MOTION (safinaMide add-On To dopamine agonist in early Idiopathic ParkinsON's disease) study design: a 24-week, double-blind, placebo-controlled study of the efficacy and safety of safinamide

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INTRODUCTION

- Dopamine agonists (DAs) are first-line agents for Parkinson's disease (PD), particularly in younger patients.[1] As disease progresses, patients may require add-on treatment to control their motor symptoms. However, to date, no drug has been approved as add-on to DAs.
- There is also an unmet need for treatments that improve the non-motor symptoms of PD. As some of these symptoms appear to be mediated by non-dopaminergic pathologies,[2] agents with a mechanism of action 'beyond dopamine' may be beneficial.
- Safinamide is an α-aminoamide in Phase III clinical development as add-on therapy to levodopa or DAs in patients with PD. It has both dopaminergic and non-dopaminergic mechanisms of action, including monoamine oxidase-B and dopamine reuptake inhibition, activity-dependent sodium channel antagonism, and inhibition of glutamate release *in vitro*.[3-5]
- Previous clinical studies have shown that safinamide significantly improves motor symptoms when used as add-on to DA therapy in early PD.[6,7]

OBJECTIVE

- The objective of the MOTION study is to further evaluate the efficacy and safety of safinamide as add-on therapy to a stable dose of DA in patients with early-stage PD. Here, we describe the MOTION study design and highlight its key features.

METHODS

Study design

- Phase III, 24-week, randomized, double-blind, placebo-controlled, multi-national study.
- The study consists of four periods: screening, treatment, taper/entry to long-term extension, and safety follow-up (Figure 1).
- Patients completing the MOTION study have the option to enter an 18-month extension study (Figure 1).
- Over 20 countries are participating in this global study, throughout five continents (Figure 2).

Patients

- Inclusion criteria:
  - Diagnosis of idiopathic PD (<5 years' duration)
  - Hoehn and Yahr Stage I–III
  - Male or female, aged 30–80 years.
- Key exclusion criteria:
  - Forms of Parkinsonism other than idiopathic PD
  - Current end-of-dose wearing-off or ON-OFF phenomena, disabling peak-dose or biphasic dyskinesia, or unpredictable or widely swinging fluctuations
  - Psychosis, depression (GRID Hamilton Rating Scale for Depression–17-item [GRID HAM-D] >17), dementia, or cognitive dysfunction.

Treatments

- At least 666 subjects will be randomized in a 1:1:1 ratio to:
  - Safinamide 50 mg/day
  - Safinamide 100 mg/day
  - Placebo.
- Patients will have been receiving treatment with a single DA at a stable dose for ⩾4 weeks before screening and throughout study treatment.
- Safinamide will be taken orally once per day, in the morning with breakfast, in addition to the morning dose of the subject's DA.
- PD treatments (other than DAs) are not permitted within 8 weeks before screening or during the study.

Outcome parameters

- Efficacy and safety parameters are shown in Figure 3.

Statistical analysis

- Sample size
  - At least 666 randomized subjects, resulting in a total of 498 evaluable subjects, will provide at least 90% power to detect a clinically meaningful difference of 2.5 points in the primary efficacy parameter, the Unified Parkinson's Disease Rating Scale (UPDRS) Section III score change from baseline to 24 weeks, between safinamide and placebo treatment groups, assuming a common standard deviation of 7 points, Type-I error rate of 5%, and a 25% drop-out rate.
- Data analysis
  - **Primary efficacy parameters and other continuous parameters:** analysis of covariance (ANCOVA) model on the change from baseline to Week 24, with baseline values as the covariate.
  - **Other parameters:** a logistic regression model will be used for Clinical Global Impression of Change (CGI-C) and Patient's Global Impression of Change (PGIC) data.
  - Data will be analyzed in a hierarchical fashion. For the primary efficacy parameter, a comparison between safinamide 100 mg/day and placebo will be conducted first and, if significant, the difference between safinamide 50 mg/day and placebo will be tested. For each sequential efficacy parameter, the 100 mg versus placebo analysis will only be conducted if the results for the previous efficacy parameter (100 mg versus placebo) were significant; the same will apply to the 50 mg versus placebo analysis.

Key features

- In addition to standard outcome parameters for motor symptoms, two common non-motor symptoms of PD will be assessed:
  - **Cognition** – the Cogtest® PD Battery
    - Specifically designed to assess the pattern of cognitive deficits seen in PD
    - Electronic collection of participant responses and automated scoring minimize examiner error
    - Interactive touch-screen interface, immediate response mechanisms, and motivational tasks engage the participant and ensure optimum outcomes.
  - **Depression** – GRID HAM-D (17-item)
    - Assesses depressed mood and the vegetative and cognitive symptoms of depression
    - Intensity and frequency are evaluated separately for each item.
- All raters will be trained on the use of the scales and, if possible, have at least two years' experience of their use. All raters will be approved, based on their performance compared with a consensus rating on one or more videotaped subject interviews or assessments. Additional training will be conducted periodically during the study.

Other features

- The following parameters are being assessed during the study:
  - Patient-reported outcomes (activities of daily living, PGIC, and quality of life)
  - Health-resource utilization
  - Ambulatory blood-pressure monitoring (in selected countries)
  - Pharmacokinetic modeling
  - Biomarker analysis.

CONCLUSIONS

- **MOTION will be the largest Phase III study evaluating the effect of add-on therapy to DAs for the treatment of patients with early PD.**
- **As well as traditional endpoints, the study will evaluate common non-motor symptoms and patient-related outcomes.**
- **The efficacy and safety of safinamide as add-on therapy to levodopa in patients with mid- to late-stage PD are also being studied, in the ongoing SETTLE study (see Poster 378).**

Figure 1. MOTION study design

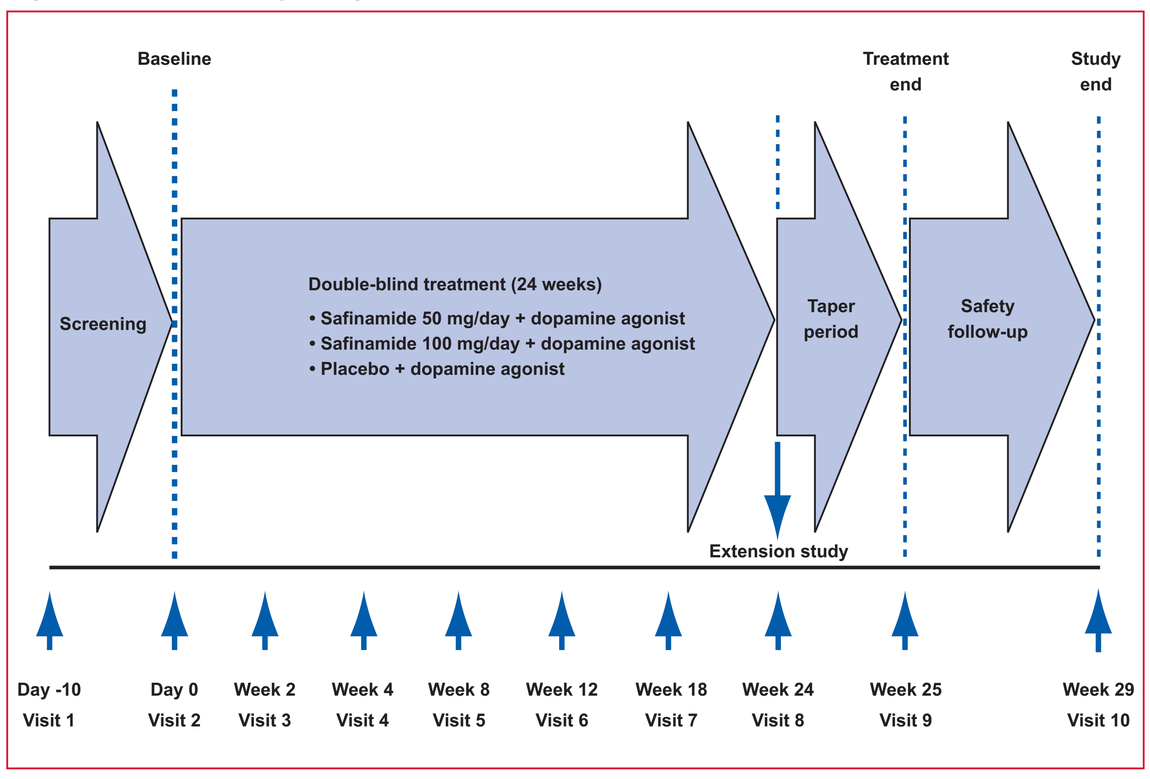

Figure 2. Countries participating in the MOTION study

Figure 3. MOTION study outcome parameters

Outcome	Parameters
Primary efficacy*	• UPDRS Part III (motor examination)
Secondary efficacy*	• UPDRS Part II (ADL) • Cogtest® PD battery (*see Key features*) • CGI-C • Proportion of subjects with scores 1, 2, 3 (showing improvement) on the CGI-C scale at Week 24 • CGI-C score at Week 24 • Proportion of responders (subjects with >30% improvement on the UPDRS Part III) • EQ-5D™ • PDQ-39 • PGIC score at Week 24
Tertiary efficacy*	• Hoehn and Yahr stage • GRID HAM-D • UPDRS Part IV (complications of therapy) • UPDRS Part I (mentation, behavior, and mood) • MMSE • Health Resource Utilization questionnaire
Safety	• TEAEs • Laboratory safety tests, ECG morphology, vital signs (including ABPM in selected countries), ophthalmologic and dermatologic examinations, impulse control disorders (QUIP), and level of daytime sleepiness
Other	• Pharmacokinetics • Biomarkers

ABPM, ambulatory blood-pressure monitoring; ADL, activities of daily living; CGI-C, Clinical Global Impression of Change; ECG, electrocardiogram; EQ-5D, EuroQol-5 Dimensions Questionnaire; GRID HAM-D, GRID version of the Hamilton Rating Scale for Depression; MMSE, Mini-Mental State Examination; PD, Parkinson's Disease; PDQ-39, Parkinson's Disease Questionnaire–39-item; PGIC, Patients Global Impression of Change; QUIP, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease; TEAE, treatment-emergent adverse events; UPDRS, Unified Parkinson's Disease Rating Scale

*Unless otherwise stated, parameters will be analyzed as a change from baseline to Week 24

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Effect of safinamide on depressive symptoms in patients with mid-late stage Parkinson's disease

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INTRODUCTION

- Depression is common in Parkinson's disease (PD): an estimated 35% of patients have clinically significant depressive symptoms, while 17% have major depressive disorder.[1] Depression is associated with poor quality of life;[2,3] it also has a negative impact on patients' ability to function[4] and increases caregiver burden.[2] PD therapy should, therefore, be focused on improving both motor and depressive symptoms.
- The precise pathology underlying depressive symptoms in PD is not known, but data suggest that both dopaminergic and non-dopaminergic mechanisms are involved.[5,6]
- Safinamide is an α-aminoamide in development for use in PD that has both dopaminergic and non-dopaminergic mechanisms of action.[7,8]

OBJECTIVE

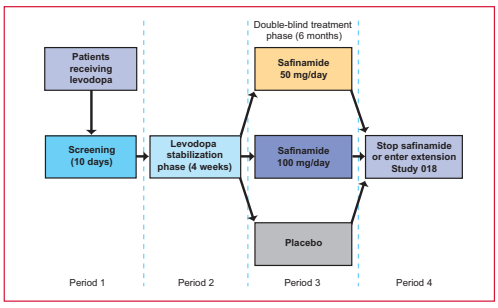
- The efficacy and safety of safinamide as add-on therapy to stable levodopa were assessed in a Phase III trial in patients with mid- to late-stage PD and motor fluctuations. Here, we describe data on the effect of safinamide on symptoms of depression in study participants.

