# Clinical Study Report

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| **Study Title:** | A Phase 3, Double-Blind, Placebo-Controlled Study to Determine the Efficacy and Safety of a Low (50 mg/day) and High (100 mg/day) Dose of Safinamide, as Add-on Therapy, in Patients with Idiopathic Parkinson's Disease with Motor Fluctuations, Treated with a Stable Dose of Levodopa and Who May be Receiving Concomitant Treatment with Stable Doses of a Dopamine Agonist, and/or an Anticholinergic |
| **Name of the Test Drug/Investigational Product:** | Safinamide |
| **EUDRACT Number:** | 2006-005860-14 |
| **Indication:** | Parkinson's Disease |
| **Study Design** | Double-blind, placebo-controlled, parallel-group, multicenter, multinational |
| **Name of the Sponsor:** | Newron Pharmaceuticals SpA. |
| **Protocol Number:** | NW-1015/016/III/2006 |
| **Development Phase of Study:** | Phase 3 |
| **Study Initiation Date (Date First Patient Screened):** | 13 January 2007 |
| **Study Completion Date (Date Last Patient Completed Last Observation):** | 28 October 2008 |
| **Name and Address of Sponsor Signatory:** | Ravi Anand, MD<br>Newron Pharmaceuticals S.p.A<br>Via Ludovico Ariosto 21, 20091 Bresso (MI), Italy<br>Tel: +39-0261034600<br>Fax: +39-0261034635 |
| **Good Clinical Practice (GCP) Statement:** | This study was conducted in accordance with good clinical practices. |
| **Date of Report:** | 20 May 2010 FINAL |

## 2. SYNOPSIS

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| **Name of Sponsor/Company:**<br>Newron Pharmaceuticals SpA. | | *(For National Authority Use Only)* |
| **Name of Finished Product:**<br>Safinamide | | |
| **Name of Active Ingredient:**<br>Safinamide | | |
| **Title of Study:**<br>A Phase 3, Double-Blind, Placebo-Controlled Study to Determine the Efficacy and Safety of a Low (50 mg/day) and High (100 mg/day) Dose of Safinamide, as Add-on Therapy, in Patients with Idiopathic Parkinson's Disease with Motor Fluctuations, Treated with a Stable Dose of Levodopa and Who May be Receiving Concomitant Treatment with Stable Doses of a Dopamine Agonist, and/or an Anticholinergic | | |
| **Study Number:**<br>NW-1015/016/III/2006 | | |
| **Investigators:**<br>See Appendix 16.1.3. | | |
| **Study Centers:**<br>The study was conducted at 52 study centers: 35 in India, 10 in Romania, and 7 in Italy. | | |
| **Publication (Reference):**<br>There were no publications based on this study. | | |
| **Study Period (Date First Patient Screened—Date Last Patient Completed Last Observation):**<br>13 January 2007—28 October 2008 | **Study Phase of Development:** 3 | |
| **Objectives:**<br>The objective of this study was to evaluate the efficacy and safety of 2 oral (PO) doses of safinamide (50 and 100 mg/day) compared with placebo, as add-on therapy in patients with idiopathic Parkinson's Disease (PD) with motor fluctuations, who are currently receiving a stable dose of levodopa. | | |
| **Methods:**<br>This study was a Phase 3, multicenter, multinational, double-blind, placebo-controlled, parallel-group study conducted in patients with idiopathic PD with motor fluctuations, who were receiving a stable dose of levodopa. The total duration of the study was approximately 108 weeks, including the Screening period (10 days), a levodopa stabilization phase (4 weeks), the treatment period (24 weeks), an optional 1-week taper phase, and the extension study (78 weeks). Eligible patients could receive treatment with either safinamide or placebo for a total of 102 weeks (a 24-week initial treatment period plus a 78-week extension of the treatment period). This was achieved by the patients' participating in 2 protocols: all randomized patients completing their participation in the double-blind treatment period in this study could enter an ongoing 78-week, double-blind extension study (Study NW-1015/018/III/2006 [Study 018]). Patients who met the entry criteria at Baseline were randomized (1:1:1) to receive 1 of the 2 doses of safinamide or placebo. Patients returned for regularly scheduled visits at Weeks 4, 8, 12, 18, and 24 (or at early discontinuation). Ophthalmologic examinations were performed by a qualified ophthalmologist at Screening, Week 12, and Week 24. | | |

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**Number of Patients (Planned and Analyzed):**

It was planned that a total of 660 patients (220 per treatment group) were to be randomized so that 568 patients completed the 24-week treatment period. A total of 900 patients were screened; 231 (25.7%) were considered screening failures. Overall, 669 were randomized to treatment (222 to placebo, 223 to safinamide 50 mg/day, and 224 to safinamide 100 mg/day) and 594 completed the study. A total of 669 patients comprised both the intent-to-treat (ITT) and safety population.

