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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Imagabalin

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: Not Applicable

NATIONAL CLINICAL TRIAL NO.: NCT00658008

PROTOCOL NO.: A5361019

PROTOCOL TITLE: 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 49 study centers: Hungary (2 study centers), Italy (2 study centers), Korea (4 study center), and the United States (41 study centers).

Study Initiation and Completion Dates: 10 April 2008 to 23 March 2009; the study was terminated prematurely.

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 Scale (HAM-A) total score at Week 8.

- To assess the safety and tolerability of PD 0332334 in subjects with GAD.

Secondary Objective:

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

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 sustained response at Week 1 (based on the HAM-A total score) of PD 0332334 in the treatment of GAD;
- To assess the effect of PD 0332334 on patient reported symptoms 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; and
- To compare the efficacy of paroxetine to placebo.

METHODS

Study Design: This study was a Phase 3, randomized, double-blind, parallel-group, multicenter, 10-week, placebo-controlled, fixed-dose study of PD 0332334/Imagabalin and paroxetine in subjects with GAD. This study consisted of 3 phases: an initial screening phase completed 7 to 14 days before randomization, an 8-week, double-blind treatment phase, and a 2-week, double-blind, dose-tapering, follow-up phase. After obtaining written informed consent, subjects underwent a washout of prior psychotropic medications, and should have been off all psychotropic medications for at least 14 days before randomization. Screening visit procedures were completed within 14 days of the randomization visit.

Subjects who fulfilled entry criteria were randomized to receive 1 of the following 5 treatments in a double-blind fashion (137 subjects planned per treatment group):

- PD 0332334 75 mg twice daily (BID) (150 mg/day);
- PD 0332334 175 mg BID (350 mg/day);
- PD 0332334 225 mg BID (450 mg/day);
- Placebo; or

- Paroxetine 20 mg once daily (QD) (20 mg/day).

Number of Subjects (Planned and Analyzed): A total of 685 subjects were planned to be enrolled in this study. Overall, 785 subjects were screened for entry into this study; of these, 493 subjects were assigned to treatment, 491 subjects received treatment, and 305 subjects completed treatment. All subjects who received treatment (N=491) were analyzed for adverse events (AEs) and 443 subjects were analyzed for laboratory data.

Diagnosis and Main Criteria for Inclusion: Subjects eligible for enrollment in this study were between the ages of 18 and 65 years, inclusive, and had a diagnosis of GAD as established by the clinician using all sources of data including the Mini International Neuropsychiatric Interview (MINI) for Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) Axis I disorders and other clinical information. Subjects with specific phobia(s) (as defined in DSM-IV) or dysthymic disorder were allowed in the study. Subjects must have had a HAM-A total score ≥20, a Covi Anxiety Scale score of ≥9 and a Raskin Depression Scale score ≤7 at Screening (Visit 1), and a HAM-A total score ≥20 at the Screening (Visit 1) and Randomization (Visit 2) visits to ensure predominance of anxiety symptoms over depression symptoms. Subjects had to be otherwise healthy men or nonpregnant, nonlactating women (women must have been using a hormonal or barrier method of contraception or 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.

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 QD dose regimen for paroxetine and placebo. Subjects randomized to receive PD 0332334 175 mg BID or PD 0332334 225 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 75 mg BID	PD 0332334 175 mg BID	PD 0332334 225 mg BID
1	75 HS	125 HS	125 HS
2	75 BID	125 BID	125 BID
3	75 BID	125 BID	125 BID
4	75 BID	125 BID	125 BID
5	75 BID	175 BID	225 BID
6	75 BID	175 BID	225 BID
7	75 BID	175 BID	225 BID

