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ORIGINAL ARTICLE

Real life evaluation of safinamide effectiveness in Parkinson's disease

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Abstract

In this retrospective study, we evaluated both efficacy and effectiveness of safinamide 50 and 100 mg in the treatment of motor fluctuations and disabling dyskinesias in a cohort of patients with idiopathic Parkinson's disease (PD). Ninety-one PD patients were evaluated during the first year of commercialization of the drug, both prior to starting safinamide and at the last available follow-up. Evaluations were based on the Unified Parkinson's Disease Scale part III (UPDRS III), Hoehn & Yahr (HY), Unified Dyskinesia Rating Scale (UDysRS) walking and balance item 9 score, daily time spent in OFF and in ON with disabling dyskinesias (1 week diary), mean daily dose of levodopa (LD), dopamine-agonists (DA), catechol-O-methyl transferase inhibitor (COMT-I), monoamine oxidase B inhibitor (MAOB-I), and their LD equivalent dose (LEDD). Eight patients withdrew safinamide within the first month for minor side effects. At the follow-up evaluation, after a mean time with safinamide of 7.5 months ± 3.4, all patients showed a significant improvement of all the scale scores, except for HY, and of the daily dosages of the drugs and the LEDD. The same results were shown by PD patients treated with safinamide 50 mg and patients who started safinamide without switching from a previous MAOBI. PD patients with safinamide 100 mg and patients who started safinamide switching from a previous MAOBI significantly improved in time spent in OFF and LEDD. In conclusion, safinamide is safe and effective in improving motor complications in patients with idiopathic PD and can be considered a useful levodopa sparing strategy.

Keywords Parkinson's disease · Motor fluctuations · Dyskinesias · Safinamide

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Introduction

Parkinson's disease (PD) is the world's second most spread chronic neurodegenerative disorder of the elderly. It rarely occurs before the age of 50 and a sharp increase in incidence is reported after the age of 60 [1, 2]. PD is traditionally defined as a progressive disorder characterized by the triad of rigidity, bradykinesia, and tremor accompanied by several non-motor symptoms that show a nonlinear progression during the course of the disease [3]. The pathogenetic changes include the loss of dopaminergic neurons in the substantia nigra pars compacta and the appearance of Lewy bodies within the pigmented neurons of the SN. It is presumed that motor symptoms occur at a loss of about 60–80% of the dopaminergic neurons in the SN. Non-dopaminergic neurotransmitter systems, such as the serotonergic, cholinergic, adrenergic, and glutamatergic are also involved in the pathophysiological of the disease [4].

Levodopa (LD) is still the gold standard of symptomatic efficacy on PD symptoms. Since the amount of its daily dose is associated with the development of motor complications

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and dyskinesias, the concomitant use of other dopaminergic and non-dopaminergic drugs is useful for realizing a LD sparing strategy [5].

Safinamide (Xadago®, Zambon S.p.A. Bresso, Italy) is an orally administered α-aminoamide derivative, that combines potent, selective and reversible inhibition of monoamino oxidase B (MAO-B) with blockade of voltage-dependent Na+ and Ca2+ channels and inhibition of stimulated glutamate release [6–11], targeting both dopaminergic and glutamatergic systems [11, 12].

The outcomes of long-term, double-blind design studies performed to investigate the effects of safinamide as an add-on therapy to LD, outline a good safety profile and a long-term efficacy on motor function (ON time without troublesome dyskinesias and wearing off) in PD patients with motor complications [13].

In 2015, safinamide was approved in the EU for the treatment of mid- to late-stage fluctuating PD as an add-on therapy to a stable dose of LD alone or in combination with other PD treatments [10, 14–16]. In 2017 safinamide received approval in USA [17]. Safinamide has been on the market in Italy since March 2016.

While efficacy of safinamide has been proved by several controlled studies, its effectiveness in usual care settings and in non-selected PD patients has still to be described.

The objective of this observational real-life study is to evaluate the effectiveness of safinamide as adjunct therapy in a cohort of patients with idiopathic PD and motor fluctuations retrospectively evaluated.

Materials and methods

Study design and population

We included in the study all the patients attending three Movement Disorders Outpatients Clinics (two in Milan and one in Novara) who were prescribed with safinamide between March 2016 and March 2017 as additional therapeutic option to a LD monotherapy or in combination with other treatments.

