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ORIGINAL RESEARCH ARTICLE

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

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Abstract

Background Levodopa remains the gold standard for the treatment of Parkinson's disease, but its long-term use is associated with motor complications whose management is still a significant challenge. Safinamide is a multimodal drug with proven efficacy as an adjunct to levodopa.

Objective The objective of this study was to investigate the efficacy and safety of safinamide as an add-on to levodopa in Chinese patients with Parkinson's disease with motor fluctuations.

Methods The XINDI study was a phase III, randomized, double-blind, placebo-controlled, multicenter study, with a 2-week screening period and a 16-week treatment period. The starting dose of safinamide (or placebo) was 50 mg once daily, increased to 100 mg once daily at day 15. Patients aged ≥ 18 years, with idiopathic Parkinson's disease of >3 years duration, Hoehn and Yahr stage 1–4, and daily OFF time ≥ 1.5 h, were eligible. Patients should follow a stable oral levodopa regimen and may receive concomitant treatment with stable doses of other anti-Parkinson drugs, except monoamine oxidase-B inhibitors. Patients with severe disabling peak-dose or biphasic dyskinesia, unpredictable or widely swinging fluctuations, other forms of parkinsonism, a history of dementia or severe cognitive dysfunction, major psychiatric illnesses, and/or clinically significant medical illnesses were excluded. The primary efficacy endpoint was the change from baseline to week 16 in the mean daily OFF time. Secondary efficacy endpoints included the Unified Parkinson's Disease Rating Scale, the Numerical Rating Scale, the Clinical Global Impression scale, and the 39-Item Parkinson's Disease Questionnaire scale. The statistical analysis of the efficacy parameters was conducted using an analysis of co-variance, except for the Clinical Global Impression scale scores that were assessed using the Wilcoxon–Mann–Whitney test. Safety was evaluated through the frequency of adverse events and serious adverse events, physical examination, vital signs, 12-lead electrocardiograms, and laboratory exams. All safety endpoints were summarized using descriptive statistics.

Results The trial enrolled 307 patients. At week 16, the difference in the change of the mean total daily OFF time between safinamide and placebo groups was 1.10 h ($p < 0.0001$). This change was significantly greater in the safinamide group starting from week 2, suggesting a rapid onset of drug efficacy. ON time, Unified Parkinson's Disease Rating Scale, Clinical Global Impression scale, and the 39-Item Parkinson's Disease Questionnaire showed statistically significant improvements. There were no significant between-group differences for adverse events or serious adverse events.

Conclusions Safinamide, as add-on therapy to levodopa, significantly reduced motor fluctuations and improved motor symptoms and quality of life of Chinese patients with idiopathic Parkinson's disease. The improvements observed in the Unified Parkinson's Disease Rating Scale total and motor scores were also clinically significant. No safety concerns were identified, confirming the good tolerability profile of the drug.

Clinical Trial Registration NCT03881371, registered on 19 March, 2019, https://clinicaltrials.gov/NCT03881371.

Qianqian Wei and Yuyan Tan contributed to the work equally.

The members of the XINDI Study Investigators Group are mentioned in Acknowledgements section.

Extended author information available on the last page of the article

Key Points

A new pivotal, multicenter, phase III, double-blind, placebo-controlled study (the XINDI trial) was conducted to evaluate, for the first time and for regulatory purposes, the efficacy and safety of safinamide in Chinese patients with Parkinson's disease with motor fluctuations.

Safinamide, as add-on therapy to levodopa, significantly reduced motor fluctuations and improved motor symptoms and quality of life of Chinese patients with idiopathic Parkinson's disease.

1 Introduction

Parkinson's disease (PD) is a disabling neurodegenerative disorder in which the loss of nigrostriatal dopaminergic neurons leads to a classical set of motor and non-motor symptoms [1]. The prevalence of PD in adults aged 65 years or older in China is estimated at 1.7% and the PD population is expected to double by 2030, suggesting an increasing demand for new PD therapies [2]. The medical expenditure of PD is one of the highest ranked of the neurological diseases, which could be the leading cause of a serious socioeconomic burden in the future aging society [3].

Traditional pharmacotherapies for PD aim to restore depleted dopamine levels in the brain, but these treatments are limited, as PD is a complicated disorder in which multiple interacting neurotransmitters, such as glutamate, are implicated [4]. Targeting non-dopaminergic systems may be thus an alternative approach [5].

Levodopa (L-dopa) remains the most effective drug, but its long-term use is associated with motor complications (fluctuations and dyskinesia) [6]. About 40% of patients experience motor complications after 4–6 years of L-dopa therapy, and 60–100% after 10 years [7]. Moreover, non-motor symptoms do not improve significantly. Motor and non-motor symptoms markedly affect the quality of life (QoL) of patients with PD and of their caregivers; therefore, comprehensive treatments for both might be very helpful for PD management [8].

