Journal of the Neurological Sciences 461 (2024) 123051

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Safinamide as adjunctive therapy to levodopa monotherapy for patients with Parkinson's disease with wearing-off: The Japanese observational J-SILVER study

Noriko Nishikawa [a,*], Taku Hatano [a], Kenya Nishioka [b], Shin-Ichi Ueno [a], Shinji Saiki [a], Ryota Nakamura [c], Asako Yoritaka [d], Takashi Ogawa [c], Yasushi Shimo [e], Wataru Sako [a], Hideki Shimura [b], Yoshiaki Furukawa [b], Takanori Kamei [f], Takayuki Ishida [f], Nobutaka Hattori [a], on behalf of the J-SILVER study group

[a] Department of Neurology, Faculty of Medicine, Juntendo University, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421, Japan
[b] Department of Neurology, Juntendo Tokyo Koto Geriatric Medical Center, 3-3-20, Shinsuna, Koto-ku, Tokyo 136-0075, Japan
[c] Department of Neurology, Juntendo University Urayasu Hospital, 2-1-1, Tomioka, Urayasu, Chiba 279-0021, Japan
[d] Department of Neurology, Juntendo University Koshigaya Hospital, 560, Fukuroyama, Koshigaya, Saitama 343-0032, Japan
[e] Department of Neurology, Juntendo University Nerima Hospital, 3-1-10, Takanodai, Nerima-ku, Tokyo 177-8521, Japan
[f] Medical HQs, Eisai Co., Ltd., 4-6-10, Koishikawa, Bunkyo-ku, Tokyo 112-8088, Japan

ARTICLE INFO

Keywords:
MAO-B inhibitor
Wearing-off
Parkinson's disease
Safinamide
Quality of life
Pain

ABSTRACT

Background: Safinamide is an effective adjunctive therapy for wearing-off in Parkinson's disease (PD); however, evidence is lacking in older patients and those in the early stages of wearing-off. This study evaluated the efficacy and safety of safinamide as adjunctive therapy in patients with PD treated with levodopa monotherapy in clinical practice.

Methods: This multicentre, open-label observational study was conducted at five sites in Japan. Patients diagnosed with PD and wearing-off initiated safinamide as adjunctive therapy with levodopa monotherapy. Efficacy endpoints were mean changes in Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) Part I, III, and IV scores; daily ON-time without dyskinesia using 24-h patient symptom diaries; and 39-item Parkinson's Disease Questionnaire (PDQ-39) scores at 18 weeks of treatment.

Results: In total, 24 patients initiated safinamide (66.7% were aged ≥75 years); the mean duration of wearing-off was 1.2 years. MDS-UPDRS Part III total score, Part IV total score, and PDQ-39 summary index decreased significantly from baseline (mean change −7.0 [$p = 0.012$], −2.4 [$p = 0.007$] and − 5.3 [$p = 0.012$], respectively). There was a non-statistically significant increase of 1.55 h in mean daily ON-time without dyskinesia. Numerical Rating Scale total score for pain ($p = 0.015$), and scores for OFF-period pain ($p = 0.012$) and nocturnal pain ($p = 0.021$) subdomains were significantly improved in the subgroup with pain. Most reported adverse events were classified as mild.

Conclusion: Safinamide improved motor and non-motor symptoms and quality of life-related measures in older patients with PD in the early stages of wearing-off without new safety concerns.

Study registration: University Hospital Medical Information Network in Japan; study ID: UMIN000044341.

Abbreviations: ADL, activities of daily living; ADR, adverse drug reaction; AE, adverse event; BMI, body mass index; CGI-I, Clinical Global Impression-Improvement; CI, confidence interval; FAS, full analysis set; KPPS, King's Parkinson's Disease Pain Scale; LOCF, last observation carried forward; MAO-B, monoamine oxidase-B; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; NRS, Numerical Rating Scale; PD, Parkinson's disease; PDQ-39, 39-item Parkinson's Disease Questionnaire; PGI-I, Patient Global Impression-Improvement; PIGD, postural instability gait difficulty; REM, rapid eye movement; SD, standard deviation.

* Corresponding author.
E-mail addresses: n.nishikawa.ts@juntendo.ac.jp (N. Nishikawa), thatano@juntendo.ac.jp (T. Hatano), nishioka@juntendo.ac.jp (K. Nishioka), sueno@juntendo.ac.jp (S.-I. Ueno), ssaiki@juntendo.ac.jp (S. Saiki), ryonaka@juntendo.ac.jp (R. Nakamura), ayori@juntendo.ac.jp (A. Yoritaka), takashio@juntendo.ac.jp (T. Ogawa), yshimo@juntendo.ac.jp (Y. Shimo), w.sako.fn@juntendo.ac.jp (W. Sako), hshimura@juntendo.ac.jp (H. Shimura), yfuruka@juntendo.ac.jp (Y. Furukawa), t2-kamei@hhc.eisai.co.jp (T. Kamei), t8-ishida@hhc.eisai.co.jp (T. Ishida), nhattori@juntendo.ac.jp (N. Hattori).

https://doi.org/10.1016/j.jns.2024.123051
Received 15 January 2024; Received in revised form 29 March 2024; Accepted 13 May 2024
Available online 17 May 2024

1. Introduction

The global population is ageing, and almost two-thirds of patients with Parkinson's disease in Japan are aged ≥75 years [1]. Parkinson's disease is a neurodegenerative disorder characterised by motor symptoms and degenerative loss of dopaminergic neurons in the substantia nigra [2]. Dopamine replacement therapy is the primary treatment for Parkinson's disease, and levodopa is the gold standard of treatment for the motor symptoms of the condition [3]. However, long-term levodopa treatment is associated with motor complications, such as wearing-off and dyskinesia onset [4]. As the disease progresses, adjunctive therapy with dopamine agonists, monoamine oxidase-B (MAO-B) inhibitors, and other anti-parkinsonian drugs becomes necessary in addition to levodopa [5].

In recent years, there has been concern that dopamine agonists are associated with a risk of impulse-control disorders in the long term [6]. In addition, the PD-MED study has re-evaluated the efficacy and tolerability of MAO-B inhibitors and shown them to be equivalent in efficacy and patient-rated quality of life to dopamine agonists [7].