METHODS

Study design

- 24-week, multi-center, randomized, double-blind, placebo-controlled, parallel-group study with four periods: screening, stabilization, treatment, and taper/entry to the long-term extension study (Figure 1).

Figure 1. Study design



Patients

- Male or female patients aged 30 to 80 years with idiopathic PD (>3 years' duration) and Hoehn and Yahr Stage I–IV.
- Patients with motor fluctuations (>1.5 hours' daily OFF time). Patients were excluded if they had wide/unpredictable fluctuations or severe, disabling peak-dose or biphasic dyskinesia.
- Patients with depression, defined as a GRID Hamilton Rating Scale for Depression–17-item (GRID HAM-D) total score >17, were also excluded.

Treatments

- Once-daily single dose of safinamide 50 mg/day, safinamide 100 mg/day, or placebo as add-on therapy to levodopa.
- The levodopa dose was to remain stable during the 24-week treatment period, if possible.
- Patients on PD therapies other than monoamine oxidase-B inhibitors were eligible for inclusion, but the dose had to remain stable during the treatment period, if possible.
- If a patient's clinical condition warranted a change (increase or decrease) in the dose of levodopa or other PD therapies (i.e. in the event of clinically significant motor deterioration or adverse events, respectively), all endpoint evaluations were carried out before the change was made.

Assessments

- The primary efficacy endpoint was the change in mean daily ON time (ON time without dyskinesia plus ON time with minor dyskinesia) recorded in patient diaries. Other efficacy variables included changes in the GRID HAM-D total score and the patient-rated 'emotional wellbeing' subscale of the PD Questionnaire (PDQ-39).
- The following post hoc analyses were carried out:
  - GRID HAM-D item scores
  - Change in GRID HAM-D total score according to baseline score (<10 and ⩾10) and antidepressant use.
- Safety assessments included treatment-emergent adverse events (TEAEs), laboratory data, and vital signs.

Statistical analysis

- Least squares (LS) means changes (baseline to Week 24) between active treatment and placebo were compared using a mixed linear model (ON time) and ANCOVA (other efficacy endpoints).

RESULTS

- In total, 669 patients were randomized to treatment (Table 1) and 594 patients (89%) completed the study.
- There were no significant differences between the treatment groups for any demographic or disease-related characteristics (Table 1).

Table 1. Patient demographics and baseline characteristics

Characteristic	Placebo (n=222)	Safinamide 50 mg/day (n=223)	Safinamide 100 mg/day (n=224)
Gender, n (%)			
Male	160 (72.1)	157 (70.4)	163 (72.8)
Race, n (%)			
White	42 (18.9)	43 (19.3)	44 (19.6)
Asian	180 (81.1)	180 (80.7)	179 (79.9)
Age, years, mean (SD)	59.4 (9.41)	60.1 (9.67)	60.1 (9.19)
Disease duration, years, mean (SD)	8.3 (3.76)	7.9 (3.98)	8.2 (3.79)
Daily ON time,[a] hours, mean (SD)	9.3 (2.15)	9.4 (2.26)	9.5 (2.43)
Daily OFF time, hours, mean (SD)	5.3 (2.06)	5.2 (2.08)	5.2 (2.16)
GRID HAM-D total score, mean (SD)	5.9 (3.70)	6.0 (3.70)	6.0 (3.55)
PDQ-39 emotional well being score, mean (SD)	30.4 (18.29)	31.1 (19.70)	30.8 (18.86)

[a]Without troublesome dyskinesia
GRID HAM-D, GRID Hamilton Rating Scale for Depression–17-item; PDQ-39, Parkinson's Disease Questionnaire; SD, standard deviation

Efficacy

- The addition of safinamide to stable doses of levodopa resulted in significant increases in total daily ON time without troublesome dyskinesia in both safinamide groups versus placebo (Table 2).

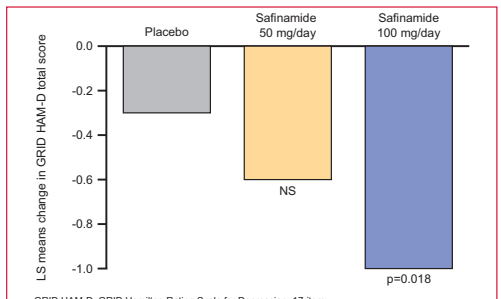
Table 2. Effect of safinamide on patient-recorded functional state: LS means difference versus placebo at Week 24

Characteristic recorded	Safinamide 50 mg/day		Safinamide 100 mg/day	
	Difference vs placebo (hours/day)	p-value	Difference vs placebo (hours/day)	p-value
ON time without dyskinesia	0.5	0.0367	0.7	0.0070
ON time with minor dyskinesia	0.0	0.9196	-0.1	0.5881
ON time with troublesome dyskinesia	0.1	0.5324	0.0	0.9931
OFF	-0.6	0.0022	-0.6	0.0027
Asleep	-0.1	0.5021	0.0	0.6727

Least squares (LS) means and p-values were calculated from an ANCOVA model based on the change from baseline to endpoint, with the baseline value as a covariate

- The improvement in GRID HAM-D total score was significantly greater for safinamide 100 mg/day versus placebo (Figure 2).

Figure 2. LS means change in GRID HAM-D total score between baseline and Week 24



GRID HAM-D, GRID Hamilton Rating Scale for Depression–17-item; LS, least squares; NS, not significant; p-value vs placebo

- Improvements in GRID HAM-D item scores for early insomnia, work and activities, and somatic anxiety were also significantly greater for safinamide 100 mg/day versus placebo; depressed mood and loss of appetite were of borderline significance (p=0.0561 and p=0.0584, respectively) (Table 3).

Table 3. LS means change in GRID HAM-D item scores between baseline and Week 24

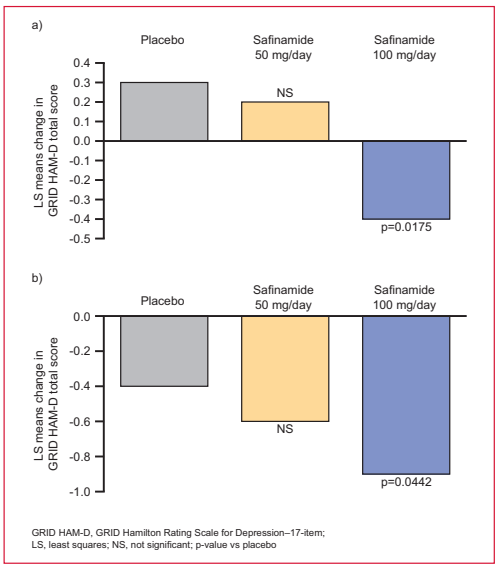
GRID HAM-D item	Placebo (n=222)	Safinamide 50 mg/day (n=223)	Safinamide 100 mg/day (n=224)
Depressed mood	-0.1	0.0	-0.2†
Guilt	0.0	-0.1	0.0
Suicide	0.0	0.0	0.0
Insomnia, early	0.0	0.0	-0.1*
Insomnia, middle	0.1	0.1	0.0
Insomnia, late	0.0	0.0	0.0
Work and activities	0.1	0.0	-0.1*
Psychomotor retardation	-0.1	-0.1	-0.1
Psychomotor agitation	0.0	0.0	-0.1
Anxiety, psychic	-0.1	-0.1	-0.1
Anxiety, somatic	0.0	-0.1†	-0.1**
Loss of appetite	-0.1	-0.1	0.0†
Somatic symptoms, general	0.0	0.0	0.0
Sexual interest	0.0	-0.1†	0.0
Hypochondriasis	0.0	0.0	0.0
Loss of weight (medical history)	0.0	-0.1	0.0
Loss of weight (psychiatrist rating)	0.1	0.2	0.1
Insight	0.0	0.0†	0.0

†p<0.1; *p<0.05; **p<0.01 vs placebo
Data rounded to one decimal place
GRID HAM-D, GRID Hamilton Rating Scale for Depression–17-item; LS, least squares

- Safinamide 100 mg/day was also associated with a significantly greater improvement in the emotional wellbeing subscale of the PDQ-39. LS means changes from baseline were -1.5 in the placebo group, -2.5 in the safinamide 50 mg/day group, and -5.0 in the safinamide 100 mg/day group (p=0.4236 and p=0.009 versus placebo, respectively).

- Most patients (>80%) had a baseline GRID HAM-D total score <10 (184/222 patients in the placebo group, 185/223 patients in the safinamide 50 mg/day group, and 187/224 patients in the safinamide 100 mg/day group) and >90% were not taking antidepressants (205, 206, and 213 patients, respectively). In both subgroups, LS means change in score at Week 24 was significantly greater for safinamide 100 mg (but not 50 mg/day) versus placebo (Figure 3). Between-group differences for the other subgroups (GRID HAM-D ⩾10 and antidepressant use) were not significant.

