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Assessment of Safety and Efficacy of Safinamide as a Levodopa Adjunct in Patients With Parkinson Disease and Motor Fluctuations
A Randomized Clinical Trial

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IMPORTANCE Although levodopa remains the most effective oral pharmacotherapy for Parkinson disease (PD), its use is often limited by wearing off effect and dyskinesias. Management of such complications continues to be a significant challenge.

OBJECTIVE To investigate the efficacy and safety of safinamide (an oral aminoamide derivative with dopaminergic and nondopaminergic actions) in levodopa-treated patients with motor fluctuations.

DESIGN, SETTING, AND PARTICIPANTS From March 5, 2009, through February 23, 2012, patients from academic PD care centers were randomized (1:1 ratio) to receive double-blind adjunctive safinamide or placebo for 24 weeks. All patients had idiopathic PD with "off" time (time when medication effect has worn off and parkinsonian features, including bradykinesia and rigidity, return) of greater than 1.5 hours per day (excluding morning akinesia). Their pharmacotherapy included oral levodopa plus benserazide or carbidopa in a regimen that had been stable for 4 weeks or longer. During screening, each patient's regimen was optimized to minimize motor fluctuations. Study eligibility required that after 4 weeks of optimized treatment, the patients still have more than 1.5 hours per day of off time. Adverse events caused the premature study discontinuation of 12 individuals (4.4%) in the safinamide group and 10 individuals (3.6%) in the placebo group.

INTERVENTIONS Patients took safinamide or placebo as 1 tablet daily with breakfast. If no tolerability issues arose by day 14, the starting dose, 50 mg, was increased to 100 mg.

MAIN OUTCOMES AND MEASURES The prespecified primary outcome was each treatment group's mean change from baseline to week 24 (or last "on" treatment value) in daily "on" time (relief of parkinsonian motor features) without troublesome dyskinesia, as assessed from diary data.

RESULTS At 119 centers, 549 patients were randomized (mean [SD] age, 61.9 [9.0] years; 334 male [60.8%] and 371 white [67.6%]): 274 to safinamide and 275 to placebo. Among them, 245 (89.4%) receiving safinamide and 241 (87.6%) receiving placebo completed the study. Mean (SD) change in daily on time without troublesome dyskinesia was +1.42 (2.80) hours for safinamide, from a baseline of 9.30 (2.41) hours, vs +0.57 (2.47) hours for placebo, from a baseline of 9.06 (2.50) hours (least-squares mean difference, 0.96 hour; 95% CI, 0.56-1.37 hours; $P < .001$, analysis of covariance). The most frequently reported adverse event was dyskinesia (in 40 [14.6%] vs 15 [5.5%] and as a severe event in 5 [1.8%] vs 1 [0.4%]).

CONCLUSIONS AND RELEVANCE The outcomes of this trial support safinamide as an effective adjunct to levodopa in patients with PD and motor fluctuations to improve on time without troublesome dyskinesia and reduce wearing off.

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Supplemental content

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Levodopa is the most effective and widely used pharmacotherapy for Parkinson disease (PD).[1,2] Unfortunately, oral levodopa use is limited by the development of motor complications (wearing off and dyskinesias), which are related in part to the daily dosage used.[3,4] Wearing off can be managed by increasing the dose or frequency of oral levodopa administration or by adding a monoamine oxidase B (MAO-B) inhibitor, catechol *O*-methyltransferase (COMT) inhibitor, or dopamine agonist.[2] However, such strategies can increase the risk of dyskinesia.

Safinamide is a water-soluble, orally administered aminoamide derivative that acts as a potent, highly selective, reversible MAO-B inhibitor.[5-7] In addition, it blocks voltage-dependent sodium and calcium channels and reduces neuronal glutamate release.[8] In early clinical studies, it was found to improve motor control in patients with PD who received it as an add-on treatment to a dopamine agonist[9-11] or as an adjunct to levodopa.[10] We describe the results of a phase 3 trial of safinamide as an adjunct to levodopa in patients with PD and motor fluctuations who were taking levodopa.

Key Points

Question Is safinamide a beneficial treatment for motor fluctuations in patients using oral levodopa for the treatment of Parkinson disease?

Findings In this 24-week, randomized clinical trial, 549 patients had more than 1.5 hours per day of "off" time despite pharmacotherapy optimized to minimize motor fluctuations. Safinamide taken once daily significantly increased daily "on" time without troublesome dyskinesia by a mean 1.42 hours vs 0.57 hour for placebo.

Meaning The study supports the use of safinamide as an effective adjunct to levodopa for fluctuating Parkinson disease.

Methods

The Safinamide Treatment as Add-on to Levodopa study was a double-blind, parallel-group, 24-week trial of safinamide (50-100 mg/d orally) vs placebo in patients taking stable dosages of levodopa and concomitant PD medications. The complete trial protocol can be found in Supplement 1. The study was conducted in accordance with the study protocol and its amendments, the Declaration of Helsinki,[12] the International Conference on Harmonisation Harmonised Tripartite Guideline[13] for good clinical practices, and all applicable local regulatory requirements, including institutional review board approval. Study investigators fully explained the trial to all patients and, before study participation, all patients provided written informed consent.

