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# Use of 3D bioreactor-based manufacturing method produced product for ARDS clinical trial (HLCM051)

HEALIOS K.K. ("Healios") is developing a treatment for patients with pneumonia induced ARDS (trial name: ONE BRIDGE) using HLCM051, a somatic stem cell regenerative medicine. As announced on March 2, 2023, we have disclosed the outline of the trial necessary for data augmentation required to advance the product to approval in Japan. In addition, we are pleased to announce that in preparation for the start of this study, we have also conducted a regenerative medicine product quality consultation with the Pharmaceuticals and Medical Devices Agency (PMDA) to receive advice on the investigational product to be used in this study, and have reached an agreement to use investigational product manufactured by our 3D bioreactor-based method.

The use of a 3D bioreactor-based method enables efficient and stable mass production of cells, and therefore allows for the supply of product in large quantities in a stable manner for commercial production after the launch of the product, as compared to the conventional 2D method utilized in prior studies. Importantly, the 3D method also promises cost efficiencies and anticipated superior economics.

Commenting on the agreement, Tadahisa Kagimoto, MD, Chairman and CEO of Healios, said:

"The challenge to date in cellular medicine has been instability in terms of both quality and quantity. Based on this agreement with the regulatory authorities, HLCM051 could be the first 3D bioreactor-approved cell product in the world. This will solve a major bottleneck in regenerative medicine and enable the delivery of stable products in large quantities to patients around the world who have no treatment options, and will lead the way to full-fledged commercialization of the technology. We believe that regenerative medicine is entering a new phase of industrialization. We have the requisite manufacturing license and know how, and will establish mass production that meets the regulations of authorities around the world. As a pioneer in this industry, we have been working to establish a de facto standard, and with our ARDS program, we will leverage our know-how and accelerate the industrialization of

regenerative medicine."

Note: At the time of publication, there are no approved allogeneic cell products that have been publicly announced to be manufactured in 3D culture (according to our own research).

This study will start after the submission of the future clinical trial plan notification and the confirmation of the official study protocol.

HLCM051 has been designated as an orphan regenerative medicine product for use in the treatment of ARDS by the Ministry of Health, Labor and Welfare in November 2019.

There is no confirmed impact of this matter on our business performance for the fiscal year ending December 31, 2023 at this time. We will promptly announce any matters that should be disclosed in the future.

*ARDS
ARDS is a general term for the symptoms of acute respiratory failure suddenly occurring in seriously ill patients. The major causes are severe pneumonia, septicemia, trauma etc. Inflammatory cells are activated in response to these diseases or injuries, causing damage to the tissue of the lungs. As a result, water accumulates in the lungs, leading to acute respiratory failure. According to the ARDS treatment guideline 2016, the mortality rate is approximately 30 to 58%. The number of patients in Japan is estimated to be approximately 28,000 (Healios estimate based on epidemiological data on incidence and population statistics). Artificial respiration using an endotracheal tube or mask is used to treat respiratory failure in an intensive care unit.