Title of Trial: A randomised, double-blind, placebo-controlled, two-period, two-sequence-crossover interaction study to assess the effect of safinamide on levodopa pharmacokinetics in subjects with Parkinson's disease.

Investigational Product: Safinamide

Trial No.: 28780

Study Centers: This study was conducted in 2 centers in Italy.

Trial Dates:

Trial Initiation Date: 23 July 2009

Trial Completion Date: 05 July 2010

Development Phase: Phase IIa

Publication (reference): None

Study Objectives:

- The primary objective was to investigate the effect of safinamide on the pharmacokinetics (PK) of levodopa, both after single and steady state dosing of safinamide.
- The secondary objective was to assess the safety and tolerability of safinamide when given together with levodopa in the applied regimen.

Methodology:

This was a randomized, double-blind, placebo-controlled, two-period, two-sequence, cross-over trial in patients with idiopathic Parkinson's disease. The trial evaluated the effect of safinamide (100 mg o.d.), compared to placebo, on levodopa pharmacokinetics, as measured by plasma concentrations of levodopa, its metabolites and carbidopa. The trial was conducted at two closely connected but distinct sites in one country which were managed by one coordinating Investigator. The total duration of the trial was approximately 9-10 weeks, including a screening examination within 3 weeks before the first treatment period, 2 treatment periods of 6 days separated by a wash out of at least 14 days and an end of study visit (EOS) 14 days after last drug administration in period 2.

Subjects meeting all eligibility criteria were randomized in a 1:1 ratio to one of the following treatment sequences: A → B or B → A.

Number of Subjects (Planned and Analyzed):

24 subjects (12 subjects per sequence) were planned to be randomized in order to provide 22 evaluable subjects across the two sites.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Male and female subjects aged ≥ 30 years, with a body mass index (BMI) in the range of 18-32 kg/m^2), diagnosed with idiopathic Parkinson's disease, Hoehn and Yahr (H&Y) stage of I-III, who are levodopa-responsive, treated with a stable dose of levodopa/decarboxylase-inhibitor and are not taking any other MAO-B inhibitor nor any drug causing dopamine release or affecting levodopa metabolism.

Study Treatment:

Safinamide 100 mg p.o. once daily administration 6 days.

Duration of Treatment: The trial consisted of two 6-day treatment periods separated by a washout period of at least 14 days.

Reference Therapies, Dose and Mode of Administration:

Matching placebo p.o. once daily administration 6 days.

Reference product:

Drug: Nacom® immediate release formulation (100 mg levodopa +25 mg carbidopa)

Criteria for Evaluation:

Pharmacokinetics:

Primary endpoints:

- C_{max} and AUC_{0-6} of levodopa on Day 1 and Day 6

Secondary endpoints:

- t_{max}, $t_{1/2}$ within a 6-h interval, AUC0-tmax of levodopa on Day 1 and Day 6
- C_{max}, AUC_{0-6}, $t_{1/2}$ within a 6-h interval, tmax of carbidopa and levodopa/dopamine metabolites, including homovanillic acid (HVA), dihydroxyphenylacetic acid (DOPAC) and 3-O-methyl-dopa (3OMD) on Day 1 and Day 6

Safety:

Safety and tolerability parameters including frequency and incidence of treatment-emergent adverse events (TEAEs) and vital signs (blood pressure, heart rate), laboratory parameters

(including biochemistry, hematology and urinalysis), 12-lead electrocardiogram (ECGs) parameters and UPDRS part III score.

Statistical Methods:

The primary endpoints, Cmax and AUC0-6 of levodopa on Day 1 and Day 6, were analyzed in an exploratory way. Statistical hypotheses were not set up. Analyses were performed on the pharmacokinetic analysis set. Parameters were log-transformed and subjected to a mixed model analysis, with fixed effects for treatment, period and sequence and random effect for subject within sequence. The treatment ratios Treatment A/Treatment B (ratios of geometric means) were estimated for each parameter and the corresponding 90% confidence intervals (CI) were calculated based on the residual error.

For treatment differences in tmax of levodopa, carbidopa and its metabolites, the Hodges-Lehman shift estimate and the corresponding 90% CI according to Tukey were calculated.