As the disease progresses, most patients will require add-on medications to improve symptomatic control while maintaining good safety and tolerability. The Chinese Parkinson's Disease and Movement Disorder Society recommends monoamine oxidase-B inhibitors as adjunct therapy to L-dopa for the treatment of fluctuations [9].

Safinamide has a new dual mechanism of action, dopaminergic (reversible monoamine oxidase-B inhibition) and non-dopaminergic (modulation of the abnormal glutamate release), which offers a unique approach to the management of motor and non-motor symptoms and motor complications [10]. In previous pivotal clinical studies, safinamide, as add-on to L-dopa, significantly reduced OFF time and increased ON time in patients with PD who were experiencing the wearing-off phenomenon [11–14]. Currently, safinamide has been approved as add-on to L-dopa in Europe, USA, Japan, and seven other countries worldwide. The objectives of this study were to evaluate the efficacy and safety of safinamide, compared with placebo, administered to Chinese subjects with PD as adjunct therapy to L-dopa.

2 Methods

2.1 Study Design

The XINDI study (NCT03881371) was a phase III, multicenter, randomized, double-blind, placebo-controlled trial in Chinese patients with PD with motor fluctuations already treated with stable doses of L-dopa (alone or in combination with other anti-Parkinson medications). The study was conducted in accordance with the International Conference on Harmonization guideline for Good Clinical Practice (ICH E6 Rev2) and the principles of the Declaration of Helsinki. The protocol and its amendments were approved by all appropriate independent ethics committees and by the Chinese regulatory authority and the selection of the patients did not start prior to these approvals. The statistical analysis plan and the protocol are available at https://clinicaltrials.gov.

A total of 307 patients were randomized. Among these, 305 patients were treated with the study drugs (151 patients in the safinamide group, 154 patients in the placebo group). The trial was performed at 32 sites in China, began in August 2019 and was completed in August 2021. A contingency plan was created, containing the measures implemented to manage the study conduct during the coronavirus disease 2019 pandemic.

The study comprised a screening period (up to 2 weeks prior to the start of treatment, with one screening visit) and a treatment period (16 weeks, with visits at weeks 0, 2, 6, 10, and 16), followed by a telephone follow-up (1 week after the end of treatment]). The end of treatment was considered the completion of the study treatment at week 16. Study participation was up to a maximum duration of 18 weeks. A diagram of the study is described in Table 1 of the Electronic Supplementary Material (ESM). The dose of L-dopa and of the other anti-Parkinson drugs (if any) was kept constant during the screening period.

Patients who met the eligibility criteria entered the treatment period and were randomized to receive orally, once daily, either safinamide or matching placebo in a 1:1 ratio. The first dose of the investigational medicinal product (IMP) was administered at the study center following completion of all baseline assessments and based on the randomization list. Patients took subsequently 50 mg/day of IMP at home (i.e., either unsupervised or with the assistance of a caregiver) in the morning (at breakfast time, in addition to the morning dose of L-dopa and other, if any, anti-Parkinson drugs) for 2 weeks. The dosage of the IMP was then increased to 100 mg once daily the day after visit 3/week 2, ideally at day 15 (at home), and maintained to week 16 through self-administration at approximately the same time each day. Study medication accountability and treatment adherence were measured throughout the treatment period using specific study medication dispensing and return record forms.

Throughout the study, patients continued to take their standard prescribed anti-Parkinson drugs; doses were required to be kept constant. In the case of intolerable dopaminergic adverse events (AEs), e.g., dyskinesia, it was suggested to decrease the dose of L-dopa by a telephone call as a first step and consider the decrease of the dose of the IMP from 100 to 50 mg once daily as a second step. In this second case, patients were required to undergo an unscheduled visit for safety reasons and maintain the 50-mg dose for the rest of the study. Patients who did not tolerate the 50-mg dose were required to withdraw from the study and complete the end-of-treatment visit assessments, when possible. At patient enrollment, the investigators contacted a centralized, computerized, interactive voice-response system, which assigned to each patient the appropriate medication, identified by kit number and provided as matching tablets of safinamide or placebo in matching blister packs. The randomization was done with blocks sized of unequal length to guarantee a good balance between safinamide and placebo at any stage of the enrolment, minimizing the procedure selection bias, and the randomization code remained blinded throughout the study.

2.2 Patients

Eligible patients were required to be ≥ 18 years old and have a diagnosis of idiopathic PD, according to the United Kingdom PD Society Brain Bank Clinical Diagnostic Criteria [15], of more than 3 years duration, a Hoehn and Yahr stage [16] between 1 and 4 inclusive during the "ON" phase, and daily OFF time ≥ 1.5 h (excluding morning akinesia). Patients were also required to be L-dopa responsive and following a stable oral L-dopa regimen with or without a catechol-O-methyltransferase inhibitor and may be receiving concomitant treatment with stable doses of dopamine agonists, anticholinergics and/or amantadine for at least 4 weeks prior to the screening visit.

