8.6)	4 (4.5)
Dyspepsia	6 (7.0)	3 (3.3)	1 (1.1)	0
Nausea	11 (12.8)	10 (10.9)	18 (19.4)	10 (11.2)
Vomiting	3 (3.5)	4 (4.3)	6 (6.5)	3 (3.4)
General Disorders and Administration Site Conditions	18 (20.9)	7 (7.6)	13 (14.0)	8 (9.0)
Fatigue	4 (4.7)	4 (4.3)	8 (8.6)	3 (3.4)
Infections and Infestations	19 (22.1)	14 (15.2)	17 (18.3)	18 (20.2)
Gastroenteritis	1 (1.2)	0	1 (1.1)	5 (5.6)
Influenza	0	1 (1.1)	0	4 (4.5)
Nasopharyngitis	4 (4.7)	0	5 (5.4)	1 (1.1)
Upper respiratory tract infection	6 (7.0)	5 (5.4)	5 (5.4)	4 (4.5)
Urinary tract infection	7 (8.1)	2 (2.2)	0	1 (1.1)
Investigations	4 (4.7)	6 (6.5)	5 (5.4)	2 (2.2)
Weight increased	4 (4.7)	3 (3.3)	0	1 (1.1)
Metabolism and Nutrition Disorders	3 (3.5)	5 (5.4)	3 (3.2)	2 (2.2)
Increased appetite	2 (2.3)	4 (4.3)	0	1 (1.1)
Musculoskeletal and Connective Tissue Disorders	5 (5.8)	10 (10.9)	9 (9.7)	4 (4.5)
Back pain	1 (1.2)	4 (4.3)	4 (4.3)	0
Nervous System Disorders	41 (47.7)	41 (44.6)	30 (32.3)	24 (27.0)
Disturbance in attention	1 (1.2)	6 (6.5)	0	0
Dizziness	11 (12.8)	18 (19.6)	4 (4.3)	2 (2.2)
Headache	12 (14.0)	12 (13.0)	18 (19.4)	13 (14.6)
Sedation	10 (11.6)	6 (6.5)	3 (3.2)	4 (4.5)
Somnolence	12 (14.0)	17 (18.5)	5 (5.4)	4 (4.5)
Psychiatric Disorders	17 (19.8)	18 (19.6)	10 (10.8)	10 (11.2)
Insomnia	6 (7.0)	4 (4.3)	3 (3.2)	3 (3.4)
Respiratory, Thoracic and Mediastinal Disorders	5 (5.8)	5 (5.4)	11 (11.8)	9 (10.1)
Oropharyngeal pain	1 (1.2)	2 (2.2)	5 (5.4)	3 (3.4)

Abbreviations: BID = twice daily, MedDRA = Medical Dictionary for Regulatory Activities
[a] MedDRA (v12.0) coding dictionary applied.

The most common AEs (all causality) reported in this study by preferred term (MedDRA, Version 12.0) were headache (55 subjects overall) and nausea (49 subjects overall). A total of 11 subjects in the paroxetine 20 mg group, 5 subjects in the placebo group, 5 subjects in the PD 0332334 225 mg BID group, and 9 subjects in the PD 0332334 300 mg BID group discontinued the study due to AEs. The most common AEs leading to permanent discontinuation were nausea (8 subjects) and dizziness (7 subjects). Table 9 summarizes discontinuations from the study due to AEs by preferred term.

A total of 9 subjects in the paroxetine 20 mg group, 5 subjects in the placebo group, 4 subjects in the PD 0332334 225 mg BID group, and 5 subjects in the PD 0332334 300 mg BID group discontinued due to AEs that were considered to be treatment-related.

