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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Imagabalin

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: Not Applicable.

NATIONAL CLINICAL TRIAL NO.: NT00658762

PROTOCOL NO.: A5361020

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: A total of 27 centers took part in the study, including 1 center in Hungary and 26 centers in the United States.

Study Initiation and Completion Dates: 14 May 2008 to 07 April 2009

The 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 (imagabalin) 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.

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 Scale [SDS] total score) 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 Phase 3, randomized, double-blind, parallel-group, multicenter, placebo-controlled, fixed-dose study of PD 0332334 and paroxetine in subjects with GAD. Approximately 528 subjects were planned for enrollment. The study consisted of 3 phases: an initial screening phase to be 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, subjects underwent a washout of prior psychotropic medications, and were to be off all psychotropic medications for at least 14 days prior to randomization. Screening visit procedures were to be completed within 14 days of the randomization visit.

Subjects who fulfilled entry criteria were randomized to receive 1 of the following 4 treatments in a double-blind fashion (132 subjects planned per treatment group):

- PD 0332334 225 mg BID (450 mg/day)
- PD 0332334 300 mg BID (600 mg/day)

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

De-identified blood samples were planned to be collected from study subjects at screening (Visit 1) according to the standard Molecular Profiling supplement to the protocol. Participation in this component was optional for study subjects. These samples were planned to be available for utilization in the future to investigate GAD genetics, expression metabonomic and protein biomarker profiles, drug response, or other genetic or biomarker questions.

Number of Subjects (Planned and Analyzed): Approximately 528 subjects were planned for enrollment. A total of 450 subjects were screened for entry into this study. Of these, 70 and 72 subjects were randomized to PD 0332334 225 mg BID and 300 mg BID, respectively. A total of 71 subjects were randomized to 20 mg paroxetine and a total 73 were randomized to placebo.

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 an 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 non-pregnant, non-lactating 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.

To be randomized into the study, subjects had to accept lifestyle restrictions, including abstinence from alcohol, avoidance of strenuous exercise for 48 hours prior to each study visit, and using caution while driving or operating heavy machinery. Subjects were also required to use acceptable contraceptive methods for at least 14 days prior to the first dose of study medication, and for the duration of the study.

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 300 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 S1.

Table S1. Titration Schedule

Day	PD0332334 300 mg BID	PD 0332334 225 mg BID
1	125 mg HS	125 mg HS
2	125 mg BID	125 mg BID
3	125 mg BID	125 mg BID
4	225 mg BID	125 mg BID
5	225 mg BID	225 mg BID
6	300 mg BID	225 mg BID
7	300 mg BID	225 mg BID

HS = at bedime, BID = twice daily

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 who were randomized to placebo received placebo BID for the duration of the 8-week treatment phase. Subjects who were randomized to paroxetine received treatment with 20 mg QD on Day 1 and 20 mg every day in the 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 S2. All subjects received placebo BID on study days 65-71.

Table S2. Dose Tapering Schedule

Day	PD 0332334 300 mg BID	PD 0332334 225 mg BID	Placebo BID	Paroxetine 20 mg QAM
57	300 mg BID	225 mg BID	placebo BID	20 mg QAM
58	225 mg BID	125 mg BID	placebo BID	10 mg QAM
59	225 mg BID	125 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

BID = twice daily, QAM = everyday in the 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 the early 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, duration, and severity of adverse events (AEs); discontinuation due to AEs; AEs occurring during and after study drug discontinuation; body weight; clinical safety laboratory parameters; 12-lead ECGs; physical examinations; vital signs; and Changes in Sexual Functioning Questionnaire (CSFQ). Suicidal ideation and suicidal behavior were monitored using the Columbia-Suicide Severity Rating 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 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 Per-Protocol Analysis Set 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: Subject disposition is summarized in Table S3. A total of 450 subjects were screened for entry into this study. Of these, 70 and 72 subjects were randomized to PD 0332334 225 mg BID and 300 mg BID, respectively, with 34 (48.6%) and 38 (52.8%) subjects completing treatment. A total of 71 subjects were randomized to 20 mg paroxetine with 40 (56.3%) subjects completing treatment and a total 73 were randomized to placebo with 33 (45.2%) completing treatment. All subjects were analyzed for AEs, and the majority was analyzed for laboratory data.