**Diagnosis and Main Criteria for Inclusion:**

Men and women, 30 to 80 years, with a diagnosis of idiopathic PD of more than 5 years duration (patients who had PD for at least 3 years or who were older than 80 could have been enrolled upon approval of the Clinical Research Organization [CRO] Medical Monitor or Newron Medical Expert, respectively), a Hoehn and Yahr stage of 1–4 during an *off* phase, and motor fluctuations with > 1.5 hours *off* time during the day. Patients in a late stage of PD who were experiencing severe, disabling peak dose or biphasic dyskinesia or unpredictable or widely swinging fluctuations in their symptoms were excluded. Patients had to be receiving a stable dose of levodopa and could have been receiving a stable dose of a dopamine (DA) agonist or anticholinergic. Additionally, patients with a history of albinism, family history of hereditary retinal disease, progressive or severe diminution of visual acuity (ie, 20/70), retinitis pigmentosa, retinal pigmentation due to any cause, any active retinopathy or ocular inflammation (uveitis), or progressive, severe diabetic retinopathy were excluded from participating in the study.

**Test Product, Dose and Mode of Administration, Batch Numbers:**

Test product: safinamide

Route and mode of administration: oral

Dose and dosage schedule:
Safinamide 50/mg/day: 2 tablets once daily (one 50-mg tablet and 1 placebo tablet) for 24 weeks during the treatment phase; 2 tablets once daily (2 placebo tablets) during the optional 1-week taper phase
Safinamide 100 mg/day: 2 tablets once daily (two 50-mg tablets) for 24 weeks during the treatment phase; 2 tablets once daily (one 50 mg tablet and 1 placebo tablet) during the optional 1-week taper phase

Batch Numbers: 0010511

**Duration of Treatment:**

24 weeks plus an optional 1-week taper phase

**Reference Products, Dose, Mode of Administration, Batch Numbers:**

Reference product: placebo

Route and mode of administration: oral

Dose and dosage schedule: 2 placebo tablets once daily for 24 weeks during the treatment phase; 2 placebo tablets once daily during the optional 1-week taper phase

Batch Numbers: 0000511, 000A0606

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**Criteria for Evaluation:**

Efficacy: The primary efficacy variable was the mean total daily *on* time without troublesome dyskinesia over 18 hours.

The secondary efficacy variables included the following: decrease in total daily *off* time, Unified Parkinson's Disease Rating Scale (UPDRS) Section 3 (motor examination) during *on* phase, Clinical Global Impression–change from Baseline (CGI-C), Cognitive Test Battery (Cogtest), decrease in mean *off* time after first morning dose of levodopa, Dyskinesias Rating Scale (DRS) during *on* phase, UPDRS Section 2 (activities of daily living [ADL]) during *on* phase, CGI–severity of illness (CGI-S), and mean percentage reduction in levodopa dose.

The tertiary efficacy variables included the following: Hoehn and Yahr staging, grid version of Hamilton rating scale for depression–17-item scale (GRID-HAMD-17), Mini-Mental State Examination (MMSE), and Parkinson's Disease Questionnaire (PDQ-39).

**Criteria for Evaluation:**

Safety**:**

Safety variables included adverse events (AEs); clinical laboratory tests results (hematology, biochemistry, and urinalysis); vital sign measurements; 12-lead electrocardiogram (ECG) findings; physical, neurological, dermatological, and ophthalmological examination findings; and Epworth Sleepiness Scale (ESS) scores.

**Statistical Methods:**

***Adverse Events***: AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 8.1, and were summarized overall and by treatment group. The summaries were presented by MedDRA System Organ Class (SOC) and Preferred Term (PT). A treatment-emergent AE (TEAE) was defined as an AE that started on or after the first administration of study drug, or AEs that started before administration of study drug but worsened after administration of study drug. TEAEs were summarized by intensity and relationship to study drug. Serious AEs (SAEs) and AEs leading to study discontinuation were summarized separately. TEAEs were compared across treatment groups using Cochran Mantel Haenszel stratified by center.

**SUMMARY—CONCLUSIONS**

EFFICACY RESULTS

*Primary Efficacy Endpoint*

The primary efficacy endpoint was the increase in mean total daily *on* time (*on* time without dyskinesia plus *on* time with minor dyskinesia) during the 18-hour diary recording period (0600 through 2400 hours). The mean total daily *on* time over 18 hours increased over time for each of the 3 treatment groups; however, at Visit 8 (Week 24), the mean (SD) change from Baseline in total daily *on* time was approximately 55% higher for the safinamide 50 mg/day and safinamide 100 mg/day groups compared with the placebo group: 0.92 (2.414) hours for the placebo group, 1.43 (2.626) hours for the safinamide 100 mg/day group, and 1.42 (2.724) hours for the safinamide 50 mg/day group. An analysis of the change in mean total daily *on* time from Baseline to Visit 8 revealed that the safinamide 100 mg/day and the safinamide 50 mg/day groups had a statistically significantly higher mean change from Baseline (LS mean, 1.32 hours for the safinamide 100 mg/day group [P = 0.0048] and 1.28 hours for the safinamide 50 mg/day group [P = 0.0082]) than the placebo group (LS mean, 0.69 hours).

Using analysis of covariance (ANCOVA), an ad hoc analysis of the primary efficacy endpoint was also performed. As observed with the primary analysis, the mean total daily *on* time over 18 hours increased over time for each of the 3 treatment groups using ANCOVA. At Visit 8 (Week 24), the mean (SD) change from Baseline in total daily *on* time was 0.6 (2.93) hours for the placebo group compared with 1.2 (2.87) hours for the safinamide 100 mg/day group and 1.0 (3.22) hours for the safinamide 50 mg/day group, an increase of 100% and

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67%, respectively. An ANCOVA analysis of the change in mean total daily *on* time from Baseline to Visit 8 revealed that the safinamide 100 mg/day and safinamide 50 mg/day groups had a statistically significantly higher mean change from Baseline (LS mean, 0.8 hours for the safinamide 100 mg/day group [$P = 0.0070$] and 0.6 hours for the safinamide 50 mg/day group [$P = 0.0367$]) than the placebo group (LS mean, 0.10 hours).

