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ORIGINAL RESEARCH

The Effects of Safinamide in Chinese and Non-Chinese Patients with Parkinson's Disease

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ABSTRACT

Introduction: Ethnicity differences are an important determinant in the clinical manifestation of Parkinson's disease (PD), but they are not yet widely recognized, particularly regarding the response to dopaminergic medications. The aim of this paper is to analyze the efficacy and safety of safinamide in Chinese patients with PD in the pivotal studies SETTLE and XINDI compared to the non-Chinese population of the SETTLE trial.

Methods: SETTLE (NCT00627640) and XINDI (NCT03881371) were phase III, randomized, double-blind, placebo-controlled, multicenter trials. Patients received safinamide or placebo as add-on to levodopa. The primary efficacy endpoint was the change in the mean total daily OFF time. Secondary efficacy endpoints included total daily ON time, ON time with no/non-troublesome dyskinesia, Unified Parkinson's Disease Rating Scale, and Parkinson's Disease Questionnaire-39 items. Safety was evaluated through the frequency of adverse events. Data from 440 non-Chinese and 109 Chinese patients in the SETTLE study, and 305 Chinese patients in the XINDI trial were considered for this post hoc analysis.

Results: Significant positive results were seen in favor of safinamide in all populations for the primary and secondary endpoints, with no differences in terms of magnitude. No "treatment by ethnicity" interaction was detected for any parameters, confirming the homogeneity of treatment effects between different populations. The safety and tolerability of safinamide in Chinese patients were similar to those in the other ethnic groups, without unexpected adverse reactions.

Conclusions: Safinamide was shown to improve PD symptoms and quality of life in different ethnic populations, without any treatment by race interaction. Further studies are warranted to investigate potential differences in a real-life situation.

Trial Registration Number: SETTLE (NCT00627640) and XINDI (NCT03881371).

Keywords: Parkinson's disease; Safinamide; Ethnicity; Motor fluctuations; Glutamate

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Key Summary Points

Why carry out his study?

The clinical manifestation of Parkinson's disease and the response to treatments may be different between ethnic groups, and in particular in Chinese subjects compared to other populations

The aim of this study was to investigate the effects of safinamide in Chinese and non-Chinese patients through the data of two pivotal studies, one performed in Europe, Asia, Pacific, and North America, the second in China

What was learned from the study?

Safinamide improved motor symptoms and motor fluctuations in different populations without any ethnicity interaction. No differences were detected in terms of safety and tolerability

Large real-life trials in different ethnic populations are warranted to confirm these findings

INTRODUCTION

Parkinson's disease (PD) is a major neurodegenerative disorder characterized by a progressive loss of nigrostriatal dopaminergic neurons leading to a dopamine deficiency. Classical motor features of PD include tremor, bradykinesia, rigidity, and gait and postural instability [1]. The disease is also associated with several non-motor symptoms, such as fatigue, pain, mood disorders, sleep disturbances, and cognitive dysfunction, with a strong impact on patients' daytime activities and well-being [2]. Beyond dopamine, other neurotransmitters are known to be involved: glutamate plays important roles in the pathogenesis of primary symptoms, motor fluctuations, dyskinesia, and neuronal cell loss [3]. The prevalence of PD increases with age, and the number of individuals with PD over age 50 is expected to double by 2030 causing a serious socioeconomic burden in the future aging society and an increasing demand for new PD therapies [4, 5]. The epidemiology of PD among various ethnic groups has been poorly studied: some preliminary data suggest that the prodromal risk of developing PD and the clinical symptom expression may vary between different ethnic groups; Chinese patients, for example, are more likely to experience dyskinesia and depression than non-Chinese or other populations [6, 7].

Safinamide is a unique treatment modulating both dopaminergic and glutamatergic systems. The glutamatergic mechanism of action is different from that of amantadine: safinamide, in fact, has an indirect effect on the glutamate release through the blockade of sodium channels, while amantadine has a direct effect due to the *N*-methyl-D-aspartate (NMDA) receptor antagonism [8].

The metabolism of safinamide is not dependent on cytochrome P (CYP) enzymes, is not influenced by any known genetic polymorphisms, and is not influenced by weight, race, age, or gender [9].