Safinamide, a selective and reversible MAO-B inhibitor that also inhibits voltage-gated sodium channels, has been used in Europe, the United States, Asia, and Japan to treat Parkinson's disease and improve wearing-off [8]. Phase II/III (ME2125–3) [9] and phase III (ME2125–4) [10] studies of safinamide have been conducted in Japan. These studies demonstrated the efficacy and safety of adjunctive therapy with safinamide for patients with Parkinson's disease treated with levodopa and experiencing wearing-off. However, patients enrolled in the Japanese studies of safinamide were generally in their late 60s, making it challenging to apply the evidence to all aspects of actual clinical practice [9,10]. Furthermore, approximately 90% of patients in the studies were treated with concomitant anti-parkinsonian drugs other than levodopa, and there were few patients treated with levodopa monotherapy. A *post hoc* analysis of two international phase III studies suggested that safinamide may be effective as a first adjunct therapy to levodopa in a small population of patients [11]. However, this analysis evaluated only the higher dose of safinamide (100 mg/day). To our knowledge, there is no other evidence of safinamide treatment in patients with Parkinson's disease treated with levodopa monotherapy other than the report by Cattaneo et al. [11].

Therefore, we conducted an observational study of the efficacy and safety of safinamide as adjunctive therapy for patients with Parkinson's disease treated with levodopa monotherapy using measures including the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS), 39-item Parkinson's Disease Questionnaire (PDQ-39) score, rating scales for pain, and patient 24-h symptom diaries. This study may complement the current evidence for safinamide in older patients and those in the early stage of wearing-off.

2. Materials and methods

2.1. Study design

This was a multicentre, open-label observational study conducted at five sites (all secondary medical institutions) in Japan from April 2021 to January 2023. The Institutional Review Board at each site reviewed and approved the study. This study was registered with the University Hospital Medical Information Network in Japan (UMIN: 000044341). All patients provided written informed consent at the time of study enrolment.

2.2. Patients and treatments

Japanese patients aged ≥20 years who were diagnosed with Parkinson's disease according to the diagnostic criteria defined by the International Parkinson and Movement Disorder Society were enrolled. All patients received treatment with an oral levodopa-containing drug (excluding levodopa/carbidopa hydrate/entacapone combination) and had wearing-off with a predictable OFF-time. Patients receiving treatment with an anti-parkinsonian drug other than an oral levodopa-containing drug within 4 weeks prior to baseline (Week 0) were excluded. Concomitant use with other MAO inhibitors, antidepressants, or selective serotonin reuptake inhibitors was prohibited based on the package insert for safinamide in Japan [12]. Patients scheduled for neurosurgical procedures for Parkinson's disease (*e.g.*, destructive surgery, deep brain stimulation) were also excluded. The complete list of inclusion and exclusion criteria is provided in the Supplementary Methods.

In all cases, safinamide was administered as add-on therapy to oral levodopa-containing drugs. Depending on symptoms, the safinamide dose could be increased from 50 mg to 100 mg once daily. Patients were observed for 18 weeks from the start of safinamide administration. Dosage adjustments and the addition or discontinuation of drug treatment were at the discretion of the physician and there were no restrictions on the duration of observation.

2.3. Efficacy evaluation

The efficacy endpoints included mean changes from baseline in MDS-UPDRS Part I, Part III, and Part IV scores, the daily OFF-time and daily ON-time without dyskinesia on 24-h patient symptom diaries, the total PDQ-39 score, the Clinical Global Impression-Improvement (CGI-I), Patient Global Impression-Improvement (PGI-I), King's Parkinson's Disease Pain Scale (KPPS), and Numerical Rating Scale (NRS) of pain. In the NRS, pain was rated on an 11-point scale (0 to 10) during ON-state, OFF-state, and sleep, and the total score (0 to 30) was calculated. Evaluation timepoints for each item are shown in Supplementary Fig. S1 and further details of the outcome analysis are described in the Supplementary Methods.

2.4. Safety evaluation

The incidences of AEs and adverse drug reactions (ADRs) occurring or worsening after the start of the study treatment were evaluated.

2.5. Statistical methods

In the efficacy analysis, data were collected from patients who had received at least one dose and were evaluable for efficacy outcomes at both baseline and the last evaluation point. This population was defined as the full analysis set (FAS). The primary analysis was an observed cases analysis, supplemented by a sensitivity analysis using last observation carried forward for missing or omitted data. A paired *t*-test was performed for each evaluation timepoint against baseline (Week 0). The safety analysis included data from patients who received at least one dose of the study drug (Safety population). The incidence of adverse events (AEs) occurring after the start of the study treatment was summarised. All tests had a two-tailed significance level of 5% and no adjustments were made for multiplicity. All analyses were conducted using SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

3. Results

3.1. Patient demographic and baseline characteristics

Of the 33 patients who provided informed consent, 24 entered the observation period. The FAS comprised 24 patients, 17 of whom continued safinamide until Week 18. Seven patients discontinued safinamide by Week 18 (Fig. 1).

Table 1 summarises the demographic and baseline characteristics of the FAS and Safety populations. The mean (standard deviation [SD]) age was 74.5 (8.6) years, and 66.7% of patients were aged ≥75 years. The mean duration of Parkinson's Disease was 5.7 years, and the mean

duration of wearing-off was 1.2 years. The mean (SD) daily dose of levodopa was 470.8 (175.0) mg/day. The safinamide dose was increased to 100 mg/day in seven of the 17 patients (41.2%) (Supplementary Table S1). Demographic data according to final safinamide dose are shown in Supplementary Table S1.

3.2. Efficacy

MDS-UPDRS Part III total score, Part IV total score, and PDQ-39 summary index decreased markedly and significantly from baseline, with mean changes of −7.0 ($p = 0.012$), −2.4 ($p = 0.007$) and − 5.3 ($p = 0.012$), respectively, at Week 18 (Fig. 2A–C). The proportion of MDS-UPDRS Part III total score responders who improved by ≥3.25 points was 68.8% at Week 18. An increase of 0.94 h and 1.55 h in mean daily ON-time without dyskinesia from baseline was found at Week 2 and Week 18, respectively, although this was not statistically significant (Fig. 2D). Scores for bradykinesia (mean [SD] −3.5 [5.8]; 95% confidence interval [CI] −6.6, −0.4; $p = 0.029$), rigidity (−1.6 [2.0]; 95% CI −2.7, −0.6; $p = 0.005$), axial symptoms (−2.0 [3.7]; 95% CI −4.0, −0.0; $p = 0.047$), and postural instability gait difficulty (−1.6 [2.4]; 95% CI −2.9, −0.3; $p = 0.018$) were significantly improved by safinamide (Table 2). Changes from baseline in MDS-UPDRS Part IV total and sub-scores at Week 18 and CGI-I and PGI-I scores at Week 18 are summarised in Supplementary Table S2. Mean CGI-I score at Week 18 was 2.6 (Supplementary Table S2); the responder rate at Week 18 was 76.5%. For MDS-UPDRS Part I total scores, the mean change from baseline to Week 18 was −1.8 ($p = 0.018$), indicating significant improvement (Table 2).