Table S3. Subject Disposition and Subjects Analyzed

Number (%) of Subjects		PD 0332334 225 mg BID	PD 0332334 300 mg BID	Paroxetine 20 mg	Placebo
Planned	528				
Screened	450				
Assigned to Treatment		70	72	71	73
Treated		70	72	71	73
Completed		34 (48.6)	38 (52.8)	40 (56.3)	33 (45.2)
Discontinued		36 (51.4)	34 (47.2)	31 (43.7)	40 (54.8)
Analyzed for Safety					
Adverse events		70 (100)	72 (100)	71 (100)	73 (100)
Laboratory data		66 (94.3)	67 (93.1)	60 (84.5)	64 (87.7)

BID = twice daily
Percentages are based on numbers of treated subjects.
Discontinuations occurring outside the lag period have been attributed to the last study treatment received.

Table S4 summarizes subject discontinuations that occurred from Day 1 to Week 10 of the study. The most common reason for subject discontinuation was study termination by the sponsor.

Table S4. Summary of Discontinuations from Day 1 to Week 10

	PD 0332334 225 mg BID	PD 0332334 300 mg BID	Paroxetine 20 mg	Placebo
Number (%) of Subjects	70	72	71	73
Related to study drug	19 (27.1)	24 (33.3)	16 (22.5)	26 (35.6)
AE	6 (8.6)	5 (6.9)	7 (9.9)	4 (5.5)
Insufficient clinical response	0	1 (1.4)	0	2 (2.7)
Study terminated by sponsor	13 (18.6)	18 (25.0)	9 (12.7)	20 (27.4)
Not related to study drug	17 (24.3)	10 (13.9)	15 (21.1)	14 (19.2)
AE	0	0	2 (2.8)	0
Lost to follow-up	9 (12.9)	5 (6.9)	8 (11.3)	8 (11.0)
Other	1 (1.4)	2 (2.8)	2 (2.8)	3 (4.1)
Protocol violation	5 (7.1)	2 (2.8)	0	2 (2.7)
Subject no longer willing to participate in study	2 (2.9)	1 (1.4)	2 (2.8)	1 (1.4)
Withdrawn due to pregnancy	0	0	1 (1.4)	0

BID = twice daily; AE = adverse events

Demography: A summary of demographic characteristics is provided in Table S5. All subjects had a primary diagnosis of GAD with the mean duration since first diagnosis across treatment groups ranging from 6.0 years (paroxetine 20 mg treatment group) to 9.2 years (PD 0332334 225 mg BID treatment group). The age range of subjects overall was 18 years to 65 years and the majority of subjects were white.

Table S5. Demographic Characteristics

	PD 0332334		Paroxetine	Placebo
	225 mg BID	300 mg BID	20 mg	
Number of Subjects	70	72	71	73
Sex				
Male	22	30	22	20
Female	48	42	49	53
Age				
Mean (SD)	41.0 (12.3)	37.2 (11.9)	37.5 (11.5)	40.8 (12.6)
Range	19-65	18-61	18-65	19-64
Race, n (%)				
White	54 (77.1)	56 (77.8)	56 (78.9)	61 (83.6)
Black	13 (18.6)	13 (18.1)	11 (15.5)	9 (12.3)
Asian	0	0	1 (1.4)	1 (1.4)
Other	3 (4.3)	3 (4.2)	3 (4.2)	2 (2.7)
Ethnicity, n (%)				
Hispanic/Latino	6 (8.6)	6 (8.3)	4 (5.6)	9 (12.3)
Not Hispanic/Latino	64 (91.4)	66 (91.7)	67 (94.4)	64 (87.7)
Height (cm)				
Mean (SD)	168.3 (10.3)	170.2 (9.5)	169.2 (9.2)	169.0 (9.9)
Range	147.3-198.1	152.4-195.6	154.5-203.2	152.0-196.0

BID = twice daily; SD = standard deviation

Primary Objective Findings: This study was terminated prematurely as a result of the program termination; as such, only safety data accompanying demographic information, and limited efficacy data (ie, HAM-A) are presented.