Concomitant treatments not permitted were L-dopa infusion, monoamine oxidase-B inhibitors other than safinamide, opioids and opiates, fluoxetine or fluvoxamine, pethidine, any other investigational agents, traditional Chinese medicine related to nervous system disease, and acupuncture for PD treatment. Patients were excluded for severe disabling peak-dose or biphasic dyskinesia or unpredictable or widely swinging fluctuations. Patients with other forms of parkinsonism, a history of dementia or severe cognitive dysfunction, major psychiatric illnesses, and/or clinically significant medical illnesses were also excluded. The study's full inclusion/exclusion criteria are described in Table 2 of the ESM. All patients signed an informed and privacy consent form. Personal data were collected, stored, and processed exclusively in a pseudoanymized format and in compliance with the regulatory requirements for the protection of subjects' confidentiality.

2.3 Efficacy Measures

The primary efficacy endpoint was the change from baseline to week 16 in the mean total daily OFF time, as assessed by 24-h patient diary cards [17]. Secondary efficacy endpoints were the changes from baseline to week 16 in the mean total daily ON time, the mean daily ON time with no/non-troublesome dyskinesia, the Unified Parkinson's Disease Rating Scale (UPDRS) total score during the ON phase, the UPDRS part II (activities of daily living) and part III (motor) scores during the ON phase, the 39-Item Parkinson's Disease Questionnaire (PDQ-39) summary of index score, the Clinical Global Impression-Change (CGI-C) and Severity (CGI-S) scores, and the Numerical Rating Scale (NRS) score for pain. Site personnel involved in performing the efficacy assessments were required to be expert in the use of the various scales and questionnaires. To ensure consistency of ratings, the same rater was required to perform the assessments where possible.

At the screening visit, patients and their caregivers were trained on the completion of the daily diary card. The investigator reviewed with the patients the definition of "ON," "OFF," and dyskinesia symptoms and agreed a consistent interpretation of when "ON" and "OFF" symptoms begin and end, and when dyskinesia occurs. "Troublesome dyskinesia" was defined as dyskinesia that interferes with functions and causes meaningful discomfort. The patients received a daily diary to fill out at home 2 days before each study visit starting from the baseline visit. The daily OFF time was the sum of all OFF hours, and the mean total daily OFF time was averaged over the 2 days prior to each study visit. In the case of complete missing or partial missing data

for a single day before the visit, and availability of diary data for the other day before visit, the endpoint was performed using data collected in the available day.

2.4 Safety Measures

Safety was assessed throughout the study, i.e., from the provision of informed consent until the last patient visit and was evaluated through the frequency of adverse events (AEs) and serious adverse events (SAEs), physical examination, vital signs, 12-lead electrocardiograms, and laboratory exams. Adverse event terms were coded with the *Medical Dictionary for Regulatory Activities* Version 23.1 [18]. Seriousness, severity, and relationship to safinamide were entered according to clinicians' judgment and classified according to a common definition of SAEs (i.e., death, life threatening, hospitalization/hospitalization prolongation, disability or permanent damage, congenital anomaly or birth defect, important medical event).

2.5 Statistical Methods

Based on a "Monte Carlo" simulation, it was estimated that a total sample size of 260 patients (130 in the safinamide group and 130 in the placebo group) ensures 90% power to detect a mean difference in the OFF time of at least 0.9 h between the safinamide and placebo groups with a two-sided significance level (alpha) of 0.05, using a two-sample *t*-test and assuming standard deviations of 2.35 for safinamide and 2.06 for placebo. Effect size and standard deviation estimates used in sample size computations were gathered from the SETTLE study statistical report [12]. Assuming an attrition rate equal to 15%, a total of approximately 306 patients were required to be randomized.

The statistical analysis was performed using SAS for Windows Version 9.4 on all "evaluable patients for the Full Analysis Set" defined as the patients satisfying all inclusion criteria and not violating any exclusion criteria, who provided informed consent, were randomized, and received at least one dose or a partial dose of the IMP. All available data from withdrawn subjects were included in the analysis up to the time of withdrawal. The analysis of the primary efficacy parameter was performed using an analysis of covariance with treatment and the center as the independent factor, baseline mean OFF time measurement as the covariate, and the change from baseline as the dependent variable. Results were reported as the least-squares mean (LSM) for treatment differences with associated two-tailed 95% confidence intervals (CIs) and corresponding two-sided *p*-values. As an additional analysis, analysis of co-variance models for the analysis of the primary endpoint were fitted again including the site-by-treatment interaction to test if that interaction was statistically significant, using an $\alpha = 0.1$.