*Secondary Efficacy Endpoints*

The mean total daily *off* time over 18 hours decreased over time for each of the 3 treatment groups. At Visit 8 (Week 24), the mean (SD) change from Baseline in total daily *off* time was reduced by 63% in both safinamide treatment groups compared with the placebo group: –0.8 (2.17) hours for the placebo group, –1.3 (2.19) hours for the safinamide 100 mg/day group, and –1.3 (2.28) hours for the safinamide 50 mg/day group. An analysis of the change in mean total daily *off* time from Baseline to Visit 8 (Week 24) revealed that the safinamide 100 mg/day and the safinamide 50 mg/day groups had a statistically significantly reduced mean change from Baseline (LS mean, –1.3 hours for the safinamide 100 mg/day group [$P = 0.0027$] and –1.3 hours for the safinamide 50 mg/day group [$P = 0.0022$]) compared with the placebo group (LS mean, –0.7 hours).

A reduction in mean UPDRS Section 3 (motor examination) scores from Baseline was observed at all visits for all 3 treatment groups. At Visit 8 (Week 24), the mean (SD) change from Baseline in UPDRS Section 3 scores was –4.8 (9.40) for the placebo group, –6.3 (9.74) for the safinamide 50 mg/day group, and –7.3 (10.77) for the safinamide 100 mg/day group. An analysis of the change in mean UPDRS scores for Section 3 from Baseline to Visit 8 (Week 24) revealed that the safinamide 100 mg/day and the safinamide 50 mg/day groups had a statistically significantly reduced mean change from Baseline (LS mean, –7.2 for the safinamide 100 mg/day group [$P = 0.0002$] and –6.4 for the safinamide 50 mg/day group [$P = 0.0075$]) compared with the placebo group (LS mean, –4.4).

Ad-hoc analyses of the UPDRS Section 3 responder rate (defined as ≥ 20% reduction in UPDRS Section 3 scores) showed that a statistically significantly higher percentage of patients in the safinamide 50 mg/day (48.9%; $P = 0.0239$) and safinamide 100 mg/day (49.6%; $P = 0.0300$) groups had ≥ 20% reduction in UPDRS Section 3 scores compared with the placebo group (41.0%). Moreover, a higher percentage of patients in the safinamide 100 mg/day (41.1%) and safinamide 50 mg/day (37.7%) groups had ≥ 30% reduction in UPDRS Section 3 scores compared with the placebo group (31.5%). The difference between the safinamide 100 mg/day group and the placebo group was statistically significant ($P = 0.0095$), but the safinamide 50 mg/day group and the placebo group were not statistically significantly different ($P = 0.0698$).

Compared with the placebo group (27.93%), a statistically significantly higher percentage of patients in the safinamide 100 mg/day (41.07%; $P = 0.0006$) and safinamide 50 mg/day (38.57%; $P = 0.0041$) groups had ≥ 20% improvement in UPDRS Section 3 scores without worsening in Section 2 and 4 scores. Moreover, a statistically significantly higher percentage of patients in the safinamide 100 mg/day (33.93%; $P = 0.0006$) and safinamide 50 mg/day (30.04%; $P = 0.0192$) groups had ≥ 30% improvement in UPDRS Section 3 scores without worsening in Section 2 and 4 scores compared with the placebo group (22.07%).

When UPDRS Section 3 scores were further analyzed by patients' use of PD medications at Baseline, there was a statistically significant difference in the safinamide 100 mg/day group (difference in LS means, –2.7; $P = 0.0010$) and the safinamide 50 mg/day group (difference in LS means, –2.4; $P = 0.0043$) compared with the placebo group in those patients who were not taking amantadine.

For the placebo and safinamide 50 mg/day groups, the percentage of patients exhibiting improvement in their clinical status increased at each subsequent visit; the percentages ranged from 43.2% at Visit 4 (Week 4) to 55.0% at Visit 8 (Week 24) for the placebo group and 53.8% at Visit 4 (Week 4) to 67.3% at Visit 8 (Week 24) for the safinamide 50 mg/day group. Whereas for the safinamide 100 mg/day group, the percentage of patients with an improvement in their clinical status increased through Visit 6 and then decreased at Visits 7 and 8. At

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Visit 8 (Week 24), the percentage of patients with improvement was statistically significantly higher for the safinamide 100 mg/day (63.8%, $P = 0.0097$) and safinamide 50 mg/day (67.3%, $P = 0.0003$) groups than for the placebo group (55%).

A reduction in mean *off* time following first morning dose of levodopa from Baseline was observed at all visits for all 3 treatment groups. At Visit 8 (Week 24), the mean (SD) change from Baseline in mean total daily *off* time following first morning dose of levodopa was reduced by approximately 70% in the safinamide treatment groups compared with the placebo group: –0.7 (2.06) hours for the placebo group, –1.2 (2.05) hours for the safinamide 100 mg/day group, and –1.2 (2.14) hours for the safinamide 50 mg/day group. An analysis of the change in mean total daily *off* time following first morning dose of levodopa from Baseline to Visit 8 (Week 24) showed that the safinamide 100 mg/day and the safinamide 50 mg/day groups had a statistically significantly decreased mean change from Baseline (LS mean, –1.2 hours for the safinamide 100 mg/day group [$P = 0.0009$] and –1.2 hours for the safinamide 50 mg/day group [$P = 0.0013$]) compared with the placebo group (LS mean, –0.6 hours).

