2. SYNOPSIS

Name of Sponsor/Company: Newron Pharmaceuticals SpA		*(For National Authority Use Only)*
Name of Finished Product: Safinamide		
Name of Active Ingredient: Safinamide		
Title of Study: A Phase III, Double-Blind, Placebo-controlled, Randomized Trial 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 Subjects with Early Idiopathic Parkinson's Disease Treated with a Stable Dose of a Single Dopamine Agonist		
Study Number: 27918		
Investigators: See Appendix 16.1.3.		
Study Centers: The study was conducted at 112 study centers in 20 countries: 8 in India, 6 in Bulgaria, 4 in Croatia, 5 in Czech Republic, 1 in Poland, 7 in Slovakia, 3 in Finland, 4 in Germany, 9 in Italy, 1 in Portugal, 5 in South Africa, 6 in Spain, 9 in Argentina, 3 in Brazil, 3 in Chile, 3 in Colombia, 4 in Mexico, 3 in Peru, 5 in Canada, and 23 in the United States.		
Publication (Reference): There were no publications based on this study.		
Study Period (Date First Subject Screened—Date Last Subject Completed Last Observation): 27 MAR 2009 – 23 JAN 2012	**Study Phase of Development:** III	
Objectives: The objectives of this trial were to evaluate the safety and efficacy of two doses of safinamide (50 and 100 mg daily [p.o.] every morning [q.a.m.]), compared with placebo, as add-on therapy in subjects with early idiopathic Parkinson's disease (PD) who were receiving a stable dose of a single dopamine agonist (DA). ***Primary*** Evaluate the changes from Baseline to Week 24 in motor symptoms (Unified Parkinson's Disease Rating Scale [UPDRS] Section III). ***Secondary*** Evaluate the changes from Baseline to Week 24 in activities of daily living, cognition, change in global clinical status, responder rates with regard to motor symptoms, and health related quality of life. ***Safety*** The safety of two doses of safinamide (50 and 100 mg p.o. q.a.m.) compared with placebo was assessed through: incidence of treatment-emergent adverse events (TEAEs) and clinically significant changes in laboratory safety tests, electrocardiogram (ECG) morphology, vital signs with a special emphasis on blood pressure (BP) monitoring, ophthalmologic and dermatological examinations, impulse control disorders, and level of daytime sleepiness.		

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Methods:

This was a double-blind, placebo-controlled, parallel-group, randomized, multicenter, multinational, Phase III trial, comparing two doses of safinamide (50 and 100 mg p.o. q.a.m.) versus placebo as add-on therapy to a stable dose of a single DA in subjects with early idiopathic PD. Subjects who met the entry criteria at Baseline were randomized (1:1:1) to receive one of the two doses of safinamide or placebo. Subjects returned for regularly scheduled visits at Weeks 2, 4, 8, 12, 18, and 24 (or at early discontinuation). Subjects who needed an increase in their anti-Parkinsonian treatments prior to Week 24 were requested to undergo all Week 24 assessments prior to the intervention and to return for all scheduled assessments up to Week 24. The trial duration was 24 weeks in the double-blind treatment phase, followed by a one-week taper phase before discontinuing treatment. Subjects may have entered an 18-month extension trial for continuing treatment. The total duration of the trial was approximately 30.5 weeks, including the Screening period (10 days), the treatment period (24 weeks), a one-week taper phase, and a safety follow-up phase (4 weeks). Subjects not entering the 18-month extension trial entered the one-week taper phase before discontinuing treatment. This period allowed for a gradual reduction in the subject's dose of study medication to minimize the possibility of any potential withdrawal effects. Subjects who continued treatment in the extension trial did not have their dose tapered prior to entry into the trial.

