No. 20-62

October 6, 2020
Eisai Co., Ltd.

INDUSTRY-ACADEMIA-GOVERNMENT JOINT DEVELOPMENT AGREEMENT AIMING FOR DRUG DISCOVERY FOR COVID-19 UTILIZING ERITORAN AND E6011 CONCLUDED, NON-CLINICAL RESEARCH ACTIVITIES COMMENCE

Adopted for the public call for AMED
"Development of therapeutic drugs for the novel coronavirus infection (COVID-19)"

Eisai Co., Ltd. (Headquarters: Tokyo, CEO: Haruo Naito, "Eisai") announced today that it has entered into a joint research agreement with four research organizations (KAN Research Institute, National Center for Global Health and Medicine, Nagasaki University, and Yokohama City University) in Japan concerning the "Development of Therapeutics to Prevent the Aggravation of the Novel Coronavirus Infectious Disease (COVID-19)"(Grant Number: 20fk0108255), which is a research project with Eisai as the representative research organization. This joint research project "Development of Therapeutics for Novel Coronavirus Infectious Disease (COVID-19)" was adopted for the second public call by the Japan Agency for Medical Research and Development (AMED) as part of its operation for promotion of the research and development of innovative treatments for emerging and re-emerging infectious diseases in fiscal year 2020.

In patients with COVID-19 due to the SARS-CoV-2 infection, severe cases such as acute respiratory distress syndrome (ARDS) and subsequent multiple organ failure have been reported. The involvement of the formation and exacerbation of vasculopathy as well as the cytokine storm* in the process of aggravation are assumed. However, at this time, the mechanism of aggravation based on the SARS-CoV-2 infection is not fully understood.

In this collaborative research, a non-clinical animal model of SARS-CoV-2 infection will be constructed. Additionally, TLR (Toll-Like Receptor) 4 antagonist eritoran, discovered by Eisai, and an anti-FKN (fractalkine) antibody E6011, discovered by Eisai's research subsidiary KAN Research Institute, will be evaluated. In addition, this project will promote biomarker research using clinical samples derived from SARS-CoV-2 infected patients. This collaborative research, aims to elucidate the mechanism of COVID-19 aggravation based on SARS-CoV-2 infection and to create drugs that prevent the aggravation of COVID-19.

In the fight against the expansion of COVID-19, based on the *human health care* (*hhc*) philosophy, Eisai will continue the development of therapeutics, stable supply of pharmaceuticals, and support activities in each country.

* Cytokine storm: a state of immune runaway, in which the production of cytokines, which play a role in activating the immune response, becomes uncontrollable and cytokines are released in large amounts.

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

[Notes to editors]

1. About TLR4 and Eritoran (E5564)

TLR(Toll-Like Receptor)s are receptors of the innate immune system, and recognize the specific molecular structure of pathogens. It is considered that TLR initiated activation of the innate immune system plays a critical role in eliminating pathogens, causing an inflammatory reaction or an antiviral response. TLR4, one of the TLRs which constitute a family of various receptors, is activated by endotoxins such as lipopolysaccharide released from bacteria. Eritoran is Eisai's in-house discovered and developed TLR4 antagonist created by natural product organic synthesis technology. It is a structural analogue of Lipid A, which is an active pharmacophore of endotoxins. It has been previously observed to have well-tolerated safety profile in 14 clinical studies including a large Phase III randomized trial in severe sepsis. Eritoran has been shown to have the effects of suppressing cytokine production and improving systemic condition in a mouse influenza virus infection model[1]. It is expected to suppress inflammation and aggravation caused by COVID-19[2,3] by inhibiting the activation of TLR4, which is the most upstream of various cytokine gene expression signaling that causes the cytokine-storm.

Eritoran has been selected as the therapeutic drug candidate in the international trial REMAP-COVID for hospitalized patients with moderate COVID-19.

2. About FKN and E6011

FKN (fractalkine) is a chemokine that has dual functions of cell migration regulation and cell adhesion, which is induced in vascular endothelial cells during inflammation. The FKN receptor (CX3CR1) is mostly expressed in monocytes, macrophages and killer lymphocytes selectively and plays a key role in efficient collection of cells to the inflamed site. It has been suggested that the FKN-CX3CR1 system relates to various chronic inflammatory diseases including inflammatory bowel disease, rheumatoid arthritis, liver disease, central nervous system disease, arteriosclerosis, dermatosis and others. E6011 is the world's first humanized anti-FKN monoclonal antibody developed by Eisai's research subsidiary KAN Research Institute, Inc., and has a novel action mechanism inhibiting cell invasion by neutralizing activity of fractalkine (FKN), unlike existing cytokine treatments. Currently, a phase II clinical trial in patients with Crohn's disease is being conducted by Eisai's subsidiary for gastrointestinal diseases business EA pharma Co., Ltd. E6011 inhibits tight binding of CD16+ monocytes (cell populations with high CX3CR1 expression), which are important for local inflammatory response, to vascular endothelial cells[4]. E6011 therefore is expected to suppress the initiation and exacerbation of vasculopathy in COVID-19[5].

[1] KA Shirey et al., *Nature*. **2013** May 23; 497(7450):498-502
[2] P Mehta et al., *The Lancet* **2020**; 395: 1033-1034
[3] C Huang et al., *The Lancet* **2020**; 395: 497-506
[4] Y Kuboi et al., *Int Immunol.* **2019** Apr 26;31(5):357
[5] H Li et al., *The Lancet* **2020**; 395: 1517-1520