Efficacy and safety of safinamide in patients with Parkinson's disease experiencing motor fluctuations: results of a 6-month Phase III, randomised, double-blind, placebo-controlled study

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INTRODUCTION

- L-dopa augments inadequate dopamine signalling and is the most effective agent available for treating the motor symptoms of Parkinson's disease (PD).[1] However, long-term use of L-dopa is associated with motor complications (motor fluctuations and dyskinesia).[1]
- Advanced PD is characterised by poor motor control with rapid oscillations between being 'ON', 'ON' with disabling dyskinesia and 'OFF'.[2]
- Therefore, there remains a need for novel approaches to PD therapy that can minimise the risk of motor complications while providing optimal control of motor symptoms.
- Safinamide is an α-aminoamide derivative with a dual mechanism of action based on enhancement of dopaminergic function (via reversible inhibition of monoamine oxidase-B and dopamine reuptake) and reduction of glutamatergic over-activity (via inhibition of glutamate release).[3]
- Safinamide has previously been shown to improve motor function, activities of daily living and quality of life in patients with early PD treated with dopamine agonists.[4,5]

OBJECTIVE

- To evaluate the efficacy and safety of low-dose (50 mg/day) and high-dose (100 mg/day) safinamide as adjunctive therapy to L-dopa in patients with mid- to late-stage PD experiencing motor fluctuations.

METHODS

Patients

Inclusion criteria

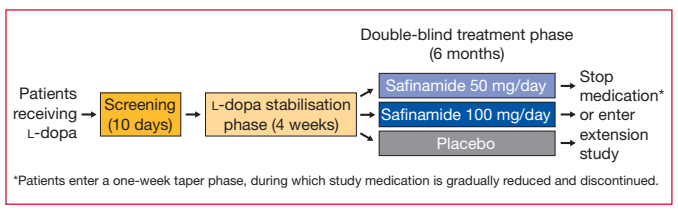
- Male or non-fecund female patients aged 30 to 80 years, with a diagnosis of idiopathic PD (>3 years' duration); Hoehn and Yahr stage I–IV while 'OFF'.
- L-dopa responsive and receiving stable L-dopa dose at screening.
- Concomitant treatment with stable doses of COMT inhibitors, DAs, anticholinergic agents and/or amantadine.
- Motor fluctuations with >1.5 hours' daily 'OFF' time.
- Ability to maintain a diary (18 hours) with or without the help of a caregiver.
- Complete ophthalmological screening.

Key exclusion criteria

- Late-stage PD with severe, disabling peak-dose or biphasic dyskinesia, or wide/unpredictable fluctuations.
- Previous stereotactic surgery to treat PD.
- History of psychosis or score ⩾3 on the UPDRS Section I, Item 2 (thought disorder) or 3 (depression).
- GRID-HAM-D total score >17.
- Evidence of dementia or cognitive dysfunction: Mini Mental State Examination <22, or UPDRS Section I, Item 1 score ⩾3.
- Active retinopathy.

COMT, catechol-O-methyltransferase; DAs, dopamine agonists; GRID-HAM-D, GRID-Hamilton Depression Rating Scale; UPDRS, Unified Parkinson's Disease Rating Scale.

Figure 1. Study design.



*Patients enter a one-week taper phase, during which study medication is gradually reduced and discontinued.

- During a 10-day screening phase, patients receiving stable doses of L-dopa and other permitted PD medications were assessed for eligibility. No adjustment to PD medication was permitted during this phase.
- Following screening, patients entered a 4-week L-dopa stabilisation phase. At the end of this period, patients were required to:
  - have achieved a stable optimal dose of L-dopa
  - still be experiencing end-of-dose wearing off (>1.5 hours/day 'OFF' time)
  - have demonstrated the ability to maintain a study diary.
- Eligible patients were randomised (1:1:1) to one of three treatment groups for 24 weeks (Figure 1).
- Stable doses of concomitant PD medications were permitted throughout the study.
- Safety and efficacy assessments were performed at baseline and at Weeks 4, 8, 12, 18 and 24.
- Patients who successfully completed the 24-week study were eligible to continue into an 18-month, double-blind extension study.

Outcome parameters

Primary efficacy variable

- Increase in mean daily 'ON' time ('ON' time without dyskinesia plus 'ON' time with minor dyskinesia) as recorded by patients or caregivers at 30-minute intervals in an 18-hour diary (0600 to 2400 h) [see Table 2].
  - Diary information was collected on the five days preceding each scheduled visit; and the last two days of recordings were used for data analysis.

