Clinical Study Report Synopsis

Clinical Study Title:	A phase III, double-blind, placebo-controlled extension trial to investigate the long-term efficacy and safety of low (50 mg/day) and high (100 mg/day) dose safinamide, as add-on therapy in subjects with early idiopathic Parkinson's disease treated with a stable dose of a single dopamine agonist
Name of Test Drug/ Investigational Product:	Safinamide
EudraCT Number:	2008-004146-88
Protocol Number:	27938
IND Number:	63,901
Indication Studied:	Early idiopathic Parkinson's disease
Study Design:	Double-blind, placebo-controlled extension trial
Comparison:	2 doses of safinamide compared to placebo
Doses:	50 mg/day and 100 mg/day as add-on therapy to a stable dose of a single dopamine agonist
Study Initiation Date (First Informed Consent Signed):	1 October 2009

This clinical study was designed, conducted, recorded, and reported in compliance with the principles of Good Clinical Practice (GCP) guidelines. These guidelines are stated in U.S. federal regulations as well as "Guidance for Good Clinical Practice," International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

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Study Completion Date (Last Subject Completed Last Observation):	28 May 2012
Duration:	Up to 83 weeks
Subject Population:	Subjects from protocol 27918 who have idiopathic early Parkinson's disease
Development Phase:	III
Report Release Date:	October 2013
Sponsor:	Newron Pharmaceuticals S.p.A. Via Ludovico Ariosto 21,20091 Bresso (MI) Italy Tel +39 02 610 3461 Fax +39 02 610 34654 E-mail: info@newron.com
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This clinical study was designed, conducted, recorded, and reported in compliance with the principles of Good Clinical Practice (GCP) guidelines. These guidelines are stated in U.S. federal regulations as well as "Guidance for Good Clinical Practice," International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

2 SYNOPSIS

Name of Sponsor/Company: Newron Pharmaceuticals S.p.A.	*(For National Authority Use Only)*
Finished Product: Safinamide	
Active Ingredient: Safinamide	
Title of Study: A phase III, double-blind, placebo-controlled extension trial to investigate the long-term efficacy and safety of low (50 mg/day) and high (100 mg/day) dose 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: 27938	**Development Phase:** III
Investigators/Study Centers: This study was conducted at 99 study centers in 20 countries.	
Publications: No publications have been generated from data resulting from this study.	
Study Duration:	Up to 83 weeks
Study Initiation:	1 October 2009
Study Completion:	28 May 2012
Objectives: To determine the long-term safety and efficacy of 2 doses of safinamide (50 mg/day and 100 mg/day) compared to placebo, as add-on therapy in subjects with early idiopathic Parkinson's disease (PD) who are currently receiving a stable dose of a single dopamine (DA)-agonist.	
Methods: Trial 27938 was an extension to the antecedent trial 27918 and was a double-blind, placebo-controlled, multi-center, multi-national, 78-week, Phase III trial, conducted to evaluate the long-term efficacy and safety of a low (50 mg/day) and high (100 mg/day) dose safinamide, compared to placebo, as add-on therapy to a stable single dose of DA-agonist in early PD. No direct enrollment into this trial occurred. Only subjects who successfully completed the previous trial (27918) were eligible to enroll in this long-term trial (27938). Upon entry into this trial, subjects continued in the same treatment group and dose level of safinamide or placebo that they received in protocol 27918, along with the same dose of DA-agonist. Subjects returned for scheduled evaluations at 12, 24, 36, 48, 60 and 78 weeks after the first dose of Investigational Medicinal Product (IMP). Subjects who completed the 78-week extension trial either entered a 1-week taper phase before discontinuing treatment or entered open-label treatment with safinamide (50-100 mg/day) in a separate open-label trial (28850). Subjects who entered the 1-week taper phase were followed for safety events for 4 weeks after the last administration of IMP. The total duration of participation from the beginning of trial 27918 to the completion of 27938 was expected to be 108.5 weeks.	
Number of Subjects: No sample-size calculations were performed for this extension study. Enrolled: 353 active, 154 placebo Completed: 153 active, 63 placebo In safety analysis: 353 active, 154 placebo In efficacy analysis: The planned efficacy analysis for this study was not performed.	

