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Submission of ARDS Clinical Trial Notification in Japan

HEALIOS K.K. and its wholly owned subsidiary ProcellCure Inc. (together "Healios") are developing a treatment for patients with pneumonia induced ARDS[*1] (trial name: ONE BRIDGE) using HLCM051[*2], a somatic stem cell regenerative medicine product. As announced on March 2, 2023, we have been preparing to conduct an additional clinical trial in Japan to reinforce the efficacy and safety data in advance of seeking approval in Japan.

To promote the development of HLCM051 for ARDS, ProcellCure has submitted a clinical trial notification for this study to the Pharmaceuticals and Medical Devices Agency (PMDA). The study will be initiated after a 14-day review period following submission of the clinical trial notification to the PMDA.

Tadahisa Kagimoto, MD, Chairman and CEO of Healios, made the following comment: "We are happy that we have reached the point where we can start the final trial for ARDS, a very serious medical need. All of us involved will continue to work steadily to obtain approval as soon as possible."

There is no confirmed impact of this matter on our business performance for the fiscal year ending December 31, 2024 at this time. We will promptly announce any matters that should be disclosed in the future.

Business framework for the development and marketing of HLCM051 for ARDS

As announced in December 27, 2023, Healios, ProcellCure, and Nobelpharma K.K. ("Nobelpharma") entered into a letter of intent for a development and marketing alliance for HLCM051 for ARDS in Japan and are currently discussing detailed terms and conditions for the development and marketing of the drug in Japan. Healios will receive an upfront payment from Nobelpharma under the agreement, which will be finalized and executed in the future. Thereafter, Healios will receive a milestone payment upon approval. After approval, Healios will supply the final manufactured product to Nobelpharma, who will in turn distribute the product to the market, and Healios anticipates that it will generate meaningful net margins from such product supply. In addition to the above, Healios expects to receive sales milestone payments of approximately 25 billion yen based on our projected sales as of the date of the basic agreement, depending on accumulated sales.

In addition to marketing the product, Nobelpharma has agreed to provide support services for the development and regulatory submission of the agreed content in the future. With the support of Nobelpharma's extensive experience and capabilities in the development and marketing of orphan drugs in Japan, for which Nobelpharma has obtained 16 drug approvals, Healios will prepare for the approval of HLCM051 for the treatment of ARDS.

In Japan, ARDS is an orphan disease with a limited number of patients (28,000 per year), while in the U.S. the number is estimated to be about 10 times as high (262,000 per year) and in China more than 20 times as high (670,000 per year). Healios has acquired the rights to develop ARDS globally and is currently preparing for an overseas clinical trial, including in the U.S. Healios will accelerate the commercialization of HLCM051 and seek to generate value through multiple partnership and alliance opportunities.

*1 Acute Respiratory Distress Syndrome (ARDS) is a general term for respiratory failure that occurs suddenly in a variety of critically ill patients. Although there are many causes of ARDS, approximately one-third of ARDS cases are caused by pneumonia, and it has been confirmed that ARDS also occurs in critically ill patients with COVID-19. There is currently no approved drug therapy that can directly improve the prognosis of patients with ARDS, and respiratory failure is treated with mechanical ventilation. The mortality rate after the onset of ARDS is 30~58%[*a], and there is a need for new therapies that can improve the prognosis of patients with ARDS. Currently, the number of patients in Japan is estimated to be approximately 28,000[*b] per year, and ARDS is designated as a rare disease. However, it is estimated that between 213,000 and 262,000[*c] patients in the United States, 133,000[*d] patients in Europe, 670,000 patients in China[*e] and more than 1.1 million patients worldwide are affected.
(Source)
*a ARDS Diagnostic Guidelines 2016
*b Healios Estimates Based on the Incidence Rate of Epidemiological Data and the Total Population of Japan by Demography
*c Diamond M et al. 2023 Feb 6. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan–. PMID: Estimates for our company based on 28613773 Data and US Population Based on the Ministry of Foreign Affairs Basic Data
*d Community Research and Development Information Service (CORDIS) 2020 7-9.
*e song-et-al-2014-acute-respiratory-distress-syndrome-emergingresearch-in-china

*2 HLCM051 is a somatic stem cell regenerative medicine product. Healios added it to its pipeline by signing an exclusive licensing agreement with the United States-based Athersys, Inc. (“Athersys”) in January 2016, whereby Healios acquired rights to develop and distribute Athersys’ proprietary stem cell product MultiStem® to treat ischemic stroke in Japan. Further, in June 2018, Healios and Athersys expanded their collaboration broadly, and as part of this expansion Healios acquired the development and distribution licenses to use MultiStem® to treat ARDS in Japan. In August 2021, an agreement was signed to expand comprehensive collaboration for commercialization, and in August 2022, licenses were obtained for the manufacture of therapeutics for both diseases, with manufacturing technology also

subsequently transferred. In October 2023, an agreement was reached to expand the above license for ARDS to cover the entire world, which is expected to significantly increase the number of eligible patients. HLCM051 was designated by the Minister of Health, Labour and Welfare as a regenerative medicine product for rare diseases for ARDS in November 2019. Two trials have been conducted with HLCM051 in ARDS, the ONE-BRIDGE study in Japan and the MUST-ARDS study in the US and UK, both of which have provided consistent and promising efficacy data.

About Healios:
Healios is Japan's leading clinical stage biotechnology company harnessing the potential of stem cells for regenerative medicine. It aims to offer new therapies for patients suffering from diseases without effective treatment options. Healios is a pioneer in the development of regenerative medicines in Japan, where it has established a proprietary, gene-edited "universal donor" induced pluripotent stem cell (iPSC) line to develop next generation regenerative treatments in immuno-oncology, ophthalmology, liver diseases, and other areas of severe unmet medical need. Healios' lead iPSC-derived cell therapy candidate, HLCN061, is a next generation NK cell treatment for solid tumors that has been functionally enhanced through gene editing. Its near-term pipeline includes the somatic stem cell product HLCM051, which has been evaluated in Japan in Phase 2/3 and Phase 2 trials in ischemic stroke and acute respiratory distress syndrome (ARDS), respectively. Healios was established in 2011 and has been listed on the Tokyo Stock Exchange since 2015 (TSE Growth: 4593).
https://www.healios.co.jp/en