SETTLE study design: a 24-week, double-blind, placebo-controlled study of the efficacy and safety of safinamide as add-on therapy to levodopa in patients with Parkinson's disease

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INTRODUCTION

- Although levodopa is very effective for treating the motor symptoms of Parkinson's disease (PD), its long-term use is associated with motor fluctuations and dyskinesia.[1] In fact, it has been estimated that ~40% of patients develop motor complications after 4–6 years of levodopa treatment.[2]
- Patients with levodopa-induced motor fluctuations usually require add-on therapy, the aim of which is to improve motor function by prolonging ON time without exacerbating (or ideally, improving) dyskinesia. Currently available add-on dopaminergic therapy may improve motor function, but this often occurs at the expense of worsening dyskinesia. Agents that combine dopaminergic and non-dopaminergic mechanisms of action may address the need for more effective and safer control of levodopa-related motor complications.
- Safinamide is an α-aminoamide in Phase III clinical development as add-on therapy to levodopa or dopamine agonists in patients with PD. It has both dopaminergic and non-dopaminergic mechanisms of action, including monoamine oxidase-B and dopamine reuptake inhibition, activity-dependent sodium channel antagonism, and inhibition of glutamate release *in vitro*.[3-5]
- Previous clinical studies have shown that safinamide significantly improves ON time without troublesome dyskinesia when used as add-on to stable doses of levodopa in patients with PD and motor fluctuations.[6]

OBJECTIVE

- The SafinamidE Treatment as add-on To LEvodopa in idiopathic PD (SETTLE) study has been designed to further evaluate the use of safinamide as add-on to stable levodopa in patients with mid- to late-stage PD and motor fluctuations. Here, we describe the SETTLE study design and highlight its key features.

METHODS

Study design

- Phase III, 24-week, randomized, double-blind, placebo-controlled, multi-national study.
- Over 20 countries are participating in this global study, throughout five continents (Figure 1).
- The study consists of five periods: screening, stabilization, treatment, taper, and safety follow-up.
- Patients completing the SETTLE study have the option to enter a long-term, open-label safety study (Figure 2).

Patients

- Key inclusion criteria:
  - Male or female, aged 30–80 years
  - Diagnosis of idiopathic PD (⩾3 years' duration)
  - Hoehn and Yahr Stage I–IV (during OFF state)
  - Stable doses of levodopa with >1.5 hours' OFF time per day.
- Key exclusion criteria:
  - Severe, disabling peak-dose or biphasic dyskinesia and/or unpredictable or widely swinging fluctuations
  - Psychosis, depression (GRID Hamilton Rating Scale for Depression–17-item [GRID HAM-D] >17), dementia, or cognitive dysfunction
  - Treatment with monoamine oxidase inhibitors.

Treatments

- Patients will be treated with safinamide 50–100 mg/day or placebo as add-on to levodopa.
  - They will receive the maximum tolerated dose of safinamide (50 or 100 mg/day), taken orally, once daily in the morning with breakfast.
- Catechol-*O*-methyl transferase inhibitors, dopamine agonists, anticholinergics, and/or amantadine are permitted, provided that they have been taken at a stable dose in the 4 weeks before screening.
- The doses of levodopa and other PD treatments can be optimized during the stabilization period, but are to remain stable during the treatment period.

Outcome parameters

- Patients will record their functional status in daily diaries using the following criteria: ON with no dyskinesia, ON with non-troublesome dyskinesia, ON with troublesome dyskinesia, and OFF.
- The primary efficacy parameter is the change (baseline to Week 24) in daily ON time without troublesome dyskinesia. Other efficacy parameters, as well as the safety parameters, are shown in Figure 3.

Statistical analysis

- Sample size
  - At least 484 randomized subjects (242 per group), resulting in 416 evaluable subjects, will provide at least 90% power to detect a clinically meaningful difference of 0.75 hours in the primary efficacy parameter, change from baseline to Week 24 in daily ON time, between the safinamide and placebo groups, assuming a common standard deviation of 2.35 hours, Type-I error rate of 5%, and a 14% drop-out rate.
- Data analysis
  - **Primary efficacy parameter and other continuous parameters:** analysis of covariance (ANCOVA), with baseline values as the covariate.
  - **Other parameters:** a logistic regression model will be used for Clinical Global Impression of Change (CGI-C) and Patient's Global Impression of Change (PGIC) data.
  - If the primary efficacy parameter is statistically significant, secondary efficacy parameters will be analyzed in a hierarchical fashion.

Key features

- In addition to standard outcome parameters for motor complications, two common non-motor symptoms of PD will be assessed:
  - **Cognition** – the Cogtest® PD Battery
    - Specifically designed to assess the pattern of cognitive deficits seen in PD
    - Electronic collection of participant responses and automated scoring minimize examiner error
    - Interactive touch-screen interface, immediate response mechanisms, and motivational tasks engage the participant and ensure optimum outcomes.
  - **Depression** – GRID HAM-D (17-item)
    - Assesses depressed mood and the vegetative and cognitive symptoms of depression
    - Intensity and frequency are evaluated separately for each item.
- All raters will be trained on the use of the scales and, if possible, have at least two years' experience of their use. All raters will be approved, based on their performance compared with a consensus rating on one or more videotaped subject interviews or assessments. Additional training will be conducted periodically during the study.
- Patient-reported outcomes
  - As motor fluctuations and dyskinesia can affect patients' ability to function, the study will also evaluate the effect of treatment on patient-reported outcomes, including the patient's opinion on his/her overall clinical status (PGIC) and quality of life (EuroQol-5 dimensions questionnaire, EQ-5D; Parkinson's Disease Questionnaire–39-item, PDQ-39).