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Diagnosis and Main Criteria for Inclusion: Eligible subjects had idiopathic PD and successfully completed all trial requirements and 24 weeks of treatment in Trial 27918. Subjects provided written informed consent for Trial 27938. Subjects that experienced a clinically significant adverse event (AE) during Trial 27918 that would have put the subject at risk or showed a clinically significant deterioration during participation in Trial 27918 were not eligible to participate in Trial 27938.	
Test Product, Dose and Mode of Administration, Batch Number: Safinamide tablets at dosage strength of 50 mg (7 mm diameter), 100 mg (9 mm diameter). Safinamide was administered orally, once per day, in the morning, in addition to the morning dose of DA-agonist.	
Duration of Treatment: The planned treatment duration was 78 weeks.	
Reference Therapy, Dose and Mode of Administration, Batch Number: Matching placebo tablets (7 or 9 mm) were provided.	
Criteria for Evaluation: The following efficacy endpoints were planned, but were not analyzed: <u>Primary Efficacy Endpoint</u>: Time from baseline to first intervention (change in the dose of DA-agonist; addition of another DA-agonist, levodopa, or other PD therapy; or discontinuation due to lack of efficacy). <u>Secondary Efficacy Endpoints</u>: • Proportion of subjects requiring intervention • Unified Parkinson's Disease Rating Scale (UPDRS) Section III (motor examination) score change from baseline to Week 78 • UPDRS Section II [Activities of Daily Living (ADL)] score change from baseline to Week 78 • Clinical Global Impression (CGI) - Change (CGI-C) scale score -minus change from Day 0 of Trial 27918 to Week 78 • CGI – Severity (CGI-S) scale score change from baseline to Week 78 • EuroQoL 5D self-report questionnaire (EQ-5D) score change from baseline to Week 78 • Parkinson's Disease Questionnaire (PDQ-39) score change from baseline to Week 78 • Cogtest® PD battery test score change from baseline to Week 78	

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Additional Efficacy Endpoints:

- Hamilton Rating Scale for Depression (GRID-HAMD; 17-item scale) score change from baseline to Week 78
- UPDRS - Section IV score change from baseline to Week 78
- UPDRS - Section I score change from baseline to Week 78
- Mini-Mental State Examination (MMSE) score change from baseline to Week 78
- Hoehn & Yahr Staging
- Health Resource Utilization parameters

Safety:

Incidence of treatment emergent adverse events (TEAEs), clinically significant changes in laboratory tests, electrocardiogram (ECG) morphology, vital signs, physical and neurological examinations, level of daytime sleepiness based on the Epworth Sleepiness Scale (ESS), and ophthalmologic and dermatological examinations.

Pharmacokinetics:

Pharmacokinetic measurements were to include area under the curve (AUC) at various times (AUC_t), maximum plasma concentration C_{max}, and time to C_{max} (t_{max}), and half-life ($t_{1/2}$).

Statistical Methods:

No sample size calculation was performed for this extension trial, as subjects were enrolled from the antecedent trial (27918). It was estimated that approximately 75% of the subjects randomized during the antecedent trial (Trial 27918) would continue into this extension trial (approximately 498 subjects).

Primary Efficacy Analysis:

For the analyses of all continuous efficacy parameters, main effects models were to be performed. In addition, full effects models consisting of the main effects (effects for treatment and country/region) as well as the interactions were to be performed. If any significant interactions were detected, the final analysis model was to include the main effects as well as the significant interactions. All statistical tests were to be 2-sided and performed at the 5% significance level.

The primary efficacy parameter (time to intervention) was to be analyzed using a Cox proportional hazards model that included effects for treatment and country/region. An approximate Chi-square test based on the Wald statistic was to be used to compare treatment groups.

Secondary and Tertiary Efficacy Analyses:

For the analyses of all continuous secondary and tertiary efficacy parameters, main effects models were to be performed as described above for the primary efficacy endpoint analyses.

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Safety Measures

Adverse events (AEs) for the treatment period were summarized by Medical Directory for Regulatory Affairs (MedDRA) system organ class and preferred term. Additional AE summaries are presented by severity and by relationship to treatment. Serious adverse events (SAEs) are listed and tabulated. Subjects who prematurely withdrew from the trial or from treatment are provided in a subject listing and summarized by primary withdrawal reason for each treatment group.

Baseline and follow-up visit results for vital signs, laboratory tests, ECG morphology, and ESS are summarized by treatment group. The physical, neurological, and dermatological examinations were collected at Trial 27918 baseline and Extension Week 78. Examinations are summarized by shift tables for analyzing the shifts in value (normal, abnormal or missing) at Extension Week 78 relative to Trial 27918 baseline value for the safety population and are provided in listings

If applicable, the change from baseline for these observed values are also summarized by treatment group. Also, shift tables for laboratory tests based on classification of values as low, normal or high with respect to the reference range and clinical significance criteria are summarized by treatment group.

Summary of Results:

Subject Population/Disposition:

Of the 610 subjects who were included in the Completer population of Trial 27918, 507 signed an ICF and were enrolled in Trial 27938. Of the 507 subjects enrolled in the trial, 174 (34.3%) were assigned to the safinamide 50 mg/day group, 179 (35.3%) to the safinamide 100 mg/day group, and 154 (30.4%) to the placebo group. A total of 216 (42.6%) subjects had a Week 78 follow-up, and therefore completed the study. There were 80 (46.0%), 73 (40.8%), and 63 (40.9%) subjects who completed the study in the safinamide 50 mg/day, safinamide 100 mg/day, and placebo groups, respectively. The majority of subjects that discontinued from the study did so due to 'Other' reasons (261 of 291 subject discontinuations), most of which were associated with the premature termination of the study.