The primary efficacy objective of this 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. Change from baseline in HAM-A total score at Week 8 was similar across treatment groups (Table S6).

Table S6. Change from Baseline in HAM-A Total Score to Week 8 (LOCF) – Full Analysis Set

	PD 0332334		Paroxetine	Placebo
	225 mg BID	300 mg BID	20 mg	
Baseline				
N	70	72	71	73
Mean (SD)	26.6 (4.8)	26.2 (3.9)	26.4 (4.4)	25.9 (3.8)
Change from baseline at Week 8 (LOCF)[a]				
N	65	71	63	67
LS mean (SE)	-12.6 (1.0)	-11.7 (0.9)	-11.7 (1.0)	-10.8 (1.0)
95% CI	-14.5, -10.7	-13.6, -9.9	-13.7, -9.8	-12.7, -8.9

BID = twice daily; 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: An overview of treatment-emergent AEs (all causality and treatment-related) is provided in Table S7. One subject each in the paroxetine 20 mg

treatment group and in the placebo group experienced a serious adverse event (SAE). No subjects in the PD 0332334 225 mg BID or 300 mg BID treatment groups experienced an SAE. The incidence of AEs was similar across the PD 0332334 225 mg BID and 300 mg BID treatment groups and the paroxetine 20 mg treatment group, and slightly less in the placebo treatment group.

The only AEs that resulted in more than 1 subject discontinuation in any treatment group were sedation (2 subjects in the PD 0332334 225 mg BID treatment group), abdominal pain (2 subjects in the paroxetine 20 mg treatment group), and nausea (2 subjects in the paroxetine 20 mg treatment group).

Table S7. Treatment-Emergent Adverse Events from Day 1 through Week 10 – Safety Analysis Set

Number (%) of Subjects	PD 0332334		Paroxetine	Placebo
	225 mg BID	300 mg BID	20 mg	
All Causality				
Subjects evaluable for AEs	70	72	71	73
Number of AEs	145	183	167	136
Subjects with AEs	50 (71.4)	56 (77.8)	55 (77.5)	49 (67.1)
Subjects with SAEs	0	0	1 (1.4)	1 (1.4)
Subjects with severe AEs	5 (7.1)	10 (13.9)	14 (19.7)	4 (5.5)
Subjects discontinued due to AEs	6 (8.6)	5 (6.9)	9 (12.7)	4 (5.5)
Subjects with dose reduced or temporary discontinuation due to AEs	0	0	1 (1.4)	0
Treatment-Related				
Subjects evaluable for AEs	70	72	71	73
Number of AEs	100	114	115	75
Subjects with AEs	42 (60.0)	45 (62.5)	40 (56.3)	36 (49.3)
Subjects with SAEs	0	0	0	0
Subjects with severe AEs	4 (5.7)	5 (6.9)	11 (15.5)	3 (4.1)
Subjects discontinued due to AEs	6 (8.6)	5 (6.9)	7 (9.9)	4 (5.5)
Subjects with dose reduced or temporary discontinuation due to AEs	0	0	0	0

BID = twice daily; AE = adverse event; SAE = serious adverse event
Except for the Number of AEs subjects are counted only once per treatment in each row.
SAEs - according to the investigator's assessment.

A summary of treatment-emergent AEs (all causality) reported in >4% of subjects is provided in Table S8. This cutoff was chosen due to very few AEs being reported in higher percentages of subjects. The most frequently reported AEs in the PD 0332334 225 mg BID and 300 mg BID treatment groups were dizziness (18.6% and 18.1% of subjects, respectively) and somnolence (17.1% and 18.1% of subjects, respectively). These AEs were also the most frequently reported treatment-related AEs the PD 0332334 225 BID mg and 300 mg BID treatment groups (dizziness: 17.1% and 18.1% of subjects; somnolence: 17.1% and 16. 7% of subjects, respectively). In the paroxetine 20 mg treatment group, the most frequently reported AEs (all causality) were nausea (11.3% of subjects) and headache (21.1% of subjects). A total of 16.9% of subjects in the paroxetine 20 mg group experienced treatment-related AEs of headache and 11.3% of subjects experienced treatment-related AEs of nausea. In the placebo treatment group, the most frequently reported AEs were nausea (16.4%) and headache (24.7%). A total of 16.4% of subjects in the placebo group

experienced AEs of headache considered to be treatment-related and 13.7% of placebo subjects experienced an AE of nausea considered to be treatment-related.