Table 9. Summary of Adverse Events (All Causalities) Leading to Permanent Discontinuation

Page 1 of 2				
System Organ Class[a] Preferred Term[a]	**PD 0332334 225 mg BID N=86**	**PD 0332334 300 mg BID N=92**	**Paroxetine 20 mg N=93**	**Placebo N=89**
Cardiac Disorders				
Tachycardia	0	0	1	0
Congenital, Familial, and Genetic Disorders				
Congenital arterial malformation	0	1	0	0
Eye Disorders				
Vision blurred	0	0	1	0
Gastrointestinal Disorders				
Diarrhea	0	0	0	1
Dry mouth	0	1	0	0
Hematemesis	0	0	0	1
Nausea	2	2	3	1
Vomiting	0	2	1	0
General Disorders and Administration Site Conditions				
Asthenia	0	0	0	1
Fatigue	0	1	0	0
Irritability	1	0	0	0
Infections and Infestations				
Subcutaneous abscess	0	1	0	0
Metabolism and Nutrition Disorders				
Anorexia	1	0	1	0
Musculoskeletal and Connective Tissue Disorders				
Myalgia	1	0	0	0
Nervous System Disorders				
Amnesia	1	0	0	0
Disturbance in attention	1	1	0	0
Dizziness	1	3	2	1
Dyskinesia	0	0	1	0
Dystonia	0	0	1	0
Headache	1	0	2	1
Lethargy	0	1	0	0
Migraine	0	0	0	1
Sedation	1	0	2	0
Somnolence	0	1	1	0
Psychiatric Disorders				
Agitation	1	0	0	0
Confusional state	0	1	0	0

Abbreviations: BID = twice daily, MedDRA = Medical Dictionary for Regulatory Activity

[a] MedDRA (v12.0) coding dictionary applied.

Table 9. Summary of Adverse Events (All Causalities) Leading to Permanent Discontinuation

Page 2 of 2				
System Organ Class[a] Preferred Term[a]	**PD 0332334 225 mg BID N=86**	**PD 0332334 300 mg BID N-92**	**Paroxetine 20 mg N=93**	**Placebo N=89**
Psychiatric Disorders				
Disorientation	0	0	1	0
Hostility	0	0	1	0
Impulse control disorder	0	1	0	0
Insomnia	1	0	1	0
Restlessness	1	0	0	0
Respiratory, Thoracic, and Mediastinal Disorders				
Dysphonia	1	0	0	0
Skin and Subcutaneous Tissue Disorders				
Rash	0	0	1	0

Abbreviations: BID = twice daily, MedDRA = Medical Dictionary for Regulatory Activity
[a] MedDRA (v12.0) coding dictionary applied.

The number and percentage of subjects by treatment group who had ≥7% increase in body weight from Baseline is summarized in Table 10.

Table 10. Incidence of ≥7% Increase in Body Weight; Safety Analysis Set

Parameters	PD 0332334 225 mg BID		PD 0332334 300 mg BID		Paroxetine 20 mg		Placebo	
	N	n (%)	N	n (%)	N	n (%)	N	n (%)
≥7% increase in body weight	86	3 (3.5)	92	1 (1.1)	93	0 (0.0)	89	0 (0.0)

Abbreviation: BID = twice daily

No subject in any treatment group completed suicide or nonsuicidal, self-injurious behavior at any post baseline assessment. Suicidal ideations were reported by subjects in each treatment group: PD 0332334 225 mg BID (3 subjects [3.7%]), PD 0332334 300 mg BID (4 subjects [4.6%]), paroxetine 20 mg (2 subjects [2.2%]), and placebo (5 subjects [5.8%]). A suicide attempt and prepatory acts toward imminent suicidal behavior were each reported in 1 subject (1.1%) in the PD 0332334 300 mg BID treatment group.

Laboratory Test Results: Table 11 provides a summary of those subjects who had normal laboratory test ranges at Baseline and had laboratory test values after the start of treatment that met the sponsor's predefined criteria for potential clinical concern. No differences were noted across treatment groups.