Number of Subjects (Planned and Analyzed):

It was planned that at least 740 subjects would need to be screened to identify at least 666 randomized subjects (i.., 222 subjects in each treatment group) to result in a total of 498 evaluable subjects (i.e., 166 evaluable subjects in each treatment group) were planned for enrollment to provide at least 90% power to detect a clinically meaningful difference of 2.5 points in the primary parameter, the UPDRS Section III score change from Baseline to Week 24, between the safinamide and placebo treatment groups. These calculations were performed using a two-sided two-sample *t* test assuming the following: a common standard deviation of seven points; a type I error rate of 5%; and a 25% nonevaluable/dropout rate. Treatment difference and standard deviation estimates used in these sample size computations considered previous results obtained in the safinamide Study 015. Subjects were randomized in a 1:1:1 ratio to safinamide 50 mg/day, safinamide 100 mg/day, or placebo.

A total of 871 subjects were screened; 192 (22.0%) were considered screening failures. Overall, 679 were randomized to treatment (227 to safinamide 50 mg/day; 227 to safinamide 100 mg/day; and 225 to placebo), and 610 completed the study. A total of 679 subjects comprised the Intent-to-Treat (ITT) population, and 678 comprised the Safety population.

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Diagnosis and Main Criteria for Inclusion:

Males and females (not of childbearing potential), 30 to 80 years of age (inclusive), with a diagnosis of idiopathic PD (based on medical history and neurological examination) of less than five years' duration and a Hoehn and Yahr Stage of I–III, who provided informed consent in writing, were eligible for the study. Subjects with other forms of PD, as well as those experiencing end-of-dose wearing off, disabling dyskinesia, or widely swinging fluctuations were excluded. Subjects with a current diagnosis of clinically significant gastrointestinal, renal, hepatic, endocrine, pulmonary, or cardiovascular disease, including acute gastric ulcer; hypertension that is not well-controlled; cardiac conditions (eg, uncontrolled atrial fibrillation, recent myocardial infarction), asthma, chronic obstructive pulmonary disease (COPD), and type I diabetes were not eligible. Subjects with a current diagnosis of human immunodeficiency virus (HIV) or hepatitis B or C (HBV/HCV) infection, clinically significant abnormal findings on laboratory tests, ECG or physical examination, a recent neoplastic disorder, or signs/symptoms of transmissible spongiform encephalopathy were excluded.

Subjects with a history of hypersensitivity to drugs similar to safinamide, as well as those taking any of the following medications, were excluded: drugs influencing absorption, metabolism or excretion of safinamide, monoamine oxidase (MAO) inhibitors, investigational drugs (within 30 days/five half-lives), PD medications other than a single dopamine agonist, opioids, serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), depot neuroleptics, or drugs with hepatotoxic or cytotoxic potential. A current/recent history of drug/alcohol abuse, psychosis, dementia, or depression was also exclusionary. Subjects with a history or current diagnosis of retinal disease or severe diminution of visual acuity were excluded.

Test Product, Dose and Mode of Administration, Batch/Lot Numbers:

Test product: Safinamide

Route and mode of administration: Oral

Dose and dosage schedule:

Safinamide 50 mg/day (small – 7 mm): two tablets (one small safinamide tablet and one large placebo tablet) once per day in the morning with breakfast/Taper Phase: two placebo tablets (one small tablet and one large tablet) once per day

Safinamide 100 mg/day (large – 9 mm): two tablets (one small placebo tablet and one large safinamide tablet) once per day in the morning with breakfast/Taper Phase: 50 mg/day (one small safinamide tablet and one large placebo tablet) once per day

Batch/Lot Numbers: 012894 (safinamide, 100 mg), 013634 (safinamide, 100 mg), 014054 (safinamide, 100 mg), 014053 (safinamide, 50 mg), 012893 (safinamide, 50 mg), 013633 (safinamide, 50 mg)

Duration of Treatment:

24 weeks plus a seven-day taper phase before treatment discontinuation and an optional 18-month, double-blind extension trial, provided that eligibility criteria were met.