At baseline, mean KPPS total score and NRS total score in patients with pain were 8.6 ($n = 19$) and 8.2 ($n = 16$), respectively. After 18 weeks of adjunctive safinamide treatment, the mean (SD) changes from baseline were − 2.6 (8.2) for KPPS and − 3.8 (4.6) for NRS (Table 2, Supplementary Fig. S2). Among subdomains of NRS, OFF-period pain ($p = 0.012$) and nocturnal pain ($p = 0.021$) were significantly improved by safinamide (Table 2). Other changes from baseline in KPPS sub-scores at Week 18 are shown in (Supplementary Table S3).

Significant changes from baseline to Week 18 for individual PDQ-39 domains were observed for mobility (−8.6 [SD 9.2]; 95% CI −13.5, −3.7; $p = 0.002$), emotional well-being (−6.8 [8.5]; 95% CI −11.3, −2.3; $p = 0.006$), and bodily discomfort (−9.4 [7.6]; 95% CI −13.7, −5.2; $p < 0.001$) (Table 3).

Table 1
Demographic data and baseline characteristics.

	FAS/Safety population ($N = 24$)
Sex, female [n (%)]	13 (54.2)
Age, years [mean (SD)]	74.5 (8.6)
Age ≥ 75 years [n (%)]	16 (66.7)
BMI [mean (SD)]	22.2 (2.4)
Duration of Parkinson's Disease, years [mean (SD)]	5.7 (3.4)
Duration of treatment with levodopa, years [mean (SD)]	4.6 (3.6)
Duration of wearing-off phenomenon, years [mean (SD)]	1.2 (1.4)
Modified Hoehn & Yahr stage (ON state) [median (min, max)]	2.0 (1,3)
Modified Hoehn & Yahr stage (OFF state) [median (min, max)]	2.8 (2, 5)
MDS-UPDRS Score [mean (SD)]	
MDS-UPDRS Part I	11.0 (4.7)
MDS-UPDRS Part III (ON state)	22.0 (8.9)
MDS-UPDRS Part IV	5.0 (2.1)
Daily OFF-time, hours [mean (SD)]	4.6 (3.2)
Daily ON-time without dyskinesia, hours [mean (SD)]	10.6 (3.5)
PDQ-39 summary index [mean (SD)]	21.3 (12.6)
King's Parkinson's Disease Pain Scale [mean (SD)]	7.1 (5.6)
Numerical Rating Scale of Pain [mean (SD)]	5.7 (6.5)
Daily dose of levodopa at baseline, mg/day [mean (SD)]	470.8 (175.0)
Daily dose of levodopa ≥400 mg/day [n (%)]	15 (62.5)
Levodopa-carbidopa [n (%)]	20 (83.3)
Levodopa-benserazide [n (%)]	4 (16.7)
History of other MAO-B inhibitors [n (%)]	9 (37.5)

BMI, body mass index; FAS, full analysis set; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; MAO-B, monoamine oxidase-B; PDQ-39, 39-item Parkinson's Disease Questionnaire score; SD, standard deviation.

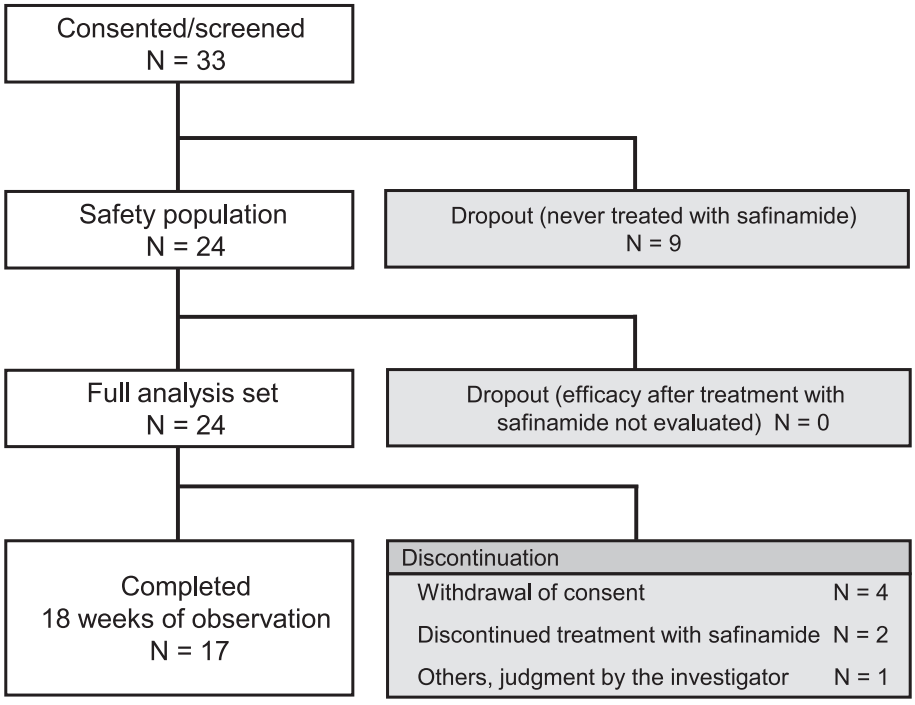

Fig. 1. Patient disposition.
Single column fitting image.