Figure 3. LS means change in GRID HAM-D total score between baseline and Week 24 in (a) patients with a GRID HAM-D score <10 at baseline and (b) not taking antidepressants at baseline



GRID HAM-D, GRID Hamilton Rating Scale for Depression–17-item; LS, least squares; NS, not significant; p-value vs placebo

Tolerability and safety

- Incidences of TEAEs were 30% for safinamide 50 mg/day, 29% for safinamide 100 mg/day, and 22.5% for placebo (p=0.209). The rate of discontinuation due to TEAEs was low (5–6%) and similar between treatment groups.
- Depression was reported as a TEAE in fewer patients in both safinamide groups compared with placebo. Although dyskinesia was reported as a TEAE more frequently in the safinamide groups versus placebo, it was generally transient and mild or moderate in severity. The most common TEAEs are shown in Table 4.
- Changes in laboratory values and vital signs were similar between treatment groups.

Table 4. Treatment-emergent adverse events reported by ⩾5% of patients in any treatment group

Event	Placebo (n=222) n (%)	Safinamide 50 mg/day (n=223) n (%)	Safinamide 100 mg/day (n=224) n (%)
Number of patients reporting at least 1 TEAE	150 (67.6)	149 (66.8)	149 (66.5)
Dyskinesia	27 (12.2)	46 (20.6)	40 (17.9)
Worsening PD	18 (8.1)	11 (4.9)	9 (4.0)
Cataract	15 (6.8)	9 (4.0)	14 (6.3)
Back pain	13 (5.9)	10 (4.5)	11 (4.9)
Depression	11 (5.0)	2 (0.9)	4 (1.8)
Headache	10 (4.5)	12 (5.4)	11 (4.9)

PD, Parkinson's disease; TEAE, treatment-emergent adverse event

CONCLUSIONS

- **In PD patients with levodopa-induced motor fluctuations and without clinical depression, safinamide 100 mg/day significantly improved both motor symptoms and depressive symptoms rated by physicians and patients. Depression was also reported less frequently as a TEAE in both safinamide groups versus placebo.**
- **Safinamide was also well tolerated in this population of patients: incidences of treatment-related TEAEs, TEAEs leading to discontinuation, and changes in laboratory and vital-sign data were similar to placebo.**
- **Depressive symptoms are also being studied in the ongoing MOTION and SETTLE studies, which are evaluating the efficacy and safety of safinamide as add-on therapy to dopamine agonists and levodopa, respectively, in patients with PD (see Posters 319 and 378).**

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Safinamide as add-on to levodopa improves motor function without worsening dyskinesia in patients with mid-late Parkinson's disease

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INTRODUCTION

- Levodopa is still regarded as the most effective drug for treating the motor symptoms of Parkinson's disease (PD).[1] However, longer-term use is associated with motor fluctuations and dyskinesia,[2] which can impact on patients' quality of life.[3]
- Patients with levodopa-induced motor fluctuations (for example, wearing off) usually require add-on therapy. However, agents that increase dopaminergic function (and therefore have the potential to improve motor function) may exacerbate dyskinesia. For this reason, there is a need for agents with a mechanism of action that extends to non-dopaminergic systems.
- Safinamide is an α-aminoamide in Phase III clinical development as an add-on therapy to dopamine agonists or levodopa. Safinamide has both dopaminergic and non-dopaminergic mechanisms of action, including monoamine oxidase-B (MAO-B) and dopamine reuptake inhibition, activity-dependent sodium channel antagonism, and inhibition of glutamate release *in vitro*.[4-6]

OBJECTIVE

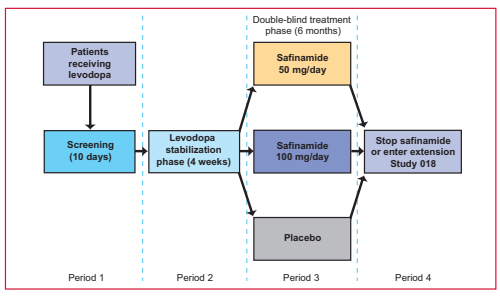
- To evaluate the effect of safinamide as add-on to stable levodopa on motor function and dyskinesia in patients with mid- to late-stage PD experiencing motor fluctuations.

METHODS

Study design

- 24-week, multi-center, randomized, double-blind, placebo-controlled, parallel-group study with four periods: screening, stabilization, treatment, and taper/entry to the long-term extension study (Figure 1).

Figure 1. Study design



Patients

- Male or female patients aged 30 to 80 years with idiopathic PD (>3 years' duration; Hoehn and Yahr Stage I–IV) and motor fluctuations (>1.5 hours' daily OFF time).
- Patients were excluded if they had wide/unpredictable fluctuations or severe, disabling peak-dose or biphasic dyskinesia.

Treatments

- Safinamide 50 mg/day, safinamide 100 mg/day, or placebo as add-on therapy to levodopa.
- The levodopa dose was to remain stable during the 24-week treatment period, if possible.
- Patients on PD therapies other than MAO-B inhibitors were eligible for inclusion, but the dose had to remain stable during the treatment period, if possible.
- If a patient's clinical condition warranted a change (increase or decrease) in the dose of levodopa or other PD therapies (i.e. in the event of clinically significant motor deterioration or adverse events, respectively), all endpoint evaluations were carried out before the change was made.

Assessments

- The primary efficacy endpoint was the change (baseline to Week 24) in mean daily ON time (ON time without dyskinesia plus ON time with minor dyskinesia). This information was recorded by patients in a daily diary.
- Secondary endpoints included the change (baseline to Week 24) in scores for the Unified Parkinson's Disease Rating Scale (UPDRS) Parts III (motor examination) and IV (complications of therapy), and the Dyskinesia Rating Scale (DRS).
- Post hoc analyses on the UPDRS subscale scores were carried out to further evaluate the effect of safinamide on motor function and dyskinesia (Table 1).
- Safety assessments included treatment-emergent adverse events (TEAEs), laboratory data, and vital signs.

Table 1. UPDRS subscale scores evaluated in the post hoc analysis

Motor function	UPDRS items
Bradykinesia	Part II, Items 23–26, 31
Rigidity	Part III, Item 22
Postural instability gait disorder	Part III, Items 13–15, 29, 30
Freezing when walking	Part II, Item 14
Dyskinesia	Part IV, Items 32–34
Dyskinesia and dystonia[a]	Part IV, Items 32–35

[a]Individual scores for Items 32–35 were also evaluated
UPDRS, Unified Parkinson's Disease Rating Scale

Statistical analysis

- Least squares means changes (baseline to Week 24) between active treatment and placebo were compared using a mixed linear model (ON time) and ANCOVA (UPDRS), and Wilcoxon rank sum test (DRS scores).

RESULTS

- In total, 669 patients were randomized to treatment (Table 2) and 594 patients (89%) completed the study.

Table 2. Patient demographics and baseline characteristics

Characteristic	Placebo (n=222)	Safinamide 50 mg/day (n=223)	Safinamide 100 mg/day (n=224)
Gender, n (%) Male	160 (72.1)	157 (70.4)	163 (72.8)
Race, n (%) White	42 (18.9)	43 (19.3)	44 (19.6)
Asian	180 (81.1)	180 (80.7)	179 (79.9)
Age, years, mean (SD)	59.4 (9.41)	60.1 (9.67)	60.1 (9.19)
Disease duration, years, mean (SD)	8.3 (3.8)	7.9 (4.0)	8.2 (3.8)
Daily ON time,[a] hours, mean (SD)	9.3 (2.2)	9.4 (2.3)	9.5 (2.4)
Daily OFF time, hours, mean (SD)	5.3 (2.1)	5.2 (2.1)	5.2 (2.2)
UPDRS Part III (motor examination) score, mean (SD)	28.7 (12.03)	27.3 (12.67)	28.3 (13.30)
Daily levodopa dose, mg, mean (SD)	660 (454)	633 (346)	601 (341)

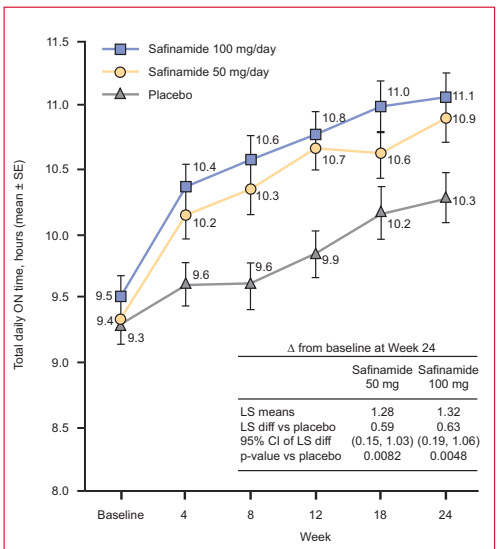
[a]Without dyskinesia or with minor dyskinesia
SD, standard deviation; UPDRS, Unified Parkinson's Disease Rating Scale

- There were no significant differences between the treatment groups for any demographic or disease-related characteristics (Table 2).
- The levodopa dose was to remain stable during the study, but there was a small increase in dose (0.27%) in the placebo group and small decreases in the safinamide 50 and 100 mg/day groups (-1.05% and -2.16%; p=0.016 for safinamide 100 mg/day versus placebo).

Efficacy

- The addition of safinamide to stable doses of levodopa resulted in significant increases in total daily ON time (without dyskinesia or with minor dyskinesia) in both safinamide groups (~1.3 h) versus placebo (0.63 h) (Figure 2). There were no significant between-group differences for the change in ON time with troublesome dyskinesia (+0.2 h for placebo, +0.3 h for safinamide 50 mg/day, and +0.2 h for safinamide 100 mg/day).