All included patients had a diagnosis of idiopathic PD according to UK Brain Bank criteria [18] and claimed motor fluctuations that were not controlled by the ongoing treatment.

The initial prescription of safinamide was of 50 mg a day, in the morning. Before starting safinamide, patients had to keep an ON/OFF diary for 1 week (with stable and unchanged therapeutic regimen), specifying how much time a day they spent in the OFF phase (in minutes) and/or in the ON phase with disabling dyskinesias (in hours).

Further information collected at the time of the first safinamide prescription (basal evaluation) were general demographic and clinical data, the Unified Parkinson's Disease part III in ON (UPDRS III) score, Hoehn & Yahr (HY) score, Unified Dyskinesia Rating Scale (UDysRS) walking and balance item 9 score [19], mean daily dose of LD, dopamine-agonists (DA), catechol-O-methyl transferase inhibitor (COMT-I), monoamine oxidase B inhibitor (MAOB-I), and their LD equivalent dose (LEDD) [20]. Patients receiving a MAOB-I had to withdraw from it 2 weeks before starting safinamide. The LEDD, both at basal evaluation and follow-up, is calculated without MAOB-I equivalent LD dose since the correspondent one of safinamide is not available yet.

Clinical data used for the comparison with basal evaluation were collected during the last available medical examination of each patient approximately 12 months later, (follow-up evaluation), and they included clinical scales, ON/OFF diaries, drugs dosages, and side effects.

Additional intermediate visits or telephone contacts, between basal and follow-up evaluation, were variably arranged according to the modalities of the individual center and the patient's needs (i.e., side effects and/or need for therapeutic dosing regimen change).

During this period, safinamide daily dose was eventually increased to 100 mg/day and dopaminergic drugs dosages were modified in relation to individual clinical needs.

Study endpoints

The primary outcome was to evaluate the effectiveness of safinamide on motor function evaluated by changes of UPDRS III score in ON phase, time spent in OFF, time spent in ON with dyskinesias and UDysRS item 9 score.

The secondary study endpoint consisted in evaluating safinamide effect on changes of daily dosages of dopaminergic therapies.

Statistical analysis

Quantitative variables were described by mean ± standard deviation if normally distributed, or by median (first quartile; third quartile) if not normally distributed. Kolmogorow-Smirnow test was used to assess the distribution of the values. When normally distributed, values were compared either by the paired *t* test or by the unpaired *t* test; when not normally distributed, they were compared by Wilcoxon test (corrected by means of method of Pratt, if necessary) or Mann Whitney test.

To detect the variation in the number of patients receiving DA or COMT-I before and after the treatment with Safinamide, Chi-square test was applied (or Fisher's exact test, when appropriate).

GraphPadPrism ® (version 6) was used for all statistical analyses.

P values < .05 were considered statistically significant.

Results

Ninety-one patients with idiopathic PD, 38 women, mean age 68.93 ± 9.68 years, median disease duration 10.48 (6.93; 14.01-first quartile; third quartile), received the prescription of safinamide as add-on therapy for motor fluctuations and or disabling dyskinesias between March 2016, baseline evaluation, and March 2017, with the last follow-up evaluation by August 2017.

Eight patients (8.8%) had to withdraw from safinamide within the first month for side effects: uneasiness (one patient), dizziness (two), insomnia (two), worsening of psychotic symptoms (one), worsening of dyskinesias (three), and five patients did not attend the control visit. Patients who discontinued treatment with safinamide (three women) had a mean age of 76.70 ± 7.58 years (significantly older than patients who continued with the treatment, $p < .006$), mean disease duration of 13.41 ± 6.89 years and UPDRS III score of 21.13 ± 12.187 in ON (significantly more severe than study population, $p < .01$). These PD patients reported side effects within 1 month of starting the treatment, during an extra visit on demand or a telephone contact. Such side effects were all minor and the onset occurred in patients with safinamide 50 mg.

Data about patients who continued treatment with safinamide (78 patients, 33 women) are shown in Table 1, where the values of all the collected parameters after the introduction of safinamide are also described. The mean daily dosage of all dopaminergic drugs showed a significant reduction after safinamide introduction as well as UPDRS III mean score in ON, UDysRS item 9 score, mean daily time spent in OFF and in ON with dyskinesias. Only the HY scale score did not show a significant change. Moreover, we observed that the DA and the COMT-I could be in some patients. In particular, 17% of patients withdrawn the DA and the 40% of patients the COMT-I during safinamide treatment.

