**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. In fact, it has been estimated that 40% of patients develop motor complications after 4–6 years of levodopa treatment.

- 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 dopamine- and non-dopaminergic mechanisms of action may address the need for more effective and safer control of levodopa-related motor complications.

- Safinamide is an N-enantiomer in Phase III clinical development as an 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.1,2

- Previous clinical studies have shown that safinamide significantly improves ON time without troublesome dyskinesia and ON time as compared with placebo in levodopa-naïve patients with PD and motor fluctuations.3

**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 design of 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 (21 participating countries), across five continents (Figure 1).

- The protocol includes five periods: 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 (≥5 years’ duration)
  - Hoehn and Yahr Stage I–IV (during OFF state)
  - Stable doses of levodopa with ≥15 hours’ OFF time per day

- Key exclusion criteria:
  - Severe, disabling peak-dose or biphasic dyskinesia and/or unpredictable or easily triggering fluctuations
  - Psychosis, depression (GRID Hamilton Rating Scale for Depression ≥17-HRMD-Q17–17), dementia, or cognitive dysfunction

- Treatment with monoamine oxidase inhibitors.

- Patients will be treated with safinamide 50–100 mg/day or placebo as add-on to levodopa.

- The primary efficacy parameter is the change (baseline to Week 24) in daily ON time without troublesome dyskinesia. Other efficacy parameters, as well as safety parameters, are shown in Figure 3.

**Statistical analysis**

- Sample size: At least 484 randomized subjects (242 per group), resulting in 418 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.

- Analysis of variance (ANOVA) with treatment as the covariate.

- Propensity score analysis and other continuous parameters: analysis of covariance (ANCOVA), with treatment as the covariate.

- Other parameters: logistic regression model will be used for Clinical Global Impression of Change (CGIC) 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.

**CONCLUSIONS**

- The SETTLE study will provide further data on the efficacy and safety of this drug with both dopaminergic and non-dopaminergic pharmacologic properties, further expanding 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 MOTOR study (see Pointer 21).

**REFERENCES**

1. HSK49432e_Schapira: HSK49432e_Schapira 24/5/10 17:35 Page 1

**Figure 1. Countries participating in the SETTLE study**

**Figure 2. SETTLE study design**

**Figure 3. SETTLE study outcome parameters**

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Key features:

- In addition to standard outcome parameters for motor complications, two common non-motor symptoms of PD will be assessed.

- Cognition – the Cogstate® PD Battery

- Cognitive function will be specifically designed to assess the pattern of cognitive deficits seen in PD

- Electronic collection of participant responses and automated scoring minimize examiner error

- Inter-rater bias by using a touch-screen interface, immediate response mechanisms, and motivational tasks engage the participant and ensure optimum outcomes

- Depression – GRID-HAM-D (17-item)

- Assess depression 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 validated 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-care utilization
  - Ambulatory blood-pressure monitoring (in selected countries)
  - Pharmacokinetic modeling
  - Biomarker analysis

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