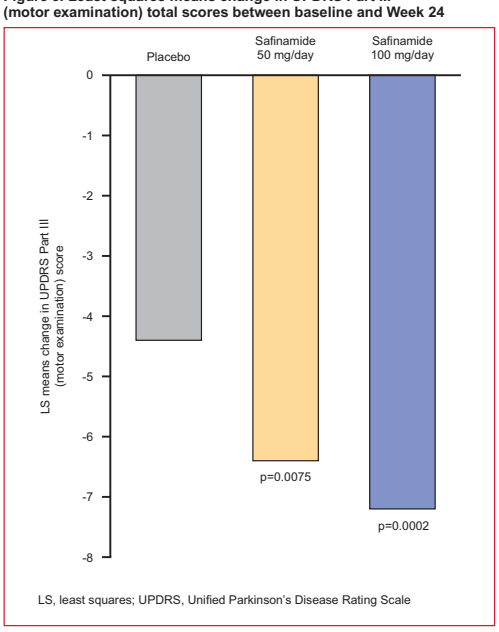
Figure 2. Mean change in ON time (ON without dyskinesia plus ON with minor dyskinesia) during the course of the study



Using an ANCOVA analysis, all time points after baseline were statistically significant when compared with placebo, with the exception of safinamide 50 mg/day at Week 18 (p=0.0739).
CI, confidence interval; LS, least squares; SE, standard error

- Both doses of safinamide were associated with significant improvements in UPDRS Part III (motor examination) scores versus placebo (Figure 3). There were also significant improvements in the UPDRS Part III subscale scores for safinamide 100 mg/day versus placebo (Table 3).

Figure 3. Least squares means change in UPDRS Part III (motor examination) total scores between baseline and Week 24



LS, least squares; UPDRS, Unified Parkinson's Disease Rating Scale

Table 3. Least squares means change in motor and dyskinesia scores between baseline and Week 24

Parameter	Placebo (n=222)	Safinamide 50 mg/day (n=223)	Safinamide 100 mg/day (n=224)
Motor			
UPDRS III, bradykinesia	-1.6	**-2.6 (p=0.014)**	**-2.7 (p=0.005)**
UPDRS III, rigidity	-1.1	-1.5 (p=0.060)	**-1.6 (p=0.017)**
UPDRS III, postural instability gait disorder	-0.2	-0.2 (p=0.278)	**-0.3 (p=0.006)**
UPDRS II, freezing when walking	-0.2	-0.2 (p=0.730)	**-0.3 (p=0.040)**
Dyskinesia			
UPDRS IV, dyskinesia	0.1	-0.1 (p=0.171)	-0.1 (p=0.0828)
UPDRS IV, dyskinesia and dystonia	-0.0	-0.1 (p=0.072)	-0.1 (p=0.094)
DRS	-0.2	-0.2 (p=0.2992)	-0.3 (p=0.2743)

DRS, Dyskinesia Rating Scale; UPDRS, Unified Parkinson's Disease Rating Scale

- There were no statistically significant differences for either dose of safinamide versus placebo for the change in UPDRS Part IV scores for dyskinesia and/or dystonia or for the DRS scores (Table 3).

Tolerability and safety

- Incidences of treatment-related TEAEs were 30% for safinamide 50 mg/day, 29% for safinamide 100 mg/day, and 22.5% for placebo (p=0.209). The rate of discontinuation due to TEAEs was low (5–6%) and similar between treatment groups.
- The most common TEAEs are shown in Table 4. Although dyskinesia was reported as a TEAE more frequently in the safinamide groups versus placebo, it was generally transient and mild or moderate in severity. Furthermore, there were no significant between-group differences for patient-reported ON time with troublesome dyskinesia, or for the physician-rated UPDRS Part IV scores (dyskinesia and/or dystonia) or DRS scores (see Table 3).
- Changes in laboratory values and vital signs were similar between treatment groups.

Table 4. Treatment-emergent adverse events reported by ≥5% of patients in any treatment group

Event	Placebo (n=222) n (%)	Safinamide 50 mg/day (n=223) n (%)	Safinamide 100 mg/day (n=224) n (%)
Number of patients reporting at least 1 TEAE	150 (67.6)	149 (66.8)	149 (66.5)
Dyskinesia	27 (12.2)	46 (20.6)	40 (17.9)
Worsening PD	18 (8.1)	11 (4.9)	9 (4.0)
Cataract	15 (6.8)	9 (4.0)	14 (6.3)
Back pain	13 (5.9)	10 (4.5)	11 (4.9)
Depression	11 (5.0)	2 (0.9)	4 (1.8)
Headache	10 (4.5)	12 (5.4)	11 (4.9)

PD, Parkinson's disease; TEAE, treatment-emergent adverse event

CONCLUSIONS

- **Based on patient diary data, add-on therapy with safinamide significantly improved ON time with non-troublesome dyskinesia in patients with levodopa-induced motor complications; it also significantly improved overall motor function in these patients.**
- **Dyskinesia reported as a TEAE was more frequent in the safinamide groups than in placebo, but was generally transient and mild or moderate in severity. All other TEAEs were similar in incidence to placebo.**
- **Safinamide was also well tolerated in this population of patients: incidences of TEAEs leading to discontinuation and changes in laboratory and vital-sign data were similar to placebo.**
- **The effects of safinamide as add-on therapy in patients with levodopa-induced motor complications are also being studied in the ongoing SETTLE study (see Poster 378).**

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SETTLE study design: a 24-week, double-blind, placebo-controlled study of the efficacy and safety of safinamide as add-on therapy to levodopa in patients with Parkinson's disease

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INTRODUCTION

- Although levodopa is very effective for treating the motor symptoms of Parkinson's disease (PD), its long-term use is associated with motor fluctuations and dyskinesia.[1] In fact, it has been estimated that ~40% of patients develop motor complications after 4–6 years of levodopa treatment.[2]
- Patients with levodopa-induced motor fluctuations usually require add-on therapy, the aim of which is to improve motor function by prolonging ON time without exacerbating (or ideally, improving) dyskinesia. Currently available add-on dopaminergic therapy may improve motor function, but this often occurs at the expense of worsening dyskinesia. Agents that combine dopaminergic and non-dopaminergic mechanisms of action may address the need for more effective and safer control of levodopa-related motor complications.
- Safinamide is an α-aminoamide in Phase III clinical development as add-on therapy to levodopa or dopamine agonists in patients with PD. It has both dopaminergic and non-dopaminergic mechanisms of action, including monoamine oxidase-B and dopamine reuptake inhibition, activity-dependent sodium channel antagonism, and inhibition of glutamate release *in vitro*.[3-5]
- Previous clinical studies have shown that safinamide significantly improves ON time without troublesome dyskinesia when used as add-on to stable doses of levodopa in patients with PD and motor fluctuations.[6]

OBJECTIVE

- The SafinamidE Treatment as add-on To LEvodopa in idiopathic PD (SETTLE) study has been designed to further evaluate the use of safinamide as add-on to stable levodopa in patients with mid- to late-stage PD and motor fluctuations. Here, we describe the SETTLE study design and highlight its key features.

METHODS

Study design

- Phase III, 24-week, randomized, double-blind, placebo-controlled, multi-national study.
- Patients completing the SETTLE study have the option to enter a long-term, open-label safety study (Figure 1).
- The study consists of five periods: screening, stabilization, treatment, taper, and safety follow-up.
- Over 20 countries are participating in this global study, throughout five continents (Figure 2).

Patients

- Key inclusion criteria:
  - Male or female, aged 30–80 years
  - Diagnosis of idiopathic PD (≥3 years' duration)
  - Hoehn and Yahr Stage I–IV (during OFF state)
  - Stable doses of levodopa with >1.5 hours' OFF time per day.
- Key exclusion criteria:
  - Severe, disabling peak-dose or biphasic dyskinesia and/or unpredictable or widely swinging fluctuations
  - Psychosis, depression (GRID Hamilton Rating Scale for Depression–17-item [GRID HAM-D] >17), dementia, or cognitive dysfunction
  - Treatment with monoamine oxidase inhibitors.

Treatments

- Patients will be treated with safinamide 50–100 mg/day or placebo as add-on to levodopa.
  - They will receive the maximum tolerated dose of safinamide (50 or 100 mg/day), taken orally, once daily in the morning with breakfast.
- Catechol-*O*-methyl transferase inhibitors, dopamine agonists, anticholinergics, and/or amantadine are permitted, provided that they have been taken at a stable dose in the 4 weeks before screening.
- The doses of levodopa and other PD treatments can be optimized during the stabilization period, but are to remain stable during the treatment period.

Outcome parameters

- Patients will record their functional status in daily diaries using the following criteria: ON with no dyskinesia, ON with non-troublesome dyskinesia, ON with troublesome dyskinesia, and OFF.
- The primary efficacy parameter is the change (baseline to Week 24) in daily ON time without troublesome dyskinesia. Other efficacy parameters, as well as the safety parameters, are shown in Figure 3.

Statistical analysis

- Sample size
  - At least 484 randomized subjects (242 per group), resulting in 416 evaluable subjects, will provide at least 90% power to detect a clinically meaningful difference of 0.75 hours in the primary efficacy parameter, change from baseline to Week 24 in daily ON time, between the safinamide and placebo groups, assuming a common standard deviation of 2.35 hours, Type-I error rate of 5%, and a 14% drop-out rate.
- Data analysis
  - **Primary efficacy parameter and other continuous parameters:** analysis of covariance (ANCOVA), with baseline values as the covariate.
  - **Other parameters:** a logistic regression model will be used for Clinical Global Impression of Change (CGI-C) and Patient's Global Impression of Change (PGIC) data.
  - If the primary efficacy parameter is statistically significant, secondary efficacy parameters will be analyzed in a hierarchical fashion.

Key features

- In addition to standard outcome parameters for motor complications, two common non-motor symptoms of PD will be assessed:
  - **Cognition** – the Cogtest® PD Battery
    - Specifically designed to assess the pattern of cognitive deficits seen in PD
    - Electronic collection of participant responses and automated scoring minimize examiner error
    - Interactive touch-screen interface, immediate response mechanisms, and motivational tasks engage the participant and ensure optimum outcomes.
  - **Depression** – GRID HAM-D (17-item)
    - Assesses depressed mood and the vegetative and cognitive symptoms of depression
    - Intensity and frequency are evaluated separately for each item.
- All raters will be trained on the use of the scales and, if possible, have at least two years' experience of their use. All raters will be approved, based on their performance compared with a consensus rating on one or more videotaped subject interviews or assessments. Additional training will be conducted periodically during the study.
- Patient-reported outcomes
  - As motor fluctuations and dyskinesia can affect patients' ability to function, the study will also evaluate the effect of treatment on patient-reported outcomes, including the patient's opinion on his/her overall clinical status (PGIC) and quality of life (EuroQol-5 dimensions questionnaire, EQ-5D; Parkinson's Disease Questionnaire–39-item, PDQ-39).

Other features

- The following parameters are being assessed during the study:
  - Health-resource utilization
  - Ambulatory blood-pressure monitoring (in selected countries)
  - Pharmacokinetic modeling
  - Biomarker analysis.