Abbreviations: HS = at bedtime, BID = twice daily

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 every morning (QAM) 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 75 mg BID	PD 0332334 175 mg BID	PD 0332334 225 mg BID	Paroxetine 20 mg QAM	Placebo BID
57	placebo BID	175 mg BID	225 mg BID	20 mg QAM	placebo BID
58	placebo BID	125 mg BID	125 mg BID	10 mg QAM	placebo BID
59	placebo BID	125 mg BID	125 mg BID	10 mg QAM	placebo BID
60	placebo BID	125 mg BID	125 mg BID	10 mg QAM	placebo BID
61	placebo BID	125 mg BID	125 mg BID	10 mg QAM	placebo BID
62	placebo BID	125 mg BID	125 mg BID	10 mg QAM	placebo BID
63	placebo BID	placebo BID	placebo BID	placebo QAM	placebo BID
64	placebo BID	placebo BID	placebo BID	placebo QAM	placebo BID

Abbreviations: QAM = every morning, BID = twice daily

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, 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 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: Subject disposition is summarized in Table 3. A total of 785 subjects were screened for entry into this study; of these, 493 subjects were assigned to treatment, 491 subjects received treatment, and 305 subjects completed treatment. All subjects who received treatment (N=491) were analyzed for AEs and 443 subjects were analyzed for laboratory data (Table 3).

Table 3. Subject Disposition and Subjects Analyzed

No. of Subjects	PD 0332334			Paroxetine 20 mg	Placebo
	75 mg BID	175 mg BID	225 mg BID		
Planned: N=685					
Screened: N=785					
Assigned to treatment	100	101	94	97	101
Treated	100	100	94	97	100
Completed	64 (64.0)	54 (54.0)	56 (59.6)	58 (59.8)	73 (73.0)
Discontinued	36 (36.0)	46 (46.0)	38 (40.4)	39 (40.2)	27 (27.0)
Analyzed for safety					
Adverse events	100 (100.0)	100 (100.0)	94 (100.0)	97 (100.0)	100 (100.0)
Laboratory data	91 (91.0)	88 (88.0)	89 (94.7)	82 (84.5)	93 (93.0)

Abbreviation: BID = twice daily
Percentages are based on the numbers of treated subjects.

Table 4 summarizes subject discontinuations that occurred from Day 1 to Week 10 of the study. Subject discontinuations from Day 1 to Week 10 overall were similar between the paroxetine 20 mg, PD 0332334 75 mg BID, PD 0332334 175 mg BID, and PD 0332334 225 mg BID treatment groups; the lowest overall number of discontinuations occurred in the placebo group. Most discontinuations (119/186 [64%]) were considered as not related to study drug (Table 4).

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

Parameters	PD 0332334 75 mg BID N=100	PD 0332334 175 mg BID N=100	PD 0332334 225 mg BID N=94	Paroxetine 20 mg N=97	Placebo N=100
Discontinuations related to study drug	17	14	13	12	11
AE related to study drug	8	9	10	6	5
Lack of efficacy	2	0	0	2	1
Study terminated by sponsor	7	5	3	4	5
Discontinuations not related to study drug	19	32	25	27	16
AE not related to study drug	2	5	1	1	1
Lost to follow-up	6	13	8	13	8
Other	3	7	9	8	5
Subject no longer willing to participate in the study	8	7	7	5	2
Total Discontinuations	36	46	38	39	27

Abbreviations: AE = adverse event, BID = twice daily

Demography: Demographic characteristics are summarized in Table 5. Overall, 307 subjects were female and 184 subjects were male. The mean age of females enrolled in the study ranged from 39.7 to 43.5 years of age. The mean age of males enrolled in the study ranged from 39.5 to 43.5 years of age. The majority of subjects (385/491 [78.4%]) enrolled in this study were white (Table 5).

All subjects had a primary diagnosis of GAD with the mean duration since first diagnosis across treatment groups ranging from 5.1 years (PD 0332334 75-mg and 225-mg treatment groups) to 7.5 years (paroxetine 20-mg treatment group).