Study Participants

In 21 countries in Europe, the Asia-Pacific region, and North America, 126 centers screened 851 patients from March 5, 2009, through February 23, 2012. All patients were required to be 30 to 80 years old and have a diagnosis of idiopathic PD by clinical evaluation and Queen Square Brain Bank criteria, with a longer than 3-year duration since diagnosis, a Hoehn and Yahr rating of stages 1 to 4 during an "off" phase (time when medication effect has worn off and parkinsonian features, including bradykinesia and rigidity, return), and daily off time greater than 1.5 hours (excluding morning akinesia). Patients were also required to be levodopa responsive and following an oral levodopa regimen (3-10 doses per day of any levodopa preparation, with or without a COMT inhibitor) that had been stable for 4 weeks. Their PD pharmacotherapy could include a dopamine agonist, anticholinergic, COMT inhibitor, and/or amantadine at stable dosage. Patients were excluded for severe, disabling peak-dose or biphasic dyskinesia and/or wide or unpredictable symptom fluctuations. The study's full exclusion criteria are summarized in the eTable in Supplement 2.

Study Design

During a 10-day screening period, each patient's PD pharmacotherapy was adjusted to minimize motor fluctuations. Patients then entered an observation phase that lasted 4 weeks (or longer, if needed to permit 4-week observation of an unchanged regimen). At the study's conclusion (the patient's baseline visit), eligibility required that the patient still be experiencing daily off time greater than 1.5 hours.

In a double-blind fashion, enrolled patients were randomized (1:1) to receive safinamide or matching placebo, taken as 1 tablet daily with breakfast (**Figure 1**). They underwent post-baseline efficacy and safety assessments at weeks 2, 4, 8, 12, 18, and 24 (or premature discontinuation). In addition, they or their caregivers were telephoned on days 7 and 21 to assess study drug tolerability. If there were no tolerability issues by day 14, the starting dosage, 50 mg/d, was increased to 100 mg/d. Patients were permitted to continue standard oral PD pharmacotherapies at stable dosage (except MAO-B inhibitors, which could not be used within 8 weeks before screening). Patients requiring an increase in antiparkinsonian treatment before week 24 were asked to participate in all further assessments. In such cases, the assessment used for the primary efficacy outcome was performed before the dose increase. Patients completing 24 weeks were eligible for an open-label extension study. Those not continuing had their study drug dosage tapered during a 1-week period (week 25), with a follow-up safety assessment 4 weeks later (week 29).

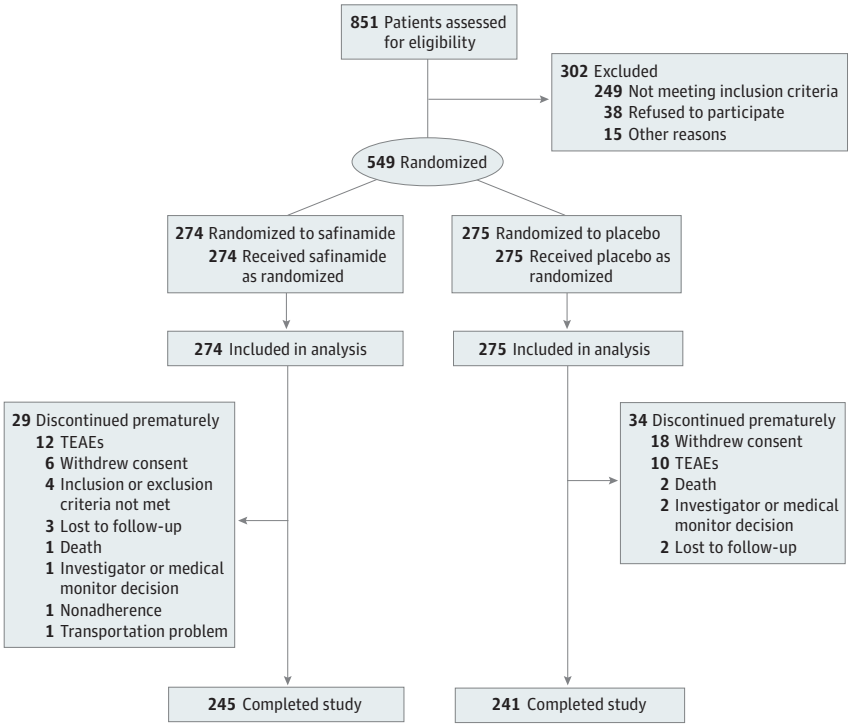
Randomization and Masking

At patient enrollment, study site personnel contacted a centralized, computerized interactive voice-response system, which created the study's randomization scheme (stratified by country or region) and assigned each patient the appropriate medication, identified by kit number and provided for each dose level of active drug or placebo as matching tablets in matching blister packs. The randomization code remained blinded throughout the study.