CONCLUSIONS

- **This large Phase III study of safinamide will provide further data on the efficacy and safety of this drug with both dopaminergic and non-dopaminergic pharmacologic properties as add-on to stable levodopa in patients with PD and motor fluctuations.**
- **In addition to traditional endpoints, including the effect of safinamide on time spent ON without troublesome dyskinesia, the study will also evaluate common non-motor symptoms and patient-reported outcomes.**
- **The efficacy and safety of safinamide as add-on therapy to dopamine agonists in patients with early PD are also being studied, in the ongoing MOTION study (see Poster 319).**

Figure 1. SETTLE study design

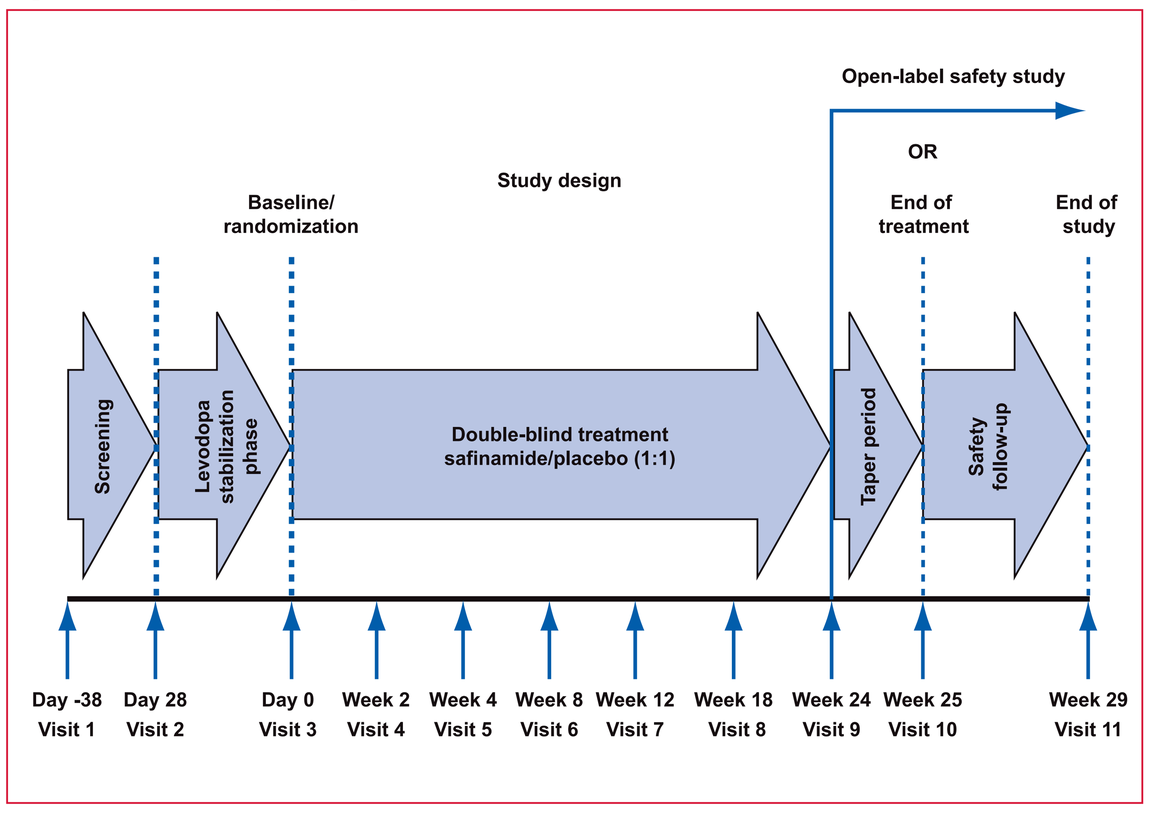

Figure 2. Countries participating in the SETTLE study

Figure 3. SETTLE study outcome parameters

Outcome	Parameters
Primary efficacy*	• Daily ON time without troublesome dyskinesia
Secondary efficacy*	• UPDRS Part II (ADL) during ON phase • Cogtest® PD battery *(see Key features)* • Dyskinesia Rating Scale during ON phase • CGI-S • Proportion of patients with an improvement (score of 1, 2, or 3) on CGI-C • CGI-C • UPDRS Part III (motor examination) during ON phase • Daily OFF time • Daily OFF time following morning levodopa dose • Change in levodopa dose • EQ-5D™ • PDQ-39 • Patient's Global Impression of Change
Tertiary efficacy*	• Hoehn and Yahr stage • GRID HAM-D • MMSE • Health Resource Utilization questionnaire • UPDRS Part I (mentation, behavior, and mood)
Safety	• TEAEs • Laboratory safety tests, ECG morphology, vital signs (including ABPM in selected countries), ophthalmologic and dermatologic examinations, impulse control disorders (QUIP), and level of daytime sleepiness
Other	• Pharmacokinetics • Biomarkers

ABPM, ambulatory blood-pressure monitoring; ADL, activities of daily living; CGI-C, Clinical Global Impression of Change; CGI-S, Clinical Global Impression of Severity; ECG, electrocardiogram; EQ-5D, EuroQol-5 Dimensions Questionnaire; GRID HAM-D, GRID version of the Hamilton Rating Scale for Depression; MMSE, Mini-Mental State Examination; PD, Parkinson's disease; PDQ-39, Parkinson's Disease Questionnaire–39-item; QUIP, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease; TEAE, treatment-emergent adverse events; UPDRS, Unified Parkinson's Disease Rating Scale
*Unless otherwise stated, parameters will be analyzed as a change from baseline to Week 24

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Cognition deficits in patients with mid- to late-stage Parkinson's disease

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INTRODUCTION

- Parkinson's disease (PD) is generally recognized as a movement disorder. However, patients may also experience non-motor symptoms such as autonomic disturbances, neuropsychiatric problems, and cognitive impairment, all of which can significantly impact on their quality of life and ability to function.[1]
- Cognitive impairment can occur early in the course of PD: studies indicate that 24–36% of newly-diagnosed patients have some degree of impairment.[2,3] Furthermore, cognitive impairment continues to decline as PD progresses,[4,5] and it has been estimated that approximately 60% of patients with cognitive impairment will progress to PD dementia.[6]
- Frontocortical functions (e.g. attention and executive function) are most commonly disrupted in early PD.[7] However, as PD progresses, patients increasingly show temporal-lobe-like deficits in learning and remote memory, as well as progressive deficits in attention and executive function.[8]

OBJECTIVE

- To use baseline data from a large Phase III study to evaluate cognitive functions in a large cohort of patients with mid- to late-stage PD.

METHODS

PD population

- The population used in the current analysis was recruited as part of a 24-week, double-blind, randomized, placebo-controlled trial to evaluate the efficacy and safety of safinamide in patients on stable levodopa with mid- to late-stage PD and motor fluctuations. Safinamide is an α-aminoamide that has both dopaminergic and non-dopaminergic mechanisms of action.
- The study consisted of four periods: screening, stabilization, treatment, and taper/entry to a long-term extension study. During the stabilization period, the dose of levodopa could be optimized if necessary.

Inclusion criteria

- Male or female patients aged 30 to 80 years.
- Diagnosis of idiopathic PD of >3 years' duration and Hoehn and Yahr Stage I–IV during an OFF period.
- Motor fluctuations (>1.5 hours' OFF time per day).

Exclusion criteria

- Wide/unpredictable fluctuations or severe, disabling peak-dose or biphasic dyskinesia.
- Psychosis or a score ⩾3 on Items 2 (thought disorder) or 3 (depression) of the Unified Parkinson's Disease Rating Scale Part I (mentation, behavior, and mood).
- Depression (GRID Hamilton Rating Scale for Depression-17-item scale score >17).
- History of (or current) substance abuse.

Baseline medications

- All patients were taking levodopa at baseline.
- Patients could also be taking other PD therapies except monoamine oxidase inhibitors.

Normative sample

Inclusion criteria

- The normative sample was generated from two separate populations. Both samples include randomly selected males and females aged 18–85 years who were fluent in English, had a minimum 8th-grade education, and provided informed consent.
- Subjects in the normative sample were considered healthy based on medical history or a Mini-Mental State Examination score >28.
- The control subjects were not age-matched with the PD patient population.

Exclusion criteria

- History of substance abuse; head injury leading to loss of function; medical or neurological conditions resulting in impaired cognitive or perceptual functions; clinically significant psychiatric conditions; unstable medical conditions.
- Subjects who had received any investigational drug within 30 days or who had used benzodiazepines or antihistamines within 24 hours of study assessment were also excluded.

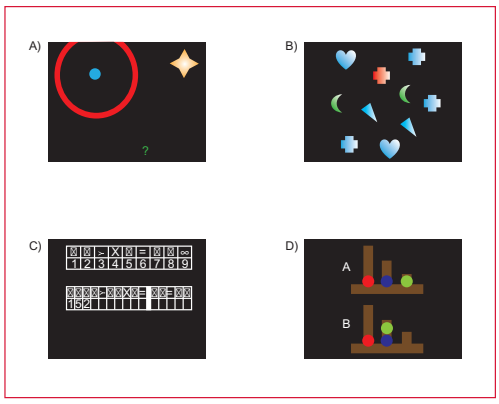
Cognitive evaluation

- Baseline cognitive functions were assessed at screening and at the end of the levodopa stabilization period.
- The following cognitive functions were assessed: declarative memory, working memory, executive function, complex attention, and psychomotor speed.
- Cognitive functions were assessed with Cogtest® (www.cogtest.com), a computerized neurocognitive test battery (Cogtest, Inc., Delaware, USA) designed for use in a variety of clinical populations and in clinical trials.
- The Cogtest® computerized console allows for accurate recording of reaction times and enhanced standardization of administration relative to conventional paper-pencil tests.