In addition, all PK parameters were presented descriptively by mean, median, geometric mean, SD, SEM, CV%, min and max values. Boxplots were prepared for the primary endpoints.

Adverse events (AEs) were analysed by intensity and relationship to drug and were summarized by frequency and incidence per treatment. All other safety parameters were presented descriptively.

Results:

Subject Disposition:

Twenty-four eligible subjects were randomized into the trial (12 subjects in each treatment sequence). Twenty-one of the 24 randomized subjects completed the trial according to the protocol.

Number of subjects planned: 24 subjects

Number of subjects randomized: 24 subjects (10 females and 14 males)

Number of subjects analyzed:

Safety population: 24 subjects

PK population: 24 subjects

Pharmacokinetic evaluation was carried out on the PK population, consisting of 24 subjects. Three subjects discontinued after the first treatment period.

Demographics and Baseline Characteristics:

Twenty-four subjects were randomized into the trial. All subjects were White. Fourteen (14) were males and ten (10) were female. The mean (SD) age of all subjects was 64.2 (9.11) years,

the mean (SD) weight was 72.7 (12.42) kg, the mean (SD) height was 167.1 (8.63) cm, and the mean (SD) BMI was 25.9 (3.41) kg/m2. The demographic characteristics were similar across the two treatment sequence groups.

Pharmacokinetic Results:

Overall, mean plasma concentration-time profiles for levodopa were similar after co-administered with safinamide (Treatment A) and after co-administration with placebo (Treatment B) both after single dose (Day 1) and at steady state (Day 6). In line PK parameters Cmax and AUC0-6 of levodopa on Day 1 and Day 6 were comparable between the two treatments.

The analysis of variance (ANOVA) point estimates for the ratio Treatment A/Treatment B on Day 1 and on Day 6 (see following Table) were close to 100% for primary parameters C_{max} and AUC_{0-6} of levodopa. For both parameters, 90% CI on Day 6 (safinamide steady-state) were within the bounds of clinical acceptability (0.75 to 1.33). However, the bioanalytical limitation must be taken into account when interpreting levodopa PK results.

	Least Squares Geometric Mean		**Ratio Estimate [%] (90% CI)**
	Treatment A (levodopa + safinamide)	**Treatment B (levodopa + placebo)**	**Treatment A / Treatment B**
Day 1			
C_{max} (ng/mL)	974.895	950.327	102.6 (88.6 - 118.8)
AUC_{0-6} (ng.h/mL)	1999.9	1734.8	115.3 (95.3- 139.5)
Day 6			
C_{max} (ng/mL)	944.322	950.325	99.4 (77.9 - 126.8)
AUC_{0-6} (ng.h/mL)	1792.2	1931.6	92.8 (82.1 - 104.8)

Descriptive statistics and ANOVA analysis of PK parameters C_{max} and AUC_{0-6} for levodopa main metabolite HVA on Day 1 and Day 6 up to 6h after dosing showed that safinamide after single dose and at steady-state does not have a relevant effect on the metabolism of levodopa into HVA.

Overall, the results of this trial are indicative that safinamide does not have a clinically relevant effect on levodopa pharmacokinetics.

Safety Results:

Safinamide was well tolerated when co-administered with levodopa.

No deaths or SAEs were reported during the trial. No subjects discontinued from the trial nor from treatment due to an AE. For the three subjects who discontinued in-between periods, reason for discontinuation was not related to safety or tolerability.

A total of 4 AEs were reported in 3 subjects (vomiting, dizziness, dyskinesia and anemia), the relationship to the treatment was assessed as unrelated or unlikely related for all 4 AEs.

Overall, clinical laboratory parameters, vital signs, ECG, and results from physical examinations showed no clinically relevant trends over time or notable individual subject changes, with the exception of one subject who experienced a clinically significant decrease in hematology parameters, which was recorded as an AE (anemia). UPDRS part III scores (ON and OFF state) were comparable between the treatments and no notable changes occurred during the trial.

Conclusions:

Safinamide after single dose and at steady-state does not appear to have a clinically relevant effect on levodopa pharmacokinetics.

The administration of safinamide 100 mg once daily in combination of levodopa for 6 days was well tolerated.