Table 5. Demographic Characteristics

Demographic Characteristics Parameters	PD 0332334						Paroxetine 20 mg N=97		Placebo N=100	
	75 mg BID N=100		175 mg BID N=100		225 mg BID N=94					
	M	F	M	F	M	F	M	F	M	F
No. of subjects	47	53	31	69	36	58	35	62	35	65
Age (years)										
18-44	29 (61.7)	33 (62.3)	19 (61.3)	37 (53.6)	23 (63.9)	29 (50.0)	16 (45.7)	32 (51.6)	23 (65.7)	35 (53.8)
45-65	18 (38.3)	20 (37.7)	12 (38.7)	32 (46.4)	13 (36.1)	29 (50.0)	19 (54.3)	30 (48.4)	12 (34.3)	30 (46.2)
Mean	39.6	39.7	39.9	41.4	40.2	43.2	43.5	43.5	39.5	43.5
SD	12.0	11.8	11.9	13.5	13.5	13.7	15.3	12.5	13.4	11.8
Range	19-63	19-62	20-63	18-65	19-65	18-64	19-65	18-65	21-65	24-65
Race										
White	31 (66.0)	39 (73.6)	23 (74.2)	55 (79.7)	25 (69.4)	47 (81.0)	27 (77.1)	53 (85.5)	29 (82.9)	56 (86.2)
Black	7 (14.9)	10 (18.9)	4 (12.9)	10 (14.5)	7 (19.4)	9 (15.5)	4 (11.4)	7 (11.3)	5 (14.3)	6 (9.2)
Asian	6 (12.8)	2 (3.8)	3 (9.7)	0	3 (8.3)	2 (3.4)	1 (2.9)	1 (1.6)	1 (2.9)	1 (1.5)
Other	3 (6.4)	2 (3.8)	1 (3.2)	4 (5.8)	1 (2.8)	0	3 (8.6)	1 (1.6)	0	2 (3.1)
Ethnicity										
Hispanic/Latino	9 (19.1)	15 (28.3)	7 (22.6)	18 (26.1)	13 (36.1)	15 (25.9)	9 (25.7)	14 (22.6)	8 (22.9)	24 (36.9)
Not Hispanic/Latino	38 (80.9)	38 (71.7)	24 (77.4)	51 (73.9)	23 (63.9)	43 (74.1)	26 (74.3)	48 (77.4)	27 (77.1)	41 (63.1)
Height (cm)										
Mean	175.9	163.1	175.7	163.7	174.0	163.5	174.7	164.0	175.5	161.2
SD	10.0	7.2	6.8	6.6	6.5	7.5	7.2	7.6	6.7	7.2
Range	143.0-193.0	148.6-178.0	160.0-190.0	148.5-182.0	160.0-187.0	152.0-182.9	160.0-186.6	137.2-182.9	160.5-190.5	137.2-175.0
N	47 (100.0)	53 (100.0)	31 (100.0)	69 (100.0)	36 (100.0)	58 (100.0)	35 (100.0)	62 (100.0)	34 (97.1)	65 (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
	75 mg BID	175 mg BID	225 mg BID		
Baseline					
No. of subjects	100	100	94	97	100
Mean (SD)	25.5 (4.1)	24.8 (3.7)	25.5 (4.1)	24.9 (4.1)	25.1 (4.2)
Change from Baseline at Week 8 (LOCF)[a]					
N	91	90	85	89	96
LS mean (SE)	-10.9 (0.7)	-10.6 (0.7)	-11.4 (0.7)	-11.1 (0.7)	-10.6 (0.7)
95% CI	-12.3, -9.5	-12.0, -9.1	-12.9, -9.9	-12.5, -9.7	-12.0, -9.2

Abbreviations: ANCOVA = analysis of covariance, BID=twice daily, CI = confidence interval, HAM-A = Hamilton Anxiety 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: One subject each in the paroxetine 20 mg treatment group, the placebo group, and the PD 0332334 175 mg BID treatment group experienced a serious adverse event (SAE). No subjects in the PD 0332334 75 mg BID or 225 mg BID treatment groups experienced an SAE. There were no subject deaths reported during this study. The incidence of AEs was similar across the PD 0332334 175 mg BID and 225 mg BID treatment groups and the paroxetine 20 mg treatment group; slightly less AEs were reported in subjects in the PD 0332334 75 mg BID treatment group and in the placebo group (Table 7).