Cognitive measures

- Six tests were used to assess the different cognitive functions. One of the tests (spatial working memory) consisted of two variables and another (word list memory test) consisted of three, so there were nine variables in total:
  - **Auditory number sequencing (assesses working memory and executive function)**: subjects heard a series of numbers (e.g. "9..3..6"; minimum=2 digits, maximum=8 digits) and were asked to repeat them in numerical order, from lowest to highest.
  - **Spatial working memory (assesses visual working memory)**: in the immediate condition, subjects had to touch a briefly presented visual target on the screen. During the delayed condition, there was a delay between target presentation and the opportunity to respond, with equal numbers of trials (randomized) involving either a 2-second or 12-second delay between target presentation and the opportunity to respond. During the delay between presentation and recall, a number of distracters of variable location appeared that had to be actively touched by the subject. The distracter condition helped prevent both the subject's visual fixation location and hand position from remaining near the target (Figure 1A).
  - **Strategic target detection test (assesses complex attention and executive function)**: subjects touched the target stimuli (shapes) directly on a touch screen and had to learn which target was correct by choosing one of the stimuli following computer-generated feedback. The target stimuli changed X times during the test (Figure 1B).
  - **Word list memory test – immediate and delayed recall (assesses verbal learning and memory)**: this is a computerized word list learning test using the selective-reminding paradigm. After hearing a list of 16 words, subjects had to repeat the words. On subsequent trials, subjects were reminded of words they did not recall from the prior trial. A total of five learning trials and a 20-minute delayed memory trial were carried out.
  - **Symbol digit substitution (assesses psychomotor speed, scanning, and complex attention)**: subjects were presented with four rows of boxes on a computer screen; the first row contained symbols, the second row contained numbers, the third row contained the same symbols as the first row, and the boxes on the fourth row were empty. The subject's task was to select the number that corresponded to the symbol. The subject had a total of 90 seconds to complete 110 symbols (Figure 1C).
  - **Tower of London (assesses spatial planning, problem solving, and executive function)**: the subject was shown two displays on the screen, one below the other, each consisting of three pegs with three colored balls on the pegs. The subject's task was to think of the minimum number of moves required for the upper display to look like the lower one and verbalize their response to the tester (Figure 1D).

Figure 1. Sample screens from Cogtest® A) spatial working memory, B) strategic target detection, C) symbol digit substitution, D) Tower of London



Statistical analysis

- Cognitive data were converted into *z*-scores, based on the performance of 250 cognitively normal control subjects from the Cogtest® normative database, separated into 10-year age cohorts.
- *Z*-scores were calculated as follows:

$$\frac{\text{(Individual subject's score)} - \text{(control group's score)}}{\text{Standard deviation (SD) of the control group}}$$

- *Z*-scores are SD units, such that a *z*-score of 0 represents average performance and a *z*-score of -1.0 represents performance 1 SD below the control mean score. A test was classified as impaired if the *z*-score fell below -1.5 SD.
- Normal cognition is represented by a *z*-score of between +1.5 and -1.5 SD. For a normally distributed variable, 86% of the population will have *z*-scores within 1.5 SD of the mean, 7% will have *z*-scores below -1.5 SD, and 7% will have *z*-scores >1.5 SD above the mean (using the Chebyshev theorem: 56% fall within 1.5 SD of the mean and 44% fall outside of the mean for any distribution).[9]

RESULTS

Patient demographics

- Demographics of the PD patients and the control population are shown in Table 1. There were differences in subject age and ethnicity between the two groups, and educational level was not matched.

Table 1. Patient demographics

Characteristic	Control population (n=250)	Patients with PD (n=656)
Mean age, years (SD)	50.0 ± 17.6	60.2 ± 9.4
Duration of PD, years (range)	N/A	8.1 (2.37–27.3)
Hoehn and Yahr stage, n (%)		
Stage 1	N/A	53 (41)
Stage 2	N/A	73 (56)
Stage 3	N/A	4 (3)
Gender, %		
Male	49	72
Female	51	28
Ethnicity, (%)		
Native American	0	0
Asian	1	81
Caucasian	78	19
African-American	10	0
Other	11	0

N/A, not applicable; PD, Parkinson's disease; SD, standard deviation.

Cognitive measures

- Cognitive data recorded at the end of the levodopa stabilization period are reported.

Impairment by variable

- 94% of patients with mid- to late-stage PD exhibited impairment in at least one of the nine cognitive variables compared with cognitively normal subjects, with the greatest proportions of patients showing impairment in two (16%), three (17%), or four (16%) variables.
- PD patients demonstrated mean *z*-scores outside of normal limits (below -1.5) for several of the cognitive variables: auditory number sequencing, spatial working memory (short delay), spatial working memory (long delay), Tower of London, and strategic target detection.

Impairment by test

- 96% of patients with mid- to late-stage PD exhibited impairment in at least one of the six tests compared with the cognitively normal subjects (Table 2).
- Overall, 28–74% of patients with mid- to late-stage PD showed impaired performance in the auditory number sequencing (74%), spatial working memory (71%), word list memory (57%), strategic target detection (48%), Tower of London (46%), and symbol digit substitution (28%) tests.

Impairment by cognitive function

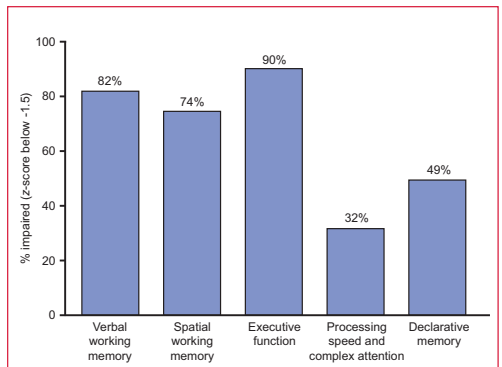
- Patients with mid- to late-stage PD exhibited impairments in all cognitive functions when compared with cognitively normal controls (Figure 2).
- 91% of patients showed impairment in at least one function, 83% showed impairment in multiple functions, and 12% showed impairment in all functions (Table 3).

Table 2. Patients with mid- to late-stage PD exhibiting impairment in at least one of the six tests* assessed by Cogtest®

Number of tests impaired (total of six tests)	Patients with impairment n (%)
0	42 (6)
1	91 (14)
2	131 (20)
3	153 (23)
4	136 (21)
5	83 (13)
6	20 (3)

*Auditory number sequencing, spatial working memory, strategic target detection test, word list memory (trial 1, learning, and delayed recall), symbol digit substitution, and Tower of London.
To be considered impaired in the word list memory and spatial working memory tests, patients had to show impairment in at least one of the variables (i.e. trial 1, total learning, or delayed recall for the former, and long or short spatial working memory for the latter).

Figure 2. Percentage of patients demonstrating impairment (z-score below -1.5) across the five functions assessed by Cogtest®



In order to be considered impaired in one of the cognitive functions, patients had to show impairment in at least one of the tests assessing that function.
Verbal working memory was assessed by the auditory number sequencing test and the word list memory, trial 1.
Spatial working memory was assessed by the spatial working memory test (short or long delay).
Executive function was assessed by the auditory number sequencing, the Tower of London, and the strategic target detection test.
Processing speed and complex attention was assessed by the symbol digit substitution test.
Declarative memory was assessed by the word list memory total learning and delayed recall tests.

Table 3. Patients with PD exhibiting impairment in at least one of the five cognitive functions assessed by Cogtest®

Number of functions impaired (total of five functions)	Patients with impairment n (%)
0	62 (9)
1	51 (8)
2	124 (19)
3	171 (26)
4	169 (26)
5	79 (12)

In order to be considered impaired in one of the cognitive functions, patients had to show impairment in at least one of the tests assessing that function.
Verbal working memory was assessed by the auditory number sequencing test and by word list memory, trial 1.
Spatial working memory was assessed the spatial working memory test (short or long delay).
Executive function was assessed by the auditory number sequencing test, the Tower of London, and the strategic target detection test.
Processing speed and complex attention were assessed by the symbol digit substitution test.
Declarative memory was assessed by the word list memory total learning and delayed recall tests.

CONCLUSIONS

- **In this study, cognitive impairment was widespread in mid- to late-stage PD, affecting 94% of patients being treated with levodopa and other PD treatments. This is higher than estimates from previous PD studies,[10,11] perhaps reflecting differences in the patient population or in the tools used to assess cognition.**
- **Impairments in executive function and verbal working memory were most common, affecting 90% and 92% of patients with mid- to late-stage PD, respectively; impairments in processing speed and complex attention were detected in approximately 32% of patients and 49% showed deficits in declarative memory compared with a cognitively normal population. Approximately 83% of patients with mid- to late-stage PD were impaired in two or more cognitive functions.**
- **A major limitation of this study was the demographic differences between the control population and the patients with PD. The age of patients, their ethnicity, and their educational level may play significant roles in the incidence of cognitive impairment, therefore, the results presented here are subject to confirmation in subsequent studies.**

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Safinamide reduces levodopa-induced dyskinesia in MPTP-lesioned primates while prolonging anti-parkinsonian efficacy

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INTRODUCTION

- Safinamide is an α-aminoamide with dopaminergic and non-dopaminergic activities currently in Phase III development for use as add-on to levodopa or dopamine agonists for patients with Parkinson's disease (PD).
- Its pharmacologic activities include selective and reversible inhibition of monoamine oxidase-B (MAO-B), use- and voltage-dependent blockade of voltage-gated Na^+ channels, Ca^{2+} channel inhibition, and reduction of induced presynaptic glutamate release *in vitro*.
- Both dopaminergic (levodopa-enhanced dopamine levels) and non-dopaminergic components (including but not limited to glutamate transmission imbalance) are implicated in levodopa-induced dyskinesia, a common treatment complication in PD patients with no currently approved therapeutic options.[1-6]
- Based on its pharmacologic profile, we hypothesized that safinamide may have antiparkinsonian and antidyskinetic activities in the monkey 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) model of PD.
- The aims of the present study were to assess whether safinamide add-on to levodopa reduces dyskinesia and to determine whether the associated antiparkinsonian response to levodopa is affected (locomotion, antiparkinsonian score, duration of levodopa effect, elapsed time before the start of levodopa effect). This study determined whether safinamide add-on to levodopa induces an exposure-behavioral effect relationship with safinamide. This was investigated in two experiments: the first was a dose-response behavioral effect of safinamide at 3 to 30 mg/kg (Experiment 1) and the second, a crossover study with 20 mg/kg safinamide (Experiment 2).

OBJECTIVE

- To understand the effects of the investigational drug, safinamide, in the MPTP monkey model of levodopa-induced dyskinesia.

METHODS

- Safinamide was tested in an animal model of levodopa-induced dyskinesia, the MPTP lesioned dyskinetic macaque monkey.[7,8] Dyskinesia and primary parkinsonian symptoms in response to individually tailored doses of levodopa and safinamide plasma levels were measured in a group of dyskinetic animals, pretreated with either vehicle or safinamide administered by oral gavage one hour before levodopa.