Efficacy Measures

The primary efficacy outcome was change from baseline to week 24 in mean daily "on" time (relief of parkinsonian motor features) without troublesome dyskinesia, as recorded by patients or caregivers in a diary[14] maintained for the 3 days

Figure 1. Trial Profile



TEAEs indicates treatment-emergent adverse events.

preceding the baseline visit and each postbaseline visit. The diaries characterized each 30-minute interval during the 18-hour day (0600 to 2400 hours) as on time, on time with nontroublesome dyskinesia, on time with troublesome dyskinesia, off time, or time asleep. To optimize their accuracy, all diary data analyses were based on entries for the second and third days.

Secondary efficacy outcomes were based on diary entries, Unified Parkinson's Disease Rating Scale (UPDRS) scores, Clinical Global Impression-Change (CGI-C) ratings, Clinical Global Impression-Severity (CGI-S) ratings, Patient Global Impression-Change (PGI-C) ratings, 39-item Parkinson Disease Questionnaire (PDQ-39) scores, EuroQoL 5 dimensions (EQ-5D) scores, change in levodopa daily dosage, Dyskinesia Rating Scale (DRS) scores, and Cogtest PD Battery scores. Five such outcomes, including mean change in daily off time, mean change in UPDRS Part III (motor examination) and Part II (activities of daily living) scores during an on phase, the proportion of patients with an improved CGI-C rating, and mean change in PDQ-39 summary index score, were predefined as key secondary outcomes. Tertiary outcomes were based on Hoehn and Yahr stage; Hamilton Rating Scale of Depression, 17-item grid version, scores; and Mini-Mental State Examination scores.

Efficacy Analyses

Among all randomized patients (intention-to-treat population), the primary efficacy outcome was tested by analysis of covariance, with treatment and country or region as fixed effects and baseline value as the covariate. For patients who discontinued or changed use of their PD medication, a week 24 value was imputed by a last observation carried forward approach. If the difference between treatment groups was statistically significant ($P \leq .05$), the key secondary end points were to be analyzed hierarchically, unless a difference between groups was statistically nonsignificant, in which case all further analyses would be performed only to obtain nominal P values. The same analysis of covariance model used for the primary efficacy analysis was used for all other outcomes, except CGI-C and PGI-C scores at week 24, which were assessed by analysis of variance with fixed effects for treatment and region, and the proportion of patients with improvement on the CGI-C, which was assessed by logistic regression with treatment and region as fixed effects. The resulting odds ratio was subjected to the Wald χ^2 test. As a sensitivity analysis, change in daily on time was examined using a mixed-effects repeated-measures model, with no imputation of missing data.

Safety Measures

The safety of safinamide was assessed by summary statistics for all patients exposed to study medication (safety population). Safety measures included treatment-emergent adverse events (TEAEs), as classified by the Medical Dictionary for Regulatory Activities, version 13.0[15]; serious adverse events (SAEs); and discontinuations attributable to TEAEs. They also included physical, neurologic, ophthalmologic, and dermatologic examinations; 12-lead electrocardiography; and clinical laboratory tests. The incidence of impulse control disorders was assessed by the Questionnaire for Impulsive-Compul-

Table 1. Baseline Characteristics of the Patients in the Intention-to-Treat Population

Characteristic	Safinamide Group (n = 274)	Placebo Group (n = 275)	*P* Value[a]
Age, mean (SD), y	61.7 (9.0)	62.1 (8.9)	.55
Sex, No. (%)			
Male	171 (62.4)	163 (59.3)	.45
Female	103 (37.6)	112 (40.7)	
Race, No. (%)			
White	183 (66.8)	188 (68.4)	.35
Asian	88 (32.1)	85 (30.9)	
Other	3 (1.1)	2 (0.7)	
Region, No. (%)			
Western Europe	109 (39.8)	110 (40.0)	>.99
Asia-Pacific	84 (30.7)	84 (30.5)	
North America	51 (18.6)	51 (18.5)	
Eastern Europe	30 (10.9)	30 (10.9)	
Weight, mean (SD), kg	72.5 (16.4)[b]	71.0 (15.8)[c]	.21
Hoehn and Yahr stage,[d] mean (SD)	2.5 (0.6)	2.5 (0.6)[c]	.80
Levodopa dosage, mean (SD), mg/d	760.8 (445.9)[e]	792.3 (400.7)[b]	.39
UPDRS score, mean (SD)			
Part I	1.3 (1.3)	1.3 (1.5)	.89
Part II[f]	10.0 (5.6)[g]	10.4 (6.3)[b]	.36
Part III[f]	22.4 (11.8)	23.4 (12.9)	.38
Part IV	5.9 (2.9)	6.0 (2.9)	.96
CGI-S rating, No. (%)			
Healthy/not at all ill	0	0[b]	.10
Borderline ill	7 (2.6)	4 (1.5)[b]	
Mildly ill	54 (19.7)	45 (16.5)[b]	
Moderately ill	162 (59.1)	160 (58.8)[b]	
Markedly ill	48 (17.5)	60 (22.1)[b]	
Severely ill	3 (1.1)	3 (1.1)[b]	
MMSE score, mean (SD)	28.7 (1.5)	28.6 (1.6)	.91
GRID-HAMD score, mean (SD)	4.7 (4.0)	5.0 (4.1)	.48

Abbreviations: CGI-S, Clinical Global Impression–Severity scale; GRID-HAMD, Hamilton Rating Scale of Depression, 17-item grid version; MMSE, Mini-Mental State Examination; UPDRS, Unified Parkinson's Disease Rating Scale.