At Baseline, the mean (SD) DRS scores for the placebo, safinamide 50 mg/day, and safinamide 100 mg/day groups were 3.4 (3.93), 3.9 (3.89), and 3.7 (4.06), respectfully. At Visits 6 (Week 12) and 8 (Week 24), reductions in DRS scores from Baseline were minimal. Among the treatment groups, there were no statistically significant differences in DRS scores during *on* phase from Baseline to Visit 8.

An ad hoc analysis of those patients who reported dyskinesia on the DRS showed that most patients reported chorea only as the most disabling dyskinesia at all study visits. A smaller number of patients reported only dystonia at all study visits.

Further hypothesis testing of subsequent variables was discontinued after the assessment of DRS scores, since the secondary efficacy variables were evaluated in a hierarchical manner, ie, testing was to be continued until the first nonsignificant difference between placebo and the safinamide 100 mg/day group was detected, Therefore, *P* values for subsequent secondary efficacy results presented after this point were not controlled for error rates and should be considered nominal values only.

Reductions in mean UPDRS Section 2 (ADL) scores from Baseline were observed at all visits for all 3 treatment groups. At Visit 8 (Week 24), the mean (SD) change from Baseline in mean UPDRS Section 2 scores was –1.5 (4.15) for the placebo group, –2.0 (4.34) for the safinamide 50 mg/day group, and –2.5 (4.24) for the safinamide 100 mg/day group. Nominal analysis of the UPDRS Section 2 scores from Baseline to Visit 8 (Week 24) revealed that the safinamide 100 mg/day group had a statistically significantly decreased mean change from Baseline (LS mean, –2.2 [$P = 0.0060$]) compared with the placebo group (LS mean, –1.2), whereas the safinamide 50 mg/day group (LS mean, –1.8 [$P = 0.0742$]) was not statistically significantly different from placebo.

At Visit 3 (Baseline), the treatment groups were similar with regard to the distribution of patients among the severity of illness categories (borderline ill, mildly ill, moderately ill, markedly ill, and severely ill). Overall, 60.2% of patients were moderately ill at Baseline (a CGI-S score of 4), 17.2% were markedly ill, and 1.3% were severely ill. Furthermore, the mean CGI-S scores were reduced from Baseline at all visits for all 3 treatment groups. At Visit 8 (Week 24), the mean (SD) change from Baseline in CGI-S scores was –0.3 (0.60) for the placebo group, –0.4 (0.69) for the safinamide 50 mg/day group, and –0.4 (0.73) for the safinamide 100 mg/day group. Nominal analysis of the change in mean CGI-S scores from Baseline to Visit 8 (Week 24) indicated that the safinamide 50 mg/day and the safinamide 100 mg/day groups had a statistically significantly reduced mean change from Baseline (LS mean, –0.4 for the safinamide 50 mg/day group [$P = 0.0038$] and –0.4 for the safinamide 100 mg/day group [$P = 0.0219$]) compared with the placebo group (LS mean, –0.2).

In the placebo group, 7.7% of patients had any reduction in their levodopa dose during the study, whereas 11.2%

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of patients in the safinamide 50 mg/day group and 11.2% of patients in the safinamide 100 mg/day group had any reduction in their levodopa dose. The 3.5% absolute difference in the percentage of patients with any reduction in their levodopa dose between the placebo and the safinamide 50 mg/day and safinamide 100 mg/day treatment groups was not statistically significant, when compared using the Cochran-Mantel-Haenszel test. Compared with the placebo group, which had a 0.27% mean percent increase in levodopa dose during the study, the safinamide 50 mg/day group had a –1.05% mean percent reduction in levodopa dose and the safinamide 100 mg/day group had a –2.16% mean percent reduction in levodopa dose. Because the median value for all 3 treatment groups was zero, a comparison using a Wilcoxon rank-sum test was performed; the results revealed that the mean percent reduction in levodopa dose was statistically significantly different from placebo for the safinamide 100 mg/day group ($P = 0.0162$), but not for the safinamide 50 mg/day group ($P = 0.0937$).

An ad-hoc analysis showed that a similar percentage of patients in the safinamide 50 mg/day group (9.4%), but a lower percentage of patients in the safinamide 100 mg/day group (4.9%), required rescue medication compared with the placebo group (9.5%). The difference between the safinamide 100 mg/day group and the placebo group was not statistically significant (P = 0.0616).

The mean reduction in levodopa dose from Baseline to Visit 8 (Week 24) was largest in the safinamide 100 mg/day group (–19.59 mg) compared with the safinamide 50 mg/day group (–11.27 mg) and the placebo group (–6.93 mg).