Table 7. Treatment-Emergent Adverse Events

No. (%) of Subjects	PD 0332334 75 mg BID N=100	PD 0332334 175 mg BID N= 100	PD 0332334 225 mg BID N=94	Paroxetine 20 mg N=97	Placebo N= 100
All Causality					
Subjects evaluable for AEs	100	100	94	97	100
Number of AEs	172	211	222	232	180
Subjects with AEs	67 (67.0)	74 (74.0)	65 (69.1)	74 (76.3)	69 (69.0)
Subjects with serious AEs	0	1 (1.0)	0	1 (1.0)	1 (1.0)
Subjects with severe AEs	7 (7.0)	10 (10.0)	10 (10.6)	11 (11.3)	8 (8.0)
Subjects discontinued due to AEs	10 (10.0)	14 (14.0)	11 (11.7)	7 (7.2)	6 (6.0)
Subjects with dose reduced or temporary discontinuation due to AEs	1 (1.0)	0	2 (2.1)	2 (2.1)	2 (2.0)
Treatment-Related					
Subjects evaluable for AEs	100	100	94	97	100
Number of AEs	123	150	166	170	121
Subjects with AEs	50 (50.0)	60 (60.0)	56 (59.6)	61 (62.9)	54 (54.0)
Subjects with serious AEs	0	0	0	0	0
Subjects with severe AEs	2 (2.0)	6 (6.0)	5 (5.3)	8 (8.2)	4 (4.0)
Subjects discontinued due to AEs	8 (8.0)	9 (9.0)	10 (10.6)	6 (6.2)	5 (5.0)
Subjects with dose reduced or temporary discontinuation due to AEs	1 (1.0)	0	1 (1.1)	2 (2.1)	1 (1.0)

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 (v11.1) coding dictionary applied.

The most common AEs reported in this study (Medical Dictionary for Regulatory Activities [MedDRA], Version 11.1) by system organ class (all causality) were gastrointestinal disorders, nervous system disorders, psychiatric disorders, general disorders and administration site conditions, and infections and infestations. The most common treatment-related AEs reported in this study (MedDRA, Version 11.1) 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 Group