Results from pivotal studies showed that safinamide has positive effects on both motor [10–14] and non-motor functions [15–17] in patients with PD, with the same efficacy in both genders [18]. A previous publication [19] has described a post hoc analysis of the SETTLE study [12] dividing the patients into two groups, Asian-Pacific and non-Chinese. The Asian-Pacific subjects came from different countries (Australia, Hong Kong, India, Korea, Malaysia, Singapore, Taiwan, Thailand, and New Zealand), but not from one unique ethnic group. The aim of this paper is to describe the results of new additional analyses comparing the non-Chinese population of the SETTLE study with the Chinese subjects of the SETTLE and the XINDI trials, aiming to confirm, as seen in a previous pharmacokinetic/pharmacodynamic study [20], that there are no differences regarding the efficacy and safety of safinamide between different populations. The two pivotal studies (SUCCESS and XINDI) have been chosen because the patients' characteristics and the

design are similar and the dosing regimens are identical (safinamide or placebo administered at 50 mg/day for 15 days, then at 100 mg/day). The study 016 [10] was excluded because of a different dosing regimen, with two fixed dose levels (50 and 100 mg/day), and because there were no Chinese patients.

METHODS

Study Design and Study Population

SETTLE (NCT00627640) and XINDI (NCT03881371) were phase III, double-blind, multicenter studies in patients with PD and motor fluctuations. The SETTLE trial enrolled patients in 21 countries of Europe, Asia, Pacific, and North America, while the XINDI study enrolled only patients in China. Patients with a diagnosis of idiopathic PD based on medical history and neurological examination [21] of more than 3 years duration, a Hoehn and Yahr (H&Y) stage 1–4 [22], and daily OFF time $\geq$ 1.5 h (excluding morning akinesia), were randomized to receive safinamide or placebo as add-on to levodopa (L-dopa). Patients with severe, disabling peak-dose or biphasic dyskinesia, wide or unpredictable fluctuations, cognitive or psychiatric problems were excluded. The efficacy was assessed by the changes in "OFF" and "ON" time from the patient diaries, the Unified Parkinson's Disease Rating Scale (UPDRS) [23], and the Parkinson's Disease Questionnaire-39 items (PDQ-39) [24]. Previous and concomitant medications were coded using the World Health Organization Drug Dictionary (WHO-DD) [25] and the adverse events (AEs) with the Medical Dictionary for Regulatory Activities (MedDRA) version 23.1 [26]. All AEs and serious adverse events (SAEs) were followed up until resolution. The studies were conducted in compliance with the last version of the Declaration of Helsinki and the Good Clinical Practices [27] and after the signature of a written informed consent by the patients and were approved by local ethics committees and national health authorities. Full details of the trials have been reported by Shapira et al. [12] and Wei et al. [14] and are also available at ClinicalTrials.gov.

Statistical Methods

Statistical analyses were performed using SAS® for Windows release 9.4 (SAS Institute, Inc., Cary, NC, USA), with two-sided tests at the significance level of $\alpha = 0.05$. Demographic data were retrieved during the baseline visit from the patient's history and hospital clinical records. Categorical variables were described as the number and percentage of subjects, while continuous variables were described by means of descriptive statistics. Conventional chi-square test or Fisher's exact test, respectively, was used to detect any difference between subgroups. Efficacy endpoints were reported by the least-squares mean (LSM) for treatment differences and two-tailed 95% confidence intervals (CIs) using the latest result computed on the basis of the numbers of patients with non-missing observations. The p values versus placebo were calculated using analysis of covariance (ANCOVA) with treatment and center as independent factor, baseline values as covariate, and the change from baseline as dependent variable. The results of the efficacy outcomes were compared between ethnicities using ANCOVA with baseline values, country, body weight, disease duration, H&Y stage, and anti-PD medications other than L-dopa as covariates. The incidence of adverse events vs placebo were analyzed using Fisher's exact test, while differences between the populations' subgroups were compared through logistic regression using country, body weight, disease duration, H&Y stage, and anti-PD medications other than L-dopa as covariates.

RESULTS

Demography

As shown in Table 1, the study populations consisted of 440 non-Chinese and 109 Chinese patients in the SETTLE study, and 305 Chinese patients in the XINDI trial. As written

Table 1 Baseline demographic and clinical characteristics of the non-Chinese population of the SETTLE study and the Chinese population of the SETTLE and the XINDI trials