[a] For continuous variables, 2-way analysis of variance with treatment and region as fixed effects; for categorical variables, Cochran-Mantel-Haenszel test stratified by region.

[b] n = 272.

[c] n = 274.

[d] During an "off" phase (the time when medication effect has worn off and parkinsonian features, including bradykinesia and rigidity, return).

[e] n = 273.

[f] During an "on" phase (the time when patients experience relief of parkinsonian motor features).

[g] n = 271.

sive Disorders in Parkinson Disease,[16] and daytime sleepiness was assessed by the Epworth Sleepiness Scale.

Sample-Size Calculation

On the basis of a 2-sided, 2-sample *t* test applied to findings of the Parkinson's Rasagiline: Efficacy and Safety in the Treatment of Off (PRESTO) study,[17] a minimum of 416 patients (208 per treatment group) would provide 90% power or greater to detect a difference of 0.75 hour in daily on time between groups, assuming an SD of 2.35 hours (for change from baseline to week 24) and a type I error rate of 5%. Assuming a dropout (or missing data) rate of 14%, a minimum of 484 patients (242 per treatment group) would need to be randomized.

Results

Participant Disposition and Characteristics

At 119 centers, 549 patients were randomized (mean [SD] age, 61.9 [9.0] years; 334 male [60.8%] and 371 white [67.6%]): 274 to safinamide and 275 to placebo (Figure 1). Among them, 245 patients (89.4%) in the safinamide group and 241 patients (87.6%) in the placebo group completed the study. In both groups, the most common reason for premature discontinuation was TEAEs (12 patients [4.4%] in the safinamide group and 10 patients [3.6%] in the placebo group). During the study, 11 patients (4.0%) taking safinamide and 21 patients (7.6%) taking placebo required a change in antiparkinsonian treatment.

The mean (SD) PD duration was 8.9 (4.6) years, and the mean (SD) levodopa dosage was 776.5 (423.8) mg/d, with 408 patients (74.3%) also taking a dopamine agonist, 166 (30.2%) taking amantadine, 95 (17.3%) taking anticholinergics, and 83 (15.1%) taking entacapone. Baseline characteristics revealed no significant differences between the treatment groups (**Table 1**).

Study Drug Exposure

Mean (SD) study drug exposure was 162.3 (37.7) days in the safinamide group and 160.7 (37.5) days in the placebo group. At day 14, a total of 219 of 241 patients (90.9%) in the safinamide group and 225 of 239 patients (94.1%) in the placebo group were prescribed the 100-mg target dose.

Efficacy Outcomes

At week 24, the mean (SD) increase in total daily on time without troublesome dyskinesia (primary efficacy outcome) was +1.42 (2.80) hours in the safinamide group and +0.57 (2.47) hours in the placebo group (least-squares [LS] mean difference, 0.96 hour; 95% CI, 0.56-1.37 hours; $P < .001$). In the mixed-effects repeated-measures model, the mean (SD) increase was +1.61 (2.81) vs +0.17 (2.38) hours (LS mean difference, 0.93 hour; 95% CI, 0.50-1.36 hours; $P < .001$).

Among key secondary outcomes (**Table 2**), the mean (SD) decrease in daily off time was -1.56 (2.35) vs -0.54 (2.21) hours (LS mean difference, -1.03 hours; 95% CI, -1.40 to -0.67 hours; $P < .001$). Mean (SD) decrease (improvement) in UPDRS Part III score rated during an on phase was -3.43 (7.72) vs -1.83 (8.23) (LS mean difference, -1.82; 95% CI, -3.01 to -0.62; $P = .003$). However, mean (SD) change in UPDRS Part II score was nonsignificant at -1.07 (3.63) vs -0.75 (3.95) (LS mean difference, -0.43; 95% CI, -1.02 to 0.16; $P = .15$). The proportion of patients with improvement (scores of 1, 2, or 3) on CGI-C was 57.7% vs 41.8% (odds ratio, 1.92; 95% CI, 1.36-2.70; nominal $P < .001$). Mean (SD) decrease (improvement) in PDQ-39 summary index score was -3.17 (10.86) vs -0.68 (10.51) (LS mean difference, -2.33; 95% CI, -3.98 to -0.68; nominal $P = .006$).