No. (%) of Subjects	PD 0332334 75 mg BID N=100	PD 0332334 175 mg BID N=100	PD 0332334 225 mg BID N=94	Paroxetine 20 mg N=97	Placebo N=100
System Organ Class[a] Preferred Term[a]					
Eye disorders	3 (3.0)	3 (3.0)	8 (8.5)	3 (3.1)	2 (2.0)
Vision blurred	2 (2.0)	3 (3.0)	4 (4.3)	1 (1.0)	1 (1.0)
Gastrointestinal disorders	32 (32.0)	32 (32.0)	32 (34.0)	45 (46.4)	34 (34.0)
Abdominal pain upper	1 (1.0)	2 (2.0)	2 (2.1)	4 (4.1)	3 (3.0)
Constipation	5 (5.0)	4 (4.0)	5 (5.3)	3 (3.1)	5 (5.0)
Diarrhea	7 (7.0)	2 (2.0)	1 (1.1)	14 (14.4)	9 (9.0)
Dry mouth	13 (13.0)	15 (15.0)	11 (11.7)	11 (11.3)	14 (14.0)
Dyspepsia	3 (3.0)	4 (4.0)	5 (5.3)	5 (5.2)	1 (1.0)
Flatulence	1 (1.0)	2 (2.0)	0	5 (5.2)	1 (1.0)
Nausea	4 (4.0)	13 (13.0)	11 (11.7)	17 (17.5)	6 (6.0)
Vomiting	3 (3.0)	4 (4.0)	6 (6.4)	5 (5.2)	1 (1.0)
General disorders and administration site conditions	15 (15.0)	12 (12.0)	16 (17.0)	15 (15.5)	16 (16.0)
Fatigue	9 (9.0)	6 (6.0)	7 (7.4)	10 (10.3)	8 (8.0)
Irritability	1 (1.0)	2 (2.0)	1 (1.1)	0	6 (6.0)
Infections and infestations	16 (16.0)	18 (18.0)	12 (12.8)	19 (19.6)	14 (14.0)
Upper respiratory tract infection	4 (4.0)	8 (8.0)	4 (4.3)	7 (7.2)	2 (2.0)
Nasopharyngitis	7 (7.0)	4 (4.0)	2 (2.1)	3 (3.1)	2 (2.0)
Urinary tract infection	2 (2.0)	5 (5.0)	3 (3.2)	3 (3.1)	2 (2.0)
Investigations	7 (7.0)	9 (9.0)	7 (7.4)	5 (5.2)	6 (6.0)
Blood creatine phosphokinase increased	1 (1.0)	2 (2.0)	2 (2.1)	1 (1.0)	4 (4.0)
Weight increased	2 (2.0)	4 (4.0)	3 (3.2)	2 (2.1)	0
Nervous system disorders	31 (31.0)	45 (45.0)	39 (41.5)	32 (33.0)	27 (27.0)
Dizziness	11 (11.0)	21 (21.0)	18 (19.1)	7 (7.2)	6 (6.0)
Headache	12 (12.0)	12 (12.0)	17 (18.1)	12 (12.4)	14 (14.0)
Sedation	2 (2.0)	8 (8.0)	1 (1.1)	2 (2.1)	0
Somnolence	10 (10.0)	17 (17.0)	18 (19.1)	7 (7.2)	6 (6.0)
Psychiatric disorders	6 (6.0)	16 (16.0)	15 (16.0)	16 (16.5)	14 (14.0)
Insomnia	1 (1.0)	2 (2.0)	5 (5.3)	6 (6.2)	7 (7.0)
Libido decreased	0	1 (1.0)	3 (3.2)	3 (3.1)	4 (4.0)
Orgasm abnormal	0	4 (4.0)	1 (1.1)	0	0
Vascular disorders	2 (2.0)	1 (1.0)	2 (2.1)	6 (6.2)	0
Hot flush	0	0	1 (1.1)	5 (5.2)	0

Abbreviations: BID = twice daily, MedDRA = Medical Dictionary for Regulatory Activities
[a] MedDRA (v11.1) coding dictionary applied.

The most common AEs (all causality) reported in this study by preferred term (MedDRA, Version 11.1) were headache (67 subjects overall), dry mouth (64 subjects), dizziness (63 subjects), somnolence (58 subjects), nausea (51 subjects), fatigue (40 subjects), and diarrhea (33 subjects). Slightly more than half (569/1017; 55.9%) of AEs (all causality) by preferred term were mild in severity. Overall, 6.5% (66/1017) of AEs (all causality) by preferred term were severe in severity. The most common treatment-related AEs reported in this study by preferred term were dizziness (62 subjects overall), dry mouth (61 subjects), somnolence (57 subjects), headache (51 subjects), nausea (43 subjects), and fatigue

(37 subjects). Slightly more than half (430/730; 58.9%) of treatment-related AEs by preferred term were mild in severity. Overall, 5.3% (39/730) treatment-related AEs by preferred term were severe in severity.

A total of 7 subjects in the paroxetine 20 mg group, 6 subjects in the placebo group, 10 subjects in the PD 0332334 75 mg BID group, 14 subjects in the PD 0332334 175 mg BID group, and 11 subjects in the PD 0332334 225 mg BID group discontinued the study due to AEs.