Animals

- Female ovariectomized cynomolgus monkeys (*Macaca fascicularis*) weighing between 2.8 and 4.4 kg were used for these experiments. The primates were handled in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals. All procedures were reviewed and approved by the Institutional Animal Care Committee of Laval University. The animals were rendered parkinsonian by continuous infusion of MPTP (Sigma-Aldrich, Canada) using subcutaneous osmotic minipumps (Alzet, 0.5 mg/24 h) until they developed a stable parkinsonian syndrome. After one to three months of recuperation, animals were treated daily with levodopa/benserazide 100/25 capsule p.o. (Prolopa, Hoffmann-La Roche) until clear and reproducible dyskinesias developed.

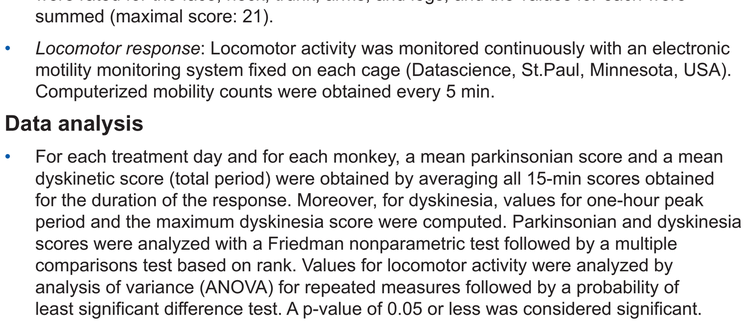
Drugs

- Safinamide was provided by Merck Serono S.A., Geneva, Switzerland. A fresh safinamide aqueous solution was prepared on every experimental day. A volume between 12 and 20 mL of the safinamide solution was administered by nasogastric gavage. Levodopa methyl ester and benserazide (Sigma-Aldrich, Canada) were dissolved in sterile 0.9% saline solution and pH adjusted to 7.

Experimental design: dose-response behavioral effect of safinamide (Experiment 1)

- Three weeks before beginning the acute study, animals were primed by repeated administration (three times per week) with levodopa/benserazide 100/25 or 50/12.5 depending on the motor response of the animals. Monkeys were first evaluated following vehicle (water) administration alone (baseline) and with vehicle + levodopa/benserazide, administered subcutaneously. Levodopa doses were adjusted for each monkey, varied from 15–35 mg/kg, and were always given simultaneously with a fixed dose of benserazide (50 mg total). Ascending doses of safinamide (3, 10, and 30 mg/kg) as add-on to levodopa were tested (Figure 1). Safinamide was given one hour before levodopa administration. Experimental days were separated by three days of washout and two days following the last oral administration of levodopa (50 or 100 mg).

Figure 1. Observation day schedule



Experimental design: behavioral effect of safinamide (crossover design) (Experiment 2)

- A crossover design was used in Experiment 2. On the observation day, half of the MPTP-treated monkeys were administered levodopa/benserazide + vehicle and the others, levodopa/benserazide + safinamide 20 mg/kg. After a one-week washout period, crossover of the treatments was performed. The observer was blind to the treatments in Experiment 2; all other experimental conditions were the same as Experiment 1.

Safinamide assays

- After the behavioral measures, a blood sample was taken five hours after administration of levodopa (six hours after safinamide administration). Blood samples (1 mL) were collected in EDTA tubes and centrifuged (10 min, 1000 x g) at 4°C. Plasma samples were then stored at -80°C for later analysis. Plasma concentrations of safinamide were assayed by liquid chromatography-mass spectrometry/mass spectrometry.

Behavioral assessment

- The animals were observed through a one-way screen and were scored "live" for antiparkinsonian and dyskinetic responses for the full duration of the levodopa response.
- *Parkinsonian score*: A disability scale developed in the author's laboratory was used to evaluate the parkinsonian syndrome in MPTP monkeys.[9,10] Behaviors were scored every 15 minutes (maximal score: 16).
- *Dyskinetic score*: Dyskinesias were scored every 15 min for the duration of the treatments according to a scale developed in the author's laboratory.[9,10] Dyskinesias were rated for the face, neck, trunk, arms, and legs, and the values for each were summed (maximal score: 21).
- *Locomotor response*: Locomotor activity was monitored continuously with an electronic motility monitoring system fixed on each cage (Datascience, St.Paul, Minnesota, USA). Computerized mobility counts were obtained every 5 min.

Data analysis

- For each treatment day and for each monkey, a mean parkinsonian score and a mean dyskinetic score (total period) were obtained by averaging all 15-min scores obtained for the duration of the response. Moreover, for dyskinesia, values for one-hour peak period and the maximum dyskinesia score were computed. Parkinsonian and dyskinesia scores were analyzed with a Friedman nonparametric test followed by a multiple comparisons test based on rank. Values for locomotor activity were analyzed by analysis of variance (ANOVA) for repeated measures followed by a probability of least significant difference test. A p-value of 0.05 or less was considered significant.

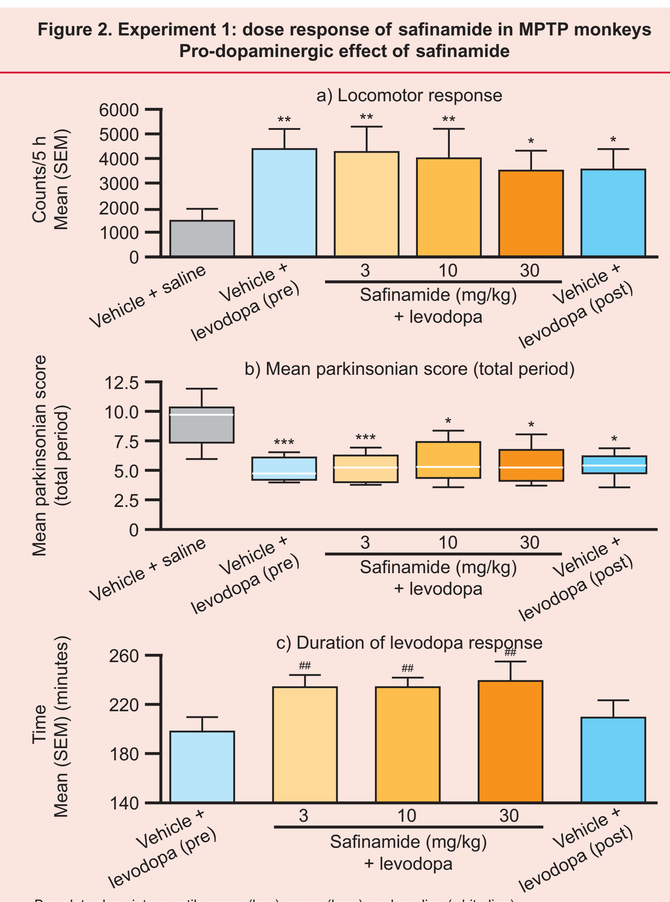
RESULTS

- As expected, levodopa induced dyskinetic motions over a period of 2–3 hours after oral administration in all animals.

Experiment 1: dose-response behavioral effect of safinamide

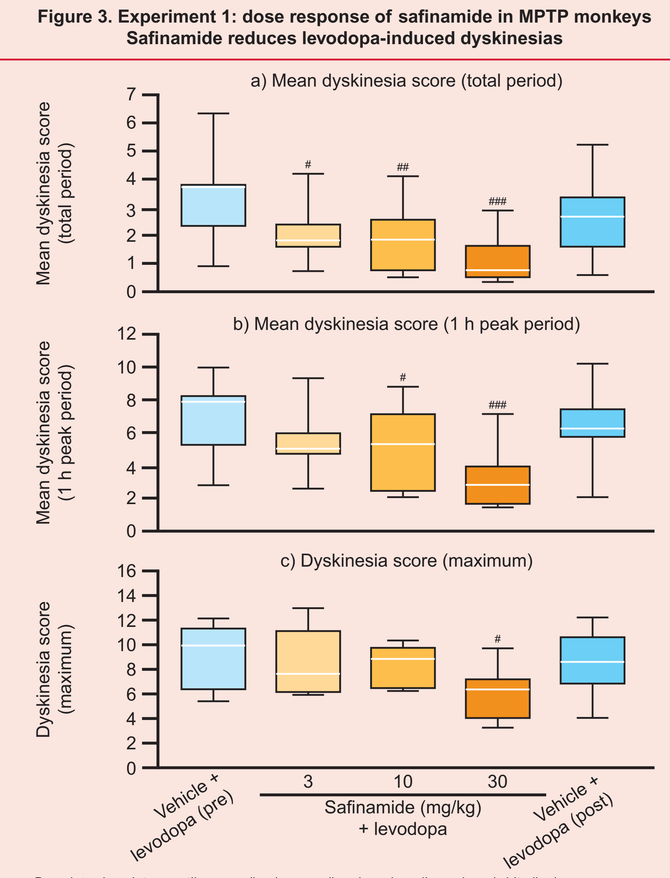
- Compared with baseline, levodopa significantly increased locomotor response; this response was maintained in animals treated with all three doses of safinamide as add-on to levodopa (Figure 2a).
- Compared with baseline, levodopa significantly reduced parkinsonian symptoms; again, this response was maintained in animals treated with all three doses of safinamide as add-on to levodopa (Figure 2b). Moreover, the duration of the levodopa response was significantly prolonged by each dose of safinamide (Figure 2c).
- Safinamide was also associated with significant dose-dependent improvements in levodopa-induced dyskinesia:
  - There were significant reductions in the mean dyskinesia score over the whole assessment period for each dose of safinamide (Figure 3a) and during the one-hour peak period for 10 and 30 mg/kg safinamide (Figure 3b).
  - The maximum dyskinesia score was significantly reduced with 30 mg/kg safinamide (Figure 3c).
  - Both dystonic and choreic dyskinesias were responsive to safinamide.
- A typical time course of dyskinesia scores is shown in Figure 4.