Table 11. Laboratory Test Abnormalities Reported by ≥2 Subjects in Any Treatment Group; Subjects With Normal Baseline

Parameter	Unit	Criteria	PD 0332334 225 mg BID		PD 0332334 300 mg BID		Paroxetine 20 mg		Placebo	
			N	n	N	n	N	n	N	n
Electrolytes										
Bicarbonate (venous)	mEq/L	<0.9 × LLN	71	1 (1%)	82	3 (4%)	81	0	73	1 (1%)
Clinical chemistry (other)										
Creatine kinase	U/L	>2.0 × ULN	69	1 (1%)	68	0	74	4 (5%)	67	0
Urinalysis (microscopy)										
Urine RBC	HPF	≥6	18	6	16	4	17	2	16	4
Urine WBC	HPF	≥6	19	6	19	3	18	1	17	4
Urine epithelial cells	HPF	≥6	19	7	18	5	14	4	16	2

Abbreviations: BID = twice daily, HPF = high-powered field, LLN = lower limit of normal, N = total number of subjects with normal or missing baseline with at least 1 observation of the given laboratory test while on study treatment or during lag time, n = number of subjects with normal or missing baseline with a laboratory abnormality meeting specified criteria while on study treatment or during lag time, RBC = red blood cell, ULN = upper limit of normal, WBC = white blood cell
Percentages are displayed for the laboratory tests having a category with ≥50 subjects.

Vital Signs Measurements and Electrocardiogram Results: There were no notable differences across treatment groups in effects on vitals signs. Table 12 summarizes the vital signs measurements that met the sponsor's predetermined criteria for potential clinical concern.

Table 12. Vital Signs Measurement Data; Safety Analysis Set

Parameter	Criteria	PD 0332334 225 mg BID		PD 0332334 300 mg BID		Paroxetine 20 mg		Placebo	
		N	n (%)	N	n (%)	N	n (%)	N	n (%)
Increase from baseline									
Maximum increase from baseline in sitting systolic BP (mm Hg)	≥30	82	0	88	4 (4.5)	90	2 (2.2)	86	1 (1.2)
Maximum increase from baseline in sitting diastolic BP (mm Hg)	≥20	82	3 (3.7)	88	6 (6.8)	90	5 (5.6)	86	4 (4.7)
Absolute values									
Sitting systolic BP (mm Hg)	<90	86	2 (2.3)	92	2 (2.2)	93	2 (2.2)	89	3 (3.4)
Sitting diastolic BP (mm Hg)	<50	86	1 (1.2)	92	1 (1.1)	93	0	89	1 (1.1)
Sitting heart rate (bpm)	<40	86	0	92	0	93	0	89	0
	>120	86	0	92	0	93	0	89	0

Abbreviations: BID = twice daily, BP = blood pressure, bpm = beats per minute, mm Hg = millimeters of mercury

Subjects with corrected QT interval with Bazett's formula (QTcB) or corrected QT interval with Fredericia's formula (QTcF) intervals 450 to <500 msec and ≥500 msec are summarized in Table 13. There were no notable differences across treatment groups in effects on ECG parameters.

Table 13. Electrocardiogram Data; Safety Analysis Set

Parameter	Criteria	PD 0332334 225 mg BID		PD 0332334 300 mg BID		Paroxetine 20 mg		Placebo	
		N	n (%)	N	n (%)	N	n (%)	N	n (%)
Maximum QTcB Interval (msec)	450 - <500	86	1 (1.2)	92	8 (8.7)	93	4 (4.3)	89	4 (4.5)
	≥500	86	0	92	1 (1.1)	93	0	89	0
Maximum QTcF Interval (msec)	450 - <500	86	0	92	1 (1.1)	93	2 (2.2)	89	2 (2.2)
	≥500	86	0	92	0	93	0	89	0

Abbreviations: BID=twice daily, msec = millisecond, QTcF = Corrected QT interval with Fredericia's formula, QTcB = corrected QT interval with Bazett's formula

Conclusions: The PD 0332334 program has been terminated because the compound does not provide meaningful benefit to subjects beyond the current standard of care. The compound was not terminated due to safety reasons. Change from Baseline in HAM-A total score at Week 8 was similar across treatment groups. Safety results from this study indicate that PD 0332334 was safe and well tolerated in this group of adult male and female subjects with GAD.