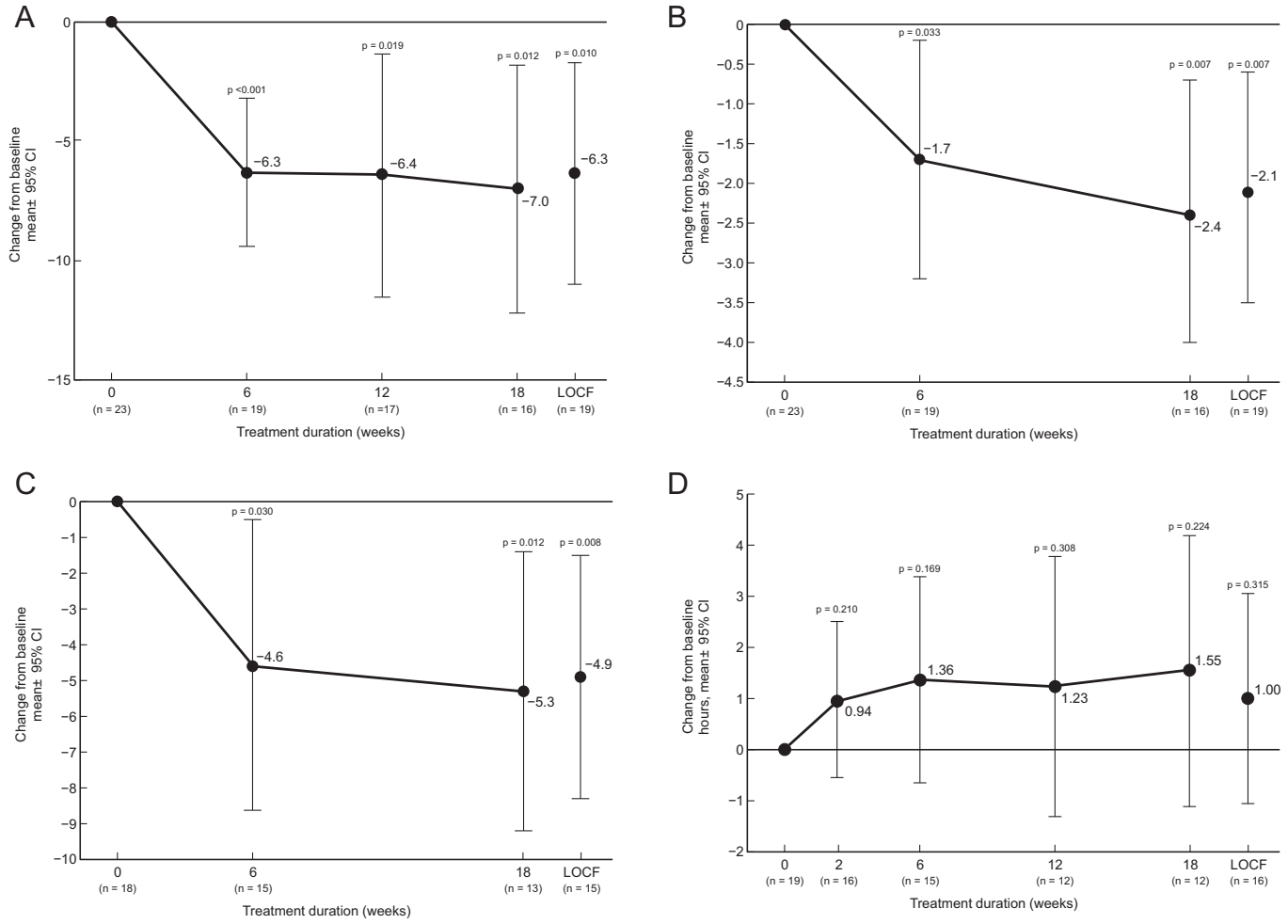

Fig. 2. Changes from baseline in A) MDS-UPDRS Part III total score, B) MDS-UPDRS Part IV total score, C) PDQ-39 summary index, and D) daily ON-time without dyskinesia.
CI, confidence interval; LOCF, last observation carried forward; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; PDQ-39, 39-item Parkinson's Disease Questionnaire score.
A paired *t*-test was performed for each evaluation timepoint against baseline (Week 0).
Two-column fitting image.

3.3. Safety

During the study period, a total of 10 AEs were reported in 24 patients, most of which were classified as mild. A joint wrist fracture was classed as a severe and serious AE, which was not causally related to safinamide. AE onset was most often observed within 2 weeks (5 of 10 patients). ADRs were reported in four patients; all were mild but three of four ADRs led to discontinuation; one ADR resulted in dose reduction. ADRs included visual hallucination, hypotension, vomiting, and hyperhidrosis (Table 4).

4. Discussion

In this study, we observed improvements in motor and non-motor symptoms when safinamide was administered to Japanese patients with Parkinson's disease with wearing-off who were being treated only with levodopa-containing preparations. To our knowledge, this is the first multicentre prospective observational study to examine the efficacy of safinamide adjunctive therapy with levodopa monotherapy, and we have confirmed that there are no new safety concerns.

Compared with the long-term phase III study conducted in Japan [10], the disease duration in this study was approximately 4 years less, and the time of wearing-off onset was approximately 2.5 years less. Thus, the present study evaluated patients in the early stages of wearing-off. Furthermore, the patients in this study had a higher mean age (74.5 years), which may reflect routine clinical practice in Japan, one of the most rapidly ageing societies in the world. All patients started treatment with safinamide 50 mg/day, and the dose of safinamide had been increased to 100 mg/day in 41.2% of patients by Week 18 depending on symptoms. The addition of other anti-parkinsonian drugs was not required in any patients.

Treatment with safinamide improved the MDS-UPDRS part III total score by a mean of −7.0 points at Week 18 compared with baseline. The proportion of responders who improved by ≥3.25 points or more, considered a minimal but clinically pertinent difference [13], was 68.8%. Together with the responder rate at 18 weeks for CGI-I (76.5%), for which the threshold for a minimal but clinically pertinent difference is 3 [13], it can be concluded that a clinically meaningful effect was observed in approximately 70% of the patients.

Of the primary motor symptoms, bradykinesia, rigidity, and axial symptoms improved with treatment with safinamide, consistent with the results of a previous phase II/III study [14]. The improvement in bradykinesia and rigidity is thought to be mainly because of dopaminergic effects from MAO-B inhibition. Safinamide has been reported to improve tremor [14], but there was no improvement in tremor scores in this study, which is perhaps attributable to the low mean tremor score at

Table 2
Changes from baseline for efficacy endpoints at Week 18 (FAS; N = 24).