Analyses of ON time, UPDRS, NRS scales, and PDQ-39 scales were performed using an analysis of co-variance model parameterized as above. The CGI-C and the CGI-S scores were assessed using the Wilcoxon–Mann–Whitney test stratified by center, whilst the point estimate of treatment differences was reported as Hodges–Lehmann estimators together with associated two-sided non-parametric 95% CIs.

Missing data on the primary endpoint were imputed using multiple imputation as the primary imputation method and last observation carried forward as the sensitivity analysis. Missing data on all the other secondary efficacy endpoints were imputed only using the last observation carried forward method. All safety endpoints were summarized using descriptive statistics for the "Safety population," defined as all patients who provide the informed consent and received at least one dose or partial dose of IMP.

3 Results

3.1 Patients' Disposition and Demography

The patients' disposition is summarized in Fig. 1. Out of the 307 patients randomized, 267 (87.0%) patients completed the study treatment [137 patients in the safinamide group (89.5%), 130 patients in the placebo group (84.4%)]. A total of 40 (13.0%) patients withdrew from the study [16 patients in the safinamide group (10.4%), 24 patients in the placebo group (15.6%)]. The most common reason for discontinuation was AEs (eight patients in the safinamide group, nine patients in the placebo group), followed by withdrawal by patient (two patients in the safinamide group, ten patients in the placebo group) and physician decision (three patients in the safinamide group, three patients in the placebo group). None of the patients withdrew from the study because of coronavirus disease 2019. The mean treatment duration was 15.4 weeks in the safinamide group and 14.4 weeks in the placebo group. At day 15, all patients received the 100-mg dose and more than 97% had a treatment adherence of 100% at week 16.

Baseline demographics and clinical characteristics were similar between the two treatment groups (Table 1). The baseline mean total daily OFF time was 5.9 h in the safinamide group and 5.6 h in the placebo group (Table 1). There were no differences in the antiparkinsonian drugs used concomitantly, with 100% of patients taking L-dopa.

3.2 Efficacy

Safinamide showed a statistically significant reduction at week 16 in the mean total daily OFF time (primary endpoint) compared with placebo ($p < 0.0001$), with a LSM difference between safinamide and placebo of 1.10 h (Fig. 2

and Table 2). TheLSM change from baseline to weeks 2, 6, and 10 in the mean total daily "OFF" time was also significantly greater in the safinamide group compared with the placebo group (all p-values $\leq$ 0.0001).

In addition, safinamide, compared with placebo, showed statistically significant improvements at week 16 in the main secondary efficacy endpoints (Table 2) including the total daily "ON" time (LSM difference 0.89 h, $p = 0.0049$, 95% CI + 0.274, + 1.515), total daily "ON" time without dyskinesia/with non-troublesome dyskinesia (LSM difference 1.07 h, $p = 0.0021$, 95% CI + 0.392, +1.753), UPDRS total score (LS mean difference 5.99 points, $p < 0.0001$, 95% CI − 8.842, − 3.141), UPDRS part II (LS mean difference 1.52 points, $p = 0.0033$, 95% CI − 2.521, − 0.511) and part III (LS mean difference 3.80 points, $p = 0.0002$, 95% CI −5.749, − 1.856) scores, and PDQ-39 summary of the index score (LS mean difference 3.36 points, $p = 0.0033$, 95% CI − 5.589, − 1.128). As for the primary endpoint, these improvements were found in all study visits.

Among other secondary findings, there were statistically significant improvements with safinamide at week 16 in PDQ-39 subscales scores for mobility ($p = 0.0038$, 95% CI − 7.732, − 1.506), activities of daily living ($p = 0.0012$, 95% CI − 9.303, − 2.326), emotional well-being ($p = 0.0047$, 95% CI − 8.843, − 1.620), stigma ($p = 0.0275$, 95% CI − 8.950, − 0.531), and in the CGI-C ($p = 0.0007$, 95% CI + 0.000, + 1.000) and CGI-S ($p = 0.0150$, 95% CI + 0.000, + 0.400) scales scores. Regarding the NRS score, most patients did not report pain at the baseline visit (NRS score = 0), allowing minimal if any margin for improvement. Therefore, despite NRS scores being numerically greater in the safinamide group versus the placebo group at the end of the study, the change did not reach statistical significance ($p = 0.8901$, 95% CI − 0.440, + 0.382).