A total of 6 subjects in the paroxetine 20 mg group, 5 subjects in the placebo group, 8 subjects in the PD 0332334 75 mg BID group, 9 subjects in the PD 0332334 175 mg BID group, and 10 subjects in the PD 0332334 225 mg BID group discontinued due to AEs that were considered to be treatment-related. The most common AEs leading to permanent discontinuation were dizziness and fatigue (6 subjects each) (Table 9).

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 75 mg BID N=100**	**PD 0332334 175 mg BID N=100**	**PD 0332334 225 mg BID N=94**	**Paroxetine 20 mg N=97**	**Placebo N=100**
Number of Occurrences					
Cardiac Disorders					
Tachycardia	0	0	0	1	0
Eye Disorders					
Diplopia	1	0	1	0	0
Vertigo	0	0	0	0	1
Vision blurred	2	0	0	0	0
Gastrointestinal Disorders					
Abdominal pain	1	0	0	0	0
Abdominal pain upper	0	1	0	0	0
Aerophagia	1	0	0	0	0
Diarrhea	1	0	0	0	0
Dry mouth	1	0	1	1	0
Nausea	1	2	0	0	1
Stomach discomfort	0	0	0	0	0
Tongue edema	0	0	0	0	0
Vomiting	0	1	0	1	0
General Disorders and Administration Site Conditions					
Asthenia	1	0	0	0	0
Chest discomfort	0	0	0	1	0
Chest pain	0	0	1	0	0
Fatigue	0	1	1	4	0
Feeling abnormal	0	0	1	0	0
Irritability	0	0	1	0	2
Sluggishness	0	1	0	0	0
Infections and Infestations					
Upper respiratory tract infection	0	0	0	1	0
Immune System Disorders					
Hypersensitivity	1	0	0	0	0
Injury, Poisoning, and Procedural Complications					
Accidental overdose	0	1	0	0	0
Investigations					
Alanine aminotransferase increased	0	1	0	1	0
Aspartate aminotransferase increased	0	1	0	0	0
Blood thyroid stimulating hormone increased	1	0	0	0	0
Red blood cells urine positive	0	1	0	0	0
Weight increased	0	1	0	0	0

Abbreviations: BID = twice daily, MedDRA = Medical Dictionary for Regulatory Activity
[a] MedDRA (v11.1) 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 75 mg BID N=100**	**PD 0332334 175 mg BID N=100**	**PD 0332334 225 mg BID N=94**	**Paroxetine 20 mg N=97**	**Placebo N=100**
Number of Occurrences					
Metabolism and Nutrition Disorders					
Fluid retention	1	0	0	0	0
Musculoskeletal and Connective Tissue Disorders					
Arthralgia	0	1	0	0	0
Intervertebral disc protrusion	1	0	0	0	0
Musculoskeletal stiffness	0	1	0	0	0
Pain in jaw	0	1	0	0	0
Sensation of heaviness	1	0	0	0	0
Nervous System Disorders					
Disturbance in attention	0	1	0	0	0
Dizziness	2	3	0	1	0
Headache	1	1	1	1	1
Sedation	1	0	0	0	0
Syncope	0	0	0	0	1
Hypoesthesia	0	1	0	0	0
Somnolence	1	0	3	0	0
Psychiatric Disorders					
Anorgasmia	0	0	0	1	0
Anxiety	0	2	0	1	0
Depression	1	0	1	0	0
Insomnia	0	0	1	0	1
Libido decreased	0	0	0	0	1
Loss of libido	0	0	1	0	0
Suicidal ideation	0	1	0	0	0
Respiratory, Thoracic, and Mediastinal Disorders					
Dyspnea	1	0	0	1	0
Pulmonary embolism	0	0	0	1	0
Skin and Subcutaneous Tissue Disorders					
Hyperhidrosis	1	0	0	0	0
Night sweats	0	0	0	0	1
Rash	0	0	1	0	0
Vascular Disorders					
Deep vein thrombosis	0	0	0	1	0

Abbreviations: BID = twice daily, MedDRA = Medical Dictionary for Regulatory Activity
[a] MedDRA (v11.1) coding dictionary applied.