Efficacy Endpoints:

The planned efficacy endpoints of the study were not analyzed, hence no results are presented.

Extent of Exposure:

The overall mean treatment compliance among all subjects was 97.7 ± 8.5%. The mean treatment compliance ranged from 97.1±10.8% in subjects treated with safinamide 100 mg/day to 98.3 ±4.5% in subjects treated with safinamide 50 mg/day. Overall, 97.4% of subjects had treatment compliance between 80% and 120%.

As expected, the mean overall exposure was approximately 2-fold higher in subjects treated with safinamide 100 mg/day (39116±16726 mg) compared to subjects treated with safinamide 50 mg/day (20636±7817 mg). The mean duration of exposure was 406 ± 160 days for all subjects.

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Safety:

A total of 309 (60.9%) subjects reported 1082 TEAEs. The percentage of subjects with ≥1 TEAE was generally similar among safinamide 50 mg/day (60.9%) safinamide 100 mg/day (58.7%), and placebo (63.6%) treated subjects.

The most common TEAEs occurring in the safinamide treatment groups were back pain (7.4%), fall (5.1%), and urinary tract infection (4.2%). In the placebo group, the most common TEAE was insomnia (7.8%). The incidence of these common TEAEs did not indicate any dose-dependency or pattern of association with safinamide treatment.

A relatively similar percentage of subjects reported moderate TEAEs in the safinamide 50 mg/day (28.2%), safinamide 100 mg/day (29.6%), and placebo (23.4%) treated groups. Likewise, a relatively similar percentage of subjects reported severe TEAEs in the safinamide 50 mg/day (5.7%), safinamide 100 mg/day (4.5%), and placebo (3.9%) treated groups. In addition, the percentage of subjects reporting TEAEs possibly (13.2% and 15.1% in the safinamide 50 mg/day and safinamide 100 mg/day groups, respectively) or probably (1.7% in both the safinamide 50 mg/day and safinamide 100 mg/day groups) related to treatment appeared to be consistent with the placebo treated group (18.8% and 2.6% of subjects reported possible or probable TEAEs, respectively).

Overall, the incidence of serious TEAEs was low among all subjects in the study. There were 9 (5.2%) subjects in the safinamide 50 mg/day group that experienced 15 SAEs, 10 subjects (5.6%) in the safinamide 100 mg/day group that experienced 14 SAEs, and 11 (7.1%) subjects in the placebo treated group that experienced 14 SAEs.

The percentage of subjects discontinuing treatment due to a TEAE was low and relatively consistent among the safinamide 50 mg/day (2.3%), safinamide 100 mg/day (5.6%), and placebo (4.5%) treated subjects. These subjects represented .4.1% of the total number of subjects. There were 2 discontinuations due to deaths in this study. The events related to these 2 deaths (1 subject receiving each of safinamide 50 mg/day and safinamide 100 mg/day) were cardiac disorders and were reported to be unrelated to study treatment.

The incidence of pre-specified ocular, cardiovascular, and hepatic TEAEs was low. There were no trends or indications of any dose-dependency or pattern of association with safinamide treatment.

Changes from Baseline and abnormal shifts in laboratory results, vital signs, physical findings, neurological and dermatological examinations, ECG findings, cardiovascular and hepatic events, and ESS appeared to be consistent among the 3 treatment groups. Ophthalmological results were also similar between all 3 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 trends or safety concerns with the use of safinamide at doses of 50 mg/day and 100 mg/day as add-on treatment in early PD patients treated with a single DA-agonist.

Pharmacokinetics (PK):

The planned PK endpoints of the study were not analyzed, hence no results are presented.

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Conclusions:

No clinically relevant pattern of adverse changes 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.

These results indicate that long-term treatment of up to 2 years with safinamide at doses of 50 and 100 mg/day was well tolerated in early PD patients treated concomitantly with a single DA-agonist.

Status of Study: In October 2011, Merck-Serono announced in a press release that it would return all rights for safinamide to Newron Pharmaceuticals. The decision was not related to safety or efficacy concerns regarding safinamide. It led to a decision to terminate the Extension Trial 27938 early, consistent with the Trial 27938 protocol. All subjects enrolled in the Extension Trial 27938 were asked to complete the following visits immediately: Week 78 / Early Termination, Week 79 (Taper Visit), and Week 83 Safety Follow-up Visit. All subjects enrolled in the trial were to be followed for safety until 4 weeks after their last administration of safinamide, as detailed in the scheduled visits described in the protocol (Week 83 Safety Follow-up Visit).

Date of Study Report:	October 2013