*Tertiary Efficacy Endpoints*

For all 3 treatment groups, the median Hoehn and Yahr stage was 3 (which was defined as moderately severe bilateral disease, significant slowing of body movements, and impairment of equilibrium) at Visit 3 (Baseline). At Visit 8 (Week 24), the median Hoehn and Yahr stage was 2.5 (which was defined as bilateral involvement and posture, gait, and balance were affected but symptoms caused minimal disability) for all 3 treatment groups. There was no statistically significant difference in mean Hoehn and Yahr stage between the placebo and safinamide 50 mg/day and safinamide 100 mg/day treatment groups at Visit 8.

Reductions in mean GRID-HAMD-17 scores from Baseline were observed at all visits for all 3 treatment groups. At Visit 8 (Week 24), the mean (SD) change from Baseline in mean GRID-HAMD-17 scores was –0.3 (3.47) for the placebo group, –0.7 (3.13) for the safinamide 50 mg/day group, and –0.9 (2.76) for the safinamide 100 mg/day group. An analysis of the GRID-HAMD-17 scores from Baseline to Visit 8 (Week 24) revealed that the safinamide 100 mg/day group had a statistically significantly decreased mean change from Baseline (LS mean, –1.0 [$P = 0.0179$]) compared with the placebo group (LS mean, –0.3), while the safinamide 50 mg/day group (LS mean, –0.6 [$P = 0.2367$]) was not statistically significantly different from placebo.

The change from Baseline to Visit 8 in the 17 individual HAMD scores were analyzed separately. For the safinamide 50 mg/day group, there were no statistically significant differences from Baseline in individual HAMD scores compared with the placebo group. The safinamide 100 mg/day group was statistically significantly different from the placebo group for the following items: insomnia early ($P = 0.0404$), work and activities ($P= 0.0292$) and anxiety, somatic ($P = 0.0064$).

A further analysis of the GRID-HAMD-17 total scores from Baseline to Visit 8 (Week 24) for the subgroup of patients from India revealed that the safinamide 100 mg/day group had a statistically significantly decreased mean change from Baseline (LS mean, –0.7 [$P = 0.0172$]) compared with the placebo group (LS mean, –0.3), while the safinamide 50 mg/day group (LS mean, –0.6 [$P = 0.3310$]) was not statistically significantly different from placebo.

At Baseline, patients in all 3 treatment groups exhibited good cognitive function, as indicated by median MMSE scores of 27.9, 28.1, and 27.9 for the placebo, safinamide 50 mg/day and safinamide 100 mg/day groups, respectively. At Visit 8 (Week 24), there was little change in MMSE scores from Baseline for any treatment

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group.

For the PDQ-39, the ADL dimension exhibited decreases in mean scores from Baseline at all visits for all 3 treatment groups. The mean change from Baseline in ADL scores for the safinamide 50 mg/day group was statistically significantly decreased (LS mean, –5.2 [P = 0.0183]) compared with the placebo group (LS mean,–1.4) at Visit 8. For the emotional well being and communication dimensions, decreases in mean scores from Baseline were observed at all visits for all 3 treatment groups. At Visit 8, the mean change from Baseline in emotional well being scores for the safinamide 100 mg/day group was statistically significantly decreased (LS mean, –5.0 [P = 0.0090]). The mean change from Baseline in communication scores for the safinamide 100 mg/day group was statistically significantly decreased (LS mean, –4.3 [P = 0.0375]) compared with the placebo group (LS mean, –1.0) at Visit 8. For the bodily discomfort dimension, the placebo group exhibited a small increase from Baseline in mean scores over time (LS mean, 0.7). Similarly, the safinamide 50 mg/day group had a small increase in mean scores over time (LS mean, 0.9). For the safinamide 100 mg/day group, the mean scores for the bodily discomfort dimension were statistically significantly decreased over time compared with the placebo group (LS mean, –3.4 [P = 0.0085]) at Visit 8. For the mobility, stigma, and social support and cognition dimensions, the safinamide 50 mg/day and safinamide 100 mg/day treatment groups were not statistically significantly different from the placebo group.

An ad hoc analysis of the total PDQ-39 scores, performed using ANCOVA, showed that decreases in total mean PDQ-39 scores from Baseline were observed at all visits for all 3 treatment groups. The mean change from Baseline in total scores for the safinamide 100 mg/day group was statistically significantly decreased (LS mean, –28.4 [*P* = 0.0267]) at Visit 8 compared with the placebo group (LS mean, –11.0), whereas the safinamide 50 mg/day group (LS mean, –19.0 [*P* = 0.3103]) was not statistically significantly different from placebo.

Results of the ad-hoc analysis of the UPDRS Section 4 (complications of therapy) items 32–34, which assess the duration, disability, and pain of dyskinesias, revealed no statistically significant difference between the safinamide 50 mg/day group versus the placebo group and the safinamide 100 mg/day group versus the placebo group; however, an ad-hoc analysis of the subgroup of patients from India showed a statistically significant mean change (P = 0.0045) from Baseline in the UPDRS Section 4 scores in the safinamide 100 mg/day group compared with the placebo group.

