**Title of Trial:** A double-blind, randomized, placebo-controlled, parallel-group, dose-escalation trial to explore the potential antidyskinetic properties of safinamide in patients with Parkinson's disease suffering from levodopa induced dyskinesias

**Investigational Product:** Safinamide

**Trial No.:** EMR701165-023

**Study Center:** This study was conducted at 9 sites in 5 countries (Austria, Canada, France, Germany and South Africa).

**Trial Period (years):**

Trial Initiation Date: 10 May 2010

Trial Completion Date: 21 November 2011

**Development Phase:** Phase IIa

**Publication (reference):** At the time of the clinical trial report, there were no publications based on the trial. A scientific publication will be prepared in collaboration with the principal investigator (Prof. Olivier Rascol, MD, PhD) and the other investigators of the trial with the approval of the sponsor.

**Study Objectives:** The purpose of this trial was to determine if safinamide (up to 300 mg/day) can attenuate levodopa (L-dopa)-induced dyskinesia (LID) in Parkinson's disease (PD).

Primary

To determine the maximum reduction in Unified Dyskinesia Rating Score (UDysRS) compared to baseline across all post-baseline dose visits.

Secondary

- To explore the impact of safinamide dose for antidyskinetic activity of safinamide in late-stage PD patients with LID, and to evaluate changes from baseline in motor fluctuations, motor function, activities of daily living, and change in global clinical status.
- To further characterize the safety and tolerability of safinamide in late-stage PD patients with LID. The safety of a dose range of safinamide 100 to 300 mg dosed orally (po) once daily in the morning (qam) compared to placebo will be assessed through: incidences of treatment emergent adverse effects (TEAEs) and clinically significant changes in laboratory safety tests, ECG morphology, vital signs, ophthalmological, and dermatological examinations.

**Methodology:** The trial was a prospective, randomized, double-blind, parallel-group, placebo-controlled, within-subject dose-escalation trial. Safinamide/matching placebo doses were administered qam. Following a screening period of approximately 2 weeks (+/- 3 days, Visit 1), dosing began at Visit 2 (Days 1 through 8) with 100-mg safinamide/matching placebo. Following efficacy and safety assessments at Visit 3 (Day 8), Visit 4 (Day 22), Visit 5 (Day 36), and Visit 6 (Day 51), safinamide doses (or matching placebo doses, as per the number of tablets administered) were escalated to: 150 mg (Days 9 through 11), 200 mg (Days 12 through 22), 250 mg (Days 23 through 25), and 300 mg (Days 26 through 66). Final efficacy and safety assessments occurred at Visit 7 (Day 66). Efficacy was evaluated based on assessments conducted at the 100-, 200-, and 300-mg dose levels. Dose reductions for tolerability were permitted. From Days 67 through 72, doses were tapered as follows: 250 mg (2 days), 200 mg (2 days), 150 mg (2 days), and 100 mg (1 day). Subjects returned at Visit 8/End of Trial (EOT, Day 101) for final safety and clinical assessments. Subjects who prematurely discontinued were required to complete Visit 8/EOT at the time of discontinuation.

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

A total of 24 subjects were planned for randomization in a 2:1 ratio to safinamide or placebo; 26 subjects were actually randomized.

**Diagnosis and Main Criteria for Inclusion/Exclusion:**

Male and female subjects aged 30 years or above with a diagnosis of idiopathic PD according to the United Kingdom Parkinson's Disease Society Brain Bank Clinical Diagnosis Criteria, who were being treated with L-dopa and suffering from temporally predictable peak-dose LID, were enrolled.

**Study Treatment:**

Active drug was supplied as 50-mg tablets of safinamide in blister packs and administered po qam. From Days 1 through 66, doses were escalated from 100 mg (2 tablets) to 150 mg (3 tablets), 200 mg (4 tablets), 250 mg (5 tablets), and 300 mg (6 tablets). From Days 67 to 72, doses were sequentially tapered from 300 mg to 250 mg, 200 mg, 150 mg, and 100 mg.

