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**PROPRIETARY DRUG NAME®/GENERIC DRUG NAME:** Imagabalin

**THERAPEUTIC AREA AND FDA APPROVED INDICATIONS:** Not Applicable.

**NATIONAL CLINICAL TRIAL NO.:** NCT00735267

**PROTOCOL NO.:** A5361022

**PROTOCOL TITLE:** A 52-Week Open-Label Safety Study of PD 0332334 in Subjects with Generalized Anxiety Disorder

**Study Centers:** 89 centers in the United States enrolled subjects

**Study Initiation Date and Primary Completion or Completion Dates:** 02 October 2008 to 14 April 2009

The study was terminated prematurely due to termination of the PD 0332334 program.

**Phase of Development:** Phase 3

**Study Objectives:**

Primary Objective:

- To assess the long-term safety and tolerability of 350 mg/day to 600 mg/day of PD 0332334 dosed twice daily (BID) in subjects with generalized anxiety disorder (GAD).

Secondary Objective:

- To assess the relationship between severity of GAD and health care utilization over a 1-year time period.

**METHODS**

**Study Design:** This study was a Phase 3, open-label, multicenter, 1-year safety study in up to 2289 subjects with GAD. Subjects received PD 0332334 (imagabalin) in an open-label fashion in doses ranging from 350 mg/day to 600 mg/day administered BID. Subjects were eligible to enroll in this study after completing all phases (screening, double-blind treatment, dose-tapering, and follow-up) of 1 of the 4 preceding qualifying double-blind short-term GAD studies (A5361017, A5361018, A5361019, or A5361020) provided subjects were at a

center that was participating in this study (A5361022) and met the inclusion and exclusion criteria.

This study was planned to consist of 3 phases: a 1-week titration phase, a 50-week flexible dosing phase, and a 1-week taper phase. Subjects who fulfilled entry criteria were titrated up to 350 mg/day (175 mg BID) of PD 0332334 over the first week of treatment. Following titration, dosing was planned to be flexible in the range of 350 mg/day to 600 mg/day, administered BID during the 50-week flexible dosing phase. At the end of the 50-week flexible dosing phase (Visit 9, Week 51), subjects were planned to be tapered off of PD 0332334 over the last week of treatment.

**Number of Subjects (Planned and Analyzed):** A total of up to 2289 subjects were planned for enrollment. A total of 502 subjects were screened for entry into this study; of these, 468 subjects were assigned to treatment, 463 subjects received treatment, and no subjects completed treatment.

**Diagnosis and Main Criteria for Inclusion:** Subjects must have completed all phases of 1 of the 4 preceding double-blind GAD studies (A5361017, A5361018, A5361019, or A5361020). Females must have continued to use adequate birth control methods and have had a negative serum pregnancy test at least 14 days (±3-day window) prior to and a negative urine pregnancy test before starting open-label PD 0332334 at Visit 1 (Day 1). Subjects who experienced a serious adverse event (SAE) during the preceding study that was judged to be related to the study drug, subjects with a serious suicide risk per the clinical investigator's judgment, and subjects who were using prohibited medications outlined in the protocol were not included in the study.

**Study Treatment:** Following completion of all phases of the preceding qualifying short-term double-blind study, subjects who enrolled in this study were assigned to receive PD 0332334 in an open-label fashion after study eligibility had been confirmed. The first dose of PD 0332334 was administered on the evening of Day 1 (Visit 1) after completion of the Day 1 (Visit 1) visit. PD 0332334 was administered to each subject as oral capsules on a BID regimen. Subjects were titrated up to 350 mg/day (175 mg BID) of PD 0332334 over the first week of treatment according to the schedule in Table 1.

**Table 1. Titration Schedule**

| Day | Dose(s) |
|---|---|
| 1 (Visit 1) | 125 mg HS |
| 2 | 125 mg BID |
| 3 | 125 mg BID |
| 4 | 125 mg BID |
| 5 | 175 mg BID |
| 6 | 175 mg BID |
| 7 | 175 mg BID |

HS = at bedtime; BID = twice daily.

Following titration to 350 mg/day (175 mg BID) of PD 0332334 during the first week, dosing was planned to be flexible in the range of 350 mg/day to 600 mg/day (175 mg BID to

300 mg BID) during the 50-week flexible dosing phase. Beginning at Visit 2 through Visit 8, based on the investigator's assessment of safety and efficacy, the investigator could adjust the dose of PD 0332334 as long as the adjusted dose was at least 350 mg/day (175 mg BID) and did not exceed 600 mg/day (300 mg BID). Dose adjustments where unequal doses were given in the morning and evening were not permitted.

