First 2-year, placebo-controlled study in Parkinson's disease patients with motor fluctuations indicates safinamide may benefit patients with more severe dyskinesia

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Objective: To assess the antidyskinetic effects of safinamide, an α-aminoamide with dopaminergic and non-dopaminergic mechanisms, as add-on to levodopa over two years in patients with Parkinson's disease (PD) and moderate/severe dyskinesia.

Background: Primary endpoint analysis (Dyskinesia Rating Scale [DRS] score) indicated a worsening in the placebo group and an improvement in safinamide-treated patients over two years (Studies 016/018) that did not reach statistical significance when all patients were evaluated. Safinamide (50, 100mg/day) did improve motor fluctuations versus placebo.

Methods: Data from the entire ITT population were used for a post-hoc analysis of the effects of safinamide on dyskinesia in patients with no/low (DRS ≤4) and moderate/severe (DRS >4) dyskinesia at baseline.

Results: Dyskinesia was absent or low in 426/669 (63.7%) patients (DRS scores 0-4) and was moderate or severe in 242/669 (36.2%) patients. Compared with DRS≤4 patients, the DRS>4 patients were younger, more likely to be female, less likely to receive dopamine agonists and received amantadine more frequently.

In the DRS>4 population, safinamide 100mg/day improved DRS and UPDRS Part IV (items 32-33) scores versus placebo (LS mean differences vs placebo [CIs], -1.22 [-2.33, -0.11] and -0.50 [-0.92, -0.08], respectively; $p<0.05$). There were no significant improvements with 50mg/day. Incidences of adverse events were similar between the safety and DRS>4 populations.

Conclusion: Post-hoc analysis from this two-year, placebo-controlled study in mid-late PD patients with motor fluctuations showed that safinamide 100mg/day improved DRS scores in patients with more severe dyskinesia at baseline.

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Safinamide as add-on to levodopa in Parkinson's disease with motor fluctuations may improve responder rates versus placebo during long-term treatment

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Objective: To determine the clinical relevance of the long-term benefits of safinamide, an α-aminoamide with dopaminergic and non-dopaminergic mechanisms, as add-on to levodopa.

Methods: Previous analyses from Study 018 (n=544), an 18-month, double-blind, placebo-controlled extension to Study 016 (6 months; n=669), which evaluated safinamide (50 or 100mg/day) added to levodopa in patients with Parkinson's disease (PD) and motor fluctuations despite optimized therapy, showed that safinamide 100 mg/day had benefits on ON and OFF time, UPDRS Part II/III/IV, PDQ-39, and GRID HAM-D scores, but no significant effect on Dyskinesia Rating Scale (DRS) scores versus placebo. The present analysis was performed to determine the clinical relevance of these effects by evaluating responder rates. A hierarchical testing procedure was implemented: if the primary endpoint (change in DRS scores) was not met, key secondary endpoints were of exploratory nature only.

Results: After 24 months, safinamide improved responder rates for a number of evaluations, including increase in ON time and decrease in OFF time with no worsening of troublesome dyskinesia (placebo [n=222] 39.2%, 50 mg/day [n=223] 45.3% [p=0.1710] and 100 mg/day [n=224] 49.6% [p=0.0100]), and for ≥30% improvement in UPDRS Part III with no worsening in UPDRS Parts II or IV (placebo 21.6%, 50 mg/day 27.4% [p=0.1002] and 100 mg/day 30.8% [p=0.0059]).

Discussion: Two-year treatment with safinamide in mid-late PD patients with motor fluctuations despite optimized antiparkinsonian therapy was associated with improvements in responder rates that may be clinically important.

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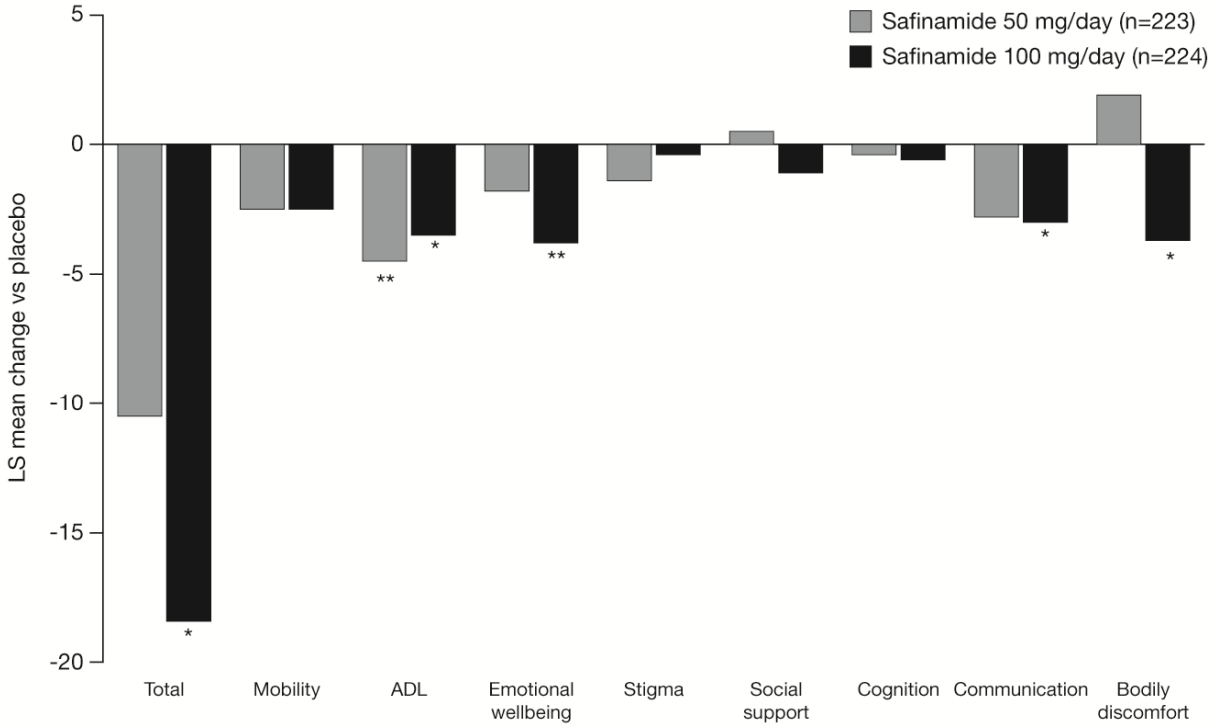
Keywords: (Five allowed [max 250 characters]): Parkinson's disease, safinamide, quality of life, depression