	Baseline	Changes from baseline		
	Mean (SD)	Mean (SD)	Two-sided 95% CI	P-value[a]
MDS-UPDRS Part III total score (ON state)	22.0 (8.9)	−7.0 (9.8)	−12.2, −1.8	0.012
Bradykinesia score	11.8 (4.5)	−3.5 (5.8)	−6.6, −0.4	0.029
Rigidity score	4.8 (3.1)	−1.6 (2.0)	−2.7, −0.6	0.005
Tremor score	0.8 (1.3)	0.1 (1.2)	−0.5, 0.8	0.684
Axial symptoms score	4.7 (3.5)	−2.0 (3.7)	−4.0, −0.0	0.047
PIGD score	3.7 (2.7)	−1.6 (2.4)	−2.9, −0.3	0.018
Daily ON-time without dyskinesia, hours	10.62 (3.54)	1.55 (4.18)	−1.10, 4.21	0.224
Daily OFF-time, hours	4.62 (3.24)	−0.95 (3.85)	−3.40, 1.49	0.409
MDS-UPDRS Part I total score	11.0 (4.7)	−1.8 (2.7)	−3.3, −0.4	0.018
Part Ia score	2.3 (2.5)	−0.9 (1.9)	−2.0, 0.1	0.069
Part Ib score	8.7 (3.1)	−0.9 (2.4)	−2.1, 0.4	0.164
KPPS total score (KPPS >0 subgroup, n = 19)	8.6 (5.0)	−2.6 (8.2)	−7.4, 2.1	0.250
NRS total score (NRS >0 subgroup, n = 16)	8.2 (6.4)	−3.8 (4.6)	−6.7, −0.9	0.015
item 1: ON-period pain	1.9 (2.3)	−0.5 (2.1)	−1.8, 0.8	0.429
item 2: OFF-period pain	3.7 (2.4)	−1.7 (1.9)	−2.9, −0.4	0.012
item 3: Nocturnal pain	2.6 (3.0)	−1.7 (2.1)	−3.0, −0.3	0.021
Daily dose of levodopa, mg/day	470.8 (175.0)	8.8 (36.4)	−9.9, 27.5	0.332

CI, confidence interval; FAS, full analysis set; KPPS, King's Parkinson's Disease Pain Scale; MDS-UPDRS, Movement Disorder Society-Unified Parkinson's Disease Rating Scale; NRS, Numerical Rating Scale; PIGD, postural instability gait difficulty; SD, standard deviation.
[a] Paired t-test for each evaluation timepoint against baseline (week 0).

Table 3
Changes from baseline for PDQ-39 domains at Week 18 (FAS; N = 24).

	Baseline	Changes from baseline			Minimal important difference
	Mean (SD)	Mean (SD)	Two-sided 95% CI	P-value[a]	
Summary Index	21.3 (12.6)	−5.3 (6.5)	−9.2, −1.4	0.012	1.6
Mobility	36.7 (25.1)	−8.6 (9.2)	−13.5, −3.7	0.002	3.2
ADL	18.5 (18.5)	−4.9 (13.0)	−11.9, 2.0	0.149	4.4
Emotional well-being	20.5 (14.0)	−6.8 (8.5)	−11.3, −2.3	0.006	4.2
Stigma	12.0 (13.8)	−0.4 (14.5)	−8.1, 7.3	0.916	5.6
Social support	9.2 (15.4)	−4.2 (8.5)	−9.1, 0.7	0.089	11.4
Cognition	26.4 (18.4)	−3.9 (8.8)	−8.6, 0.8	0.096	1.8
Communication	13.6 (20.5)	−4.4 (8.3)	−9.0, 0.1	0.056	4.2
Bodily discomfort	23.1 (15.0)	−9.4 (7.6)	−13.7, −5.2	<0.001	2.1

ADL, activities of daily living; CI, confidence interval; FAS, full analysis set; PDQ-39, 39-item Parkinson's Disease Questionnaire score; SD, standard deviation.
[a] Paired t-test for each evaluation timepoint against baseline (week 0).

baseline (0.8 points).

Treatment with safinamide improved ON-time without dyskinesia by a mean of 1.55 h as assessed by 24-h patient symptom diaries, although this was not statistically significant. In this study, ON-time improved by 0.94 h from 2 weeks after safinamide administration, confirming the rapid onset of efficacy observed in the SETTLE [15] and XINDI [16] studies.

Table 4
AEs and ADRs (Safety population; N = 24).

	Patients with AEs, N	Patients with ADRs, N
All events	10	4
Serious AEs/ADRs	1	0
Severe AEs/ADRS	1	0
AEs/ADRs leading to discontinuation	4	3
AEs/ADRs		
Visual hallucination	1	1
REM sleep behaviour disorder	1	0
Headache	1	0
Hypotension	1	1
Nausea	1	0
Vomiting	1	1
Hyperhidrosis	1	1
Lumbar spinal canal stenosis	1	0
Fatigue	1	0
Wrist joint fracture	1	0
Tooth fracture	1	0

ADR, adverse drug reaction; AE, adverse event; REM, rapid eye movement.
One patient experienced two AEs.

Treatment with safinamide significantly improved the MDS-UPDRS Part IV total score, which was attributed to improved wearing-off. Although very few patients in this study had dyskinesia at baseline, the duration and severity of dyskinesia did not worsen. The results are consistent with the *post hoc* analysis of the Japanese phase III study by Hattori et al. [17].

In this study, treatment with safinamide significantly improved the MDS-UPDRS Part I total score, suggesting that safinamide improves non-motor symptoms. In addition, the KPPS total score showed a trend toward improvement in pain over the minimal clinically significant difference, with a significant improvement at Week 6 [18]. Of note, the Japanese version of the KPPS has been validated and reported to be a useful tool for objective pain assessment in Japanese patients with Parkinson's disease [19]. The KPPS total score at baseline in this study was 7.1 points, a lower trend than in previous studies where safinamide improved KPPS [20,21]. Interestingly, validation in a subpopulation excluding patients who did not have pain at baseline showed a significant improvement in the patient-rated NRS total score, especially off-state and nocturnal pain, with the administration of safinamide. In the domain related to non-motor symptoms of the PDQ-39, a subjective rating scale, the emotional well-being and bodily discomfort domains were significantly improved, and they exceeded the minimal clinically important difference for PDQ-39 [22].