At Visit 9 (Week 51), subjects were to be tapered off PD 0332334 according to the taper schedule in Table 2.

**Table 2. Dose Tapering Titration Schedule**

| | Taper Schedule | | |
|---|---|---|---|
| **Day** | **175-200 mg BID** | **225-250 mg BID** | **275-300 mg BID** |
| 358 (Visit 9) | 175 mg BID | 225 mg BID | 225 mg BID |
| 359 | 175 mg BID | 175 mg BID | 225 mg BID |
| 360 | 125 mg BID | 175 mg BID | 225 mg BID |
| 361 | 125 mg BID | 125 mg BID | 125 mg BID |
| 362 | 125 mg BID | 125 mg BID | 125 mg BID |
| 363 | 125 mg BID | 125 mg BID | 125 mg BID |
| 364 | 125 mg BID | 125 mg BID | 125 mg BID |

BID = twice daily.



**Efficacy Evaluations:** No efficacy evaluations were performed for this study.

**Pharmacokinetic and Other Evaluations:** Although pharmacokinetic samples were collected, the Health Care Utilization Questionnaire (HCU) was administered, and GAD symptom severity was measured by the Hamilton Rating Scale for Anxiety (HAM-A), the Clinical Global Impression of Severity (CGI-S), and the Daily Diary (DD), no analyses were performed due to termination of the PD 0332334 development program.

**Safety Evaluations:** Safety endpoints for this study included the nature, incidence, and severity of adverse events (AEs); discontinuations due to AEs; and AEs occurring during and after study drug discontinuation. Body weight, clinical safety laboratory parameters, 12-lead electrocardiograms (ECGs), physical examinations, and vital signs were monitored in this study.

During AE monitoring, it was expected that the investigators would be alert to AEs that were suicide-related. If a suicide-related AE was identified, the investigator was to contact the sponsor immediately regarding the continuation of the subject in the study and a suicide risk assessment was to be performed to determine appropriate clinical follow-up. This assessment was to be performed by a clinician with experience in suicide risk assessment. If a suicide-related AE was identified, the investigational staff was to complete the Columbia-Suicide Severity Rating Scale (C-SSRS). This information was then to be used to generate a narrative of the suicide-related AE. In addition, Pfizer periodically performed a search of the safety database to identify any further suicide-related AEs.

**Statistical Methods:** The safety analysis set consisted of all subjects who were treated. Safety and demographics data were summarized using data tabulations and descriptive statistics.

## RESULTS

**Subject Disposition and Demography:** Subject disposition is summarized in Table 3. A total of 463 subjects received treatment and no subjects completed treatment. All subjects who received treatment (N=463) were analyzed for AEs and 445 subjects were analyzed for laboratory data (Table 3).

### Table 3. Subject Disposition and Subjects Analyzed

| Number (%) of Subjects | PD 0332334 |
|---|---|
| Screened: N=502 | |
| Assigned to treatment | 468 |
| Treated | 463 |
| Completed | 0 |
| Discontinued | 463 (98.9) |
| Analyzed for safety | |
| Adverse events | 463 (98.9) |
| Laboratory data | 445 (95.1) |

All subjects treated in this study were discontinued. Most of the discontinuations (367 [79.3%]) were due to the fact that the study was terminated by the sponsor. Most of the discontinuations not due to the study being terminated were considered not related to study drug (Table 4).

Table 4 summarizes subject discontinuations that occurred during the study.

### Table 4. Subject Discontinuations from Study

| Parameters | PD 0332334 |
|---|---|
| Number (%) of subjects | 463 |
| Discontinuations related to study drug | 403 (87.0) |
| Adverse event | 26 (5.6) |
| Insufficient clinical response | 10 (2.2) |
| Study terminated by sponsor | 367 (79.3) |
| Discontinuations not related to study drug | 60 (13.0) |
| Adverse event | 6 (1.3) |
| Lost to follow-up | 26 (5.6) |
| Other | 2 (0.4) |
| Protocol violation | 11 (2.4) |
| Subject no longer willing to participate in the study | 13 (2.8) |
| Withdrawn due to pregnancy | 2 (0.4) |
| Total discontinuations | 463 (100) |

Demographic characteristics are summarized in Table 5. Overall, 283 of the subjects were female and 180 subjects were male. The age of both females and males enrolled in the study ranged from 19 to 66 years of age, with a mean of 42.7 years overall. The majority of subjects (367/463 [79.3%]) enrolled in this study were white (Table 5).

Primary diagnoses and durations were available for 462 subjects. All of these subjects had a primary diagnosis of GAD with the duration since first diagnosis across treatment groups ranging from 0.0 to 56.4 years, with a mean of 8.6 years.