Other features

- The following parameters are being assessed during the study:
  - Health-resource utilization
  - Ambulatory blood-pressure monitoring (in selected countries)
  - Pharmacokinetic modeling
  - Biomarker analysis.

CONCLUSIONS

- **This large Phase III study of safinamide will provide further data on the efficacy and safety of this drug with both dopaminergic and non-dopaminergic pharmacologic properties as add-on to stable levodopa in patients with PD and motor fluctuations.**
- **In addition to traditional endpoints, including the effect of safinamide on time spent ON without troublesome dyskinesia, the study will also evaluate common non-motor symptoms and patient-reported outcomes.**
- **The efficacy and safety of safinamide as add-on therapy to dopamine agonists in patients with early PD are also being studied, in the ongoing MOTION study (see Poster 319).**

Figure 1. Countries participating in the SETTLE study

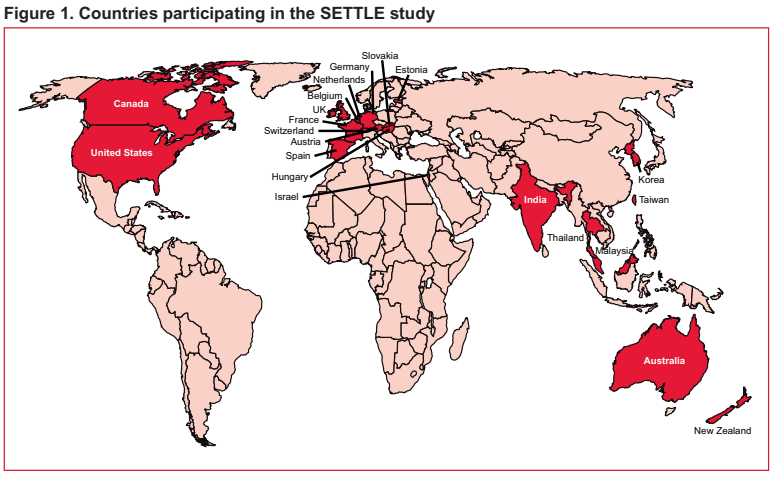

Figure 2. SETTLE study design

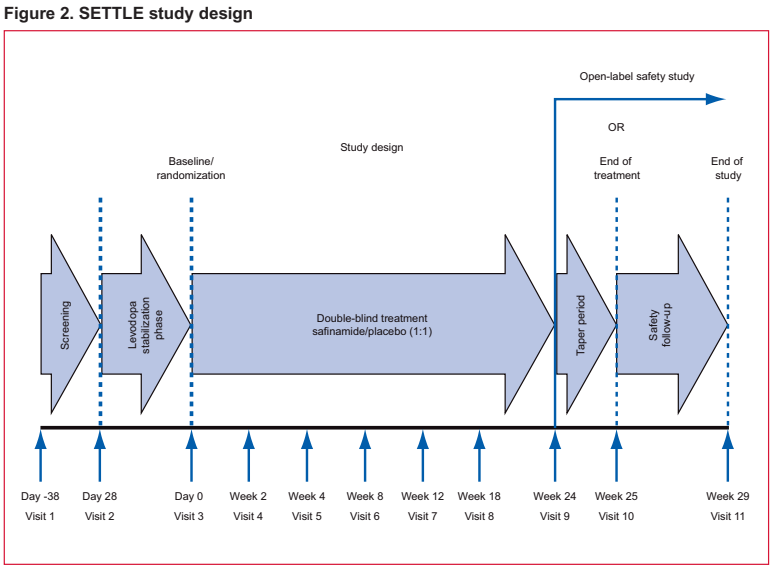

Figure 3. SETTLE study outcome parameters

Outcome	Parameters
Primary efficacy*	• Daily ON time without troublesome dyskinesia
Secondary efficacy*	• UPDRS Part II (ADL) during ON phase • Cogtest® PD battery (*see Key features*) • DRS during ON phase • CGI-S • Proportion of patients with an improvement (score of 1, 2, or 3) on CGI-C • CGI-C • UPDRS Part III (motor examination) during ON phase • Daily OFF time • Daily OFF time following morning levodopa dose • Change in levodopa dose • EQ-5D™ • PDQ-39 • PGIC
Tertiary efficacy*	• Hoehn and Yahr stage • GRID HAM-D • MMSE • Health Resource Utilization questionnaire • UPDRS Part I (mentation, behavior, and mood)
Safety	• TEAEs • Laboratory safety tests, ECG morphology, vital signs (including ABPM in selected countries), ophthalmologic and dermatologic examinations, impulse control disorders (QUIP), and level of daytime sleepiness
Other	• Pharmacokinetics • Biomarkers

ABPM, ambulatory blood-pressure monitoring; ADL, activities of daily living; CGI-C, Clinical Global Impression of Change; CGI-S, Clinical Global Impression of Severity; DRS, Dyskinesia Rating Scale; ECG, electrocardiogram; EQ-5D, EuroQol-5 Dimensions Questionnaire; GRID HAM-D, GRID version of the Hamilton Rating Scale for Depression; MMSE, Mini Mental State Examination; PD, Parkinson's disease; PDQ-39, Parkinson's Disease Questionnaire–39-item; PGIC, Patients Global Impression of Change; QUIP, Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease; TEAE, treatment-emergent adverse events; UPDRS, Unified Parkinson's Disease Rating Scale.
*Unless otherwise stated, parameters will be analyzed as a change from baseline to Week 24

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