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Reference Products, Dose, Mode of Administration, Batch/Lot Numbers:

Reference product: Placebo

Route and mode of administration: Oral

Dose and dosage schedule:

Placebo: two tablets (one small tablet and one large tablet) once per day in the morning with breakfast/Taper Phase: two placebo tablets once per day (one small tablet and one large tablet)

Batch/Lot Numbers: 013631 (placebo, 100 mg), 013632 (placebo, 100 mg), 013629 (placebo, 50 mg), 013630 (placebo, 50 mg), 012895 (placebo, 100 mg), 012948 (placebo, 50 mg),

Criteria for Evaluation:

Efficacy:

The primary efficacy parameter was the UPDRS Section III score change from Baseline to Week 24.

The key secondary efficacy parameters were UPDRS Section II activities of daily living (ADL) score change from Baseline to Week 24; Proportion of subjects with scores 1, 2, or 3 (showing improvement) on the Clinical Global Impression change scale (CGI-C) score at Week 24; Parkinson's Disease Questionnaire (PDQ)-39 score change from Baseline to Week 24; Cogtest® PD Battery test (Strategic Target Detection Test [STDT] and Auditory Numbering Sequence [ANS]) score change from Baseline to Week 24. Other secondary efficacy parameters were Clinical Global Impression severity scale (CGI-S) score at Week 24; CGI-S score change from Baseline to Week 24; Proportion of responders (subjects with at least 30% improvement on the UPDRS Section III score change from Baseline to Week 24); Patients' Global Impression of Change (PGIC) scale score at Week 24; Euro-QoL 5D (EQ-5D) score change from Baseline to Week 24; Cogtest® PD Battery test (Spatial Working Memory [SWM], Continuous Performance Test [CPT] Flanker version, and Tower of London [TOL]) score change from Baseline to Week 24.

The tertiary efficacy parameters were Hoehn and Yahr Staging score change from Baseline to Week 24; GRID-HAM-D (17-item) score change from Baseline to Week 24; MMSE score change from Baseline to Week 24; UPDRS Section IV score change from Baseline to Week 24; UPDRS Section I score change from Baseline to Week 24; Health Resource Utilization parameters.

Criteria for Evaluation:

Safety:

Safety was assessed through incidences of TEAEs and clinically significant changes in laboratory safety tests, ECG morphology, vital signs with a special emphasis on BP monitoring, physical, neurological, ophthalmological and dermatological examinations, impulse control disorders, and level of daytime sleepiness.

Adverse Events (AE): The incidence and frequency of AEs were summarized by Medical Dictionary for Regulatory Activities (MedDRA) Version 13.0, system organ class (SOC) and preferred term (PT). Treatment-emergent adverse events were defined as AEs that started on or after the first dose of the study medication or AEs that started before the first dose of study medication, but worsened after the start of the study medication. The incidence and frequency of all TEAEs were summarized by SOC and preferred term. All TEAEs were summarized by severity and by relationship to treatment. Serious TEAEs were summarized by SOC and preferred term. Time from the first dose of the study medication to the first occurrence of any serious adverse events (SAEs) was summarized. Time from the first dose of the study medication to the first occurrence of any SAEs or TEAEs leading to premature discontinuation also was summarized. All AEs of special interest were prespecified and summarized.

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Statistical Methods:

Demographic and Other Subject Characteristics: Demographic data (e.g., age, gender, race) and disease characteristics were the last recorded data prior to the first administration of randomized treatment. These data were summarized by treatment group and overall using descriptive statistics.

Statistical analyses (efficacy and safety) were carried out using SAS software 8.2 or higher (SAS Institute, Inc., USA). Continuous variables were summarized by descriptive statistics (number of subjects, mean, standard deviation (SD), minimum, median, and maximum). Categorical data were presented by number of subjects (n) and relative frequencies (%).

If not otherwise specified, Baseline value was defined as the last available measurement before the first dose of study medication (at Visit 2/Baseline).

Efficacy Evaluations:

Primary Efficacy Analysis:

The primary efficacy parameter was the UPDRS Section III score change from Baseline to Week 24.