Duration of Treatment: The duration of treatment was 10 to 11 weeks, including a 1-week taper phase. A safety evaluation was conducted 4 weeks after administration of the last dose.

Reference Therapies, Dose and Mode of Administration:

Placebo was supplied as tablets matching the 50-mg safinamide tablets, in blister packs and administered po qam. From Day 1 (Visit 2) through Day 66 (Visit 7), doses were escalated and tapered by increasing or decreasing the number of tablets administered in accordance with the number taken to achieve safinamide dosing.

**Criteria for Evaluation:**

Efficacy:

- Unified Dyskinesia Rating Scale (UDysRS, primary efficacy variable)
- Hauser Subject Diary (all parts), recording predominant status during 30-minute intervals over an 18-hour period (06:00 to 24:00 hour) each day, as per the following categories: 'asleep', 'OFF', 'ON without dyskinesia', 'ON with non-troublesome dyskinesia', and 'ON with troublesome dyskinesia'.
- MDS-UPDRS (Movement Disorder Society Sponsored revised Unified Parkinson's Disease Rating Scale)
- PDYS-26 (Parkinson Disease Dyskinesia Scale – 26 items)
- CGI (Clinical Global Impression) – Severity scale (CGI-S) and CGI – Change scale (CGI-C)
- PGI (Patient Global Impression) - Severity scale (PGI-S) and PGI – Change scale (PGI-C)

Pharmacokinetics:

- Safinamide plasma concentrations

Pharmacodynamics

Not applicable.

Safety:

- Physical, neurological, ophthalmological, and dermatological examination findings
- Medical history
- Adverse event assessments
- Hematologic, clinical chemistry, and urinalysis results
- Electrocardiogram (ECG) results

**Statistical Methods:**

Analysis Populations:

- Intent-to-Treat (ITT) Population: All subjects randomized to either safinamide or placebo.
- Per Protocol (PP) Population: Subjects from the ITT Population who completed the treatment period (66 days/Visit 7) without a major protocol deviation.

Safety Population: All subjects who received at least 1 dose of planned trial treatment (either safinamide or placebo) and had a subsequent safety assessment.

The ITT and Safety Populations were the analysis populations for the efficacy and safety analyses, respectively. The PP Population was used for supportive analyses of the efficacy endpoints.

Evaluation of Efficacy

Primary Efficacy Analysis: The primary efficacy endpoint, the maximum UDysRS total score reduction from baseline across all post-baseline visits (Days 8, 22, 36, and 66), was descriptively summarized (mean, SD, median, minimum [min], and maximum [max]) by treatment group. In addition, an Analysis of Covariance (ANCOVA) model including treatment as the factor and baseline UDysRS score as the covariate was computed. The least square (LS) mean of treatment difference (safinamide versus placebo) and the associated 95% confidence intervals (CIs) were derived from the ANCOVA model. Also, the treatment by baseline measure interaction was to be checked, and if it was significant at the 0.10 level, then a subgroup analysis was to be explored based on the quartiles of the baseline value. Furthermore, the time at which the subject first reached the maximum UDysRS reduction was summarized by number and percent of subjects, by treatment group and visit (Days 8, 22, 36, and 66).

Secondary Efficacy Analyses: The secondary efficacy endpoints, including UDysRS and subscales, MDS-UPDRS and subscales, Hauser Subject Diary data, PDYS-26, CGI, and PGI were descriptively summarized by treatment and visit. In addition, a repeated measures ANCOVA model was applied to each secondary endpoint.

All analyses were exploratory in nature.

Evaluation of Pharmacokinetics

Safinamide plasma concentrations were summarized descriptively by timepoint and treatment group.

Evaluation of Safety

Safety endpoints were summarized descriptively by treatment group and visit for the Safety Population.