To further understand the effects of safinamide, we analyzed the values of all the collected parameters in different subgroups, calculating the changes both in the single subgroups and then with a comparison between the changes of the two subgroups.

Groups receiving different safinamide dosages (group 50 and group 100) (Table 2)

At the basal evaluation, the two groups had similar demographic and clinical characteristics, except for the time spent in OFF that was significantly longer in group 100 (90 min, first quartile; third quartile 60;120) than in group 50 (60 min, first quartile; third quartile 60;72.5) ($p < .0014$). Group 50 showed a significant improvement in the clinical scales, time spent in OFF and in ON with dyskinesias, (except for HY), and in all the treatment dosages. Group 100 did not show an improvement in clinical scales scores but did have a benefit in time spent in OFF and a visible reduction of the time in ON with dyskinesias, even though it did not reach statistical significance. Group 100 showed a significant reduction only of the LEDD. The duration of treatment with safinamide was similar for the two groups. The comparison between the changes demonstrated by the two groups did not show any significant difference except for a more significant reduction

Table 1 Population who continued treatment with safinamide: demographic and clinical data at basal and follow-up evaluations

	Basal	Follow-up	$p <$
Age, years (mean ± sd)	68.09 ± 9.58	–	–
Disease duration, years [median (1st quartile; 3rd quartile)]	10.46 (6.92; 13.95)	–	–
UPDRS III in ON (70) [median (1st quartile; 3rd quartile)]	12 (5; 18.25)	10 (5; 15.25)	.0001
Hoehn & Yahr (77) [median (1st quartile; 3rd quartile)]	3 (2.5; 3)	3 (2.5; 3)	ns
Time in OFF, minutes (70) [median (1st quartile; 3rd quartile)]	60 (60; 90)	30 (0; 60)	.0001
Time in ON with Dyskinesias, hours (63) [median (1st quartile; 3rd quartile)]	1 (0; 1)	0 (0; 1)	.0008
UDysRS item 9 (63) [median (1st quartile; 3rd quartile)]	1 (0; 1)	0 (0; 1)	.0001
LD daily dose, mg (mean ± sd)	723.2 ± 306.9	667.4 ± 297	.0001
DA LEDD, mg (52 ≥ 43) [median (1st quartile; 3rd quartile)]	210 (130; 311.3)	160.0 (65; 240.0)	.0002
MAOBI LEDD, mg (21) [median (1st quartile; 3rd quartile)]	100 (100; 100)	–	–
COMTI LEDD, mg (20 ≥ 12) [median (1st quartile; 3rd quartile)]	264 (66; 330)	264 (0; 264)	.0039
LEDD, mg, (mean ± sd)	950.1 ± 390.7	826.8 ± 357	.0001
Safinamide daily dose, mg (mean ± sd)	–	65.38 ± 23.23	–
Time with safinamide, months (mean ± sd)	–	7.5 ± 3436	–

Number of patients for which the clinical data are always available or at basal evaluation and ≥ at follow-up evaluation

UPDRS III ON Unified Parkinson's Disease score part III in ON, *UDysRS* Unified Dyskinesia Rating Scale walking and balance ITEM 9 score, *LD* levodopa, *LEDD* levodopa equivalent daily dosage, *DA* Dopamino-Agonist, *COMTI* catechol-O-methyl transferase inhibitor, *MAOBI* Monoamine oxidase B inhibitor, *ns* not significant