An ad-hoc analysis of patients who had a ≥ 30-minute improvement in *on* time, *off* time, and *on* time plus *off* time revealed a statistically significantly higher percentage of patients in the safinamide 50 mg/day group (60.99%; *P* = 0.0060) and the safinamide 100 mg/day group (63.39%; *P* = 0.0009) had ≥ 30-minute improvement in *on* time than the placebo group (49.55%). Although a higher percentage of patients in the safinamide 50 mg/day group (65.92%) and the safinamide 100 mg/day group (65.18%) had a ≥ 30-minute improvement in *off* time compared with the placebo group, the difference between the safinamide 100 mg/day group versus the placebo group (*P* = 0.0657) and the safinamide 50 mg/day group versus the placebo group (*P* = 0.0883) was not statistically significant. A statistically significantly higher percentage of patients in the safinamide 50 mg/day group (54.26%; *P* = 0.0244) and the safinamide 100 mg/day group (55.80%; *P* = 0.0068) had ≥ 30-minute improvement in *on* time plus *off* time compared with the placebo group (45.05%).

Patients who had a ≥ 30-minute improvement in *on* time and *on* time plus *off* time, with no increase in troublesome dyskinesia, were further summarized. Improvement in *on* time with no increase in troublesome dyskinesia was statistically significantly higher in the safinamide 100 mg/day group (55.8%; *P* < 0.0001) than in the placebo group (39.6%). Additionally, an improvement in *on* time and *off* time with no increase in troublesome dyskinesia was statistically significantly higher in the safinamide 100 mg/day group (52.2%; *P* = 0.0008) than in the placebo group (39.2%).

For the subgroup of patients from India, an ad-hoc analysis of the total daily *on* time with troublesome

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dyskinesia showed no statistically significant difference among the treatment groups in mean total daily *on* time with troublesome dyskinesia for the subgroup of patients from India.

Additional ad-hoc analyses were performed on the change from Baseline in various diary times (*on* time, *on* time with minor dyskinesia, *on* time plus *on* time with minor dyskinesia, *off* time, *on* time with troublesome dyskinesia, and asleep time) by patients' PD medication at Baseline. The following subgroups of patients were analyzed (patients receiving only levodopa alone (N = 87); patients receiving only levodopa and Comtan (N = 30); patients receiving only levodopa and Comtan or Stalevo (N = 46); patients receiving only levodopa, Comtan or Stalevo, and DA agonists (N = 126); patients receiving only levodopa, Comtan or Stalevo, DA agonists, and anticholinergics (N = 29); patients receiving amantadine (N = 80); and patients not receiving amantadine (N = 589).

Of the 87 patients (25 on placebo, 37 on safinamide 50 mg/day, and 25 on safinamide 100 mg/day) who were receiving only levodopa alone, the change from Baseline to Visit 8 (Week 24) in *on* time was statistically significantly different for the safinamide 50 mg/day group (difference in LS means, 1.3 hours; $P = 0.0475$) and the safinamide 100 mg/day group (difference in LS means, 1.5 hours; $P = 0.0412$) compared with the placebo group; the *on* time plus *on* time with minor dyskinesias was statistically significantly different for the safinamide 50 mg/day group (difference in LS means, 1.7 hours; $P = 0.0183$) compared with the placebo group; and the *off* time was statistically significantly different for the safinamide 50 mg/day group (difference in LS means, –1.2 hours; $P = 0.0386$) compared with the placebo group.

There were no statistically significant differences among the treatment groups in the subgroup of patients receiving only levodopa and Comtan (entacapone) (a total of 30 patients) for any diary time.

For those 46 patients (14 on placebo, 8 on safinamide 50 mg/day, and 24 on safinamide 100 mg/day) receiving only levodopa and Comtan (entacapone) or Stalevo (carbidopa + levodopa + entacapone), the change from Baseline to Visit 8 (Week 24) in *off* time was statistically significantly different for the safinamide 100 mg/day group compared with the placebo group (difference in LS means, –1.9 hours; $P = 0.0348$).

For those 126 patients receiving only levodopa and Comtan or Stalevo, and DA agonists, the change from Baseline to Visit 8 (Week 24) in *off* time was statistically significantly different for the safinamide 50 mg/day group (difference in LS means, –1.1 hours; $P = 0.0176$) and the safinamide 100 mg/day group (difference in LS means, –1.4 hours; $P = 0.0154$) compared with the placebo group.

For those 29 patients receiving only levodopa, Comtan or Stalevo, DA agonists, and anticholinergics, the change from Baseline to Visit 8 (Week 24) in *off* time was statistically significantly different for the safinamide 50 mg/day group compared with the placebo group (difference in LS means, –2.7 hours; $P = 0.0259$).

For those 80 patients receiving levodopa and amantadine, the change from Baseline to Visit 8 (Week 24) in *on* time with minor dyskinesia was statistically significantly different for the safinamide 100 mg/day group compared with the placebo group (difference in LS means, –1.6 hours; $P = 0.0283$).

Of the 589 patients (196 on placebo, 196 on safinamide 50 mg/day, and 197 on safinamide 100 mg/day) receiving levodopa but not amantadine, the change from Baseline to Visit 8 (Week 24) in *on* time was statistically significantly different for the safinamide 50 mg/day group (difference in LS means, 0.6 hours; $P = 0.0175$) and the safinamide 100 mg/day group (difference in LS means, 0.7 hours; $P = 0.0077$) compared with the placebo group; the *on* time plus *on* time with minor dyskinesias was statistically significantly different for the safinamide 50 mg/day group (difference in LS means, 0.6 hours; $P = 0.0051$) and the safinamide 100 mg/day group (difference in LS means, 0.7 hours; $P = 0.0016$) compared with the placebo group; and the *off* time was statistically significantly different for the safinamide 50 mg/day group (difference in LS means, –1.3 hours; $P = 0.0029$) and the safinamide 100 mg/day group (difference in LS means, –1.3 hours; $P = 0.0027$) compared with the placebo group.