Table S8. 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

Number (%) of Subjects	PD 0332334		Paroxetine	Placebo
	225 mg BID	300 mg BID	20 mg	
All Causality				
Eye disorders	3 (4.3)	4 (5.6)	4 (5.6)	0
Vision blurred	3 (4.3)	4 (5.6)	2 (2.8)	0
Gastrointestinal disorders	23 (32.9)	24 (33.3)	25 (35.2)	22 (30.1)
Constipation	2 (2.9)	7 (9.7)	2 (2.8)	7 (9.6)
Diarrhea	4 (5.7)	3 (4.2)	6 (8.5)	4 (5.5)
Dry mouth	9 (12.9)	8 (11.1)	6 (8.5)	2 (2.7)
Dyspepsia	5 (7.1)	3 (4.2)	1 (1.4)	2 (2.7)
Nausea	6 (8.6)	5 (6.9)	8 (11.3)	12 (16.4)
Infections and infestations	9 (12.9)	15 (20.8)	10 (14.1)	10 (13.7)
Upper respiratory tract infection	2 (2.9)	3 (4.2)	5 (7.0)	2 (2.7)
Nasopharyngitis	2 (2.9)	3 (4.2)	1 (1.4)	2 (2.7)
Urinary tract infection	0	3 (4.2)	1 (1.4)	1 (1.4)
Metabolism and nutrition disorders	0	2 (2.8)	3 (4.2)	0
Decreased appetite	0	0	3 (4.2)	0
Musculoskeletal and connective tissue disorders	8 (11.4)	6 (8.3)	5 (7.0)	9 (12.3)
Arthralgia	2 (2.9)	1 (1.4)	1 (1.4)	3 (4.1)
Nervous system disorders	29 (41.4)	39 (54.2)	28 (39.4)	28 (38.4)
Disturbance in attention	3 (4.3)	3 (4.2)	0	0
Dizziness	13 (18.6)	13 (18.1)	7 (9.9)	2 (2.7)
Dysgeusia	1 (1.4)	0	0	0
Headache	7 (10.0)	9 (12.5)	15 (21.1)	18 (24.7)
Sedation	2 (2.9)	4 (5.6)	0	0
Somnolence	12 (17.1)	13 (18.1)	5 (7.0)	4 (5.5)
Tension headache	1 (1.4)	3 (4.2)	2 (2.8)	2 (2.7)
Psychiatric disorders	11 (15.7)	11 (15.3)	19 (26.8)	7 (9.6)
Abnormal dreams	0	0	3(4.2)	0
Anorgasmia	0	2 (2.8)	3 (4.2)	0
Anxiety	1 (1.4)	3 (4.2)	2 (2.8)	0
Insomnia	1 (1.4)	2 (2.8)	7 (9.9)	1 (1.4)
Libido decreased	1 (1.4)	2 (2.8)	3 (4.2)	0
Respiratory, thoracic, and mediastinal disorders	7 (10.0)	7 (9.7)	5 (7.0)	7 (9.6)
Sinus congestion	1 (1.4)	2 (2.8)	1 (1.4)	3 (4.1)

BID = twice daily
Subjects are counted only once per treatment in each row.