**Results:**

Subject Disposition:

Subject disposition is displayed in the following table. A total of 26 subjects were randomized and 23 completed the trial. Despite the 2:1 randomization, 20 subjects were randomized to safinamide and only 6 to placebo. Four subjects were discontinued from

treatment due to protocol violations (n=1, placebo) or "other" reasons (n=3, safinamide); for the same reasons, 3 subjects of these 4 subjects were also discontinued from the trial.

| **Characteristics (n [%])** | **Safinamide N=20** | **Placebo N=6** | **Total N=26** |
|---|---|---|---|
| Subjects randomized - ITT Population | 20 (100.0) | 6 (100.0) | 26 (100.0) |
| Safety Population | 20 (100.0) | 6 (100.0) | 26 (100.0) |
| Per Protocol Population | 17 (85.0) | 5 (83.3) | 22 (84.6) |
| Completed the trial | 18 (90.0) | 5 (83.3) | 23 (88.5) |
| Discontinued from treatment | 3 (15.0) | 1 (16.7) | 4 (15.4) |
| Protocol violation | -- | 1 (16.7) | 1 (3.8) |
| Other | 3 (15.0) | -- | 3 (11.5) |
| Discontinued from the trial | 2 (10.0) | 1 (16.7) | 3 (11.5) |
| Protocol violation | -- | 1 (16.7) | 1 (3.8) |
| Other | 2 (10.0) | -- | 2 (7.7) |

Baseline Characteristics:

The mean (SD) age of the trial population was 64.0 (7.9) years. All subjects were Caucasian. The median BMI was higher in the placebo group versus the safinamide group (29.13 $mg/m^2$ versus 25.64 $mg/m^2$). A higher proportion of subjects in the placebo group were male (67% versus 50% for the safinamide group) and positive for a history of smoking (33% versus 15% for the safinamide group). These differences did not reach statistical significance, but the number of subjects analyzed was small.

The mean (SD) duration of PD was 11.0 (4.8) years in the safinamide group and 12.2 (7.2) years in the placebo group. For UDysRS III, UDysRS III+IV, MDS-UPDRS (II), MDS-UPDRS (III), and MDS-UPDRS (I – IV), higher mean and median values were reported in the placebo group compared to the safinamide group. While these between-group differences did not reach statistical significance, the number of subjects analyzed was small.

Efficacy Results:

As shown in the table below, for the primary efficacy endpoint analysis, maximum reduction in UDysRS Total Score, there were changes from baseline in both groups, but no clinically or statistically significant differences emerged between treatment groups. There were also improvements from baseline in the secondary efficacy analyses in both groups (maximum reduction in UDysRS I+II Score and UDysRS III+IV Score), but no clinically or statistically significant differences emerged between treatment groups.

| Characteristics | Safinamide LS Mean (SE) of change from baseline | Placebo LS Mean (SE) of change from baseline | LS Difference (SE) between Safinamide and Placebo | 95% CI of the LS Difference | p-value versus placebo |
|---|---|---|---|---|---|
| Maximum reduction in UDysRS Total | -13.11 (2.78) | -12.98 (5.10) | -0.12 (5.83) | (-12.18, 11.93) | 0.983 |
| Maximum reduction in UDysRS I+II | -9.37 (1.75) | -6.39 (3.20) | -2.97 (3.65) | (-10.52, 4.57) | 0.423 |
| Maximum reduction in UDysRS III +IV | -5.03 (1.45) | -7.84 (2.70) | 2.81 (3.11) | (-3.62, 9.24) | 0.375 |

The time to reach maximum reduction is summarized in the following table. In the safinamide group, nearly half of subjects reached their maximum UDysRS Total Score reduction by Day 22. In the placebo group, nearly half of subjects reached their maximum UDysRS Total Score reduction by Day 36.

| First time to reach maximum reduction (n [%]) | Safinamide N=20 | Placebo N=6 |
|---|---|---|
| Visit 3 / Day 8 | 4 (20.0) | 1 (16.7) |
| Visit 4 / Day 22 | 5 (25.0) | 1 (16.7) |
| Visit 5 / Day 36 | 6 (30.0) | 1 (16.7) |
| Visit 7 / Day 66 | 4 (20.0) | 3 (50.0) |