Characteristic	Non-Chinese population in SETTLE study (*n* = 440)	Chinese population in SETTLE study (*n* = 109)	Chinese population in XINDI study (*n* = 305)	*p* value for interaction*
Mean (SD) age (years)	61.9 (8.9)	59.9 (8.8)	61.6 (9.3)	0.5550
Female (*n*, %)	199 (45.2)	45 (41.3)	128 (42.0)	0.5345
Male (*n*, %)	241 (54.8)	64 (58.7)	177 (58.0)	0.4905
Mean weight (kg)	68.8 (10.1)	62.9 (10.3)	64.5 (10.6)	0.1598
Mean BMI (kg/m^2)	24.7 (3.2)	23.0 (3.2)	23.9 (3.1)	0.7787
Mean (SD) Hoehn & Yahr stage	2.5 (0.6)	2.4 (0.5)	2.3 (0.5)	0.8116
Mean (SD) duration of PD (years)	8.4 (4.6)	7.9 (4.3)	8.3 (4.8)	0.2208
Mean (SD) total daily OFF time (h)	5.4 (2.0)	5.6 (2.8)	5.8 (2.9)	0.3928
Mean (SD) total daily ON time (h)	9.5 (2.5)	9.8 (2.2)	10.2 (2.9)	0.2414
Mean (SD) total daily ON time with no/non-troublesome dyskinesia (h)	9.2 (2.5)	9.3 (2.4)	9.7 (2.7)	0.4177
Mean (SD) UPDRS part III score	23.4 (13.0)	22.3 (10.9)	27.1 (12.9)	0.0751
Mean (SD) PDQ-39 summary of index score	27.1 (14.7)	24.7 (14.1)	24.8 (13.0)	0.0900
Mean (SD) total daily levodopa dose (mg)	776.5 (423.8)	756.4 (384.5)	510.0 (185.0)	0.0371
Concomitant antiparkinson drugs (*n*, %)				
Levodopa	440 (100.0)	109 (100.0)	305 (100.0)	0.8677
Pramipexole	224 (51.0)	54 (49.5)	155 (50.8)	0.9160
COMT inhibitors	176 (40.0)	40 (36.6)	110 (36.0)	0.3132
Amantadine	133 (30.2)	36 (33.0)	98 (32.1)	0.1236
Anticholinergics	75 (17.0)	24 (22.0)	42 (13.7)	0.0914

Percentages (%) were computed by column

n number of patients, *SD* standard deviation, *BMI* body mass index, *PD* Parkinson's disease, *h* hours, *UPDRS* Unified Parkinson's Disease Rating Scale, *PDQ-39* Parkinson's Disease Questionnaire-39 items

**p* value for interaction between subgroups of patients was calculated using chi-square test for categorical variables and Fisher's exact test for continuous variables

previously, data of the SETTLE non-Chinese population were compared with those of the Chinese patients in the SETTLE and XINDI trials, considered as distinct subgroups of patients. There were no differences at baseline between ethnic groups in the demographic and clinical characteristics except for the mean total daily levodopa dose that was higher in the SETTLE compared to the XINDI study (SETTLE non-Chinese population: 776.5 ± 423.8 mg; SETTLE Chinese subgroup: 756.4 ± 384.5 mg; XINDI: 510.0 ± 185.0 mg; *p* value for interaction between subgroups of patients = 0.0371).

Efficacy

Changes from baseline to end of study in the efficacy parameters, comparing safinamide to placebo, are reported in Table 2. Significant positive results were seen in favor of safinamide in the three populations for all parameters analyzed. There was a statistically significant reduction of the OFF time (primary endpoint) with an LSM difference versus placebo of − 1.07 h ($p < 0.0001$) in the non-Chinese population of the SETTLE study, − 0.95 h ($p = 0.0321$) in the Chinese patients in the SETTLE, and − 1.10 h ($p < 0.0001$) in the Chinese subjects of the XINDI trial. Regarding the other main secondary efficacy endpoints, safinamide, compared with placebo, showed statistically significant improvements in the total daily ON time (SETTLE non-Chinese population: LSM difference + 0.86 h, $p = 0.0096$; SETTLE Chinese subgroup: LSM difference + 0.90 h, $p = 0.0034$; XINDI: LSM difference + 0.89 h, $p = 0.0049$), total daily ON time with no/non-troublesome dyskinesia (SETTLE non-Chinese population: LSM difference + 1.01 h, $p < 0.0001$; SETTLE Chinese subgroup: LSM difference + 0.93 h, $p = 0.0459$; XINDI: LSM difference + 1.07 h, $p = 0.0021$), UPDRS part III scores (SETTLE non-Chinese population: LSM difference − 2.63, $p = 0.0142$; SETTLE Chinese subgroup: LSM difference − 2.82, $p = 0.0040$; XINDI: LSM difference − 3.80, $p = 0.0002$), PDQ-39 summary of the index score (SETTLE non-Chinese population: LSM difference − 2.63, $p = 0.006$; SETTLE Chinese subgroup: LSM difference − 2.98, $p = 0.0049$; XINDI: LSM difference − 3.36, $p = 0.0033$), and the PDQ-39 subscale scores for mobility (SETTLE non-Chinese population: LSM difference − 4.86, $p = 0.001$; SETTLE Chinese subgroup: LSM difference − 4.39, $p = 0.0190$; XINDI: LSM difference − 4.62, $p = 0.0038$), activities of daily living (SETTLE non-Chinese population: LSM difference − 4.59, $p = 0.006$; SETTLE Chinese subgroup: LSM difference − 5.03, $p = 0.0035$; XINDI: LSM difference − 5.81, $p = 0.0012$), emotional well-being (SETTLE non-Chinese population: LSM difference − 3.66, $p = 0.019$; SETTLE Chinese subgroup: LSM difference − 3.76, $p = 0.0036$; XINDI: LSM difference − 5.23, $p = 0.0047$), and stigma (SETTLE non-Chinese population: LSM difference − 2.76, $p = 0.061$; SETTLE Chinese subgroup: LSM difference − 2.52, $p = 0.099$; XINDI: LSM difference − 4.74, $p = 0.0275$).