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An ad-hoc analysis of mean daily *on* time plus *on* time with minor dyskinesia, by whether or not the patient changed dopaminergic medication within 60 days of randomization, showed that for the approximately 88% of patients who had no change in their dopaminergic medication within 60 days of randomization, there was a statistically significant difference in mean daily *on* time plus *on* time with minor dyskinesia between the safinamide 50 mg/day group and the placebo group (difference in LS means, 0.5 hours; $P = 0.0292$) and between the safinamide 100 mg/day group and the placebo group (difference in LS means, 0.7 hours; $P = 0.0033$). For the approximately 12% of patients who had a change in their dopaminergic medication within 60 days of randomization, the safinamide 50 mg/day group was statistically significantly different compared with the placebo group (difference in LS means, 1.7 hours; $P = 0.0431$) with regard to mean daily *on* time plus *on* time with minor dyskinesia.

Overall, 80.6% (539 of 669) of patients were from India, 15.8% (106 of 669) were from Romania, and 3.6% (24 of 669) were from Italy.

For the subgroups of patients from India and Romania, the 3 treatment groups were generally similar with respect to the demographic variables (age, sex, ethnicity group, race, height, and weight). For the subgroup of patients from Italy, the placebo, safinamide 50 mg/day, and safinamide 100 mg/day groups were dissimilar with regard to age (median, 64 years, 71 years, and 60 years, respectively); gender (male:female, 5:2, 1:8, and 5:3, respectively), ethnicity group (hispanic:nonhispanic, 0:7, 3:6, and 2:6, respectively); height (mean, 167.71 cm, 162.11 cm, and 170.75 cm, respectively), and weight (mean, 77.67 kg, 60.56 kg, and 78.13 kg, respectively). These disparities are most likely due to the small number of patients from Italy.

Among the 3 treatment groups, disposition by country was generally similar.

For the subgroup of patients from India, compared with the placebo group, the mean change from Baseline in *on* time plus *on* time with minor dyskinesia was statistically significantly increased in the safinamide 50 mg/day (difference in LS means, 0.6 hours; $P = 0.0075$) and safinamide 100 mg/day (difference in LS means, 0.6 hours; $P = 0.0066$) groups; mean change from Baseline in *off* time was statistically significantly decreased in the safinamide 50 mg/day (difference in LS means, –0.6 hours; $P = 0.0063$) and safinamide 100 mg/day (difference in LS means, –0.5 hours; $P = 0.0138$) groups; and mean change from Baseline in UPDRS Section 3 (motor examination) scores were statistically significantly decreased in the safinamide 100 mg/day group (difference in LS means, –2.6; $P = 0.0025$).

Furthermore, for the subgroup of patients from India, the percentage of patients on levodopa alone, levodopa plus Stalevo, levodopa and DA agonists, and levodopa and other anticholinergics were generally similar among the 3 treatment groups.

For the subgroup of patients from Romania, the mean change from Baseline in UPDRS Section 3 scores was statistically decreased in the safinamide 50 mg/day (difference in LS means, –4.9; $P = 0.0042$) and safinamide 100 mg/day (difference in LS means, –3.7; $P = 0.0295$) groups compared with the placebo group.

For the subgroup of patients from Italy, the mean change from Baseline in *off* time was statistically decreased in the safinamide 100 mg/day group (difference in LS means, –2.8 hours; $P = 0.0357$) compared with the placebo group.

Results of the additional exploratory analyses were consistent with the initial findings.

SAFETY RESULTS

Overall, 448 of 669 (67.0%) patients experienced TEAEs, and the percentage of patients with 1 or more TEAE was generally similar among the 3 groups (67.6% of patients in the placebo group, 66.8% of patients in the safinamide 50 mg/day group, and 66.5% of patients in the safinamide 100 mg/day group). The most commonly reported TEAEs that occurred in > 5.0% of patients in any treatment group were cataract, back pain, dyskinesia,

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headache, and worsening of PD. Except for dyskinesia, these AEs occurred in a similar or higher percentage of patients in the placebo group than in both safinamide treatment groups. Dyskinesia, the most frequently reported TEAE, occurred more frequently in patients in the safinamide 50 mg/day group (20.6%) compared with the safinamide 100 mg/day group (17.9%) and the placebo group (12.2%). The results of an ad hoc analysis showed that, of the approximately 12% of patients in each treatment group who were using amantadine at Baseline, a higher percentage of patients in the safinamide 100 mg/day (33.3% [9 of 27]) and safinamide 50 mg/day (25.9% [7 of 27]) treatment groups experienced dyskinesia TEAEs compared with the placebo (19.2% [5 of 26]) group.

A similar percentage of patients in the placebo (7.7%) and safinamide 100 mg/day groups (7.1%) reported severe TEAEs, whereas a slightly lower percentage of patients in the safinamide 50 mg/day group (4.0%) reported severe TEAEs. A total of 79 nonlaboratory SAEs (29 in the placebo group, 13 in the safinamide 50 mg/day group, and 37 in the safinamide 100 mg/day group) were reported during the study. No specific pattern of occurrence of SAEs was observed. Overall, a statistically significantly lower percentage of patients ($P = 0.0139$) in the safinamide 50 mg/day group (3.1%) experienced an SAE, but a similar percentage of patients in the safinamide 100 mg/day group (9.8%) experienced an SAE, compared with the placebo group (8.1%).