3.3 Safety

As reported in Table 3, during the study, 105 patients (69.5%) in the safinamide group and 88 patients (57.1%) in the placebo group experienced adverse events (AEs). The percentage of patients experiencing AEs related to the IMP was 35.7% in the safinamide group and 25.9% in the placebo group. These slight differences were not statistically nor clinically significant. No differences were detected in the percentage of patients experiencing AEs leading to discontinuation of IMP or leading to withdrawal from the study. All the AEs observed were those already described in the patients' leaflet and the majority (> 95%) were rated as mild or moderate. The most frequent AEs (≥ 3% of patients) were dyskinesia, worsening of PD, dizziness, constipation, and nausea. Worsening of PD and constipation were reported more frequently in patients receiving placebo, while dyskinesia was observed with a higher prevalence in subjects receiving safinamide (11.9%) compared with placebo

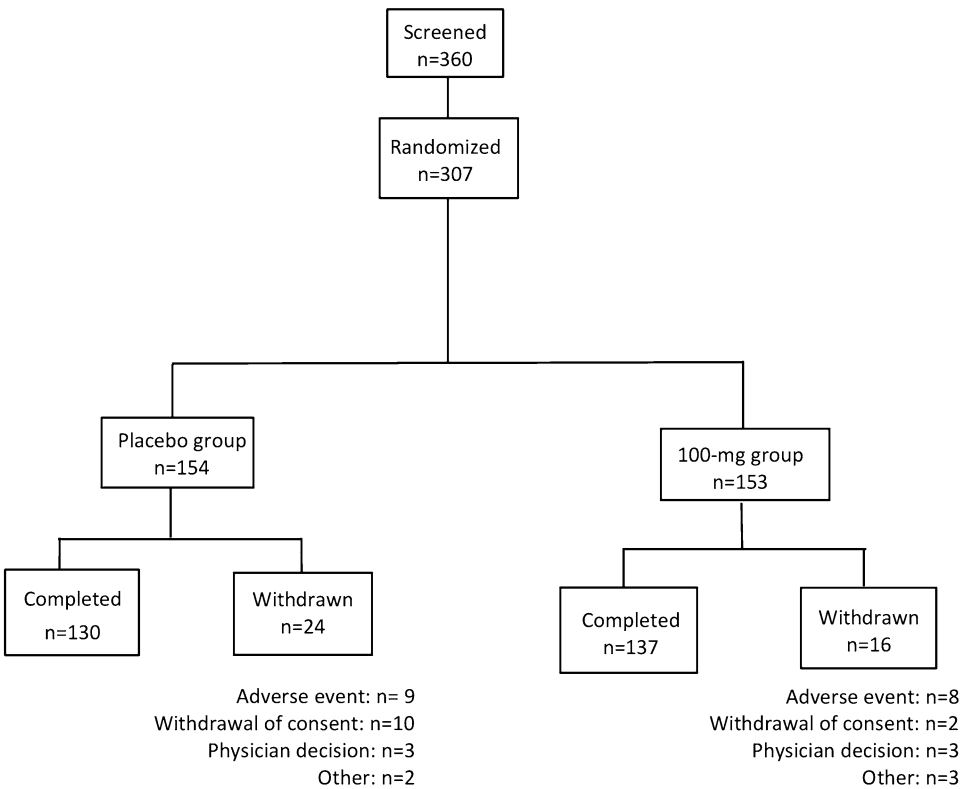

Fig. 1 Patients' disposition

Table 1 Baseline patients' demographic and clinical characteristics (FAS population)

	Safinamide ($n = 151$)	Placebo ($n = 154$)
Mean (SD) age (years)	61.4 (9.3)	61.8 (9.3)
Chinese ethnicity, *n* (%)	151 (100.0)	154 (100.0)
Sex, *n* (%)		
Male	92 (60.9)	85 (55.2)
Female	59 (39.1)	69 (44.8)
Mean weight (kg)	64.5 (10.4)	64.5 (10.7)
Mean BMI (kg/m^2)	23.9 (3.0)	23.9 (3.1)
Idiopathic PD diagnosis, *n* %	151 (100.0)	154 (100.0)
Mean (SD) duration of PD (years)	8.3 (4.9)	8.2 (4.8)
Hoehn & Yahr stage		
1	5 (3.3)	6 (3.9)
1.5	9 (6.0)	7 (4.5)
2	66 (43.7)	71 (46.1)
2.5	34 (22.5)	22 (14.3)
3	36 (23.8)	42 (27.3)
4	1 (0.7)	6 (3.9)
Mean (SD) total daily OFF time (h)	5.9 (2.8)	5.6 (3.1)
Mean (SD) total daily ON time (h)	10.1 (2.8)	10.3 (3.1)
Mean (SD) total daily ON time with no/non-troublesome dyskinesia (h)	9.7 (2.6)	9.8 (2.9)
Mean (SD) UPDRS Total score (ON phase)	46.4 (16.6)	45.7 (19.9)
Mean (SD) UPDRS part II score (ON phase)	12.0 (5.2)	12.0 (5.9)
Mean (SD) UPDRS part III score (ON phase)	27.4 (12.3)	26.8 (13.5)
Mean (SD) PDQ-39 summary of index score	25.3 (12.6)	24.3 (13.5)
Mean (SD) Total daily levodopa dose (mg)	516.5 (176.5)	505.4 (173.3)
Concomitant antiparkinson drugs, *n* (%)		
Levodopa	151 (100.0)	154 (100.0)
Pramipexole	83 (54.9)	72 (46.7)
Entacapone	55 (36.4)	55 (35.7)
Amantadine	51 (33.8)	47 (30.5)
Anticholinergics	21 (13.9)	21 (13.6)