The *p* value for the "treatment by ethnicity" interaction was non-significant for all parameters, confirming the homogeneity of treatment effects between different populations.

Stratifications according to the administration of baseline medications as add-on to levodopa other than safinamide or placebo were not performed since concomitant multiple adjunctive treatments were administered and subgroups partly overlapped.

Adverse Events and Serious Adverse Events

As reported in Table 3, the percentage of patients experiencing adverse events (AEs) and serious adverse events (SAEs) was similar among the three subgroup of patients. No significant differences were detected in the percentage of patients experiencing AEs/SAEs related to the investigational medicinal product (IMP) or leading to withdrawal from the studies. The *p* value for the "treatment by ethnicity" interaction was non-significant for all these data. As reported by Wei et al. [14], the slight difference in the incidence of AEs observed in the XINDI study between safinamide and placebo was not statistically significant. The majority of AEs/SAEs were rated as mild or moderate, were completely resolved at the end of the study, and

Table 2 Summary of the main efficacy endpoints in the non-Chinese population of the SETTLE study and the Chinese population of the SETTLE and the XINDI trials

Efficacy endpoint	Non-Chinese population in SETTLE study (n = 440)		Chinese population in SETTLE study (n = 109)		Chinese population in XINDI study (n = 305)		All Chinese vs SETTLE non-Chinese population
	LS mean difference vs placebo (95% CI)	p value[a]	LS mean difference vs placebo (95% CI)	p value[a]	LS mean difference vs placebo (95% CI)	p value[a]	p value for interaction[b]
Total daily OFF time (h)	− 1.07 (− 1.40, − 0.67)	< 0.0001	− 0.95 (− 0.90, − 0.82)	0.0321	− 1.10 (− 1.64, − 0.55)	< 0.0001	0.7554
Total daily ON time (h)	+ 0.86 (+ 0.50, + 1.36)	0.0096	+ 0.90 (+ 0.50, + 1.30)	0.0034	+ 0.89 (+ 0.27, + 1.51)	0.0049	0.6581
Total daily ON time with no/non-troublesome dyskinesia (h)	+ 1.01 (+ 0.56, + 1.37)	< 0.0001	+ 0.93 (+ 0.86, + 0.91)	0.0459	+ 1.07 (+ 0.39, + 1.75)	0.0021	0.4177
UPDRS III score (motor symptoms)	− 2.63 (− 3.01, − 0.62)	0.0142	− 2.82 (− 2.98, − 2.65)	0.0040	− 3.80 (− 5.74, − 1.85)	0.0002	0.0659
PDQ-39 SI score	− 2.63 (− 4.08, − 0.72)	0.006	− 2.98 (− 5.94, − 0.01)	0.0049	− 3.36 (− 5.58, − 1.12)	0.0033	0.0710
PDQ-39 mobility score	− 4.86 (− 5.00, − 0.14)	0.001	− 4.39 (− 5.71, − 0.60)	0.0190	− 4.62 (− 7.73, − 1.50)	0.0038	0.3983
PDQ-39 ADL score	− 4.59 (− 4.64, − 0.05)	0.006	− 5.03 (− 6.74, − 0.33)	0.0035	− 5.81 (− 9.30, − 2.32)	0.0012	0.0642
PDQ-39 emotional well-being score	− 3.66 (− 6.71, − 0.60)	0.019	− 3.76 (− 6.29, − 1.23)	0.0036	− 5.23 (− 8.84, − 1.62)	0.0047	0.0670
PDQ-39 stigma score	− 2.76 (− 2.81, − 1.05)	0.061	− 2.52 (− 5.52, − 0.48)	0.099	− 4.74 (− 8.95, − 0.53)	0.0275	0.0703