Among other secondary findings (Table 2), mean improvements in the safinamide group (vs placebo) had nominal $P \leq .05$ for CGI-C, PGI-C, and CGI-S scores, off time after the morning levodopa dose, EQ-5D index score, and levodopa daily dosage, representing decreases in 18 patients (6.6%) taking safinamide and 4 patients (1.5%) taking placebo. On the UPDRS Part IV (complications of therapy), the safinamide group had an approximately 0.1-point increase (worsening) in scores on items 32 to 34 and 32 to 35. For both increases, the LS mean difference from placebo was 0.26 point (95% CI, 0.02-0.50 for items 32 -24 and 0.01-0.52 for items 32-35; nominal $P = .04$ for both).

In a post hoc efficacy analysis, the safinamide group exhibited a significant increase vs placebo in daily on time without troublesome dyskinesia while receiving treatment with 50 mg/d at the end of week 2, the first postbaseline assessment time point (mean [SD], 1.04 [2.24] hours vs 0.40 [1.81] hours; $P < .001$ by paired, 2-sided t test). This benefit was maintained at all subsequent time points (**Figure 2**).

Safety

Overall, 186 patients (67.9%) in the safinamide group and 190 patients (69.1%) in the placebo group reported TEAEs (**Table 3**). Among the TEAEs most frequently reported, dyskinesia was more common in the safinamide group than in the placebo group (40 [14.6%] vs 15 [5.5%]). The incidence of TEAEs rated as severe was lower in the safinamide group than in the placebo group (19 [6.9%] vs 25 [9.1%]). However, dyskinesia was reported as severe in 5 patients (1.8%) taking safinamide compared with 1 patient (0.4%) taking placebo.

Eighteen patients (6.6%) taking safinamide and 26 patients (9.5%) taking placebo experienced treatment-emergent SAEs. The SAEs in more than 1 patient in either group were breast cancer and visual hallucinations, each in 2 patients taking safinamide; and diarrhea, hallucinations, and myocardial ischemia, each in 2 patients taking placebo. Fourteen patients (5.1%) in the safinamide group and 12 patients (4.4%) in the placebo group had TEAEs that led to interruption of study drug treatment. In the safinamide group, 12 of these patients discontinued participation in the trial, 1 decided to withdraw, and 1 remained in the trial. In the placebo group, 10 patients discontinued participation in the trial, 1 decided to withdraw, and 1 died. Six patients (2.2%) taking safinamide and 1 (0.4%) taking placebo interrupted their treatment because of nervous system events: dyskinesia in 3 patients in the safinamide group, PD worsening in 2 patients in the safinamide group, paraesthesia in 1 patient in the safinamide group, and dizziness in 1 patient in the placebo group. There were 3 deaths: 1 (0.4%) in the safinamide group (PD worsening, considered unlikely to be related to study medication) and 2 (0.7%) in the placebo group (myocardial ischemia and acute lymphocytic leukemia).

The treatment groups exhibited no clinically meaningful mean changes in physical findings, laboratory values, or electrocardiographic data, and abnormal postbaseline shifts had similar incidences across groups. Questionnaire for Impulsive-Compulsive Disorders in Parkinson Disease and Epworth Sleepiness Scale total scores showed little change. (In the safinamide group, the mean changes were -0.03 and -0.28, respectively.) Results of ophthalmologic examinations were similar in both groups and revealed no significant worsening.

Discussion

At 100 mg/d, safinamide significantly increased mean daily on time without troublesome dyskinesia by 0.96 hour more than placebo in patients taking a stable dose of levodopa. The increase was established by 2 weeks and was subsequently maintained. In addition, safinamide reduced mean daily off time, improved motor function (UPDRS Part III), improved quality of life (PDQ-39, EQ-5D), and revealed a global benefit (CGI). Early-morning off time was also reduced.

Overall, the study's diary data suggest safinamide effects similar or superior to those reported for MAO-B or COMT inhibitors evaluated as levodopa adjuncts to reduce off time for advanced PD. Notwithstanding the limitations of cross-trial comparisons, including potential differences in patients' demographic and PD characteristics, the reduction in off time for the safinamide group, 1.03 hours vs placebo, identified at 24 weeks as a secondary efficacy outcome, may be compared with that of the 26-week PRESTO study,[17] in which the reduction vs placebo was 0.49 hour for 0.5 mg of rasagiline and 0.94 hour for 1 mg of rasagiline (as the primary efficacy outcomes), and the 18-week Lasting Effect in Adjunct Therapy With Rasagiline Given Once Daily (LARGO) study,[18] in which it was 0.78 hour for 1 mg of rasagiline and 0.80 hour for entacapone (as the primary efficacy outcomes). For on-time improvement, the safinamide outcome, an increase of 0.96 hour vs placebo in on time without troublesome dyskinesia (primary efficacy outcome), was accompanied by a statistically insignificant increase of 0.08 hour in on time with troublesome dyskinesia (as an exploratory outcome). In the PRESTO study,[17] the total increase was 0.56 hour for 0.5 mg of rasagiline, with no