Percentages (%) were computed by column

BMI body mass index, *FAS* full analysis set, *h* hours, *n* number of patients, *NRS* Numerical Rating Scale, *PD* Parkinson's disease, *PDQ-39* 39-Item Parkinson's Disease Questionnaire, *SD* standard deviation, *UPDRS* Unified Parkinsons' Disease Rating Scale

(3.9%), although at a lower frequency than those observed in a previous pivotal clinical trial. Dyskinesia was generally transient and did not lead to discontinuations in the safinamide group.

Serious AEs were rare and occurred in 13 patients: eight (5.3%) in the safinamide group and five (3.2%) in the placebo group. Their frequency was < 1%, mostly with mild or moderate intensity, and the majority of serious AEs were completed resolved.

The analyses of laboratory evaluations, vital signs, body weight, electrocardiograms, and physical examinations did not reveal any significant findings. No ophthalmological AEs were observed.

4 Discussion

Motor fluctuations have been reported to occur in ~50% of patients with PD after only 2 years of L-dopa treatment and are often associated with non-motor symptoms such as mood deterioration and autonomic and cognitive disturbances [19, 20]. A multicenter survey performed in Chinese patients with PD receiving L-dopa showed a 46.5% mean prevalence rate of fluctuations, increasing up to 68.3% after 10 years of L-dopa therapy [21].

Motor fluctuations appear as transitions between a good response to medication with good motor function ("ON"

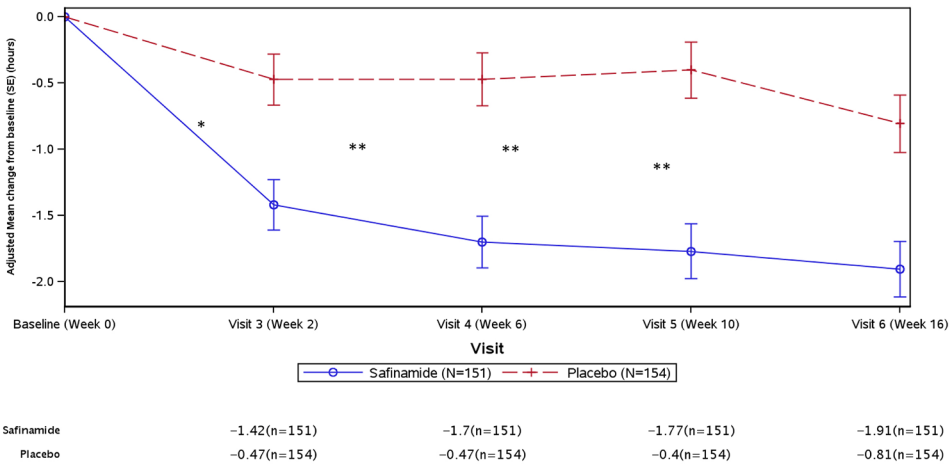

Fig. 2 Changes from baseline in mean total daily OFF time for full analysis set population. Analysis was based on acovariance model (ANCOVA) with treatment and center as independent factors, baseline value as covariate andchange from baseline as dependent variable.*p = 0.0001; **p < 0.0001

FAS: Full Analysis Set; SE: Standard Error; n: number of patients

*p = 0.0001; **p < 0.0001

Note: analysis was based on a covariance model (ANCOVA) with treatment and center as independent factors, baseline value as covariate and change from baseline as dependent variable.

Table 2 Changes from baseline at week 16 for primary and main secondary endpoints in the FAS population

