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SBI Pharmaceuticals Co., Ltd.
University of Oxford

Start of Phase II Clinical Trial using 5-ALA by the University of Oxford and SBI Pharmaceuticals

SBI Pharmaceuticals Co., Ltd., (Head office: Minato-ku, Tokyo; Representative Director & President: Yoshitaka Kitao; “SBI Pharmaceuticals”), a subsidiary of SBI Holdings, Inc., engaged in research and development of pharmaceuticals, health foods and cosmetics using 5-aminolevulinic acid (“5-ALA”)*1 and the University of Oxford in the United Kingdom hereby announce that the University of Oxford has initiated a dose-finding Phase II clinical trial [Pre-operative 5-Aminolevulinic acid to activate haem oxygenase to improve outcomes in cardiac surgery: A dose finding study (Eudra CT Number: TALEN - 2020-001135-27)] (the "Clinical Trial") to develop a cardioprotective agent combining 5-ALA hydrochloride and Sodium ferrous citrate (iron) for the mitigation of ischemia-reperfusion injury in response to cardiac surgery under cardiopulmonary bypass (CPB) under the terms of the clinical trial sponsorship agreement between the two parties. The first patient has been dosed at the John Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust.

Recently, the University of Oxford has obtained the approvals of the Medicines and Healthcare products Regulatory Agency (MHRA) and the Health Research Authority (HRA) to perform the clinical trial in the United Kingdom. This investigator-initiated clinical trial is performed by a research team based in Experimental Therapeutics at the Radcliffe Department of Medicine, University of Oxford and Cardiothoracic Surgical and Critical Care Investigators at the Oxford Heart Centre, with financial support and the investigated drug provided by SBI Pharmaceuticals.

Cardiac surgery such as coronary artery bypass surgery with cardioplegic arrest and CPB causes an ischemia-reperfusion injury (*2) in the heart and stimulation of a systemic inflammatory response. These can result in complications such as cardiac arrhythmia, myocardial stunning, low cardiac output state/cardiogenic shock, perioperative myocardial infarction, prolonged hospital stay, and extracardiac organ

dysfunction such as acute kidney injury or lung injury. In pre-clinical models, a combination of 5-ALA hydrochloride and ferrous iron administered before ischemia-reperfusion injury demonstrated a protective effect through the function of an enzyme (Heme oxygenase-1 *3) induced by 5-ALA hydrochloride and iron (*4). Based on this and the cytoprotective actions of heme oxygenase-1, administration of 5-ALA hydrochloride and iron before cardiac surgery has the potential to improve outcomes through induction of heme oxygenase-1 in myocardial cells and potentially in other tissues (e.g. kidney) to ameliorate cardiac ischemia-reperfusion injury attendant upon cardioplegic arrest and systemic inflammation promoted by CPB.

SBI Pharmaceuticals will continue to pursue various potential applications of 5-ALA, and focus on research and development to provide pharmaceuticals that satisfy the unmet medical needs of as many people as possible around the world.

(*1) 5-aminolevulinic acid (5-ALA)
An amino acid produced in mitochondria. It is an important substance that serves as a functional molecule related to energy production in the form of heme and cytochromes, and its productivity is known to decrease with age. 5-ALA is contained in food such as shochu lees, red wine and Asian ginseng. It is also known as a material forming chloroplasts in plants.

(*2) Cardiac ischemia-reperfusion injury
The tissue damage caused at reperfusion (when blood supply returns to the tissue) after a period of ischemia (shortage of oxygen).

(*3) Heme oxygenase-1
An enzyme that is induced by heme produced from 5-ALA and has the function of degradation of heme. Heme oxygenase-1 has been reported to have various functions such as anti-inflammation in vivo.

(*4) Jiangang Hou. et al. 5-Aminolevulinic acid combined with ferrous iron induces carbon monoxide generation in mouse kidneys and protects from renal ischemia-reperfusion injury. Am J Physiol Renal Physiol. 2013 Oct 15;305(8):F1149-57. doi: 10.1152/ajprenal.00275.2013.

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