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Eisai Co., Ltd.

EISAI SUBMITS NEW DRUG APPLICATION FOR MECOBALAMIN ULTRA-HIGH DOSE PREPARATION AS TREATMENT FOR AMYOTROPHIC LATERAL SCLEROSIS IN JAPAN

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") announced today that it has submitted a new drug application for mecobalamin (development code: E0302) as a treatment for amyotrophic lateral sclerosis (ALS) in Japan.

ALS is an intractable, progressive, neurodegenerative disease that causes severe muscle atrophy and weakness in the muscles. Since there is only one medicine approved for suppressing the progression of ALS in Japan, there is a significant unmet medical need for new treatment options.

Mecobalamin is approved and marketed as a treatment for peripheral neuropathies and other conditions. Since the 1990s, clinical research has been carried out on the effect of ultra-high dose mecobalamin in ALS by a study group on neurodegenerative disease, funded through the Ministry of Health, Labour and Welfare's Specified Disease Treatment Research Program. The results of this research suggested efficacy for ultra-high dose mecobalamin in ALS. In light of these findings, Eisai began clinical trials on ultra-high dose mecobalamin in 2004 and a Phase II/III clinical study (Study 761) was initiated in 2006. Study 761 was conducted as a double-blind, placebo-controlled study with the primary endpoints being time to event (use of ventilation, or death) and change in total score of the Japanese version of the ALS Functional Rating Scale-Revised (ALSFRS-R).

Although the results of Study 761 showed a trend for mecobalamin (both 25 mg and 50 mg groups) of a longer time to event and a trend in slowing the decline in ALSFRS-R scores when compared to placebo, a statistically significant difference could not be confirmed. On the other hand, the results of an additional analysis showed that ultra-high dose mecobalamin extends time to event and slows decline in ALSFRS-R scores in patients who commenced treatment within 12 months of ALS onset. Furthermore, ultra-high dose mecobalamin demonstrated a similar effect in patients with lower serum lipid levels. Meanwhile, the incidence of side effects was similar between the groups.

Considering ALS is an intractable, progressive disease with a poor prognosis that poses considerable impediments to daily life and greatly requires new treatment options, Eisai believes the agent can be useful in clinical settings for ALS given these results, and therefore has submitted an application for approval.

The results of Study 761 were presented at the 67th Annual Meeting of the American Academy of Neurology[1] held in Washington D.C, the United States from April 18 to 25, 2015, and was presented at the 56th Annual Meeting of the Japanese Society of Neurology[2] held in Niigata, Japan from May 20 to May 23, 2015.

Eisai considers neurology a therapeutic area of focus and is committed to new drug development in this field. Furthermore, as a maker and discoverer of new drugs, Eisai is carrying out various initiatives including research into uncovering new indications and value for existing drugs such as mecobalamin in order to fulfill unmet medical needs in neurology and further contribute to increasing the benefit for patients and their families.

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[Notes to editors]

1. About Amyotrophic Lateral Sclerosis (ALS)

ALS is an intractable, progressive, neurodegenerative disease that results in severe muscle atrophy and weakness in the muscles due to motor neuron dysfunction. As the main cause of death is respiratory failure due to paralysis of the respiratory muscles, without the use of an artificial respirator, death occurs within approximately 3 and 6 years from the onset of the disease. In Japan, the incidence rate of ALS ranges between 1.1 to 2.5 per 100,000 people, and onset most often occurs between the ages of 50 to 60. According to the number of patients issued a Certificate of the Recipient of Specified Disease Treatment, there were 9,240 patients with ALS in Japan in 2013. Currently, there is no curative treatment established for ALS, and since there is only one medicine approved for suppressing the progression of ALS in Japan, this is a disease with significant unmet medical needs.

2. About Mecobalamin

Mecobalamin (development code: E0302) is approved and marketed as Methycobal, a 500 μg injection of mecobalamin indicated for the treatment of peripheral neuropathies and megaloblastic anemia caused by vitamin B_{12} deficiency. Methycobal is also approved as a tablet formulation as well as a fine granule formulation indicated for the treatment of peripheral neuropathies. While the mechanism of action of mecobalamin in ALS is not known, it has been suggested in non-clinical research that mecobalamin may have efficacy through a neuroprotective effect and regeneration of nerve axons. Since the 1990s, clinical research has been carried out on ultra-high dose mecobalamin in ALS by a study group on neurodegenerative disease, funded through the Ministry of Health, Labour and Welfare's Specified Disease Treatment Research Program. Short- and long-term trials of intramuscular injection of mecobalamin at 25 mg and 50 mg per day, which is respectively 50 and 100 times the approved dosage of Methycobal, suggested that ultra-high dose mecobalamin could have a clinical effect in ALS, and therefore Eisai has been promoting clinical studies since 2004. Mecobalamin is highly sensitive to light and therefore Eisai has refined its formulation to specifically develop a new freeze-dried injectable preparation that can be administered at a high dose and is easy to use.

3. About the Phase II/III Clinical Study (Study 761) Conducted in Japan

1) Outline of study:

Title of Study	A Phase II/III Study in Patients with Amyotrophic Lateral Sclerosis (ALS)
Study Design	Multicenter, randomized, placebo-controlled, parallel-group, double-blind, comparative study
Treatment Dosage and Administration	Intramuscular injection of mecobalamin 25 mg, 50 mg or placebo twice a week for 182 weeks
Number of Subjects	370 patients (25 mg group: 124 patients, 50 mg group: 123 patients, placebo: 123 patients)

Objectives	Primary Endpoints: ● Time to event (full-time use of non-invasive ventilation, use of invasive ventilation, or death) ● Change in the total ALSFRS-R score from the time of completion of the observation period to the final time point

2) Results of study:

Overall Results	Placebo group	25 mg group	50 mg group
Time to event (median)	880 days	1147 days	954 days
Change in total ALSFRS-R score (median)	-24.0	-22.0	-21.0
Subgroup of patients who enrolled within 12 months of ALS onset			
Time to event (median)	570 days	1087 days	1197 days
Change in total ALSFRS-R score (median)	-26.5	-26.5	-22.0
Subgroup of patients with lower serum lipid (less than 130 mg/dL)			
Time to event (median)	767 days	1099 days	911 days
Change in total ALSFRS-R score (median)	-26.0	-23.1	-19.0
Regarding safety, the incidence of side effects was similar between the three treatment groups (placebo: 4.1%, 25 mg group: 7.3%, 50 mg group: 5.7%), and the only side effects to occur in two or more patients in the entire E0302 group (247 cases) were increased white blood cell count (3 cases) and abnormal hepatic function (2 cases).			

[1] R Kaji, et al. “Ultra-high dose methylcobalamin (E0302) prolongs survival of ALS: Report of 7 years’ randomised double-blind, Phase III clinical trial.” Abstract. *American Academy of Neurology Meeting* 2015; P7.060.

[2] T Imai, et al. “A Phase II/III study of ultra-high dose mecobalamin in amyotrophic lateral sclerosis (ALS) patients.” Abstract. *Japanese Society of Neurology Meeting* 2015; B-03-5.