Overall, 39 patients withdrew from the study due to TEAEs. The treatment groups were generally similar with regard to the percentage of patients who withdrew from the study due to TEAEs: 5.0% of patients withdrew due to TEAEs in the placebo group, 4.9% of patients in the safinamide 50 mg/day group, and 7.6% of patients in the safinamide 100 mg/day group.

Six deaths were reported during the study, none of which were considered to be related to the study drug.

The 3 treatment groups were generally similar with regard to hematology parameters, renal and liver function tests, biochemistry analytes, and urinalysis parameters. The frequency of individual changes in clinical laboratory test results was similar among the treatment groups. Overall, 36.9% of patients in the placebo group, 36.8% of patients in the safinamide 50 mg/day group, and 28.6% of patients in the safinamide 100 mg/day group had at least 1 clinically notable laboratory value throughout the study.

Across the treatment groups, there were minimal changes from Baseline in vital signs data at Visit 8. Except for weight, there were few clinically notable changes in vital sign data at any visit. The percentage of patients with a clinically notable change in weight increased with each visit across the treatment groups: at Visit 8 (Week 24) or endpoint, 9.5% of patients in the placebo group, 7.6% of patients in the safinamide 50 mg/day group, and 12.1% of patients in the safinamide 100 mg/day group had a clinically notable change from Baseline in weight.

Physical and dermatological examination results were similar across treatment groups at Baseline and at Visit 8 (Week 24). For all 3 treatment groups, there was a reduction in neurological findings (ie, tremor at rest, bradykinesia, rigidity, gait abnormalities, balance impairment, handwriting impairment, end-of-dose wearing off phenomenon, on-off phenomena, dyskinesia, motor fluctuations, hypomimic facial expression, and other signs) at Visit 8 (Week 24) compared with Baseline.

With regard to ESS total scores, for the safinamide 50 mg/day and safinamide 100 mg/day groups, the mean ESS total scores decreased slightly at each subsequent visit, whereas for the placebo group the mean ESS total score decreased at Visit 6 (Week 12) and then increased slightly at Visit 8 (Week 24).

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**CONCLUSION:**

- Safinamide at doses of 50 mg/day and 100 mg/day effectively increased total daily *on* time compared with placebo in patients with idiopathic PD with motor fluctuations, who were receiving a stable dose of levodopa.
- Over the 24-week study, safinamide 100 mg/day exhibited statistically significant reductions in total daily *off* time, UPDRS Section 2 (ADL) scores, UPDRS Section 3 (motor examination) scores, CGI-S scores, levodopa dose, GRID-HAMD-17 scores, and total PDQ-39 and bodily discomfort dimension scores.
- Over the 24-week study, safinamide 50 mg/day exhibited statistically significant reductions in total daily *off* time, UPDRS Section 3 (motor examination) scores, and CGI-S scores.
- In patients with idiopathic PD with motor fluctuations, who were receiving a stable dose of levodopa, safinamide at doses of 50 mg/day and 100 mg/day, improved symptoms of PD including ADL and motor symptoms (as measured by the UPDRS), patient's health status and QOL (as measured by the PDQ-39), severity of depression symptoms (as measured by the GRID-HAMD-17), and mental status (as measured by the CGI).
- Apart from dyskinesia, which occurred more frequently in patients in both safinamide groups, no major safety concerns have been identified. There were no significant findings with regard to tolerability of safinamide in this study.
- Considering the benefits seen with safinamide across numerous variables in patients with PD, and the low number of observed AEs, the benefits outweigh the risks of treatment with safinamide 50 mg/day and 100 mg/day.

**DATE OF THE REPORT:**

20 May 2010 FINAL

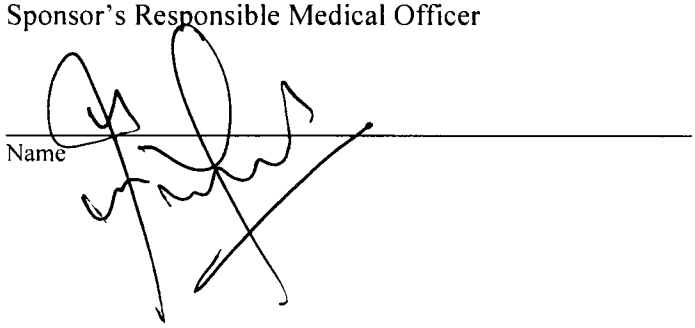
## Appendix 16.1.5
## Signature of Responsible Medical Officer

**Study Number:** NW-1015/016/III/2006

**Study Title:** A Phase III, Double-Blind, Placebo-Controlled Study to Determine the Efficacy and Safety of a Low (50 mg/Day) and High (100 mg/Day) Dose of Safinamide, as Add-On Therapy, in Patients with Idiopathic Parkinson's Disease with Motor Fluctuations, Treated with a Stable Dose of Levodopa and Who May Be Receiving Concomitant Treatment with Stable Doses of a Dopamine Agonist, and/or an Anticholinergic

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Sponsor's Responsible Medical Officer



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May 27th, 2010.

Date