**Table 5. Demographic Characteristics**

| | PD 0332334 | | |
|---|---|---|---|
| **Parameters** | **Male** | **Female** | **Total** |
| Number (%) of subjects | 180 | 283 | 463 |
| Age, years | | | |
| <18 | 0 | 0 | 0 |
| 18-44 | 98 (54.4) | 166 (58.7) | 264 (57.0) |
| 45-64 | 79 (43.9) | 111 (39.2) | 190 (41.0) |
| ≥65 | 3 (1.7) | 6 (2.1) | 9 (1.9) |
| Mean | 43.2 | 42.4 | 42.7 |
| SD | 11.4 | 12.3 | 12.0 |
| Range | 19-66 | 19-66 | 19-66 |
| Race | | | |
| White | 149 (82.8) | 218 (77.0) | 367 (79.3) |
| Black | 18 (10.0) | 50 (17.7) | 68 (14.7) |
| Asian | 5 (2.8) | 5 (1.8) | 10 (2.2) |
| Other | 8 (4.4) | 10 (3.5) | 18 (3.9) |
| Ethnicity | | | |
| Hispanic/Latino | 27 (15.0) | 44 (15.5) | 71 (15.3) |
| Not Hispanic/Latino | 153 (85.0) | 239 (84.5) | 392 (84.7) |

SD = standard deviation.

**Efficacy Results:** No efficacy evaluations were performed in this study.

**Safety Results:** A total of 7 subjects in this study experienced an SAE (Table 6 and Table 9). There were no subject deaths reported during this study. A total of 891 AEs were reported in 345 subjects in this study. A total of 31 subjects discontinued due to a treatment-emergent AE, and 31 subjects had a temporary discontinuation or dose reduction due to an AE (Table 6).

## Table 6. Treatment-Emergent Adverse Events

| Number (%) of Subjects | PD 0332334 |
|---|---|
| ***All Causality*** | |
| Subjects evaluable for AEs | 463 |
| Number of AEs | 891 |
| Subjects with AEs | 345 (74.5) |
| Subjects with serious AEs | 6 (1.3)[a] |
| Subjects with severe AEs | 29 (6.3) |
| Subjects discontinued due to AEs | 31 (6.7) |
| Subjects with dose reduced or temporary discontinuation due to AEs | 31 (6.7) |
| ***Treatment-Related*** | |
| Subjects evaluable for AEs | 463 |
| Number of AEs | 537 |
| Subjects with AEs | 270 (58.3) |
| Subjects with serious AEs | 2 (0.4)[a] |
| Subjects with severe AEs | 17 (3.7) |
| Subjects discontinued due to AEs | 25 (5.4) |
| Subjects with dose reduced or temporary discontinuation due to AEs | 27 (5.8) |

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.
AEs = adverse events; MedDRA = Medical Dictionary for Regulatory Activities.
[a] An additional subject reported an SAE of abortion spontaneous 57 days post-therapy, which is not included in this table.



The most common AEs reported in this study (Medical Dictionary for Regulatory Activities [MedDRA], Version 12.0) by system organ class (all causality) were nervous system disorders, gastrointestinal disorders, infections and infestations, psychiatric disorders, and general disorders and administration site conditions. The most common treatment-related AEs reported in this study (MedDRA, Version 12.0) by system organ class were nervous system disorders, gastrointestinal disorders, and psychiatric disorders. Table 7 provides a summary of AEs by system organ class and preferred term (all causality) in >2% of subjects in any treatment group. This cutoff was chosen due to very few AEs being reported in higher percentages of subjects.

The most common AEs (all causality) reported in this study by preferred term (MedDRA, Version 12.0) were dizziness (61 subjects), headache (54 subjects), somnolence (53 subjects), dry mouth (30 subjects), upper respiratory tract infection (29 subjects), sedation (27 subjects), and nausea (25 subjects). Slightly more than half (495/891; 55.6%) of AEs (all causality) were mild in intensity. Overall, 4.0% (36/891) of AEs (all causality) were severe in intensity. The most common treatment-related AEs reported in this study by preferred term (MedDRA, Version 12.0) were dizziness (58 subjects), somnolence (52 subjects), headache (43 subjects), dry mouth (29 subjects), and sedation (26 subjects). More than half (352/537; 65.5%) of the treatment-related AEs were mild in intensity. Overall, 3.7% (20/537) of the treatment-related AEs were severe in intensity.

