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Submission of Clinical Trial Notification in Japan for the Global Phase 3 REVIVE-ARDS Study

HEALIOS K.K. announces that we have submitted a clinical trial plan notification to the Pharmaceuticals and Medical Devices Agency (PMDA) for a clinical trial to be conducted in Japan as part of the Global Phase 3 trial (REVIVE-ARDS*[1]) for HLCM051 (invimestrocel) for the treatment of ARDS*[2] (Acute Respiratory Distress Syndrome). Following a 14-day review period after submitting the clinical trial plan notification to PMDA, we plan to commence this trial.

Outline of REVIVE-ARDS Study

Conditions	Placebo-Controlled, Double-Blind, Randomized (IP administered within 48 hours of meeting ARDS diagnosis criteria)
Subjects	Patients with pneumonia-induced ARDS
Region	US, Japan, APAC, EU
Enrollment	Up to 550 (HLCM051 [n=275], placebo [n=275]) Interim analyses will be conducted at the 300-case and 400-case milestones. If IP demonstrates statistically significant efficacy at any interim analysis, the trial will be terminated early. *Number of enrolled patients per region undetermined
Primary Endpoint	VFD (the number of days out of 28 during which a ventilator was not used for the patient)
Secondary Endpoint (examples)	Mortality (90 days after administration)

As announced in "Completion of Formal Regulatory Consultation for ARDS and Agreement on the Global Phase 3 Trial (REVIVE-ARDS Study)"(April 23, 2025) the PMDA has agreed that the REVIVE-ARDS study can enroll Japanese subjects as part of the post-approval verification studies for conditional and time-limited approval of HLCM051 (invimestrocel) in Japan. The REVIVE-ARDS study plans to initiate patient enrollment in Japan first, followed by enrollment globally in parallel and thereafter, primarily in the United States. As part of this global trial, we have now submitted the clinical trial notification in Japan. We plan to announce updates on the progress of the REVIVE-ARDS study as appropriate.

As announced in "Development and Application Policy for HLCM051 (ARDS and Ischemic Stroke Treatment)" (December 9, 2025), we are prioritizing the development of HLCM051 (invimestrocel), our somatic stem cell regenerative medicine, as a treatment for ARDS. In Japan, we are commencing patient enrollment domestically as part of the REVIVE-ARDS study and will continue preparations for submitting an application for conditional and time-limited approval, obtaining approval, and launching product sales.

As announced in "Decision to Apply for Conditional and Time-Limited Approval for ARDS in Japan and ARDS Development Strategy Update" (October 2, 2024), in Japan, following discussions with the PMDA, we have decided to submit an application for conditional and time-limited approval. This application is based on the positive results from the Phase 2 trial already completed in Japan (ONE-BRIDGE Study*[3]) and the Phase 2 trial conducted in the US and UK (MUST-ARDS trial), with the REVIVE-ARDS trial to be conducted as a confirmatory trial.

Future Outlook

This matter has no impact on our consolidated financial results of the fiscal year ending December 31, 2026. We will promptly announce any matters that should be disclosed in the future.

*1 REVIVE-ARDS

REVIVE-ARDS is a pivotal, global Phase 3 study to demonstrate and confirm the efficacy and safety of HLCM051 (invimestrocel) for ARDS caused by pneumonia, primarily in the United States. We held an End-of-Phase 2 consultation with the FDA (Food and Drug Administration) in September, 2024, as for the study design, we agreed with the FDA on the use of a primary endpoint based on VFD (Ventilator Free Days: the number of days a patient does not require mechanical ventilation out of 28 days post administration in REVIVE-ARDS study, which is consistent with that utilized in the ONE-BRIDGE study previously completed in Japan). Interim analyses will be conducted at the 300 and 400 patient stages, and the REVIVE-ARDS study can be completed when statistical significance is confirmed. The maximum number of patients is 550. We also confirmed the framework for utilizing 3D investigational product in this study.

*2 Acute Respiratory Distress Syndrome (ARDS)

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

*3 ONE-BRIDGE Study
A Phase 2 clinical trial that tested invimestrocel for patients with pneumonia-induced ARDS in Japan. In August and November 2021, Healios presented data on the endpoints at 90 and 180 days after treatment with the product, which showed positive results.

About HEALIOS K.K.:
HEALIOS K.K. 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 and owns proprietary, global platforms utilizing both somatic stem cells and iPS cells.

In the somatic stem cell field, Healios is developing invimestrocel (HLCM051), a proprietary cell product comprised of multipotent adult progenitor cells ("MAPCs") derived from the bone marrow of healthy adult donors. Invimestrocel has been shown to exhibit powerful anti-inflammatory and immunomodulatory properties with applicability in a range of disease states, has been tested in hundreds of patients in late stage clinical trials, is manufactured consistently at scale in 3D bioreactors, and has demonstrated both safety and suggested efficacy in hundreds of patients across multiple indications. Healios is seeking to advance invimestrocel on a global basis for ARDS, ischemic stroke, and trauma.

In the iPSC regenerative medicine field, Healios is developing HLCN061, a next generation NK cell treatment for solid tumors that has been functionally enhanced through gene-editing. These cells have demonstrated robust anti-tumor efficacy in animal models, benefit from a scalable 3D bioreactor manufacturing process, and are currently being prepared for initial human testing in collaboration with Akatsuki Therapeutics. The company has also established a proprietary, gene-edited "universal donor" induced pluripotent stem cell line to develop next generation regenerative treatments in immuno-oncology, ophthalmology, liver diseases, and other areas of severe unmet medical need.

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