Figure 2. Experiment 1: dose response of safinamide in MPTP monkeys
Pro-dopaminergic effect of safinamide



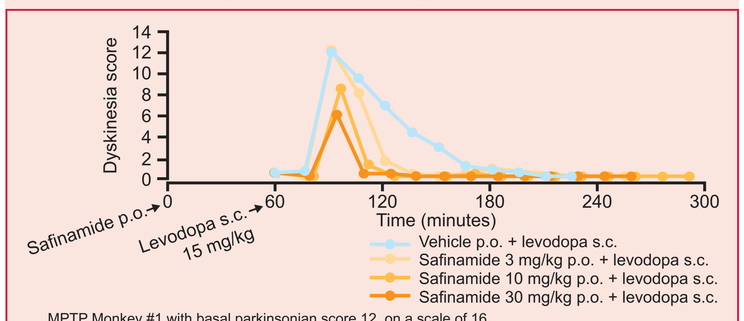
Box plots show interquartile range (box), range (bars), and median (white line)
*p<0.05; **p<0.01; ***p<0.001 vs vehicle + saline
##p<0.01 vs vehicle + levodopa (pre)

Figure 3. Experiment 1: dose response of safinamide in MPTP monkeys
Safinamide reduces levodopa-induced dyskinesias



Box plots show interquartile range (box), range (bars), and median values (white line)
#p<0.05; ##p<0.01; ###p<0.001 vs vehicle + levodopa (pre)

Figure 4. Experiment 1: dose response of safinamide in MPTP monkeys
Example of time course of dyskinesia scores

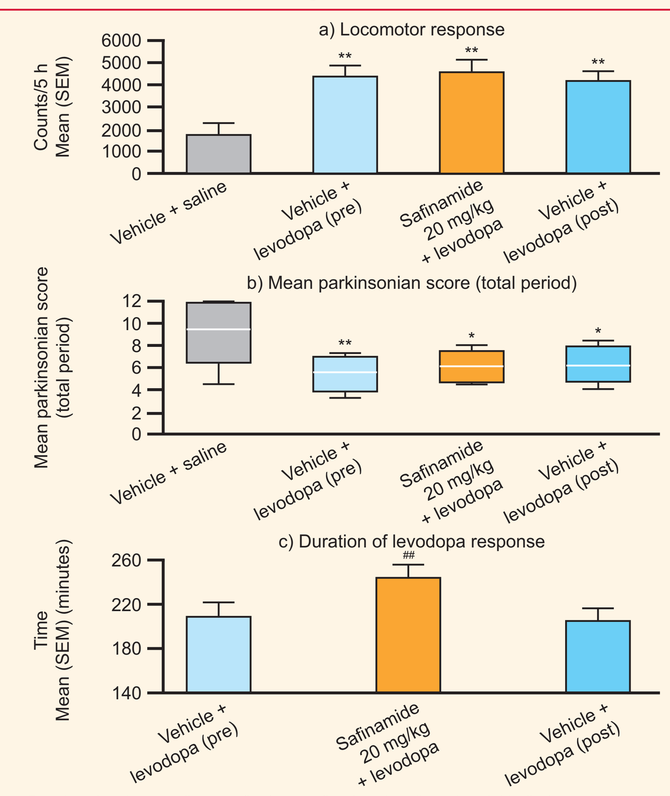


MPTP Monkey #1 with basal parkinsonian score 12, on a scale of 16

Experiment 2: behavioral effect of safinamide (crossover design)

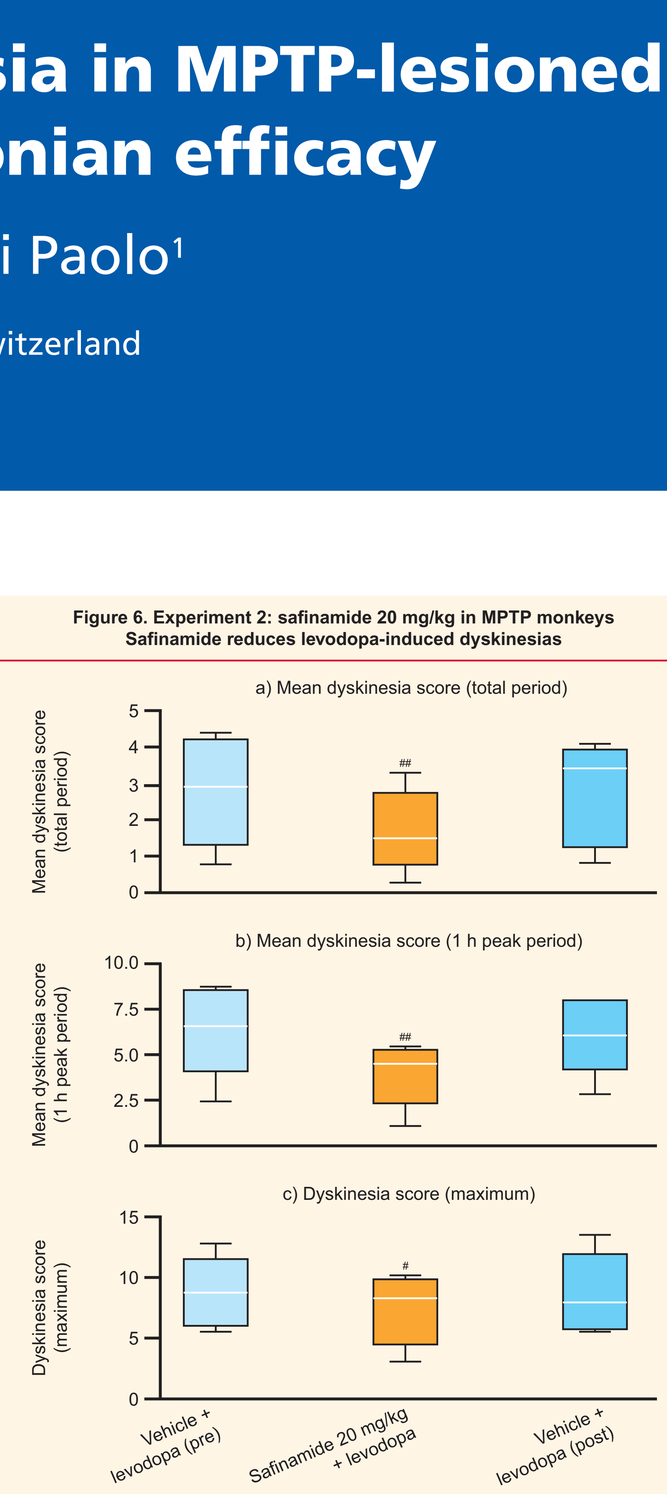
- The results obtained in the crossover experiment were very similar to those obtained with the dose-response experiment:
  - The locomotor and antiparkinsonian effects of levodopa were maintained with add-on safinamide (Figures 5a and 5b, respectively), and the duration of the levodopa response was significantly prolonged (Figure 5c).
  - Add-on safinamide significantly reduced all three measures of levodopa-induced dyskinesia (Figures 6a–c).
- A typical time course of dyskinesia scores is shown in Figure 7.

Figure 5. Experiment 2: safinamide 20 mg/kg in MPTP monkeys
Pro-dopaminergic effect of safinamide



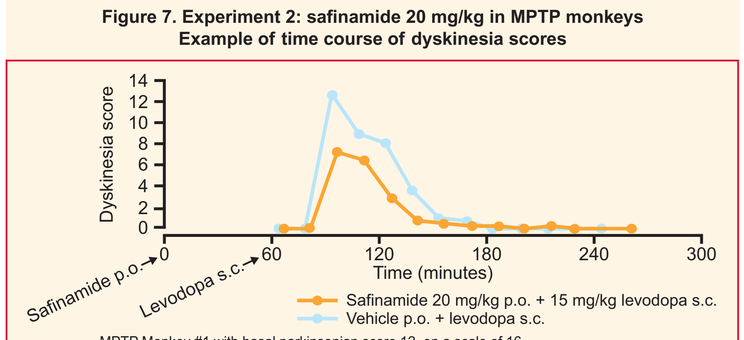
Box plots show interquartile range (box), range (bars), and median values (white line)
*p<0.05; **p<0.01 vs vehicle + saline
##p<0.01 vs vehicle + levodopa (pre)

Figure 6. Experiment 2: safinamide 20 mg/kg in MPTP monkeys
Safinamide reduces levodopa-induced dyskinesias



Box plots show interquartile range (box), range (bars), and median values (white line)
#p<0.05; ##p<0.01 vs vehicle + levodopa (pre)

Figure 7. Experiment 2: safinamide 20 mg/kg in MPTP monkeys
Example of time course of dyskinesia scores



MPTP Monkey #1 with basal parkinsonian score 12, on a scale of 16

Pharmacokinetic analysis

Table 1. Plasma safinamide levels on observation day, 6 hours after dosing

Safinamide dose	Safinamide plasma concentration at 6 h, mean micromolar (SD)
3 mg/kg	0.49 (0.09)
10 mg/kg	1.9 (0.72)
20 mg/kg	4.92 (1.5)
30 mg/kg	10.4 (3.1)

DISCUSSION

- In MPTP-treated monkeys, safinamide pretreatment reduced dyskinesia scores in all cases, compared with vehicle, in two independent experiments. Its antidyskinetic effect was dose-related and both peak intensity and duration of the dyskinetic motions were reduced; in addition, both dystonic and choreic dyskinesias were responsive to safinamide. Safinamide (at all doses tested) increased the duration of the antiparkinsonian effect of levodopa by more than half an hour and maintained the antiparkinsonian and locomotor intensity of the levodopa effect.
- Six-hour plasma levels of safinamide associated with efficacy ranged from 0.5 to 10 μM. Pharmacokinetic profiles for safinamide in normal macaque monkeys suggest that plasma safinamide levels during the active period for dyskinesia (1.5 to 3 hours after safinamide dosing) may have been two- to three-fold higher. Plasma levels in patients taking 100 and 200 mg/day safinamide are 4–9 μM.
- These results support the potential therapeutic use of safinamide for the management of treatment-associated dyskinesia and wearing-off. The increased duration of the antiparkisonian effect of levodopa is likely due to the MAO-B activity of safinamide and was maximal at the doses tested. The antidyskinetic activity of safinamide was dose-related and was likely due to the other pharmacologic activities of this compound.

CONCLUSIONS

- **In this study, safinamide reduced the dyskinesia that appears in parkinsonian primates in response to levodopa administration. This activity was associated with plasma drug levels similar to those achieved using doses currently being tested in clinical trials.**
- **Safinamide did not reduce dyskinesia by simply antagonizing the dopaminergic action of levodopa since it simultaneously prolonged the antiparkinsonian efficacy of levodopa.**

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