**Table 7. Summary of Treatment-Emergent Adverse Events (All Causality) in >2% of Subjects; Safety Analysis Set**

| Number (%) of Subjects | PD 0332334 |
|---|---|
| **All Causality** | |
| Gastrointestinal disorders | 109 (23.5) |
| Constipation | 13 (2.8) |
| Diarrhea | 12 (2.6) |
| Dry mouth | 30 (6.5) |
| Dyspepsia | 15 (3.2) |
| Flatulence | 10 (2.2) |
| Gastroesophageal reflux disease | 10 (2.2) |
| Nausea | 25 (5.4) |
| General disorders and administrative site conditions | 63 (13.6) |
| Fatigue | 14 (3.0) |
| Irritability | 13 (2.8) |
| Infections and infestations | 101 (21.8) |
| Influenza | 12 (2.6) |
| Nasopharyngitis | 19 (4.1) |
| Sinusitis | 15 (3.2) |
| Upper respiratory tract infection | 29 (6.3) |
| Investigations | 28 (6.0) |
| Weight increased | 14 (3.0) |
| Metabolism and nutrition disorders | 17 (3.7) |
| Increased appetite | 10 (2.2) |
| Musculoskeletal and connective tissue disorders | 46 (9.9) |
| Back pain | 11 (2.4) |
| Nervous system disorders | 187 (40.4) |
| Disturbance in attention | 10 (2.2) |
| Dizziness | 61 (13.2) |
| Headache | 54 (11.7) |
| Sedation | 27 (5.8) |
| Somnolence | 53 (11.4) |
| Psychiatric disorders | 69 (14.9) |
| Insomnia | 15 (3.2) |

Subjects are counted only once per treatment in each row. 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.

The most common AEs leading to subject discontinuation in this study (MedDRA, Version 12.0) included the following (subjects could have multiple AEs leading to discontinuation): dizziness (5 AEs), peripheral edema (4 AEs), anxiety (4 AEs), and somnolence (3 AEs). A summary of all AEs leading to discontinuation is provided in Table 8.

## Table 8. Summary of Adverse Events (All Causalities) Leading to Permanent Discontinuation

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| Number of Occurrences | PD 0332334 |
|---|---|
| System Organ Class<br>MedDRA (v12.0) preferred term | |
| Cardiac disorders | |
| Palpitations | 1 |
| Ear and labyrinth disorders | |
| Tinnitus | 1 |
| Gastrointestinal disorders | |
| Abdominal pain | 1 |
| Abdominal pain upper | 1 |
| Constipation | 1 |
| Gastroesophageal reflux disease | 1 |
| Nausea | 1 |
| Pancreatitis acute | 1 |
| General disorders and administration site conditions | |
| Chest pain | 1 |
| Face oedema | 1 |
| Fatigue | 1 |
| Feeling abnormal | 1 |
| Feeling jittery | 1 |
| Irritability | 1 |
| Oedema peripheral | 4 |
| Infections and infestations | |
| Gastroenteritis | 1 |
| Lung infection | 1 |
| Investigations | |
| Heart rate increased | 1 |
| Nervous system disorders | |
| Dizziness | 5 |
| Headache | 2 |
| Hypersomnia | 1 |
| Somnolence | 3 |
| Psychiatric disorders | |
| Anorgasmia | 1 |
| Anxiety | 4 |
| Confusional state | 1 |
| Depression | 2 |
| Insomnia | 1 |
| Nightmare | 1 |
| Reproductive system and breast disorders | |
| Ejaculation delayed | 1 |

MedDRA = Medical Dictionary for Regulatory Activities.

**Table 8. Summary of Adverse Events (All Causalities) Leading to Permanent Discontinuation**

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| Number of Occurrences | PD 0332334 |
|---|---|
| System Organ Class<br>MedDRA (v11.1) preferred term | |
| Respiratory, thoracic and mediastinal disorders | |
| Choking sensation | 1 |
| Nasal dryness | 1 |
| Wheezing | 1 |
| Skin and subcutaneous disorders | |
| Skin fissures | 1 |
| Vascular disorders | |
| Hypotension | 1 |

MedDRA = Medical Dictionary for Regulatory Activities.

A listing of SAEs is provided in Table 9. A total of 7 subjects reported a total of 10 SAEs, 5 of which were considered to be related to study treatment. No deaths were reported during the study.