Table 2. Efficacy Findings in the Intention-to-Treat Population (Last Observation Carried Forward)

Outcome	Safinamide Group, Mean (SD) (n = 274)			Placebo Group, Mean (SD) (n = 275)			LS Mean Difference in Change (95% CI)[a]	*P* Value[a]
	Baseline	Week 24	Change	Baseline	Week 24	Change		
Primary Outcome								
"On" time without troublesome dyskinesia,[b] h/d	9.30 (2.41)	10.73 (2.75)	+1.42 (2.80)	9.06 (2.50)	9.63 (2.77)	+0.57 (2.47)	+0.96 (+0.56 to +1.37)	<.001
Key Secondary Outcomes								
"Off" time,[b] h/d	5.34 (1.97)	3.77 (2.56)	-1.56 (2.35)	5.38 (2.01)	4.84 (2.59)	-0.54 (2.21)	-1.03 (-1.40 to -0.67)	<.001
UPDRS Part III score[c]	22.26 (11.66)	18.83 (10.87)	-3.43 (7.72)	23.05 (12.65)	21.22 (11.78)	-1.83 (8.23)	-1.82 (-3.01 to -0.62)	.003
UPDRS Part II score[c]	9.97 (5.53)	8.90 (5.44)	-1.07 (3.63)	10.43 (6.29)	9.68 (5.94)	-0.75 (3.95)	-0.43 (-1.02 to +0.16)	.15
Patients with improvement on CGI-C, %[d]	NA	57.7	NA	NA	41.8	NA	1.92 (1.36 to 2.70)[e]	<.001[e,f]
PDQ-39 score	27.47 (14.61)	24.31 (13.73)	-3.17 (10.86)	26.94 (14.83)	26.26 (14.92)	-0.68 (10.51)	-2.33 (-3.98 to -0.68)	.006[e]
Other Secondary Outcomes								
CGI-C rating	NA	3.31 (1.10)	NA	NA	3.76 (1.02)	NA	-0.44 (-0.62 to -0.27)[f]	<.001[e,g]
CGI-S rating	3.95 (0.72)	3.75 (0.79)	-0.20 (0.69)	4.05 (0.70)	3.94 (0.72)	-0.11 (0.67)	-0.13 (-0.24 to -0.03)	.01[e]
Off time after the morning levodopa dose, h/d	0.83 (0.57)	0.57 (0.56)	-0.26 (0.59)	0.86 (0.65)	0.76 (0.71)	-0.09 (0.79)	-0.18 (-0.28 to -0.09)	<.001[e]
DRS score	2.79 (3.50)	2.67 (2.99)	-0.11 (2.86)	2.57 (3.08)	2.33 (2.69)	-0.24 (2.50)	+0.23 (-0.14 to +0.60)	.22[e]
Change in levodopa dose, %	NA	NA	-1.11 (11.43)	NA	NA	+0.78 (6.45)	-1.89 (-3.44 to -0.33)	.02[e]
PGI-C rating	NA	3.28 (1.10)	NA	NA	3.67 (1.01)	NA	-0.40 (-0.57 to -0.22)[f]	<.001[e,g]
UPDRS Part IV items 32-34 score	1.89 (1.98)	1.99 (2.08)	+0.10 (1.79)	1.89 (1.99)	1.74 (1.81)	-0.15 (1.38)	+0.26 (+0.02 to +0.50)	.04[e]
UPDRS Part IV items 32-35 score	2.18 (2.12)	2.27 (2.17)	+0.08 (1.86)	2.24 (2.12)	2.04 (1.95)	-0.20 (1.47)	+0.26 (+0.01 to +0.52)	.04[e]
EQ-5D index score	0.68 (0.18)	0.71 (0.18)	+0.03 (0.19)	0.67 (0.20)	0.65 (0.21)	-0.03 (0.19)	+0.06 (+0.03 to +0.09)	<.001[e]
Cogtest PD Battery scores								
Auditory No. sequencing	-0.65 (0.93)	-0.73 (0.94)	-0.08 (0.95)	-0.62 (0.98)	-0.53 (0.95)	+0.09 (1.07)	-0.19 (-0.33 to -0.05)	.01[e]
Spatial working memory	2.81 (3.95)	2.60 (3.26)	-0.21 (4.11)	2.34 (3.33)	2.57 (3.59)	+0.24 (3.66)	-0.14 (-0.66 to +0.38)	.60[e]
Strategic target detection	1.01 (1.32)	1.28 (1.39)	+0.27 (1.65)	1.08 (1.36)	1.21 (1.30)	+0.13 (1.61)	+0.09 (-0.13 to +0.30)	.44[e]
Word list memory	-0.91 (1.50)	-0.70 (1.61)	+0.21 (1.45)	-0.92 (1.43)	-0.65 (1.38)	+0.27 (1.31)	-0.05 (-0.26 to +0.15)	.61[e]
Symbol digit substitution	-2.54 (0.86)	-2.50 (0.92)	+0.05 (0.77)	-2.62 (0.86)	-2.48 (0.87)	+0.14 (0.68)	-0.07 (-0.18 to +0.04)	.24[e]
Tower of London	-0.19 (0.99)	-0.02 (0.97)	+0.17 (1.03)	-0.18 (0.99)	0.08 (0.91)	+0.26 (1.00)	-0.10 (-0.24 to +0.04)	.16[e]
Word list memory delayed	-1.09 (1.58)	-1.01 (1.55)	+0.09 (1.55)	-1.15 (1.57)	-0.99 (1.45)	+0.16 (1.44)	-0.05 (-0.26 to +0.17)	.68[e]
Tertiary Outcomes								
Hoehn and Yahr stage	2.48 (0.59)	2.43 (0.58)	-0.05 (0.45)	2.49 (0.61)	2.44 (0.62)	-0.05 (0.51)	-0.01 (-0.08 to +0.07)	.88[e]
GRID-HAMD score	4.74 (4.04)	4.82 (4.33)	+0.07 (3.61)	4.95 (4.09)	5.28 (4.91)	+0.32 (4.11)	-0.31 (-0.93 to +0.30)	.32[e]
MMSE score	28.66 (1.46)	28.46 (1.93)	-0.20 (1.50)	28.64 (1.58)	28.59 (1.60)	-0.05 (1.61)	-0.14 (-0.39 to +0.10)	.26[e]