Other efficacy variables

- Decreases in total daily 'OFF' time and mean 'OFF' time following the first morning dose of L-dopa.
- UPDRS scores on Sections I (mentation, behaviour and mood), II (activities of daily living), III (motor) scores during 'ON' phase and IV (complications of therapy).
- Clinical Global Impression (CGI) 'Change' and 'Severity of Illness' scores.
- Dyskinesia Rating Scale.[6]
- GRID-HAM-D (Depression) total score.
- Response rate to 50 and 100 mg/day safinamide:
  - ⩾30-min increase in daily 'ON' time from baseline
  - ⩾30-min decrease in 'OFF' time from baseline
  - ⩾30% improvement in UPDRS III (motor) scores from baseline.

Safety

- Safety was evaluated by monitoring adverse events (AEs), clinical laboratory evaluations, 12-lead electrocardiograms, vital signs, and physical and neurological examinations.

RESULTS

Patients

- 669 patients were randomised to treatment, all of whom were included in the safety and intent-to-treat populations (Table 1).
- 594 (89%) patients completed 24 weeks' treatment, with 25, 21 and 29 patients withdrawing from the placebo, 50 mg/day and 100 mg/day treatment groups, respectively.
- 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.

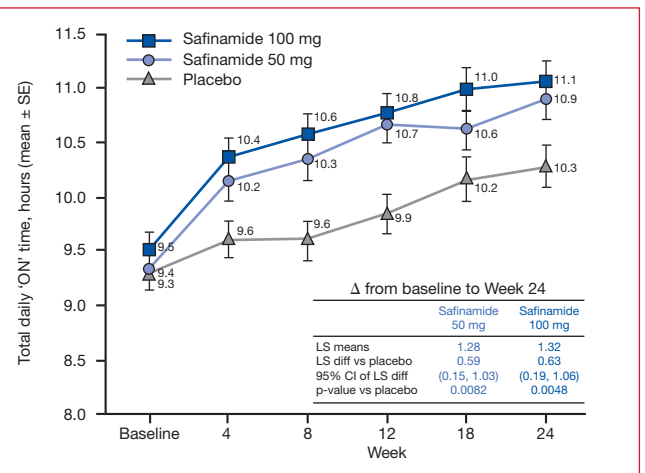
Characteristic	Placebo (n=222)	Safinamide 50 mg/day (n=223)	Safinamide 100 mg/day (n=224)
Gender, n (%)			
Male	160 (72.1)	157 (70.4)	163 (72.8)
Race, n (%)			
Asian	180 (81.1)	180 (80.7)	179 (79.9)
White	42 (18.9)	43 (19.3)	45 (20.1)
Age, years, mean (SD)	59.4 (9.41)	60.1 (9.67)	60.1 (9.19)
H&Y stage, mean (SD)	2.8 (0.7)	2.8 (0.6)	2.8 (0.6)
Disease duration, years, mean (SD)	8.3 (3.8)	7.9 (4.0)	8.2 (3.8)
Daily 'OFF' time, hours, mean (SD)	5.3 (2.1)	5.2 (2.1)	5.2 (2.2)
Daily 'ON' time, hours, mean (SD)	9.3 (2.2)	9.4 (2.3)	9.5 (2.4)
UPDRS III score 'ON', mean (SD)	28.7 (12.0)	27.3 (12.7)	28.3 (13.3)
Concomitant PD drug, n (%)			
L-dopa[a]	222 (100)	223 (100)	224 (100)
Dopamine agonist	136 (61.3)	142 (63.7)	128 (57.1)
Entacapone[b]	89 (40.1)	82 (36.8)	91 (40.6)
Anticholinergic	86 (38.7)	73 (32.7)	85 (37.9)
Amantadine	32 (14.4)	29 (13.0)	30 (13.4)

H&Y, Hoehn and Yahr; PD, Parkinson's disease; SD, standard deviation; UPDRS, Unified Parkinson's Disease Rating Scale.
[a]Includes various formulations of L-dopa such as Sinamet (immediate release/controlled release) and Madopar.
[b]Includes entacapone administered as monotherapy and as a combination therapy (e.g. Stalevo).

Efficacy

- The addition of safinamide to stable doses of L-dopa resulted in significant increases in total daily 'ON' time in both the 50 mg/day and the 100 mg/day groups compared with placebo (Figure 2).
- Increases in mean daily 'ON' time were not associated with any increase in 'ON' time with troublesome dyskinesia (Table 2).
- Following the morning L-dopa dose, both 50 and 100 mg/day safinamide significantly reduced 'OFF' time compared with placebo (treatment difference -0.6 hours/day for both groups; p=0.0013 and p=0.0009, respectively).
- Treatment with safinamide was not associated with any worsening on the Dyskinesia Rating Scale (Table 3) and UPDRS I score (Figure 3).