	Safinamide, LSM (SE)	Placebo, LSM (SE)	Difference safinamide-placebo, LSM (SE)	95% CI	*P*-value
Mean total daily OFF time (h)	− 1.91 (0.21)	− 0.81 (0.21)	− 1.10 (0.27)	− 1.643, − 0.555	<0.0001
Mean total daily ON time (h)	+ 1.33 (0.23)	+ 0.43 (0.24)	+ 0.89 (0.31)	+ 0.274, + 1.515	0.0049
Mean total daily ON time with no/non-troublesome dyskinesia (h)	+ 1.19 (0.26)	+ 0.12 (0.27)	+ 1.07 (0.34)	+ 0.392, + 1.753	0.0021
UPDRS Total score (ON phase)	− 12.42 (1.08)	− 6.43 (1.12)	− 5.99 (1.44)	− 8.842, − 3.141	<0.0001
UPDRS part II score (ON phase)	− 2.63 (0.38)	− 1.12 (0.39)	− 1.52 (0.51)	− 2.521, − 0.511	0.0033
UPDRS part III score (ON phase)	− 8.11 (0.73)	− 4.31 (0.77)	− 3.80 (0.98)	− 5.749, − 1.856	0.0002
PDQ-39 summary of index score	− 6.20 (0.85)	− 2.84 (0.88)	− 3.36 (1.13)	− 5.589, − 1.128	0.0033
PDQ-39 mobility score	− 9.03 (1.18)	− 4.41 (1.23)	− 4.62 (1.58)	− 7.732, − 1.506	0.0038
PDQ-39 ADL score	− 9.76 (1.32)	− 3.95 (1.38)	− 5.81 (1.77)	− 9.303, − 2.326	0.0012
PDQ-30 emotional well-being score	− 8.26 (1.37)	− 3.03 (1.42)	− 5.23 (1.83)	− 8.843, − 1.620	0.0047
PDQ-39 stigma score	− 6.91 (1.59)	− 2.17 (1.66)	− 4.74 (2.13)	− 8.950, − 0.531	0.0275
CGI-C score	+ 3.00 (1.12)	+ 3.40 (1.03)	+ 0.40 (0.10)	+ 0.000, + 1.000	0.0007
CGI-S score	+ 3.60 (0.80)	+ 3.80 (0.95)	+ 0.20 (0.00)	+ 0.000, + 0.400	0.0150
NRS score	+ 0.08 (0.15)	+ 0.11 (0.16)	− 0.03 (0.21)	− 0.440, + 0.382	0.8901

Analysis was based on an analysis of covariance model with treatment and center as independent factors, baseline measurement as the covariate, and the change from baseline as the dependent variable and on the Wilcoxon–Mann–Whitney test stratified by center (CGI-C and CGI-S only)

ADL activities of daily living, *CGI-C* Clinical Global Impression of Change, *CGI-S* Clinical Global Impression of Severity, *CI* confidence interval, *FAS* full analysis set, *h* hours, *LSM* least-squares mean, *NRS* Numerical Rating Scale, *PDQ-39* 39-Item Parkinson's Disease Questionnaire, *SE* standard error, *UPDRS* Unified Parkinsons' Disease Rating Scale

phases) and periods of poor drug response, usually associated with increased PD-related disability ("OFF" phases). There is a significant association between OFF episodes and reduced QoL, with an increase of QoL deterioration linked to the increase of the daily OFF time [22]. Moreover, costs of PD closely correlate with the presence or absence of motor fluctuations: more than a half of the total costs of PD are generated among fluctuating patients [23]. Treatment strategies capable of reducing or delaying motor fluctuations would be expected to increase QoL and lower the economic burden of PD.

In the XINDI study, safinamide reduced by >1 hour the daily OFF time and contemporarily significantly increased the daily ON time and the ON time with no/non-troublesome dyskinesia. The latter is the "good" ON time and correlates with patients' perceived duration of

Table 3 Summary of AEs in the safety population

	Safinamide ($n = 151$)	Placebo ($n = 154$)	P-value*
All AEs	105 (69.5%)	88 (57.1%)	n.s.
AEs related to IMP	54 (35.7%)	40 (25.9%)	n.s.
AEs leading to withdrawal	8 (5.3%)	9 (5.8%)	n.s.
All SAEs	8 (5.3%)	5 (3.2%)	n.s.
SAEs related to IMP	4 (2.6%)	3 (1.9%)	n.s.
SAEs leading to withdrawal	3 (1.9%)	1 (0.6%)	n.s.
Most frequent AEs (reported by ≥ 3% of patients in any group)			
Dyskinesia	18 (11.9%)	6 (3.9%)	n.s.
Dizziness	10 (6.6%)	10 (6.4%)	n.s.
Worsening of PD	7 (4.6%)	14 (9.0%)	n.s.
Constipation	6 (3.9%)	8 (5.1%)	n.s.
Nausea	6 (3.9%)	6 (3.9%)	n.s.
AEs leading to withdrawal			
Dizziness	4 (2.6%)	2 (1.2%)	n.s.
Nausea	3 (1.9%)	2 (1.2%)	n.s.
Worsening of PD	1 (0.6%)	3 (1.9%)	n.s.
Freezing of gait	0 (0.0%)	2 (1.2%)	n.s.
SAEs			
Dizziness	1 (0.6%)	0 (0.0%)	n.s.
Nausea	1 (0.6%)	0 (0.0%)	n.s.
Headache	1 (0.0%)	0 (0.0%)	n.s.
Worsening of PD	0 (0.0%)	1 (0.6%)	n.s.
Hypertension	1 (0.6%)	1 (0.6%)	n.s.
Ventricular extrasystoles	1 (0.6%)	1 (0.6%)	n.s.
Angina unstable	0 (0.0%)	1 (0.6%)	n.s.
Hemorrhoids	1 (0.6%)	0 (0.0%)	n.s.
Depression	1 (0.6%)	1 (0.6%)	n.s.
Back pain	1 (0.6%)	0 (0.0%)	n.s.