A summary of SAEs is provided in Table 10. SAE presentations were derived from a separate, centralized AE monitoring database that was continuously updated based on rapidly communicated reports from the investigators to the sponsor. The clinical study database was based on information provided from the Case Report Forms (CRFs) and Data Collection Tool (DCTs). Consequently, occasional differences in data may exist between the centralized safety database and the clinical study database.

Table 10. Serious Adverse Events

Subject	System Organ Class	Preferred Term	Treatment Phase (Dose[a])	Adverse Event		
				Study Start Day[b]/ Study Stop Day[b]	Severity/ Outcome	Action/ Causality
Treatment group: PD 0332334 75 mg BID						
26-year-old female	Unknown	Pancreatitis	Active (75 mg)	44/ Unknown	Unknown[c]/ resolved	Unknown
Treatment group: PD 0332334 175 mg BID						
31-year-old female	Hepatobiliary disorders	Cholecystitis	Active (350 mg)	25/ 30	Severe/ resolved	Treatment given/ other – history of cholecystitis
Treatment group: Paroxetine 20 mg						
54-year-old female	Respiratory, thoracic, and mediastinal disorders	Pulmonary embolism	Active (20 mg)	8/ 92	Moderate/ resolved	Permanently discontinued/ other illness – idiopathic
	Vascular disorders	Deep vein thrombosis	Active (20 mg)	8/ 92	Severe/ resolved	Permanently discontinued/ other illness – idiopathic
Treatment group: Placebo						
58-year-old male	Ear and labyrinth disorders	Vertigo	Active (0 mg)	2/ 3	Severe/ resolved	Permanently discontinued, vestibular physical therapy given in the hospital/ Other illness – benign positional paroxysmal vertigo
	Nervous system disorders	Syncope	Active (0 mg)	2/ 2	Severe/ resolved	Permanently discontinued/ Other illness – benign positional paroxysmal vertigo

Abbreviations: BID = twice daily, SAE = serious adverse event

[a] Dose at onset of adverse event.

[b] Day relative to start of study treatment; first day of study treatment = Day 1.

[c] Subject experienced this SAE post-therapy, the severity is unknown, the action/causality is also unknown. Serious adverse event as determined by investigator assessment.

The number and percentage of subjects by treatment group who had ≥7% increase in body weight from Baseline is summarized in Table 11.

Table 11. Incidence of ≥7% Increase in Body Weight; Safety Analysis Set

Parameter	Criteria	PD 0332334 175 mg BID		PD 0332334 225 mg BID		Paroxetine 20 mg	
		N	n (%)	N	n (%)	N	n (%)
Increase in body weight	≥7%	100	4 (4.0)	94	4 (4.3)	97	1 (1.0)

Abbreviation: BID = twice daily

No subject in any treatment group completed suicide and no subjects in any treatment group made a suicide attempt, did preparatory acts toward imminent suicidal behavior, or displayed nonsuicidal self-injurious behavior at any post baseline assessment. Overall, 2 (2.2%), 3 (3.1%), 1 (1.1%), and 1 (1.1%) subject in the paroxetine 20 mg, PD 0332334 75 mg BID, PD 0332334 175 mg BID, and PD 0332334 225 mg BID treatment groups, respectively, reported suicidal ideations at any postbaseline visit.