Abbreviations: CGI-C, Clinical Global Impression–Change; CGI-S, Clinical Global Impression–Severity; DRS, Dyskinesia Rating Scale; EQ-5D, EuroQoL 5 dimensions; GRID-HAMD, Hamilton Rating Scale of Depression, 17-item grid version; LS, least-squares; MMSE, Mini-Mental State Examination; NA, not applicable; PD, Parkinson disease; PDQ-39, 39-item Parkinson Disease Questionnaire; PGI-C, Patient Global Impression–Change; UPDRS, Unified Parkinson's Disease Rating Scale.

[a] Calculated, unless noted otherwise, from an analysis of covariance model with treatment and region as fixed effects and baseline value as covariate.

[b] From patient diary data. "Off" time is defined as the time when medication effect has worn off and parkinsonian features, including bradykinesia and rigidity, return.

[c] During an "on" phase (the time when patients experience relief of Parkinsonian motor features).

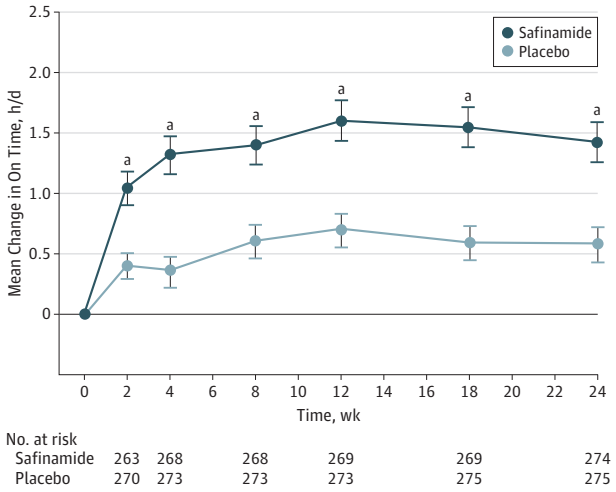
[d] Scores of 1, 2, or 3.

[e] Nominal *P* value, following a nonsignificant difference between treatment groups on an earlier test in the study's hierarchical test sequence.

[f] Odds ratios and 95% CIs estimated by logistic regression model with treatment and region as fixed effects; *P* value calculated with the Wald χ^2 test.

[g] Calculated from an analysis of variance model with fixed effects for treatment and region.

Figure 2. Change in "On" Time Without Troublesome Dyskinesia During Double-blind Treatment in the Intention-to-Treat Population (Last Observation Carried Forward)



Results are based on patient diary data. "On" time indicates when patients experience relief of parkinsonian motor features. Error bars indicate SE.

[a] $P < .001$ (unpaired, 2-sample t test).