The effects of safinamide on sensory symptoms and pain have been reported in several studies, including Tsuboi et al. (improvement of

MDS-UPDRS part II, item17) [23] and a *post hoc* analysis by Cattaneo et al. (PDQ-39 bodily discomfort domain) [24], which aligns with our findings of numerical improvements in KPPS and NRS. In the present study, safinamide improved pain in OFF-time and at night but did not improve pain in ON-time. These findings suggest that patients with Parkinson's disease have a lowered pain threshold in OFF-time [25] and that safinamide may exert its effect on the lowered pain threshold through dopaminergic and non-dopaminergic effects. This is supported by a non-clinical study indicating that safinamide improved pain threshold in a dose-dependent manner in a rat model of neuropathic pain [26] and in a mouse model of PD [27].

The effects of safinamide on depression and apathy have been reported by Hattori et al. (improvement of MDS-UPDRS part I, item 3) [28] and Cattaneo et al. (improvement of PDQ-39 emotional well-being) [29], and, because other MAO-B inhibitors also improve PDQ-39 emotional well-being [30], it is reasonable to assume that safinamide improved depressive symptoms and mood *via* the dopaminergic effects of MAO-B inhibition.

Of the 24 patients, AEs occurred in 10 patients (41.7%) in this study; four (16.7%) were causally related to safinamide. In the Japanese long-term phase III study (n = 203, 52 weeks, mean age 67.4 years), approximately half of the patients were up-titrated to 100 mg/day of safinamide [10]. AEs and ADRs were reported in 78.3% and 38.9% of patients, respectively, of which the most common were nasopharyngitis and dyskinesia [10]. No specific AEs of dyskinesia were observed in this study. As this study was conducted in patients in the early stages of wearing-off, it is likely that dyskinesia did not develop or worsen. One case each of hallucination, hypotension, vomiting, and excessive sweating were reported as ADRs. In the Japanese phase III long-term study [10], ADRs of visual hallucination and nausea were observed in 2.5% of patients, and ADRs of hypotension were also reported in an international phase III study [31]. Excessive sweating may be an effect of the sweating disorder observed as an autonomic symptom of the underlying disease. These symptoms are also commonly observed in the pathogenesis of Parkinson's disease, and there is no concern about new adverse effects caused by safinamide in older patients.

This study has some limitations to consider when interpreting the findings. It included a single arm of patients treated with safinamide for pre- and post-treatment comparisons. As the study was conducted under routine clinical practice, and safinamide doses were increased according to individual symptoms, analysis by safinamide dose was not performed. Furthermore, the fact that two patients received an increased dose of levodopa during the observation period is a limitation. The results may have been confounded by the placebo effect and the variance of raters from different study sites in the evaluation of MDS-UPDRS and KPPS scores. A placebo effect has been reported to exist for Parkinson's disease, depression, and pain [32], and the effect of safinamide shown in this study may include a placebo effect. Regarding the results of the 24-h patient symptom diaries, it should be noted that in some cases, the diaries were not accurate because the study included a large number of older patients, and this was not as strictly controlled as in a randomised clinical trial. The analysis in this study was based on 24 cases, and it is possible that the power was insufficient to detect statistically significant differences. Finally, regarding the assessment of dyskinesia, tremors and non-motor symptoms, caution is required in interpreting the results, as not all patients had symptoms before the start of treatment.

This study showed that safinamide improved motor and non-motor symptoms and quality of life-related measures in older patients with Parkinson's disease in the early stages of wearing-off without new safety concerns. Unlike previous randomised controlled trials in general, this is an observational study examining the efficacy and safety of safinamide treatment under routine clinical practice conditions; therefore, the results of this study may be helpful in predicting response to the drug in real-life clinical settings. In the future, it will be necessary for such observational studies to re-evaluate the usefulness of the drug in actual clinical practice.

J-SILVER study group investigators

Maya Ando, Hiroto Eguchi, Jiro Fukae, Yoshiaki Furukawa, Atsuhito Fuse, Taku Hatano, Nobutaka Hattori, Naohide Kurita, Toshiki Nakahara, Asuka Nakajima, Sho Nakajima, Ryota Nakamura, Noriko Nishikawa, Kenya Nishioka, Kotaro Ogaki, Takashi Ogawa, Yutaka Oji, Genko Oyama, Shinji Saiki, Wataru Sako, Yasushi Shimo, Hideki Shimura, Shin-Ichi Ueno, Takao Urabe, Masao Watanabe, Kazuo Yamashiro, Asako Yoritaka. The affiliations of the investigators are listed in Supplementary Table S4.

Ethics statement

The study protocol and its amendments were reviewed and approved by all appropriate ethics committees. The patients/participants provided their written informed consent to participate in this study.

Funding

This research was funded by Eisai Co., Ltd. The employees of Eisai were involved in study design; in the interpretation of data; and in the decision to submit the article for publication.

CRediT authorship contribution statement

Noriko Nishikawa: Conceptualization, Methodology, Investigation, Writing – original draft, Writing – review & editing, Project administration. **Taku Hatano:** Writing – review & editing. **Kenya Nishioka:** Investigation, Writing – review & editing. **Shin-Ichi Ueno:** Investigation, Writing – review & editing. **Shinji Saiki:** Investigation, Writing – review & editing. **Ryota Nakamura:** Investigation, Writing – review & editing. **Asako Yoritaka:** Investigation, Writing – review & editing. **Takashi Ogawa:** Investigation, Writing – review & editing. **Yasushi Shimo:** Investigation, Writing – review & editing. **Wataru Sako:** Investigation, Writing – review & editing. **Hideki Shimura:** Investigation, Writing – review & editing. **Yoshiaki Furukawa:** Investigation, Writing – review & editing. **Takanori Kamei:** Conceptualization, Methodology, Writing – review & editing, Project administration. **Takayuki Ishida:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing, Project administration. **Nobutaka Hattori:** Conceptualization, Methodology, Writing – review & editing, Supervision.

Declaration of competing interest

N.N., S.S. and W.S. report honoraria and consultation fees from Eisai Co., Ltd. during the conduct of the study. T.H., K.N., R.N., A.Y., Y.S. and H.S. report honoraria from Eisai Co., Ltd. during the conduct of the study. S.-I.U., T.O. and Y.F. have no competing interests to declare. T.K. and T.I. are employees of Eisai Co. Ltd. N.H. reports honoraria, consultation fees and grants from Eisai Co., Ltd. during the conduct of the study.