Figure 2. Effect of safinamide on primary endpoint of total and mean change in 'ON' time from baseline ('ON' time without dyskinesia plus 'ON' time with minor dyskinesia).



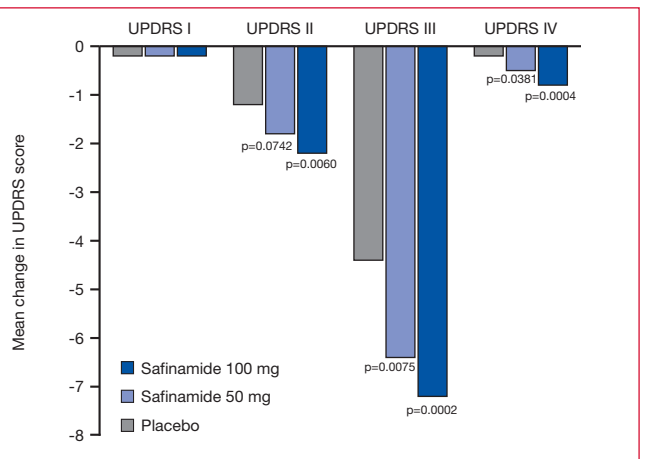
Using an ANCOVA analysis (mixed model repeated measures), all time points after baseline were statistically significant when compared with placebo, with the exception of safinamide 50 mg/day at Week 18 (p=0.0739). CI, confidence interval; LS, least squares; SE, standard error.

Table 2. Effect of safinamide 50 and 100 mg/day 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.

Figure 3. Mean changes from baseline in UPDRS I–IV scores.



Least squares means and p-values were calculated from an ANCOVA model based on the change from baseline with the baseline value as a covariate. UPDRS, Unified Parkinson's Disease Rating Scale.

- Compared with placebo, the addition of both 50 and 100 mg/day safinamide to stable L-dopa dose significantly reduced total daily 'OFF' time (Table 2), UPDRS III scores during 'ON' phase (Figure 3), UPDRS IV scores (Figure 3), CGI 'Change' and 'Severity of Illness' scores (Table 3).
- Safinamide 100 mg/day induced significant improvements in UPDRS II scores (Figure 3) and GRID-HAM-D ratings (Table 3).

Table 3. Effect of safinamide on secondary efficacy parameters.

Parameter	Placebo (n=222)	Safinamide 50 mg/day (n=223)		Safinamide 100 mg/day (n=224)	
	Change from baseline	Change from baseline	p-value vs placebo	Change from baseline	p-value vs placebo
CGI improvement in at least 1 category, % patients	55.0	67.3	0.0003	63.8	0.0097
CGI 'Severity'[a]	-0.2	-0.4	0.0038	-0.4	0.0219
GRID-HAM-D[a]	-0.3	-0.6	0.2367	-1.0	0.0179
UPDRS IV (items 32-34)[a]	0.1	-0.1	0.2947	-0.2	0.1168
Dyskinesia Rating Scale (mean ± SD)[b]	-0.2 ± 2.14	-0.2 ± 2.55	0.2992	-0.3 ± 3.16	0.2734

[a]Least squares 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.
[b]p-value calculated using Wilcoxon rank-sum test comparing active versus placebo at endpoint.
CGI, Clinical Global Impression; GRID-HAM-D, GRID-Hamilton Depression Rating Scale; SD, standard deviation; UPDRS, Unified Parkinson's Disease Rating Scale.

Clinically significant benefits of safinamide 50 and 100 mg/day

- Significantly more patients receiving safinamide 50 and 100 mg/day exhibited a ⩾30-minute increase in 'ON' time, ⩾30-minute decrease in 'OFF' time and a ⩾30% improvement in UPDRS III scores compared with placebo (Table 4).

Table 4. Summary of patient response rates to safinamide 50 or 100 mg/day.

Parameter	Placebo (n=222)	Safinamide 50 mg/day (n=223)		Safinamide 100 mg/day (n=224)	
	Responders, n (%)	Responders n (%)	p-value vs placebo	Responders n (%)	p-value vs placebo
Increase in 'ON' time,[a] n (%)	88 (39.6)	106 (47.5)	0.0641	125 (55.8)	<0.0001
Improvement in 'ON' and 'OFF' time,[b] n (%)	87 (39.2)	99 (44.4)	0.2069	117 (52.2)	0.0008
UPDRS III, ⩾30% improvement from baseline, n (%)	70 (31.5)	84 (37.7)	0.0698	92 (41.1)	0.0095
⩾30-minute improvement in 'ON' and 'OFF' time and ⩾30% improvement in UPDRS III scores	42 (18.9)	60 (26.9)	0.0177	66 (29.5)	0.0016

[a]⩾30-minute increase in 'ON' time from baseline without increase in troublesome dyskinesia, based on analysis of daily diaries.
[b]⩾30-minute increase in 'ON' time from baseline without increase in troublesome dyskinesia and ⩾30-minute decrease in 'OFF' time, based on analysis of daily diaries.
UPDRS, Unified Parkinson's Disease Rating Scale.