Table 2 Changes of the clinical data in group 50 and group 100 and between them

	Safinamide 50 mg (54)			Safinamide 100 mg (24)			50 vs 100
	Basal	Follow-up	$p <$	Basal	Follow-up	$p <$	$p <$
Age, years (mean ± sd)	68.50 ± 9106	–	–	67,18 ± 10,73	–	–	ns
Disease duration, years [median (1st quartile; 3rd quartile)]	10.42 (6.86; 13.46)	–	–	11,16 (6,56; 14,68)	–	–	ns
UPDRS III (50–20) [median (1st quartile; 3rd quartile)]	12 (5; 18)	10 (5; 15.25)	.0001	9.5 (4; 19.75)	9.5 (4; 15.75)	ns	ns
H&Y (53–24) [median (1st quartile; 3rd quartile)]	2.5 (2; 3)	2.5 (2; 3)	ns	3 (2.1; 3)	2.75 (2.1; 3)	ns	ns
Time in OFF, minutes (50–20) [median (1st quartile; 3rd quartile)]	60 (60; 72.5)	30 (0; 56.25)	.0001	90 (60; 120)	60 (30; 75)	.0001	ns
Time in ON with dyskinesias, hours (46–17) [median (1st quartile; 3rd quartile)]	1 (0; 1)	0 (0; 1)	.0029	1 (0; 1.5)	0 (0; 1)	.0625	ns
UDysRS (46–17) [median (1st quartile; 3rd quartile)]	1 (0; 1)	0 (0; 1)	.0001	0 (0; 1)	0 (0; 1)	ns	ns
LD daily dose, mg (mean ± sd)	681.5 ± 286.5	6233 ± 281.2	.0001	817.2 ± 335.9	766.7 ± 313.5	.0683	ns
DA LEDD, mg (35 ≥ 29–17 ≥ 13) (mean ± sd)	225.3 ± 132.9	159.2 ± 121.5	.0076	242.4 ± 105.3	183.2 ± 128.6	.0624	ns
MAOBI LEDD, mg (12–9) [median (1st quartile; 3rd quartile)]	100 (100; 100)	–	–	100 (75; 100)	–	–	ns
COMTI LEDD, mg (11 ≥ 5–9 ≥ 7) [median (1st quartile; 3rd quartile)]	264 (264; 330)	0 (0; 264)	.0156	264 (132; 264)	264 (33; 264)	ns	.0353
LEDD, mg (mean ± sd)	896.3 ± 384.1	753.4 ± 317.1	.0001	1071 ± 390.2	962.45 ± 370	.0137	ns
Time on safinamide, months (mean ± sd)	–	7429 ± 3775	–	–	7391 ± 2.84	–	ns

Number of patients for which the clinical data are always available or at basal evaluation and ≥ at follow-up evaluation

UPDRS III ON Unified Parkinson's Disease score part III in ON, *UDysRS* Unified Dyskinesia Rating Scale walking and balance ITEM 9 score, *LD* levodopa, *LEDD* levodopa equivalent daily dosage, *DA* Dopamino-Agonist, *COMTI* catechol-O-methyl transferase inhibitor, *MAOBI* Monoamine oxidase B inhibitor, *ns* not significant

of COMT-I daily dose/number of patients with COMT-I at basal in Group 50 than in Group 100.

Groups with and without a previous MAOB-I (Group MAOBI and Group No MAOBI) (Table 3)

Before starting safinamide, 17 patients were on rasagiline (2 patients with 0.5 mg, 15 patients with 1 mg), and 4 patients on selegiline (1 with 5 mg, 3 with10 mg). Rasagiline and selegiline were withdrawn 2 weeks before starting safinamide. The MAO-I was changed because of the persistence of motor fluctuations and/or disabling dyskinesias.

We considered these 21 patients as a single group (Group MAOBI). We evaluated differences between their clinical values showed during MAOB-I treatment and the ones during safinamide therapy and we made a comparison between Group MAOBI and the rest of the population that did not receive a treatment with a MAOB-I before safinamide (Group No MAOBI). At the basal evaluation, Group No MAOBI showed a significant higher score of UPDRS III and HY than Group MAOBI.

Moreover, Group No MAOBI showed a significant improvement in all the scale scores, except from HY, and a significant reduction of all the drugs dosages. Group MAOBI improved significantly in time in OFF and LD and LEDD daily dosage significantly decreased. No significant differences were observed in the intragroup analysis.

Discussion

This is the first observational retrospective study reporting on the effects of safinamide 50 or 100 mg/day on the motor function of consecutive PD patients observed for 1 year after the Italian commercialization of the drug in the real life setting of three Movement Disorders Centers.

The results confirm that safinamide can be considered an effective and safe add-on therapy for the treatment of motor fluctuations and/or disabling dyskinesias, with a dropout rate for complications of 8.8%. Patients who discontinued safinamide for minor side effects were significantly older and with a significantly more severe form of PD than patients who continued the treatment: the data can be considered the first evidence describing the clinical profile of the most appropriate population of patients for the treatment with safinamide.

Safinamide efficacy is demonstrated by the significant improvement of the motor scales scores (UPDRS III in ON phase, and UDysRS item 9): its effectiveness is further confirmed by the reduction of daily time spent in OFF and in ON with disabling dyskinesias.