Topic: Parkinsonism

Change in PDQ total and subscale scores after 24 months' treatment with safinamide (end of Study 018)



LS, least squares
*p<0.05; **p≤0.01

Long-term efficacy of safinamide as add-on to levodopa in Parkinson's disease (PD) using an 'on' and 'on-off' treatment analysis

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Objective: To evaluate the efficacy of safinamide as add-on to levodopa using 'on' and 'on/off' treatment population analyses.

Methods: The two-year, double-blind, placebo-controlled Study 016/018 evaluated safinamide (50, 100mg/day) added to levodopa and other antiparkinsonian medications in PD with motor fluctuations. Previously, 'on' treatment analyses (censored at intervention to exclude effects of other PD medications) were reported (Anand AAN 2011). This exploratory analysis evaluated the efficacy of safinamide in patients who required intervention ('on/off' treatment – a wider, more conservative population).

Results: Comparisons between 'on' and 'on/off' populations revealed similar results in Dyskinesia Rating Scale (DRS) scores and improvements in ON time with safinamide after two years (Table). While DRS scores were not significantly improved for all patients randomized; significant improvement was observed with 100mg/day for patients with more severe dyskinesia (baseline DRS>4) in the 'on' treatment population ($p=0.0317$). Improvements in ON time with no/minor dyskinesia were comparable in both 'on' and 'on/off' analyses.

Discussion: In this two-year study, safinamide improved ON time with no/minor dyskinesia using both 'on' and 'on/off' treatment analyses, showing that the potential benefits of safinamide were unaffected by additional therapeutic interventions.

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Table. 'On' and 'on/off' treatment analyses vs placebo

	Safinamide 50 mg/day 'on treatment'		**Safinamide 100 mg/day 'on treatment'**		**Safinamide 50 mg/day 'on/off treatment'**		**Safinamide 100 mg/day 'on/off treatment'**	
	Least squares difference (95% CI)	**p-value**	**Least squares difference (95% CI)**	**p-value**	**Least squares difference (95% CI)**	**p-value**	**Least squares difference (95% CI)**	**p-value**
DRS score (n=669)	-0.51 (-1.32, 0.29)	0.2125	-0.59 (-1.40, 0.21)	0.1469	-0.19 (-0.84, 0.47)	0.5787	-0.37 (-1.03, 0.28)	0.2641
DRS score in patients with DRS>4 at baseline (n=242)	-0.73 (-1.84, 0.39)	0.1999	-1.22 (-2.33, -0.11)	0.0317	-0.68 (-1.76, 0.40)	0.2144	-1.02 (-2.12, 0.08)	0.0689
ON time with no/minor dyskinesia (n=440; patients who completed Study 018)	0.6 (0.1, 1.1)	0.0243	0.6 (0.1, 1.1)	0.0176	0.6 (0.1, 1.2)	0.0216	0.7 (0.2, 1.2)	0.0109

Two-year, placebo-controlled safety and tolerability data for safinamide as add-on to levodopa in patients with Parkinson's disease (PD)

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Objective: To evaluate the long-term safety and tolerability of safinamide as add-on to levodopa in patients with PD and motor fluctuations.

Methods: Study 018 was an 18-month, double-blind, placebo-controlled extension to a previous six-month trial (Study 016), evaluating safinamide (50, 100mg/day) as add-on to levodopa. Patients continued with existing PD therapies (except MAO-B inhibitors). Safety assessments included adverse events (AEs), laboratory, vital sign, and ECG data.

Results: 544 of 669 patients in Study 016 entered Study 018; ~80% in total completed the extension. Discontinuations due to AEs, incidences of serious AEs and deaths over two years were similar between placebo and safinamide 50mg/day, and slightly increased with 100mg/day. The three most common newly emergent AEs during Study 018 were ongoing PD, dyskinesia, and cataract. Incidences of treatment-emergent AEs for Studies 016/018 combined were similar across treatment groups over two years, except for dyskinesia, which occurred more frequently in safinamide groups, reflecting a slight excess in the first six months (Study 016). The three most common re-emergent events in Study 018 were dyskinesia, dry mouth, and back pain. Other measures (Dyskinesia Rating Scale and diary data) indicated no worsening or potential improvement of dyskinesia with safinamide treatment. There were no clinically relevant differences in other safety and tolerability assessments among groups.

Conclusions: In this two-year, prospective, placebo-controlled study in patients with mid-late PD, safinamide treatment was generally well tolerated.

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