n number of patients, *LS* least squares, *CI* confidence interval, *h* hours, *UPDRS* Unified Parkinson's Disease Rating Scale, *SI* summary index, *PDQ-39* Parkinson's Disease Questionnaire-39 items, *ADL* activities of daily living

[a]ANCOVA with treatment, center, and study as fixed effects and baseline values as continuous covariate

[b]ANCOVA with baseline values, country, body weight, disease duration, H&Y stage, and anti-PD medications other than L-dopa as covariates

Table 3 Summary of the AEs/SAEs in the non-Chinese population of the SETTLE study and the Chinese population of the SETTLE and the XINDI trials

	Non-Chinese population in SETTLE study (n = 440)		Chinese population in SETTLE study (n = 109)		Chinese population in XINDI study (n = 305)		All Chinese vs SETTLE overall population
	Safinamide (n = 219)	Placebo (n = 221)	Safinamide (n = 59)	Placebo (n = 50)	Safinamide (n = 151)	Placebo (n = 154)	p value for interaction[a]
All AEs	146 (66.7%)	157 (71.0%)	40 (67.7%)	33 (66.0%)	105 (69.5%)	88 (57.1%)	0.8554
AEs related to IMP	63 (28.7%)	64 (28.9%)	15 (25.4%)	12 (24.0%)	54 (35.7%)	40 (25.9%)	0.7581
AEs leading to withdrawal	12 (5.5%)	9 (4.0%)	0 (0.0%)	1 (2.0%)	8 (5.3%)	9 (5.8%)	0.0877
All SAEs	15 (6.8%)	24 (10.8%)	3 (5.0%)	2 (4.0%)	8 (5.3%)	5 (3.2%)	0.0759
SAEs related to IMP	3 (1.3%)	6 (2.7%)	0 (0.0%)	0 (0.0%)	4 (2.6%)	3 (1.9%)	0.8810
Most frequent AEs (reported by ≥ 5% of patients in either treatment group)							
Dyskinesia	32 (14.6%)	12 (5.4%)	8 (13.5%)	3 (6.0%)	18 (11.9%)	6 (3.9%)	0.1670
Fall	16 (7.3%)	9 (4.0%)	2 (3.3%)	1 (2.0%)	2 (1.3%)	0 (0.0%)	0.0660
Urinary tract infection	15 (6.8%)	11 (5.0%)	2 (3.3%)	1 (2.0%)	1 (0.6%)	0 (0.0%)	0.1960
Nausea	15 (6.8%)	13 (5.9%)	1 (1.6%)	2 (4.0%)	6 (3.9%)	6 (3.9%)	0.0922
Headache	10 (4.6%)	15 (6.8%)	2 (3.3%)	2 (4.0%)	5 (3.3%)	2 (1.3%)	0.7166

Patients were counted once

AE adverse event, *SAE* serious adverse event, *IMP* investigational medicinal product, *n* number of patients, *%* percentage of patients

[a]Logistic regression using country, body weight, disease duration, H&Y stage, and anti-PD medications other than L-dopa as covariates

were those described in the patients' leaflet. The most frequent AEs were dyskinesia, fall, urinary tract infection, nausea, and headache. Dyskinesia was observed with higher prevalence in all subjects receiving safinamide (SETTLE non-Chinese population: 14.6%; SETTLE Chinese subgroup: 13.5%; XINDI: 11.9%) compared with placebo (SETTLE non-Chinese population: 5.4%; SETTLE Chinese subgroup: 6.0%; XINDI: 3.9%), but was generally of mild or moderate intensity, transient, and did not lead to withdrawal from the study or IMP interruption. Drugs that increase the dopaminergic tone are known to increase dyskinesia; however, most patients with PD who complained of dyskinesia had presented this motor complication since the beginning of the study with no further aggravation. Moreover, as seen in previous

pivotal trials, safinamide did not deteriorate ON time with troublesome dyskinesia [10, 11].