The following posthoc analyses of the primary efficacy endpoint were performed for the ITT Population:

- An analysis of the Maximum Reduction in UDysRS (ANCOVA) in subjects who had taken at least 1 dose of 300 mg revealed a moderate difference between groups (LS difference [SE] = 4.45 [7.19]; p-value = 0.544) favoring the placebo group. However, the sample size was too small to draw any conclusion from this subgroup analysis.
- An analysis of the Maximum Reduction in UDysRS (ANCOVA) in subjects with baseline UDysRS total score not below the median (overall) revealed a moderate difference between groups (LS difference [SE] = 3.59 [7.86]; p-value= 0.658) favoring placebo group. However, the sample size was too small to draw any conclusion from this subgroup analysis.
- An analysis of the Maximum Reduction in UDysRS (ANCOVA) in subjects with baseline UDysRS total score below the median (overall) revealed a moderate difference between groups (LS difference [SE] = -8.64 [7.06]; p-value = 0.249) favoring the safinamide group. However, the sample size was too small to draw any conclusion from this subgroup analysis.
- An analysis of the Maximum Reduction in UDysRS (ANCOVA) in subjects who had taken at least 1 dose of 300 mg revealed no difference between groups (LS difference [SE] = 4.45 [7.19]; p-value = 0.544).
- An analysis of the Maximum Reduction in UDysRS (ANCOVA) in subjects with baseline UDysRS total score not below the median (overall) revealed no difference between groups (LS difference [SE] = 3.59 [7.86]; p-value= 0.658).

- An analysis of the Maximum Reduction in UDysRS (ANCOVA) in subjects with baseline UDysRS total score below the median (overall) revealed no difference between groups (LS difference [SE] = -8.64 [7.06]; p-value = 0.249).

For the secondary efficacy endpoints (MDS-UPDRS [Total and Subparts I, II, III, IV, or IV – Item 6], ON Time, ON Time with no dyskinesia, OFF Time, or PDYS-26), there were improvements from baseline in both groups, but no clinically or statistically significant differences emerged between treatment groups. Lastly, there were no clinically or statistically significant between-group differences in investigator- or subject-assessed change from baseline in general health status, the CGI-C or PGI-C scales, respectively.

Pharmacokinetic Results:

Analysis of safinamide plasma concentrations in this trial confirmed appropriate treatment exposure; postdose safinamide concentrations across the different visits were in the expected range and increased according to the actual dose received.

Safety Results:

The mean (SD) duration of treatment was 64.3 (20.3) days in the safinamide group and 65.0 (30.3) days in the placebo group. In the safinamide group, compliance ranged from 96.1% to 100.0%, with a mean (SD) compliance rate of 99.73% (0.91). In the placebo group, compliance ranged from 90.9% to 100.0%, with a mean (SD) compliance rate of 97.47% (4.03).

No deaths occurred during the trial and no subjects discontinued from treatment or the trial due to a treatment-emergent adverse event (TEAE). A total of 4 treatment-emergent serious adverse events (SAEs) occurred in 4 subjects, all on safinamide: ulcerative colitis, eczema, macular edema, and rib fracture. Only macular edema was considered by the investigator to be possibly related to treatment. Eczema and macular edema were considered severe. Ulcerative colitis and rib fracture were considered to be mild and moderate, respectively. At the end of the trial, the rib fracture and eczema had resolved, the macular edema resolved with sequelae, and the ulcerative colitis was ongoing.

During the trial, 6 TEAEs in 3 subjects out of 20 (15%) in the safinamide group were assessed as severe: the above-mentioned SAE macular edema (n=1); blood creatine phosphokinase increased (n=1); and sleep disorder, dry skin, eczema, and hyperkeratosis (n=1, all occurring in a single subject). There were no severe TEAEs in the placebo group.