The primary analysis of the primary endpoint (UPDRS Section III score) was performed for confirmatory testing based on the ITT population using the On-Treatment Approach (i.., approach in which only the On-Treatment efficacy data were used for analysis). This primary endpoint was analyzed using an analysis of covariance (ANCOVA) model on the change from Baseline to Week 24, with fixed effects of treatment and region and the Baseline value of the UPDRS Section III score as the covariate. Regions were defined in the statistical analysis plan. Treatment-group comparisons were based on evaluating the differences in Type III least-squares (LS) mean changes from the ANCOVA main model.

A hierarchical procedure was used for the comparison of the primary parameter between each safinamide dose to placebo. First, the safinamide 100-mg/day dose was compared with placebo. If this comparison was statistically significant, then the safinamide 50-mg/day dose was compared with placebo; otherwise, the comparison of the safinamide 50-mg/day dose to placebo was not performed.

The treatment-by-region interaction and treatment-by-Baseline interaction were evaluated. If the interaction was statistically significant ($p < 0.1$), then further sensitivity analysis using a nonparametric ANCOVA main model was conducted and reported.

Secondary Efficacy Analyses:

The key secondary efficacy endpoints were:

- UPDRS Section II (ADL) score change from Baseline to Week 24
- Proportion of subjects with scores 1, 2, or 3 (showing improvement) on the CGI change scale at Week 24
- PDQ-39 score change from Baseline to Week 24
- Cogtest® PD Battery test score change from Baseline to Week 24 (STDT and ANS)

Testing of the key secondary efficacy analyses was performed in a hierarchical fashion – both across the secondary parameters and for the treatment tests within each secondary parameter. Testing was performed in the above prespecified order with all parameters tested sequentially first for safinamide 100 mg/day versus placebo and then for safinamide 50 mg/day versus placebo once all parameters completed the 100-mg/day test successfully. The test for the next parameter/dose was only to proceed if the test for the preceding parameter was significant. The Cogtest® PD Battery for both safinamide doses was tested only after completing testing for both groups for the other

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parameters.

The hierarchical order of the secondary parameters was specified in the prospective statistical analysis plan prior to unblinding the treatment groups.

The same ANCOVA model used for the primary efficacy parameter was used for the continuous secondary clinical parameters using the Baseline value of the parameter to be analyzed as a single covariate. If parametric model assumptions were not met, then the data at Baseline and Week 24 were ranked, and a nonparametric ANCOVA on ranked data using the same model as that for the primary efficacy parameter was performed.

The proportion of subjects with scores 1, 2, or 3 on the CGI-C/PGIC scales was analyzed using a logistic regression model with treatment and region effects.

Exploratory secondary efficacy parameters included:

- CGI change scale score at Week 24
- CGI severity scale score change from Baseline to Week 24
- Proportion of responders (subjects with at least 30% improvement on the UPDRS Section III score change from Baseline to Week 24)
- PGIC scale score at Week 24
- EQ-5D score change from Baseline to Week 24
- Cogtest® PD Battery test score change from Baseline to Week 24 (SWM, CPT, and TOL)

These parameters were analyzed using the same methodology as the key secondary efficacy parameters.

The quality-of-life parameters were analyzed by a third party with statistical methodology described in a separate analysis plan.

Tertiary Efficacy Analyses:

The tertiary efficacy parameters were:

- Hoehn and Yahr Staging score change from Baseline to Week 24
- GRID-HAM-D (17-item) score change from Baseline to Week 24
- UPDRS Section IV score change from Baseline to Week 24
- UPDRS Section I score change from Baseline to Week 24
- MMSE score change from Baseline to Week 24
- Health Resource Utilization parameters

The same ANCOVA model used for the analysis of the primary and continuous secondary efficacy parameters were used for the tertiary parameters, using the Baseline value of each parameter to be analyzed as a single covariate.

The health resource utilization parameters were analyzed by a third party with statistical methodology described in a separate analysis plan.

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Safety Evaluations:

Safety data analyses were based on the Safety Population. Descriptive summaries by treatment group were presented for all safety data.