Safety

- Safinamide was generally well tolerated as add-on to stable L-dopa therapy. A total of 448 patients reported at least one treatment-emergent AE (TEAE). The most common TEAEs (⩾5% incidence) are shown in Table 5.

Table 5. Treatment-emergent adverse events (TEAEs) [⩾5% in one or more groups].

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)

- Serious AEs occurred in 18 (8.1%), 7 (3.1%) and 22 (9.8%) in the placebo, 50 mg/day safinamide group and 100 mg/day safinamide group, respectively. Serious AEs caused 3 (1.4%), 2 (0.9%) and 4 (1.8%) withdrawals from each group, respectively.
- There were 6 deaths during the study; two in the placebo group and four in the safinamide 100 mg/day group. Two of the deaths in the safinamide group were considered not related to treatment and two were of unknown cause.
- Eight patients (3.6%) receiving placebo withdrew from the study due to non-serious AEs, compared with 9 patients (4.0%) in each of the two safinamide groups.
- Clinically notable laboratory values were reported for 82 (36.9%), 82 (36.8%) and 64 (28.6%) of patients on placebo, low- or high-dose safinamide, respectively.

CONCLUSIONS

- **When used as add-on to stable L-dopa therapy for 24 weeks in patients with mid- to late-stage PD, safinamide 50 and 100 mg/day:**
  - **significantly increased total daily 'ON' time without increasing troublesome dyskinesia, indicating that safinamide improved motor fluctuations**
  - **significantly reduced 'OFF' time after the first morning L-dopa dose, total daily 'OFF' time, UPDRS III score during 'ON' phase, UPDRS IV scores and CGI 'Change' and 'Severity of Illness' scores**
  - **the clinical significance of changes associated with safinamide was reflected in the responder analysis.**
- **Safinamide 100 mg/day also significantly improved activities of daily living and may also reduce depressive symptoms associated with PD.**
- **Safinamide treatment was well tolerated in this study; no systematic differences were observed between the groups in the incidence of withdrawals, serious AEs or clinically notable AEs, indicative of a good safety profile for safinamide.**

- **This study had a high completion rate (89%); and of 669 patients enrolled, 544 (81%) continued into the 18-month extension study assessing dyskinesia as the primary endpoint.**

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ABSTRACT

Objective: To evaluate the efficacy and safety of safinamide as adjunctive therapy to L-dopa in patients with Parkinson's disease (PD) experiencing motor fluctuations.

Background: Safinamide is an α-aminoamide derivative combining dopaminergic enhancement with inhibition of glutamate release. Safinamide improves motor function, activities of daily living (ADL) and quality of life in clinical trials of patients with early PD concurrently treated with dopamine agonists.

Methods: Patients with mid- to late-stage PD, aged 30-80 years, experiencing motor fluctuations (>1.5 hour/day 'OFF' time) while on a stable dose of L-dopa and other PD therapies were enrolled in this 6-month, Phase III, double-blind, placebo-controlled, multicentre study. After a 4-week L-dopa stabilisation phase, patients were randomised to safinamide at 50 mg/day (n=223) or 100 mg/day (n=224), or placebo (n=222). The primary efficacy endpoint was increase in mean daily 'ON' time (without dyskinesia and with minor dyskinesia). Safety assessments included vital signs, adverse events (AEs) and laboratory tests.

Results: 594 of 669 (89%) patients enrolled in the study completed 6 months' treatment. Addition of 50 or 100 mg/day safinamide significantly increased 'ON' time (each 1.3 hour/day) compared with placebo (0.7 hour/day; p=0.0082 and p=0.0048, respectively) without increasing troublesome dyskinesia (both p>0.05). Both doses also induced statistically significant reductions in UPDRS IV scores (p=0.0381 and p=0.0004, respectively), daily 'OFF' time, 'OFF' time after the first morning L-dopa dose, UPDRS III during 'ON' phase, and CGI change and severity scores for both doses. Significant improvements were also noted in UPDRS II and in GRID-HAM-D ratings after 100 mg/day safinamide. The discontinuation rate, serious and non-serious AEs were similar across treatments. Common AEs (>5% in one group or more) were cataract, back pain, dyskinesia, headache, worsening PD and depression.

CONCLUSIONS

In patients with mid- to late-stage PD, safinamide (50 and 100 mg/day) given as adjunct to L-dopa improves 'ON' and 'OFF' times, motor function and ADL without worsening dyskinesia.