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Merck KGaA Initiates SETTLE, the Second Phase III Clinical Trial of Safinamide in Advanced Parkinson's Disease

- **Additional important effects of safinamide noted in ongoing analyses of first Phase III clinical trial done in similar patient population (study 016)**

Darmstadt, May 7, 2009 – Merck KGaA and its partner Newron Pharmaceuticals SpA (SWX: NWRN) announced today the initiation of the SETTLE[1] study. This study will evaluate the efficacy and safety of a dose range of safinamide (50-100 mg once daily) as add-on therapy to a stable dose of levodopa, in mid- to late-stage Parkinson's disease patients with motor fluctuations compared to placebo.

The SETTLE study is one of the Phase III trials that constitute the clinical development program designed to support an application for marketing authorization as discussed with regulatory authorities. SETTLE is a six-month (24-week), randomized, double-blind, international Phase III trial. The trial will involve more than 450 patients with mid- to late-stage idiopathic Parkinson's disease (more than five years of disease duration) treated with a stable dose of levodopa for at least four weeks who have motor fluctuations with more than one and a half hours of "OFF"[2] time during the day. Additionally, patients may be receiving concomitant treatment with stable doses of a dopamine agonist, a COMT inhibitor, an anticholinergic and/or amantadine. After a four-week levodopa dosage stabilization phase, study participants will be randomized in one of the two arms of the trial (1:1) to receive either safinamide or matching placebo tablets, as adjunctive treatment to levodopa therapy.

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News Release

The primary endpoint of the trial is the change in daily “ON” time, as assessed by the recordings of diary cards maintained by patients after prior training, from baseline to week 24. Secondary endpoints include changes in measures of activities of daily living, global clinical status and health-related quality of life.

“Managing motor fluctuations and reducing the time during which anti-Parkinson drugs are not working and symptoms return, the so-called ‘OFF’ times, are still unmet medical needs for patients with mid- to late-stage Parkinson’s disease,” said Bernhard Kirschbaum, head of global Research and Development of the Merck Serono division. “After the encouraging results we obtained for study 016, we aim to confirm the efficacy of safinamide as an add-on therapy to levodopa in a flexible dosing regimen.”

Additional results from the analyses of study 016

Additional results from the analyses of study 016 (for which top-line data were reported previously, showing that safinamide significantly improved motor function in patients with advanced Parkinson’s disease) are now available and will be shared in detail at the Movement Disorder Society’s 13th International Congress in Paris in June: safinamide was shown to have a significant benefit on motor fluctuations (increase in “ON” time, decrease in “OFF” time) at both 50 and 100 mg doses without any increase in “ON” time with troublesome dyskinesias. A statistically significant reduction in the UPDRS[3] part IV scale was seen at both doses. The 100 mg dose was also shown to improve depressive symptoms in this non-depressed patient population as measured by the GRID-HAMD[4] scale total score, and to result in an improvement of the emotional well-being as measured by a subscale of the PDQ-39[5].

“The additional results from study 016 are encouraging and suggest that safinamide could have benefits beyond motor symptoms, motor fluctuations and activities of daily living. The increase in ‘ON’ time without any increase in troublesome dyskinesia is critical for patients and physicians,” said Ravi Anand, Newron’s Chief Medical Officer. “Depressive symptoms are important aspects of PD and the ability of safinamide to improve some of these symptoms in addition to the other benefits is promising and warrants further studying safinamide as a potential new treatment option.”

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Merck Serono has exclusive worldwide rights to develop, manufacture and commercialize safinamide in Parkinson's disease, Alzheimer's disease and other therapeutic applications, as per the agreement signed with Newron in 2006.

Footnotes

[1] SETTLE - **S**afinamid**E** **T**reatment as add-on **T**o **LE**vodopa in idiopathic Parkinson's disease with motor fluctuations

[2] "OFF" time refers to the times when people with Parkinson's disease have a decrease in the ability to move (hypomobility) and other symptoms that cause difficulty rising from a chair, speaking, walking or performing their usual activities. "OFF" episodes occur because the person's dose of levodopa has worn off or suddenly stopped providing benefit.

[3] The Unified Parkinson's Disease Rating Scale (UPDRS) is one of the most widely used rating scales used to follow the course of Parkinson's disease. It is made up of 44 items, scored from 0 to 4, to establish individual patients' mental status, activities of daily living, motor function and complications of therapy. These are evaluated by interview and clinical observation. Part IV rates complications of therapy. This includes several questions about the duration and the severity of dyskinesias and motor fluctuations.

[4] The GRID-HAMD is an improved version of the Hamilton Rating Scale for Depression (HAMD), the de facto international gold standard for the assessment of depression. It was developed to provide standardized explicit scoring conventions and a structured interview guide for administration and scoring of the HAMD.

[5] The Parkinson's Disease Questionnaire (PDQ-39) is the most widely used Parkinson's-disease-specific measure of health status. It contains thirty-nine questions, covering eight aspects of quality of life. The instrument was developed on the basis of interviews with people diagnosed with the disease. It has been widely validated, and translated into over fifty languages.

About safinamide

Safinamide, an alpha-aminoamide derivative that is orally formulated, is currently being developed by Merck Serono and Newron as an add-on treatment for patients with Parkinson's disease. Safinamide is believed to have a novel dual mechanism of action based on the enhancement of the dopaminergic function (through reversible inhibition of monoamine oxidase-B [MAO-B] and dopamine uptake) and reduction of glutamatergic activity by inhibiting glutamate release.

News Release

About Parkinson’s disease

Parkinson's disease is a degenerative disorder of the central nervous system that often impairs the patient’s motor skills and speech. Parkinson's disease belongs to a group of conditions called movement disorders. It is characterized by muscle rigidity, tremor, a slowing of physical movement (bradykinesia) and, in extreme cases, a loss of physical movement (akinesia). The primary symptoms are the results of decreased stimulation of the motor cortex by the basal ganglia, normally caused by the insufficient formation and action of dopamine, which is produced in the dopaminergic neurons of the brain. Secondary symptoms may include high-level cognitive dysfunction and subtle language problems. Parkinson’s disease is both chronic and progressive. It is estimated that more than 3 million people in the industrialized countries suffer from Parkinson’s disease.

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