Adverse Events: Incidence and frequency of AEs were summarized by system organ class and preferred term. The incidence of all individual TEAEs, including TEAEs leading to discontinuation and SAEs, were analyzed using the Fisher exact method, with p value presented for exploratory purposes. The most common TEAEs occurring in at least 1% of subjects in any treatment group were summarized by preferred term and sorted by the overall unique subject count by most-frequent preferred term. Other TEAEs (not including SAEs) reported in at least 5% of subjects in any treatment group were summarized by SOC and preferred term.

Time from the first dose of study medication to the first occurrence of any TEAE, SAE, death, and TEAE leading to premature discontinuation from the study were summarized. Time from the first dose of the study medication to the first occurrence of each individual TEAE for those TEAEs reported in at least 5% of subjects in any treatment group was summarized. Percentiles of the time to event were estimated from Kaplan-Meier survival curves. Incidence and frequency of the total TEAEs and individual TEAEs reported in at least 2% of subjects in any treatment group were summarized by the following Baseline characteristics, respectively: age group (<65 years, ≥65 years and ≤ 74 years, ≥75 years); gender; weight (≤ median, > median); body mass index (BMI), by World Health Organization (WHO) International Classification of Adult BMI (Underweight: <18.50, Normal range: 18.50-24.99, Overweight: 25.00-29.99, Obese: ≥30.00).

Clinical Laboratory Evaluation: Clinical laboratory samples (hematology, chemistry, and urinalysis) were collected at the visits specified in the schedule of evaluations, and evaluated in the central laboratories.

The following data analyses were performed: summary statistics (number of subjects, mean, standard deviation (SD), minimum, median, and maximum), divided into hematology, biochemistry, and urinalysis (for continuous variables) for each visit and the absolute change from Baseline to each of the visits.

Incidences of clinically significant laboratory results were presented by visit. Shift tables were presented between Baseline and Endpoint (worst observation carried forward; WOCF) by Low, Normal, and High relative to the laboratory normal range. Shift tables were presented between Baseline and endpoint (WOCF) by combining the criteria of clinical significance (CS) and the laboratory normal ranges into the categories of Low (CS), Low (non-CS), Normal, High (non-CS), and High (CS) relative to the laboratory normal range. Specifically:

- Low (CS): below the normal range and further below the clinically significant criteria.
- Low (non-CS): below the normal range but not below the clinically significant criteria.
- Normal: within normal range.
- High (non-CS): above the normal range but not above the clinically significant criteria.
- High (CS): above the normal range and further above the clinically significant criteria.

Vital Signs: Vital signs were presented descriptively for each vital sign measurement for Baseline (before study medication administration) and the change from Baseline to endpoint for the Safety Population. An endpoint (last observation carried forward; LOCF) at Week 24 for vital signs parameters was defined as the last post-Baseline observation on study, including any unscheduled visits. The endpoint (LOCF) was used in summary statistics. If a Baseline value was missing, then change from Baseline was considered as missing.

Other Safety Parameters: Ambulatory blood-pressure monitoring (ABPM) was performed during the trial, but the protocol did not impose dietary restrictions with regard to tyramine-containing foods on subjects.

Analysis of ECGs was performed at the visits specified in the schedule of evaluations to evaluate QT and QTc outliers and any safinamide-related QT and/or QTc prolongation or shortening in subjects with early idiopathic

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Parkinson's disease, to evaluate treatment-emergent morphological abnormalities including CS arrhythmias and other rhythm problems, conduction abnormalities, and any evidence of myocardial ischemia or infarction, and to evaluate effect of safinamide on PR interval, QRS duration, and other ECG intervals.

Ophthalmologic analysis was performed to detect and assess the safety signal of clinical concern using data from the ophthalmologic examinations. The main analysis was the incidence of clinically significant worsening as assessed by the central reviewer. The difference in the incidence of clinically significant worsening from central review was assessed by a categorical method.