Data availability

The datasets generated during and/or analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Acknowledgements

We thank all participating patients and their families, as well as investigators, physicians, nurses, and clinical research coordinators at all investigational sites. We would also like to thank Tomoko Ozawa and Mitsuyo Yoshida of Eisai Co., Ltd. and Tomohito Ide of APO PLUS STATION Co., Ltd. for their help in the study operation, Fumio Kusano of

APO PLUS STATION Co., Ltd. for statistical analysis, which were funded by Eisai Co., Ltd. We thank Keyra Martinez Dunn, MD and Helen Roberton of Edanz (www.edanz.com) for providing medical writing support, which was funded by Eisai Co., Ltd. in accordance with Good Publication Practice 2022 guidelines (https://www.ismpp.org/gpp-2022).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2024.123051.

References

[1] M. Seki, Y. Kawata, A. Hayashi, M. Arai, S. Fujimoto, Prescribing patterns and determinants for elderly patients with Parkinson's disease in Japan: a retrospective observational study using insurance claims databases, Front. Neurol. 14 (2023) 1162016, https://doi.org/10.3389/fneur.2023.1162016.

[2] L.V. Kalia, A.E. Lang, Parkinson's disease, Lancet 386 (2015) 896912, https://doi.org/10.1016/S0140-6736(14)61393-3.

[3] A. Lees, E. Tolosa, F. Stocchi, J.J. Ferreira, O. Rascol, A. Antonini, W. Poewe, Optimizing levodopa therapy, when and how? Perspectives on the importance of delivery and the potential for an early combination approach, Expert. Rev. Neurother. 23 (2023) 15–24, https://doi.org/10.1080/14737175.2023.2176220.

[4] E.L. Lane, L-DOPA for Parkinson's disease-a bittersweet pill, Eur. J. Neurosci. 49 (2019) 384–398, https://doi.org/10.1111/ejn.14119.

[5] R. Gilbert, P. Khemani, Treatment of advanced Parkinson's disease, J. Geriatr. Psychiatry Neurol. 35 (2022) 12–23, https://doi.org/10.1177/0891988720988904.

[6] J.C. Corvol, F. Artaud, F. Cormier-Dequaire, O. Rascol, F. Durif, P. Derkinderen, A. R. Marques, F. Bourdain, J.P. Brandel, F. Pico, L. Lacomblez, C. Bonnet, C. Brefel-Courbon, F. Ory-Magne, D. Grabli, S. Klebe, G. Mangone, H. You, V. Mesnage, P. C. Lee, A. Brice, M. Vidailhet, A. Elbaz, DIGPD Study Group, Longitudinal analysis of impulse control disorders in Parkinson disease, Neurology 91 (2018) e189–e201, https://doi.org/10.1212/WNL.0000000000005816.

[7] R. Gray, S. Patel, N. Ives, C. Rick, R. Woolley, S. Muzerengi, A. Gray, C. Jenkinson, E. McIntosh, K. Wheatley, A. Williams, C.E. Clarke, PD MED Collaborative Group, Long-term effectiveness of adjuvant treatment with catechol-o-methyltransferase or monoamine oxidase b inhibitors compared with dopamine agonists among patients with Parkinson disease uncontrolled by levodopa therapy: the PD MED randomized clinical trial, JAMA Neurol. 79 (2022) 131–140, https://doi.org/10.1001/jamaneurol.2021.4736.

[8] K. Kurihara, T. Mishima, S. Fujioka, Y. Tsuboi, Efficacy and safety evaluation of safinamide as an add-on treatment to levodopa for Parkinson's disease, Expert Opin. Drug Saf. 21 (2022) 137–147, https://doi.org/10.1080/14740338.2022.1988926.

[9] N. Hattori, Y. Tsuboi, A. Yamamoto, Y. Sasagawa, M. Nomoto, ME2125-3 Study Group, Efficacy and safety of safinamide as an add-on therapy to L-DOPA for patients with Parkinson's disease: a randomized, double-blind, placebo-controlled, phase II/III study, Parkinsonism Relat. Disord. 75 (2020) 17–23, https://doi.org/10.1016/j.parkreldis.2020.04.012.

[10] Y. Tsuboi, N. Hattori, A. Yamamoto, Y. Sasagawa, M. Nomoto, ME2125-4 Study Group, Long-term safety and efficacy of safinamide as add-on therapy in levodopa-treated Japanese patients with Parkinson's disease with wearing-off: results of an open-label study, J. Neurol. Sci. 416 (2020) 117012, https://doi.org/10.1016/j.jns.2020.117012.

[11] C. Cattaneo, M. Sardina, E. Bonizzoni, Safinamide as add-on therapy to levodopa in mid- to late-stage Parkinson's disease fluctuating patients: post hoc analyses of studies 016 and SETTLE, J. Parkinsons Dis. 6 (2016) 165–173, https://doi.org/10.3233/JPD-150700.

[12] Pharmaceuticals and Medical Devices Agency, Equfina® TABLETS 50 mg Package Insert. https://www.info.pmda.go.jp/go/pack/1169018F1020_2_02/, 2020 (accessed 29 November 2023).

[13] K. Horváth, Z. Aschermann, P. Ács, G. Deli, J. Janszky, S. Komoly, E. Balázs, K. Takács, K. Karádi, N. Kovács, Minimal clinically important difference on the motor examination part of MDS-UPDRS, Parkinsonism Relat. Disord. 21 (2015) 1421–1426, https://doi.org/10.1016/j.parkreldis.2015.10.006.

[14] M. Nomoto, T. Ishida, M. Koebis, T. Kamei, I. Suzuki, N. Hattori, Y. Tsuboi, Characteristics of wearing-off and motor symptoms improved by safinamide adjunct therapy in patients with Parkinson's disease: a post hoc analysis of a Japanese phase 2/3 study, J. Neurol. Sci. 434 (2022) 120083, https://doi.org/10.1016/j.jns.2021.120083.

[15] A.H. Schapira, S.H. Fox, R.A. Hauser, J. Jankovic, W.H. Jost, C. Kenney, J. Kulisevsky, R. Pahwa, W. Poewe, R. Anand, Assessment of safety and efficacy of safinamide as a levodopa adjunct in patients with Parkinson disease and motor fluctuations: a randomized clinical trial, JAMA Neurol. 74 (2017) 216–224, https://doi.org/10.1001/jamaneurol.2016.4467.