Moreover, both in the whole sample and in subgroups there is a significant reduction of total daily dopaminergic load, in particular of LEDD total dose, but also the prescription of the

Table 3 Changes of the clinical data in Group MAOBI and Group No MAOBI and between them

	Group No MAOBI (57)			Group MAOBI (21)			No MAOBI vs MAOBI
	Basal	Follow-up	$p <$	Basal	Follow-up	$p <$	$p <$
Age, years (mean ± sd)	68.36 ± 9381	–	–	66.82 ± 10.57	–	–	ns
Disease duration, years (mean ± sd)	11.49 ± 6336	–	–	9626 ± 3671	–	–	ns
UPDRS III (51–19) [median (1st quartile; 3rd quartile)]	12 (6; 22)	10 (6; 18)	.0001	5 (3; 15)	5 (3; 13)	ns	ns
H&Y (55–20) [median (1st quartile; 3rd quartile)]	3 (2.5; 3)	3 (2.5; 3)	ns	2.5 (2; 3)	2.5 (2; 2.88)	ns	ns
Time in OFF, minutes (51–19) [median (1st quartile; 3rd quartile)]	60 (60; 90)	30 (0; 60)	.0001	60 (60; 90)	30 (0; 60)	.0001	ns
Time in ON with dyskinesias, hours (44–19) [median (1st quartile; 3rd quartile)]	1 (0; 1)	0 (0; 1)	.0016	0 (0; 1)	0 (0; 1)	ns	ns
UDysRS (44–19) [median (1st quartile; 3rd quartile)]	1 (0; 1)	0 (0; 1)	.0001	0 (0; 1)	0 (0; 1)	ns	ns
LD daily dose, mg (mean ± sd)	725.9 ± 305.9	674.1 ± 287.0	.0005	716.1 ± 317	649.1 ± 329.5	.0023	ns
DA LDeq daily dose, mg ($32 \geq 25–18 \geq 15$) (mean ± sad)	234.2 ± 132.7	174.2 ± 153.7	.0052	224.7 ± 108.2	195.3 ± 127.2	ns	ns
COMTI LEDD, mg ($11 \geq 6–7 \geq 6$) [median (1st quartile; 3rd quartile)]	264 (264; 330)	66 (0; 264)	.0156	264 (264; 330)	264 (132; 264)	ns	ns
LEDD, mg (mean ± sd)	931.8 ± 365.0	809.3 ± 325.2	.0001	999.8 ± 463.6	857.4 ± 453.6	.0039	ns
Safinamide dosage, mg (mean ± sd)	–	63.16 ± 22.21	–	–	71.43 ± 25.35	–	ns
Time on safinamide, months (mean ± sd)	–	7250 ± 3641	–	–	8048 ± 2991	–	ns

Number of patients for which the clinical data are always available or at basal evaluation and ≥ at follow-up evaluation

UPDRS III ON Unified Parkinson's Disease score part III in ON, *UDysRS* Unified Dyskinesia Rating Scale walking and balance ITEM 9 score, *LD* levodopa, *LEDD* levodopa equivalent daily dosage, *DA* Dopamino-Agonist, *COMTI* catechol-O-methyl transferase inhibitor, *MAOBI* Monoamine oxidase B inhibitor, *ns* not significant

COMTI and of the DA is reduced. The change of dopaminergic drugs dose was requested because the introduction of safinamide caused an improvement of time spent in OFF but also an increase of time with dyskinesias in our population; subsequently, by reducing the daily dose of LD and suspending or reducing the dose of the DA or of the COMTI there was a consequent improvement of dyskinesias. The choice to suspend or to reduce the dose of DA or COMT-I or to reduce the dose of LD was made in relation to the clinical characteristic of the patient.

Safinamide is a potent MAOB inhibitor, more than the other two irreversible ones [8, 21]. This could be the explanation why it is possible to reduce the total LEDD, also improving both the OFF time and the ON time with dyskinesias.

The evaluation of dopaminergic therapy dosage changes after the introduction of safinamide suggests that safinamide can be considered an effective levodopa- sparing strategy. In fact, both the global sample and in the Group 50 showed an improved control of motor complications despite the significant reduction of all dopaminergic drugs.