Physical, neurological, and dermatological examinations were collected at Baseline and Week 24. Each examination was analyzed by a shift table between Baseline and Week 24 on the Safety population.

The Epworth Sleepiness Scale (ESS), an 8-item subject-rated assessment of the subject's level of daytime sleepiness with items rated on a 4-point scale, scores were collected at Baseline, Week 12, and Week 24. A score of 0 indicated that the subject would never doze or sleep during the activity. A score of 1, 2, or 3 indicated a slight, moderate, or high chance of dozing or sleeping, respectively.

The Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease (QUIP), a self-administered questionnaire (full version) specifically designed to identify current impulsive-compulsive behaviors in Parkinson's disease, scores were collected at Baseline, Week 12, and Week 24. Each question was rated by a response of "Yes," "No," or "Not Answered."

SUMMARY—CONCLUSIONS

EFFICACY RESULTS

Primary Efficacy Endpoint

At Week 24, the safinamide 100-mg/day group had a mean (SD) change in score on the UPDRS III of –1.96 (5.53), the safinamide 50-mg/day group had a mean (SD) change in score of –1.95 (7.35), and the placebo group had a mean (SD) change in score of –1.10 (6.17). The LS mean (SE) difference between the safinamide and placebo groups was –1.04 (0.58) for the 100-mg/day dose and –0.65 (0.58) for the 50-mg/day dose, indicating greater improvement in motor symptoms with safinamide. Using a parametric ANCOVA model, ITT population, and On-Treatment Approach, a borderline statistically significant difference between the safinamide 100-mg/day group and the placebo group (LS mean difference = –1.04, p = 0.073) was observed, while there was no significant difference between the safinamide 50-mg/day treatment group and the placebo group (LS mean difference = –0.65, p = 0.259) in UPDRS Section III score change from Baseline to Week 24. Similar results were observed using the MMRM model, the ITT population, and the On-Treatment Approach. Additional analyses for the UPDRS III, requested by the FDA, using a modified ITT (FDA-mITT) population, defined as all treated patients with a baseline value and at least one post-baseline assessment, ANCOVA-LOCF and MMRM models, and an On-and-Off-Treatment Approach, showed results similar to the primary efficacy analysis.

In contrast to what was observed for the total ITT population, the analysis of the change from Baseline to Week 24 for the UPDRS III, which included only those subjects receiving DA-agonist monotherapy, showed a statistically significant (p = 0.0396) LS mean (SE) treatment difference of –1.20 (0.58) for the safinamide 100-mg/day group, compared with the placebo group. This indicates that inclusion of data from subjects who were not receiving monotherapy with a DA-agonist at Baseline and were in violation of the protocol may have adversely affected the primary efficacy analysis.

Secondary and Tertiary Endpoints

Additional analyses were performed for all secondary and tertiary endpoints. Statistical trends ($p < 0.10$) toward improvement in the safinamide 100-mg/day group compared with placebo were seen for the mean change from Baseline in the UPDRS Section II and the EQ-5D Index score, as well as for the safinamide 50-mg/day group versus

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placebo for any improvement in the CGI-C. The PDQ-39 summary index score was statistically significantly improved for the safinamide 100-mg/day group compared with the placebo group. No statistically significant improvements or trends were seen for either safinamide group compared with the placebo group for the Cogtest results, CGI-S, PGIC, Hoehn and Yahr, GRID-HAM-D, MMSE, UPDRS IV, and UPDRS I.

SAFETY RESULTS

A total of 468 subjects (69.0%) reported 1650 TEAEs. In the three treatment groups, the percentage of subjects with one or more TEAEs was similar among the groups: 66.4% of subjects (150 of 226) in the safinamide 50-mg/day group; 68.3% of subjects (155/227) in the safinamide 100-mg/day group; and 72.4% of subjects (163/225) in the placebo group.

The most common TEAEs that occurred in >5.0% of subjects in any treatment group were nausea, nasopharyngitis, arthralgia, back pain, dizziness, headache, and somnolence. The incidence of these common TEAEs did not indicate any dose-dependency or pattern of association with safinamide treatment.