Most subjects reported at least 1 TEAE during the trial (14 safinamide subjects [70%] and 6 placebo subjects [100%]). In the safinamide group, TEAEs reported in 10% or more subjects included dyskinesia (n=5, 25% of subjects), back pain, muscle spasms, and anxiety (n=2, 10% each). Of these TEAEs, only dyskinesia was reported in a higher proportion of subjects on placebo (n=2, 33%).

In the safinamide group, 7 TEAEs of dyskinesia occurred in 5 subjects. All were considered possibly or probably related to investigational medicinal product [IMP]. The severity of

dyskinesia was considered mild in 6 cases and moderate in 1 case. The events were reported as TEAEs from 4 to 67 days after the first IMP dose and lasted for 1 to 44 days. For 3 subjects, dosing was interrupted and for 4 subjects, doses were either adjusted downward or not escalated further. Dosing was never discontinued due to dyskinesia, and in all instances, dyskinesia resolved.

In the placebo group, both TEAEs of dyskinesia were considered to be of moderate severity and possibly related to IMP. These were reported as TEAEs at 32 and 36 days after the first IMP dose and lasted for 29 days and approximately 4 months. Dosing was never discontinued for dyskinesia, although it was interrupted and reduced for both subjects. In both instances, dyskinesia resolved.

While dyskinesia was reported as the most frequent TEAE in the safinamide group, it is impossible to conclude whether safinamide worsens or improves dyskinesia based on the results of this small trial with disparity in the number of subjects in each treatment group. Dyskinesia as a TEAE was reported in 33% of subjects on placebo versus 25% of subjects on safinamide. Furthermore, dyskinesia is a fluctuating symptom, and any exacerbation from baseline over the 66-day treatment period would have been reported as a TEAE. Lastly, as reflected in the efficacy findings, average dyskinesia ratings actually improved slightly over the course of the trial for the safinamide group, although not to a degree different from placebo.

TEAEs considered related to IMP are described below.

- In the safinamide group, dyskinesia (7 events in 5 subjects [25%]) and muscle spasm (2 events in 2 subjects [10%]) were the only TEAEs considered possibly or probably related to IMP and reported for ≥10% of subjects.
- In the placebo group, dyskinesia was reported as possibly related to IMP (2 events in 2 subjects [33.3%]) and muscle spasm was not reported as possibly or probably related to IMP.

“Pre-specified AEs” of interest with safinamide treatment were defined to include Dyskinesia (including Dyskinesia, Akathisia, and Dystonia), Ocular, Cardiovascular, and Hepatic associated events.

- In the safinamide group, TEAEs in the dyskinesia (5 subjects [25%]), ocular (2 subjects [10%]), and cardiovascular (2 subjects [10%]) categories occurred in ≥10% of subjects. By PT, these presepcified TEAEs included dyskinesia (5 subjects [25%]), cataract, macular edema, blood creatine phosphokinase increased, orthostatic hypotension, and aspirate aminotransferase increased (each occurring in 1 subject [5%]). Increased AST, a hepatic presepcified TEAE, occurred in only 1 subject (5%).
- In the placebo group, only TEAEs in the dyskinesia (2 subjects [33.3%]) and ocular (1 subject [16.7%]) categories occurred in ≥10% of subjects. By PT, these presepcified TEAEs included dyskinesia (2 subjects [33.3%]), cataract and visual impairment (each occurring in a single subject [16.7%]).

Over the course of the trial, there were no notable changes in laboratory parameters for either treatment group. Similarly, no notable safety findings were observed in either group for ECGs; vital signs; ocular, dermatologic, neurologic, or physical examinations.

**Conclusions:**

A total of 26 subjects were enrolled in this small, double-blind, placebo-controlled, randomized, dose-escalation trial evaluating 100 to 300 mg/day of safinamide versus placebo (2:1 ratio) in subjects with LID. Modest improvements from baseline were observed for the primary and secondary efficacy endpoints, in both the placebo and safinamide groups, but no clinically or statistically significant differences were observed between the groups. Analysis of safinamide plasma concentrations was in line with previous data. No new notable safety findings concerning safinamide emerged from this trial.