Patients were counted only once. AEs were classified according to the *Medical Dictionary for Regulatory Activities* Version 23.1. Percentages are calculated on the number of patients (n) in the safety analysis set by the investigational product

AE adverse event, *IMP* investigational medicinal product, *n* number of patients, *n.s.* not significant, *PD* Parkinson's disease, *SAE* serious adverse event, % percentage of patients, *two-sided p-value

a good response to the therapy throughout the day [17]. The reduction in OFF time is not only statistically, but also clinically significant based on the difference versus placebo defined by Hauser and Auinger [24]. Furthermore, the improvements were observed after only 2 weeks of safinamide treatment, suggesting a rapid onset of the efficacy of the drug. Despite the limitations of indirect comparisons between different studies, the reduction in OFF time observed with safinamide (1.10 h vs placebo) was significantly higher than the same reduction observed with rasagiline (0.5 h) in Chinese patients with PD [25]. The subjects enrolled in this study were already on an optimized regimen of anti-Parkinson medications and may be explained by the peculiar glutamatergic modulation of safinamide. It is known, in fact, that glutamate and other neurotransmitters, in addition to dopamine, are involved in the pathogenesis of motor fluctuations [26, 27].

Safinamide treatment also improved the UPDRS total score and the UPDRS part III (motor) score with a magnitude that was not only statistically, but also clinically significant, representing a moderate clinically important difference according to the criteria developed by Shulman et al. [28]. A clinically important difference is the amount of change on a measure that patients recognize as clinically significant and valuable and is one of the most important tools for patient-centered studies [29]. Moreover, the improvement in the UPDRS motor score observed with safinamide (− 3.80 points vs placebo) was twice that observed with rasagiline (− 1.60 points) by Zhang et al. [25]. These positive outcomes were reflected by the significant improvements seen

in the patients' health-related QoL scales (UPDRS II, CGI, and PDQ-39): these findings are in line with previous reports showing the beneficial effect of safinamide in a real-life setting [30, 31]. Furthermore, the improvements seen in the "emotional well-being" domain of the PDQ-39 score confirm the previous published data on the efficacy of safinamide on depression [32, 33].

Safinamide did not show any pattern of adverse effects based on laboratory tests, vital signs, electrocardiograms, or physical or neurological examinations. Except for dyskinesia, AEs occurred with a similar frequency compared to the placebo group. Drugs that increase the dopaminergic tone are expected to increase dyskinesia; however, it is important to note that most patients with PD who complained of dyskinesia have presented with these abnormal movements since the beginning of the study with no further aggravation. Furthermore, in the XINDI trial, safinamide did not deteriorate the ON time with troublesome dyskinesia, as seen in previous studies [11–13, 34], and a past meta-analysis showed a significant higher incidence of dyskinesia with entacapone compared with safinamide treatment [35]. This positive outcome was achieved without any reduction in L-dopa or other dopaminergic drugs. This effect may be related to the dual mechanisms of safinamide, which modulates dopaminergic and glutamatergic pathways. It is known, in fact, that several neurotransmitters, in addition to dopamine, contribute to the appearance of L-dopa-induced dyskinesia, including overactive glutamate transmission [34]. Overall, the safety profile of safinamide in the XINDI trial was similar to that of the studies performed in Caucasian and Asian-Pacific subjects, and there were no AEs specific to Chinese patients, confirming the tolerability of the drug.

There are some limitations owing to the relatively short-term treatment duration, the eligibility criteria, and the high frequency of medical examinations that do not completely reflect the routine clinical practice. A generalization of the results of this study is limited by the characteristics of patients outlined by the inclusion and exclusion criteria. Further longer real-life trials in the Chinese PD population are warranted to confirm the beneficial effects of safinamide in the long term, despite the progression of the pathology. Another limitation is the lack of an arm with another active drug, preventing a direct comparison.

5 Conclusions

In the XINDI study, safinamide, as add-on therapy to L-dopa, significantly reduced motor fluctuations and improved motor symptoms and the QoL of Chinese patients with idiopathic PD. Despite some AEs common to dopaminergic drugs, no safety concerns were identified, confirming the good tolerability profile of the drug. These results suggest that safinamide can be an effective and safe option for the management of fluctuating patients.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40263-022-00958-6.

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Declarations

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Ethics approval The study was approved by all appropriate independent ethics committees and by the Chinese regulatory authority.

Consent to participate All study participants provided informed consent.

Consent for publication Not applicable.

Availability of data and material The data that support the findings of this study are available from Zambon S.p.A but restrictions apply to the availability of these data, which were used under license for the current study, and thus are not publicly available. However, data are available from the authors upon reasonable request and with permission of Zambon S.p.A.

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