A similar percentage of subjects in the safinamide 50-mg/day group (23.0% [52/226]), the safinamide 100- mg/day group (20.3% [46/227]), and the placebo group (24.9% [56/225]) reported moderate TEAEs. A slightly higher percentage of subjects in the safinamide 50-mg/day group (4.9% [11/226]) reported severe TEAEs compared with the safinamide 100-mg/day group (2.6% [6/227]) and the placebo group (3.6% [8/225]).

The incidence of prespecified ocular, cardiovascular, and hepatic TEAEs was low and did not indicate any dose-dependency or pattern of association with safinamide treatment.

Overall, the incidence of SAEs was low. In the safinamide 50-mg/day group, nine subjects (4.0%) experienced a total of 12 SAEs. In the safinamide 100-mg/day group, eight subjects (3.5%) experienced a total of 12 SAEs. In the placebo group, five subjects (2.2%) experienced a total of six SAEs ($p = 0.610$). There were no deaths in this study.

The percentage of subjects discontinuing from the study because of AEs was significantly lower ($p = 0.036$) in the safinamide 50-mg/day treatment group (three subjects [1.3%]) and the safinamide 100-mg/day treatment group (five subjects [2.2%]) than in the placebo group (12 subjects [5.3%]). These 20 subjects represented 2.9% of the total number of subjects.

Changes from Baseline and abnormal shifts in laboratory results, vital signs, physical findings, ESS, and QUIP were similar among all three treatment groups. Ophthalmological results were also similar among all three treatment groups, and no significant overall worsening was observed in the safinamide groups relative to the placebo group, as determined by a blinded central reviewer.

These data do not suggest any safety concerns with the use of safinamide at doses of 50- and 100-mg/day as add-on treatment in this population of early PD patients receiving treatment with a single dopamine agonist.

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CONCLUSION:

- The results for the primary efficacy measure showed that, at Week 24, the LS mean (SE) difference between the safinamide and placebo groups was –1.04 (0.58) for the 100-mg/day dose and –0.65 (0.58) for the 50-mg/day dose, indicating greater improvement in motor symptoms with safinamide. Using a parametric ANCOVA (LOCF) model, the ITT population, and On-Treatment data, there was a borderline statistically significant difference (p = 0.073) between the safinamide 100-mg/day group and the placebo group, but no significant difference (p = 0.259) between the safinamide 50-mg/day treatment group and the placebo group, in UPDRS Section III score change from Baseline to Week 24.
- However, an analysis of the primary efficacy measure for the DA-agonist mono-therapy population, which excluded data from 13 subjects that were not receiving mono-therapy with a DA-agonist at baseline, showed a statistically significant (p=0.0396) LS mean (SE) treatment difference of -1.20 (0.58) for the safinamide 100 mg/day group, compared to placebo. This indicates that inclusion of data from these 13 subjects may have adversely affected the primary efficacy analysis for the ITT population.
- Beneficial effects of safinamide on measures of activities of daily living and quality of life were also observed in both the ITT and DA-agonist monotherapy analysis populations.
- There was no significant difference among the three treatment groups in the incidence of TEAEs or SAEs, while a greater proportion of subjects in the placebo group, compared with the safimamide groups, discontinued treatment due to AEs.
- No clinically relevant pattern of adverse change associated with safinamide treatment was noted with regard to laboratory tests, vital signs, ECGs, or physical, neurological, dermatological, or ophthalmological examinations.
- Safinamide treatment was not associated with an increase in daytime sleepiness or impulsive-compulsive behavior.
- In summary, treatment with safinamide at doses of 50 and 100 mg/day was well tolerated in this population of early PD patients treated with a single DA-agonist. Improvements in motor symptoms as well as quality of life and functioning were observed with safinamide 100 mg/day.

DATE OF THE REPORT:

25 Oct 2013 Final v1.0