The majority of AEs reported in this study were mild or moderate in severity. In the PD 0332334 225 mg BID and 300 mg BID treatment groups, a total of 8/145 events (6 of which were treatment-related) and 13/183 events (6 of which were treatment-related) were considered to be severe. In the paroxetine 20 mg treatment group, a total of 26/167 events (16 of which were treatment-related) were considered to be severe. In the placebo group 5/136 events (3 of which were treatment-related) were considered to be severe. The only

severe treatment-related AEs reported in more than 1 subject in any treatment group were: headache and insomnia (each occurring in 3 subjects in the paroxetine 20 mg treatment group); nausea (2 subjects in the paroxetine 20 mg treatment group); and anxiety (2 subjects in the PD 0332334 300 mg BID treatment group).

A summary of AEs leading to discontinuation is provided in Table S9. In the PD0332334 treatment groups and in the placebo treatment group, all AEs leading to discontinuation were represented by single occurrences with the exception of sedation (2 subjects in the 225 mg BID group). In the paraxetine 20 mg treatment group, nausea and abdominal pain resulted in discontinuation in 2 subjects each. Other AEs leading to discontinuation in this treatment group were represented by single occurrences.

Table S9. Summary of Adverse Events Leading to Discontinuation

Number (%) of Subjects	PD 0332334		Paroxetine	Placebo
	225 mg BID	300 mg BID	20 mg	
Ear and labyrinth disorders				
Tinnitus	0	0	1	0
Eye disorders				
Eye pain	0	1	0	0
Vision blurred	0	1	1	0
Gastrointestinal disorders				
Abdominal discomfort	0	1	0	0
Abdominal pain	0	0	2	0
Nausea	0	0	2	0
General disorders and administration site conditions				
Energy increased	0	1	0	0
Feeling jittery	0	0	1	0
Injury, poisoning and procedural complications				
Overdose	0	0	1	0
Nervous system disorders				
Crying	0	1	0	0
Dizziness	1	0	1	1
Headache	0	1	1	1
Lethargy	0	0	1	0
Sedation	2	0	0	0
Somnolence	0	0	0	1
Psychiatric disorders				
Agitation	1	1	0	1
Anxiety	0	1	1	0
Disorientation	1	0	0	0
Insomnia	0	1	0	0
Mania	1	0	0	0

BID = twice daily

Three subjects experienced a ≥7% increase in body weight during the study: 2 subjects in the PD 0332334 300 mg BID treatment group and 1 subject in the paroxetine 20 mg treatment group.

C-SSRS data indicates that no subjects in any treatment group completed suicide, made a suicide attempt, or performed preparatory acts toward imminent suicidal behavior at any post baseline assessment. Non-suicidal self-injurious behavior was reported in 1 subject (PD 0332334 225 mg BID treatment group) and 3 subjects in each treatment group reported suicidal ideations at a post baseline assessment.

A summary of SAEs is provided in Table S10. 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 CRFs/DCTs. Consequently, occasional differences in data may exist between the centralized safety database and the clinical study database. No PD 0332334 treated subjects experienced an SAE during the study. A total of 2 placebo treated subjects, 1 paroxetine treated subject, and 1 non-randomized subject reported an SAE; none of which were considered to be related to study treatment. One death was reported during the study (placebo subject died from an SAE of pulmonary embolism that occurred post-therapy).

Table S10. Serious Adverse Events

Subject	Preferred Term	Total Daily Dose	Adverse Event		
			Event Onset Day[a]	Clinical Outcome	Causality
Treatment group: Paroxetine 20 mg					
61-year-old female	Appendicitis	20 mg	27	Recovered	Unrelated
Treatment group: Placebo					
60-year-old female	Pulmonary embolism	Placebo	98 (post-therapy)	Fatal	Unrelated
41-year-old female	Appendicitis	Placebo	36	Recovered	Unrelated
Pre-Randomization					
64-year-old-male	Cerebral disorder	NA[b]	NA[b]	Recovered	NA[b]

[a] Days are relative to the day of starting double-blind/active therapy (Day 1)
[b] This event occurred prior to randomization thus the subject did not receive study treatment.

Laboratory Test Results: No differences were noted across treatment groups with respect to laboratory results.

Vital Signs Measurements and Electrocardiogram Results: There were no notable differences across treatment groups in treatment effects on vital signs measurements or ECG parameters.

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.