DISCUSSION

The role of ethnicity in PD is poorly understood and underinvestigated, despite differences observed in epidemiology, clinical manifestation, and response to treatments. Several factors might play a role, such as pharmacogenetic, sociocultural, and environmental [28]. This is the first publication that analyzes potential differences, after safinamide administration, comparing Chinese patients with PD with other ethnic populations from the USA, Europe, Asia, and Pacific.

Safinamide significantly improved motor fluctuations and motor symptoms in all subjects, without any significant interaction between treatment and race. The improvements observed with the UPDRS part III (motor score) were not only statistically but also clinically significant according to the criteria of Shulman et al. [29] and were confirmed by the positive results seen in the mobility domain of the PDQ-39 scale. These results may be explained by the dual mechanism of action of safinamide, dopaminergic (MAO-B inhibition) and non-dopaminergic (glutamate modulation). Safinamide prevents the degradation of dopamine, thereby raising its levels and prolonging its effects. This mechanism is expected to improve both the quality and the duration of fluctuations. Moreover, glutamate is known to be involved, together with dopamine and other neurotransmitters, in the deterioration of motor symptoms and in the development of motor complications [30, 31]. Significant improvements were seen in three other PDQ-39 domains—activities of daily living, emotional well-being, and stigma—and were reflected by a general improvement of patient's quality of life, as shown by the PDQ-39 summary of index scores. The benefit seen in the emotional well-being domain of the PDQ-39 score, in particular, is consistent with previous published data on the efficacy of safinamide on depression and apathy [16, 32]. Despite a different baseline levels of levodopa dosages, which could reflect different therapeutic strategies, the L-dopa equivalent daily dose (LEDD) did not changed during the study periods [12, 14], confirming that safinamide treatment does not require an increase of L-dopa dose [33]. Overall, the safety profile of safinamide in Chinese patients was similar to that in the other ethnicities, without any unexpected adverse reaction. Adverse events occurred with a similar frequency in both safinamide and placebo groups except for dyskinesia, which was prevalent with safinamide, although non-significant. Its incidence resembled that reported for rasagiline and opicapone in patients with fluctuating PD [34–37]. Previous trials have shown that safinamide does not deteriorate the ON time with troublesome dyskinesia and improves dyskinesia scales [11, 38], and therefore this frequency difference could be due to the increase of the dopaminergic tone mitigated by the glutamatergic modulation of the drug.

There are some limitations to be considered in this post hoc analysis. The original trials were not designed nor powered to investigate differences between ethnic subgroups and did not consider genetic and socioeconomic factors. The results could be also limited by the short-term treatment duration, the eligibility criteria, and the frequency of visits that do not reflect the routine clinical practice. There was only one pre-specified dosage level of safinamide and data were compared versus placebo, without a direct comparison with another active treatment. These findings should therefore be considered as exploratory and must be confirmed in larger real-life trials in different ethnic populations.

CONCLUSIONS

Increased knowledge on the role of ethnicity in PD may help to evaluate more appropriately symptom expression and treatment response, improve the diagnosis, and prescribe personalized medicines. Our post hoc analyses of the SETTLE and XINDI studies have shown that safinamide was effective in improving motor symptoms and motor fluctuations in different populations without any ethnicity interaction,

and with a favorable safety profile. Further epidemiological studies are needed to investigate the effects of safinamide in different ethnic populations and in usual care setting.

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Author Contributions. Carlo Cattaneo and Jaime Kulisevsky contributed to analyzing the data, interpreting the findings, writing and reviewing the paper, collecting and analyzing the literature, designing the tables, and approved the final manuscript.

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Data Availability. The data supporting the conclusions of this article will be made available by the corresponding author on reasonable request. Full details of the trials SUCCESS and XINDI have been reported by Shapira et al. [12] and Wei et al. [14], respectively, and are also available at ClinicalTrials.gov. (SETTLE: NCT00627640; XINDI: NCT03881371).

Declarations

Conflict of Interest. Carlo Cattaneo is an employee of Zambon SpA; Jaime Kulisevsky has received compensation for consultancy and speaker related activities from Zambon SpA.

Ethical Approval. This article is based on the data of the previously conducted studies SUCCESS and XINDI that have been approved in all countries by ethical national committees and national health authorities and were performed according to the guidelines of the Declaration of Helsinki. The authors received permission to access the data. No new studies with human participants have been performed for this publication. Written informed and privacy consents to participate in the studies SUCCESS and XINDI, collect, analyze, and report anonymized and aggregated data were obtained from all patients.

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