Laboratory Test Results: Table 12 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 12. Laboratory Test Abnormalities Reported by ≥2 Subjects in Any Treatment Group; Subjects With Normal Baseline

Parameter	Unit	Criteria	PD 0332334 75 mg BID		PD 0332334 175 mg BID		PD 0332334 225 mg BID		Paroxetine 20 mg		Placebo	
			N	n	N	N	n	N	n	n	N	n
Electrolytes												
Bicarbonate (venous)	mEq/L	<0.9 × LLN	90	0	85	2 (2%)	85	5 (6%)	78	1 (1%)	87	2 (2%)
Clinical chemistry (other)												
Creatine kinase	U/L	>2.0 × ULN	77	1 (1%)	79	3 (4%)	78	5 (6%)	64	4 (6%)	85	4 (5%)
Urinalysis (microscopy)												
Urine RBC	HPF	≥6	28	5	24	5	22	5	24	5	23	4
Urine WBC	HPF	≥6	29	5	22	3	22	5	23	4	24	1
Urine epithelial cells	HPF	≥6	26	8	20	6	20	5	22	15	22	6

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 13).

Table 13. Vital Signs Measurement Data; Safety Analysis Set

Parameter	Criteria	PD 0332334 75 mg BID		PD 0332334 175 mg BID		PD 0332334 225 mg BID		Paroxetine 20 mg		Placebo	
		N	n (%)	N	N	n (%)	N	n (%)	n (%)	N	n (%)
Increase from baseline											
Maximum increase from baseline in sitting systolic BP (mm Hg)	≥30	95	1 (1.1)	95	5 (5.3)	91	1 (1.1)	93	5 (5.4)	98	2 (2.0)
Maximum increase from baseline in sitting diastolic BP (mm Hg)	≥20	95	2 (2.1)	95	5 (5.3)	91	0	93	6 (6.5)	98	5 (5.1)
Absolute values											
Sitting systolic BP (mm Hg)	<90	100	0	100	1 (1.0)	94	2 (2.1)	97	0	100	0
Sitting diastolic BP (mm Hg)	<50	100	0	100	1 (1.0)	94	0	97	0	100	0
Sitting heart rate (bpm)	<40	100	0	100	0	94	0	97	0	100	0
	>120	100	0	100	0	94	0	97	0	100	0

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

Five subjects had a total of 6 AEs of increased BP during the study: PD 0332334 75 mg BID treatment group (1 AE; mild/ resolved; not related), PD 0332334 175 mg BID treatment group (1 AE; moderate/ resolved; not related), PD 0332334 225 mg BID treatment group (1 AE; mild/ resolved; related), placebo treatment group (2 AEs [mild/ resolved, not related and mild/ still present, not related), and paroxetine 20 mg treatment group (1 AE; mild/ still present, related).

Subjects with corrected QT interval with Bazett's (QTcB) or corrected QT interval with Fredericia's formula (QTcF) intervals 450 to <500 msec and ≥500 msec are summarized in Table 14. One subject in the PD 0332334 175-mg BID treatment group had a QTcB interval ≥500 msec after the start of study treatment; the QTc intervals recorded for this subject are summarized in Table 15. There were no notable differences across treatment groups in effects on ECG parameters.

Table 14. Electrocardiogram Data; Safety Analysis Set

Parameter	Criteria	PD 0332334 75 mg BID		PD 0332334 175 mg BID		PD 0332334 225 mg BID		Paroxetine 20 mg		Placebo	
		N	n (%)	N	N	n (%)	N	n (%)	n (%)	N	n (%)
Maximum QTcB Interval (msec)	450 - <500	100	3 (3.0)	100	7 (7)	94	5 (5.3)	97	5 (5.2)	100	8 (8)
	≥500	100	0	100	1 (1)	94	0	97	0	100	0
Maximum QTcF Interval (msec)	450 - <500	100	1 (1.0)	100	5 (5.0)	94	0	97	2 (2.1)	100	3 (3.0)
	≥500	100	0	100	0	94	0	97	0	100	0

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

Table 15. QTc Intervals ≥500 msec

Treatment Phase/ Study Day	QTcB Interval (msec)	QTcF Interval (msec)
Subject with QTcB interval ≥500 msec after the start of study treatment; PD 0332334 175-mg BID treatment group		
Prestudy/ -6	457	415
Active/ 43	502	467
Active/ 57	509	468
Active/ 71	484	448

Abbreviations: BID = twice daily, 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 the 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.