Table 3. TEAEs in the Safety Population

TEAE	No. (% of Group) Safinamide Group (n = 274)	Placebo Group (n = 275)
Summary		
Any TEAE	186 (67.9)	190 (69.1)
Mild	163 (59.5)	161 (58.5)
Moderate	85 (31.0)	72 (26.2)
Severe	19 (6.9)	25 (9.1)
Any study drug-related TEAE[a]	78 (28.5)	76 (27.6)
Any SAE	18 (6.6)	26 (9.5)
Any study drug-related SAE[a]	3 (1.1)	6 (2.2)
Any TEAE causing discontinuation from study	12 (4.4)	10 (3.6)
Death	1 (0.4)	2 (0.7)
By preferred term[b]		
Dyskinesia	40 (14.6)	15 (5.5)
Fall	18 (6.6)	10 (3.6)
Urinary tract infection	17 (6.2)	12 (4.4)
Nausea	16 (5.8)	15 (5.5)
Headache	12 (4.4)	17 (6.2)
Constipation	11 (4.0)	11 (4.0)
Somnolence	10 (3.6)	8 (2.9)
Insomnia	10 (3.6)	5 (1.8)
Back pain	9 (3.3)	14 (5.1)
Nasopharyngitis	9 (3.3)	11 (4.0)
Hypoesthesia	8 (2.9)	2 (0.7)
Arthralgia	7 (2.6)	13 (4.7)
Dizziness	7 (2.6)	8 (2.9)
Diarrhea	7 (2.6)	7 (2.5)
Parkinson disease	7 (2.6)	5 (1.8)
Dyspepsia	7 (2.6)	3 (1.1)
Hallucination	6 (2.2)	6 (2.2)
Anxiety	6 (2.2)	4 (1.5)
Cough	6 (2.2)	3 (1.1)
Hypertension	4 (1.5)	6 (2.2)
Fatigue	3 (1.1)	8 (2.9)
Muscle spasms	3 (1.1)	6 (2.2)
Abdominal pain upper	0	6 (2.2)

Abbreviations: SAE, serious adverse event; TEAE, treatment-emergent adverse event.

[a] Recorded relation to study drug was probable, possible, or missing.

[b] Listed types, by Medical Dictionary for Regulatory Activities, version 13.0[15] preferred term, are all those reported in more than 2.0% of either treatment group.

increase in troublesome dyskinesia. For 1 mg of rasagiline, however, on time with troublesome dyskinesia accounted for 32% of a total increase of 1.15 hours. In the LARGO study,[18] it accounted for 21% of a total 1.08-hour increase for 1 mg of rasagiline and 17% of a total 1.03-hour increase for entacapone. In the present trial, the safinamide CGI outcome was -0.44 vs placebo (Table 2). In the PRESTO study, it was -0.68 for 0.5 mg of rasagiline and -0.39 for 1.0 mg of rasagiline,[17] and in the LARGO study, it was -0.49 for 1.0 mg of rasagiline and -0.36 for entacapone.[18]

The outcomes of the present trial support those of a previous double-blind study of safinamide as an adjunct to levodopa, in which 669 patients with motor fluctuations following stable regimens of levodopa and other PD pharmacotherapies were randomized to adjunctive placebo or 50 or 100 mg/d of safinamide for 24 weeks.[19] Safinamide significantly increased daily on time without troublesome dyskinesia by an LS mean, compared with placebo, of 0.51 hour for 50 mg/d and 0.55 hour for 100 mg/d. Significant reductions were observed in daily off time, in off time after first morning levodopa dose, and in UPDRS Part III scores while on. After an additional 18 months, the benefits of safinamide at 100 mg/d remained significant vs placebo by outcome measures, including daily on time without troublesome dyskinesia, daily off time, UPDRS Part III score, and PDQ-39 score.[20]

In the present trial, nondiary measures of dyskinesia in the safinamide group revealed either no change (DRS score) or a small increase of nominal significance (UPDRS Part IV dyskinesia subscores). As a TEAE, dyskinesia was reported more frequently with safinamide than with placebo. Its incidence (14.6% during 24 weeks vs 5.5% for placebo) resembled that reported for rasagiline in patients with fluctuating PD (18% during 26 weeks vs 10% for placebo[17]). In the previous safinamide trial, there was no apparent association between dosage and the frequency of dyskinesias, which was 21.1% for 50 mg/d and 18.3% for 100 mg/d compared with 12.6% for placebo at 24 weeks[19] and 31.2% for 50 mg/d and 27.8% for 100 mg/d compared with 21.7% for placebo at 2 years.[20] In both studies,[19,20] safinamide was generally well tolerated, as indicated by high study completion rates (approximately 89% in the present trial) and low rates of safinamide treatment discontinuation attributable to TEAEs (approximately 5% in the present trial).

Limitations

Limitations to the interpretation of the present study's outcomes include the study's duration of 24 weeks and its testing of only 1 prespecified dosage level (100 mg). The study also did not obtain overnight diary data and did not analyze the data from the first day of each 3-day diary-keeping period.

Conclusions

The management of motor complications in PD remains a significant challenge in which all available pharmacologic options carry the risk of inducing or exacerbating dyskinesias.[2] In the present study, safinamide increased on time and decreased off time to levels comparable to those seen for MAO-B and COMT inhibitors and had a low risk of inducing or exacerbating dyskinesia categorized as troublesome. For safinamide, these effects may be related to dopaminergic and nondopaminergic drug actions. It is notable that in a nonprimate model of levodopa-induced dyskinesias, safinamide reduced the intensity and duration of dyskinesias and also prolonged the motor benefits of levodopa.[21] Despite this study's limitations, it provides evidence that supports safinamide as an effective once-daily adjunct to levodopa for fluctuating PD. We anticipate that the results are generalizable across the PD population and suggest that safinamide offers an additional option for the control of motor fluctuations by oral medication before considering infusion therapies or deep brain stimulation.

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