**Table 9. Serious Adverse Events**

| Subject | Preferred Term | Total Daily Dose | Adverse Event | | |
|---|---|---|---|---|---|
| | | | Event Onset Day[a] | Clinical Outcome | Causality[e] |
| 58-year-old female | Pericardial effusion | 350 mg<br>450 mg | 48<br>19 | Recovered | Related |
| 55-year-old female[b] | Headache<br>Hypoaesthesia<br>Visual impairment | 600 mg<br>600 mg<br>600 mg | 12<br>12<br>12 | Recovered<br>Recovered<br>Recovered | Related<br>Related<br>Related |
| 41-year-old male | Chest pain | 500 mg | 103 | Recovered | Unrelated |
| 44-year-old male | Diverticulitis[c] | 400 mg | 12 | Recovered | Unrelated |
| 26-year-old female | Abortion spontaneous | 250 mg | 109 | Recovered | Related |
| 49-year-old female[d] | Chest pain<br>Headache | 350 mg<br>350 mg | 73<br>73 | Recovered<br>Recovered | Unrelated<br>Unrelated |
| 43-year-old female[d] | Pancreatitis | 400 mg | 17 | Recovered | Unrelated |

Medical Dictionary for Regulatory Activities (MedDRA, v12.0) coding dictionary applied.
[a] Days are relative to the day of starting active therapy (Day 1).
[b] The dose was reduced in response to these serious adverse events.
[c] The subject was temporarily withdrawn from the study due to this event.
[d] The subject was permanently withdrawn from the study due to these events.
[e] As determined by investigator assessment.

A total of 36 subjects reported possible suicide-related AEs during the study.

The number and percentage of subjects 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**

| | | | PD 0332334 |
|---|---|---|---|
| **Parameter** | **Criteria** | **N** | **n (%)** |
| Increase in body weight | ≥7% | 463 | 14 (3.0) |

N = number of subjects evaluated; n = number of subjects with a ≥7% increase in body weight.

Table 11 provides a summary of laboratory test abnormalities in ≥2 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. A total of 445 subjects were evaluable for laboratory abnormalities, and 51 (11%) subjects with normal baseline values reported abnormalities.

**Table 11. Laboratory Test Abnormalities in ≥2 Subjects; Subjects With Normal Baseline**

| | | | PD 0332334 | |
|---|---|---|---|---|
| **Parameter** | **Unit** | **Criteria** | **N** | **n** |
| ***Hematology*** | | | | |
| Hemoglobin | g/dL | <0.8x LLN | 406 | 2 |
| Hematocrit | % | <0.8x LLN | 415 | 2 |
| White blood cell count | $10^3/mm^3$ | >1.5x ULN | 416 | 2 |
| ***Electrolytes*** | | | | |
| Potassium | mEq/L | >1.1x ULN | 411 | 3 |
| ***Clinical chemistry (other)*** | | | | |
| Glucose | mg/dL | >1.5x ULN | 377 | 2 |
| Creatine kinase | U/L | >2.0x ULN | 390 | 8 |
| ***Urinalysis (dipstick)*** | | | | |
| Urine blood/hemoglobin (qual) | — | ≥1 | 412 | 25 |
| Urine urobilinogen | — | ≥1 | 442 | 2 |

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; qual = qualitative; ULN = upper limit of normal.

A summary of the incidence of vital signs values reaching the level of potential clinical concern is provided in Table 12.

**Table 12. Categorical Summary of Vital Signs Measurement Data; Safety Analysis Set**

| Parameter | Criteria | PD 0332334 N | PD 0332334 n (%) |
|---|---|---|---|
| ***Increase from baseline*** | | | |
| Maximum increase from baseline in sitting systolic BP (mm Hg) | ≥30 | 456 | 18 (3.9) |
| Maximum increase from baseline in sitting diastolic BP (mm Hg) | ≥20 | 456 | 19 (4.2) |
| ***Absolute values*** | | | |
| Sitting systolic BP (mm Hg) | <90 | 460 | 2 (0.4) |
| Sitting diastolic BP (mm Hg) | <50 | 460 | 2 (0.4) |
| Sitting heart rate (bpm) | <40 | 460 | 0 |
| Sitting heart rate (bpm) | >120 | 460 | 0 |

BP = blood pressure; bpm = beats per minute; mm Hg = millimeters of mercury; N = number of subjects evaluated; n = number of subjects with value of potential clinical concern.

Three subjects had 1 AE each of increased BP during the study.

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. One subject had a QTcB interval ≥500 msec prior to the start of study treatment.

**Table 13. Categorical Summary of Electrocardiogram Data; Safety Analysis Set**

| Parameter | Criteria | PD 0332334 N | PD 0332334 n (%) |
|---|---|---|---|
| Maximum QTcB interval (msec) | 450 - <500 | 468 | 35 (7.5) |
| | ≥500 | 468 | 1 (0.2) |
| Maximum QTcF interval (msec) | 450 - <500 | 468 | 9 (1.9) |
| | ≥500 | 468 | 0 |

N = number of subjects evaluated; n = number of subjects with value of potential clinical concern; 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. 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.