No. 19-53

July 18, 2019
Eisai Co., Ltd.

EISAI PRESENTS NONCLINICAL RESEARCH RESULTS OF ELENBECESTAT OF WITHOUT SIGNIFICANT EFFECTS ON SYNAPTIC FUNCTION IN BRAIN BY SPINAL DENSITIY EVALUATION AT EFFECTIVE DOSE TO DECREASE AMYLOID BETA LEVEL IN CEREBROSPINAL FLUID AT ALZHEIMER'S ASSOCIATION INTERNATIONAL CONFERENCE (AAIC) 2019

Eisai Co.,Ltd.(Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") announced its latest data of nonclinical research which examined the effect to the synaptic function in the brain by spinal densities[*1] in regard to oral BACE (beta-site amyloid precursor protein cleaving enzyme) inhibitor elenbecestat[*2] were presented at the Alzheimer's Association International Conference (AAIC) held in Los Angeles, California, United States, from July 14 to 18, 2019 (Poster Presentation No.: P2-064).

BACE is a key enzyme in the production of Aβ peptides, which inhibits β site of amyloid precursor protein (APP). BACE inhibitor may decrease the formation of toxic Aβ peptide aggregates in the brain, thereby thought to exert disease modifying effects and may have potential to slow the disease progression. On the other hand, in addition to APP, the other substrates with physiological role in synapse formation and function are known as a substance (substrate) changed by BACE. At this time, the effect to Aβ level in CSF and synaptic damage were examined after 4 weeks of administration of BACE inhibitors using novel preclinical model mouse. For the examination compounds, elenbecestat (in-house discovery), verubecestat, and lanabecestat were used. In addition, the effect to the synapse formation and function were evaluated by setting the numerous spinal densities on dendrite of brain cortex (number of spines per 10 μm of dendrites) and mitochondrial function (mitochondrial oxygen efficiency) of hippocampal synaptosomes (isolated presynaptic terminal) as an index. It is believed that decreases in spinal densities and mitochondrial function damage the synaptic function and deteriorate the cognitive function.
The dose of each BASE inhibitor was adjusted so as to be equivalent to the dose for clinical study in accordance with exploratory data of lowering effect of Aβ in mouse CSF.

As a result, elenbecestat did not show significant effects on spinal density and mitochondrial function at dose of 3, 10mg/kg with significant decline of Aβ level in CSF ($p<0.001$).
As for the verubecestat, significant decline of spinal density was shown at the dose of 10, 30mg/kg ($p<0.05$) with significant decline of Aβ level in CSF ($p<0.001$).
Also, as for lanabecestat, significant decline of spinal density was shown at the dose of 30, 100mg/kg ($p<0.05$) with the significant decline of Aβ level in CSF ($p<0.001$), as well as the significant decline of mitochondrial function was shown at the dose of 100mg/kg ($p<0.05$).
These results suggest that elenbecestat does not affect the synaptic function in the brain with an effective

dose to decline the Aβ level in CSF.

Eisai aims to realize the prevention and cure of dementia through a multi-dimensional and holistic approach with a foundation of over 35 years of experience of drug discovery activities in the area of Alzheimer's disease and dementia. Eisai strives to create innovative medicines as soon as possible to further contribute to addressing the unmet medical needs of, as well as increasing the benefits provided to, patients and their families.

*1 There are more than 100 billion nerve cells (neurons) in the brain, the information is transmitted by forming each bond, called a synapse. This synapse is formed between the axon terminal (presynaptic neuron) sending information and the neuron dendrite (postsynaptic neuron) receiving information. Many supraspinal structures on the neuron dendrite which forms synapse is called spine.

*2 Elenbecestat, is being jointly developed by Eisai and Biogen Inc. (Headquarters: Cambridge, Massachusetts, United States, "Biogen").

Media Inquiries:
Public Relations Department,
Eisai Co., Ltd.
+81-(0)3-3817-5120

[Notes to editors]

1. About Elenbecestat (generic name, development code: E2609)

Discovered by Eisai, elenbecestat is an investigational next-generation oral candidate for the treatment of Alzheimer's disease (AD) that inhibits BACE (beta amyloid cleaving enzyme). By inhibiting BACE, a key enzyme in the production of Aβ peptides, elenbecestat reduces Aβ production, and by reducing amyloid plaque formations in the brain, exerts disease modifying effects of potentially slowing the progression of AD. Currently, two global Phase III clinical studies (MISSION AD1/2) of elenbecestat in early AD including mild cognitive impairment (MCI) due to AD or the mild AD are underway. In addition, the U.S. Food and Drug Administration (FDA) has granted Fast Track designation for the development of elenbecestat, a process allowing priority reviews by the FDA for drugs deemed as having potential to treat serious conditions and tackle key unmet medical needs.

2. About joint development agreement between Eisai and Biogen for Alzheimer's disease

Eisai and Biogen are collaborating on the joint development and commercialization of Alzheimer's disease treatments. Eisai serves as the lead in the co-development of elenbecestat, a BACE inhibitor, and BAN2401, an anti-amyloid beta (Aβ) protofibril antibody, and the companies plan to pursue marketing authorizations for the two compounds worldwide. If approved, the companies will also co-promote the products in major markets, such as the United States, the European Union and Japan. As to BAN2401 and elenbecestat, both companies will equally split overall costs, including research and development expenses. Eisai will book all sales for elenbecestat and BAN2401 following marketing approval and launch, and profits will be equally shared between the companies.