[16] Q. Wei, Y. Tan, P. Xu, E. Tao, Z. Lu, X. Pan, B. Wang, C. Liu, X. Dong, Y. Tian, X. Sun, C. Cattaneo, S. Chen, H. Shang, XINDI Study Investigators Group, The XINDI study: a randomized phase III clinical trial evaluating the efficacy and safety of safinamide as add-on therapy to levodopa in Chinese patients with Parkinson's disease with motor fluctuations, CNS Drugs 36 (2022) 1217–1227, https://doi.org/10.1007/s40263-022-00958-6.

[17] N. Hattori, T. Kamei, T. Ishida, I. Suzuki, M. Nomoto, Y. Tsuboi, Long-term effects of safinamide adjunct therapy on levodopa-induced dyskinesia in Parkinson's disease: post-hoc analysis of a Japanese phase III study, J. Neural Transm. (Vienna) 129 (2022) 1277–1287, https://doi.org/10.1007/s00702-022-02532-2.

[18] G. Taghizadeh, S.M. Fereshtehnejad, S. Goudarzi, S. Jamali, M. Mehdizadeh, Minimal clinically important difference of the King's Parkinson's disease pain scale, Disabil. Rehabil. 45 (2023) 1680–1683, https://doi.org/10.1080/09638288.2022.2074152.

[19] K. Kurihara, S. Fujioka, Y. Mizutani, H. Watanabe, K. Iwaoka, T. Maeda, M. Seki, T. Tezuka, J. Nakahara, T. Konno, T. Ishiguro, O. Onodera, Y. Asano, K. Takahashi, A. Rizos, K.R. Chaudhuri, Y. Tsuboi, Validation study of the Japanese version of the King's Parkinson's disease pain scale and the King's Parkinson's disease pain questionnaire, Parkinsonism Relat. Disord. 120 (2024) 106012, https://doi.org/10.1016/j.parkreldis.2024.106012.

[20] D. Santos García, R. Yáñez Baña, C. Labandeira Guerra, M.I. Cimas Hernando, I. Cabo López, J.M. Paz González, M.G. Alonso Losada, M.J. Gonzalez Palmás, C. Cores Bartolomé, C. Martínez Miró, Pain improvement in Parkinson's disease patients treated with safinamide: results from the SAFINONMOTOR study, J. Pers. Med. 11 (2021) 798, https://doi.org/10.3390/jpm11080798.

[21] C. Geroin, I.A. Di Vico, G. Squintani, A. Segatti, T. Bovi, M. Tinazzi, Effects of safinamide on pain in Parkinson's disease with motor fluctuations: an exploratory study, J. Neural Transm. (Vienna) 127 (2020) 1143–1152, https://doi.org/10.1007/s00702-020-02218-7.

[22] V. Peto, C. Jenkinson, R. Fitzpatrick, Determining minimally important differences for the PDQ-39 Parkinson's disease questionnaire, Age Ageing 30 (2001) 299–302, https://doi.org/10.1093/ageing/30.4.299.

[23] Y. Tsuboi, M. Koebis, Y. Kogo, T. Ishida, I. Suzuki, M. Nomoto, N. Hattori, Effects of safinamide adjunct therapy on pain in patients with Parkinson's disease: post hoc analysis of a Japanese phase 2/3 study, J. Neurol. Sci. 429 (2021) 118070, https://doi.org/10.1016/j.jns.2021.118070.

[24] C. Cattaneo, P. Barone, E. Bonizzoni, M. Sardina, Effects of safinamide on pain in fluctuating Parkinson's disease patients: a post-hoc analysis, J. Parkinsons Dis. 7 (2017) 95–101, https://doi.org/10.3233/JPD-160911.

[25] S. Sung, N. Vijiaratnam, D.W.C. Chan, M. Farrell, A.H. Evans, Pain sensitivity in Parkinson's disease: systematic review and meta-analysis, Parkinsonism Relat. Disord. 48 (2018) 17–27, https://doi.org/10.1016/j.parkreldis.2017.12.031.

[26] Y. Kogo, M. Koebis, Y. Kobayashi, T. Ishida, T. Maeda, Analgesic effect of safinamide mesylate in a rat model of neuropathic pain, Behav. Brain Res. 452 (2023) 114555, https://doi.org/10.1016/j.bbr.2023.114555.

[27] L.G. Zhang, J. Cheng, M.Q. An, C.J. Li, L.G. Dong, J.M. Wang, C.F. Liu, F. Wang, C. J. Mao, Safinamide alleviates hyperalgesia via inhibiting hyperexcitability of DRG neurons in a mouse model of Parkinson's disease, Behav. Brain Res. 459 (2023) 114787. Advance online publication, https://doi.org/10.1016/j.bbr.2023.114787.

[28] N. Hattori, Y. Kogo, M. Koebis, T. Ishida, I. Suzuki, Y. Tsuboi, M. Nomoto, The effects of safinamide adjunct therapy on depression and apathy in patients with Parkinson's disease: post-hoc analysis of a Japanese phase 2/3 study, Front. Neurol. 12 (2022) 752632, https://doi.org/10.3389/fneur.2021.752632.

[29] C. Cattaneo, T. Müller, E. Bonizzoni, G. Lazzeri, I. Kottakis, C. Keywood, Long-term effects of safinamide on mood fluctuations in Parkinson's disease, J. Parkinsons Dis. 7 (2017) 629–634, https://doi.org/10.3233/JPD-171143.

[30] N. Hattori, A. Takeda, Y. Hanya, T. Kitagawa, M. Arai, Y. Furusawa, H. Mochizuki, M. Nagai, R. Takahashi, Effects of rasagiline on Parkinson's disease questionnaire (PDQ-39) emotional well-being domain in patients with Parkinson's disease: a post-hoc analysis of clinical trials in Japan, PLoS One 17 (2022) e0262796, https://doi.org/10.1371/journal.pone.0262796.

[31] R. Bhidayasiri, T. Ishida, F. Kamei, R.E. Husni, I. Suzuki, S.L. Wu, J.W. Cho, Safinamide as an adjunct to levodopa in Asian and Caucasian patients with Parkinson's disease and motor fluctuations: a post hoc analysis of the SETTLE study, J. Mov. Disord. 16 (2023) 180–190, https://doi.org/10.14802/jmd.22196.

[32] D. Murray, A.J. Stoessl, Mechanisms and therapeutic implications of the placebo effect in neurological and psychiatric conditions, Pharmacol. Ther. 140 (2013) 306–318, https://doi.org/10.1016/j.pharmthera.2013.07.009.