Safinamide is effective in improving motor function and in reducing drug dosages at 50 mg, which is the dose received by the majority of our patients (76%). The decision to increase the dose to 100 mg in the other 24% of the population was taken after 1–3 months of treatment, at the first control visit after the basal evaluation, if the patient did not show or report a satisfactory improvement. After 1 year of follow-up, most of the patients of this cohort did not need an increase in the dosage of safinamide, still showing a stable improvement of motor function. A further observational study lasting more than 1 year will be able to delineate when, how, and why the increase from 50 to 100 mg will be appropriate.

In the current 1-year follow up study, we analyzed the differences between Group 50 and Group 100. The patients of the latter showed a significant longer basal time in OFF and, even so, time in OFF is the only parameter that improved significantly at the follow up evaluation, along with the reduction of LEDD. Moreover, the reduction of the dose or the suspension of the DA and the COMT-I was not significant in Group 100. A possible explanation is that these patients presented a more severe form of the disease as indicated by the longer time in OFF, and the improvement was possible reducing moderately the dopaminergic drugs dosages. The results of this study do not allow a deep discussion about the effect of safinamide 100 mg on dyskinesias. Patients of group 100 showed only a trend toward improvement of time in ON with dyskinesias but at the basal evaluation they had a mildly lower score of the UDysRS item 9 than group 50, even if not significant. Therefore, these results allow us to infer that patients who needed and have benefited from the increase of the dose of safinamide from 50 to 100 mg were those with longer OFF phases and not excessively long ON phases with disabling dyskinesias.

Subsequently, we analyzed the differences between patients that started safinamide switching from another MAOB-I, rasagiline or selegiline, Group MAOBI (20%), and patients No MAOBI (80%).

Group No MAOBI showed a significant improvement of all parameters and drug dosages, except for HY, while Group MAOI significantly improved only in time in OFF, LD daily dose, and LEDD. At the basal evaluation, Group No MAOBI showed a significantly more severe form of the disease than Group MAOBI. The small sample size of the Group MAOBI does not allow for observation of further possible differences between the changes of the two groups, but we can speculate that patients with a previous therapy with a MAOB-I showed a less severe disease with a narrower margin of improvement, with a lower UPDRS III and HY score at basal evaluation.

This non-blinded, non-randomized cohort retrospective study has several limitations. Although we recruited consecutive PD patients, there could be a selection bias, so participants enrolled into the study cannot be considered a representative selection of the background population. In fact, a small sample of older patients with a severe form of PD withdrew for side effects. It is possible that throughout the study we avoided prescribing safinamide to other patients who presented with this profile. Nevertheless, the minimal inclusion and exclusion criteria allowed the enrollment of a heterogeneous population that tended to reflect the type of case physicians seen in their clinics.

A further limitation of the study is the not standardized methodology in relation to when, how, and why the therapeutic regimen gets changed. In the absence of randomization, the severity of the disease and patient's peculiar characteristics can influence the treatment decisions (confounding by indication). This bias has been partially controlled by the fact that the physicians of the three different Movement Disorders Centers managed the therapeutic changes in a similar way, demonstrating the adherence to real clinical practice of this study, but also that a possible standardization exists in clinical practice of specialized Movement Disorders Centers.

The absence of blinding in this observational study did not permit for balancing factors potentially influencing the outcomes. We tried to limit this bias by choosing objective outcome measures (scale scores, time in ON and in OFF, and drugs dosages) which can be poorly influenced by the patient's and physician's awareness of the assigned treatment.

Conclusions

Safinamide can be considered a safe, efficient, and effective treatment of motor fluctuations and disabling dyskinesias in idiopathic PD patients and an active effective levodopa, DA, and COMT-I-sparing strategy in the middle stage of the disease.

Further, conclusions obtained from this study indicate that patients with an intermediate stage of the disease can benefit from the treatment better than more advanced and older patients.

In this population, the dose of 50 mg of safinamide was effective in most of the patient for the first year of treatment, and the 100 mg was useful in patients with longer OFF phases and less disabling dyskinesias.

Patients switching to safinamide from a previous MAOB-I treatment can benefit of further reduction of the duration of time spent in OFF but to a lesser extent in the reduction of DA or COMT-I dosages.

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Compliance with ethical standards

Conflict of interests Francesca Mancini has received speaker honoraria from Zambon and Abbvie.

Alessio Di Fonzo has received a speaker honorarium from Sanofi Genzyme.

Giulia Lazzeri has no conflict of interest.

Linda Borellini has no conflict of interest.

Vincenzo Silani serves on the Board of Cytokinetics for the Vitality trial in ALS and he received consulting fees.

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Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

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