March 13, 2025

Company Name: HEALIOS K.K.
Representative: Hardy TS Kagimoto, Chairman & CEO
(TSE Growth Code: 4593)

ONE-BRIDGE Trial in ARDS: Peer-Reviewed Publication in Japan

In our announcement dated January 15, 2025, titled "Status of Conditional and Time-Limited Approval Application for ARDS in Japan (Clinical Part)", Healios decided that it will submit the Conditional and Time-Limited Approval Application in Japan, based on the positive results of the Phase 2 study (ONE-BRIDGE study*[1]) completed in Japan and the Phase 2 study (MUST-ARDS study*[2]) completed in the U.S. and the U.K., and on the premise that a pivotal, global Phase 3 trial (REVIVE-ARDS study*[3]) of HLCM051 for ARDS*[4], to be run mainly in the United States, would act as a confirmatory study.

We hereby announce that a portion of the clinical data, which is scheduled to be submitted as part of this application, has been published in the peer-reviewed journal Regenerative Therapy published by The Japanese Society for Regenerative Medicine, the leading domestic journal in the field of regenerative medicine. The publication not only demonstrates the academic recognition garnered by the ONE-BRIDGE study, but also enhances the credibility of the submission data and will contribute to post-launch activities of the product.

This paper has been authored under the leadership of Dr. Kazuya Ichikado, Director, Department of Respiratory Medicine, Saiseikai Kumamoto Hospital and the principal investigator of the ONE-BRIDGE Study. The paper presents the results of a statistical analysis comparing historical data on ARDS patients collected at Saiseikai Kumamoto Hospital with data from patients administered HLCM051 in the ONE-BRIDGE study. The analysis, performed on well-matched groups, demonstrated an extension of ventilator-free days (VFD: the number of days within 28 days post-treatment during which a patient was not on mechanical ventilation) by an average of 8.1 days, and a reduction in mortality at 180 days post-treatment by approximately 33.7%. These results, consistent with the findings of the ONE-BRIDGE study, confirm the therapeutic trend of our product in the treatment of ARDS. For further details, please refer to the article via the link provided below.

There is no confirmed impact of this matter on our business performance for the fiscal year ending December 31, 2025 at this time. We will promptly announce any matters that should be disclosed in the future.

<Article>
Title: Clinical efficacy of invimestrocel for acute respiratory distress syndrome caused by pneumonia: Comparison with historical data using propensity score analysis - ScienceDirect
Journal: https://www.sciencedirect.com/journal/regenerative-therapy
DOI: 10.1016/j.reth.2025.02.018

*1 ONE-BRIDGE Study
This Phase II trial was conducted in Japan using HLCM051 cell therapy for patients with ARDS secondary to pneumonia. In this open-label, placebo-controlled study, Cohort 1 (pneumonia-derived ARDS) comprised 20 patients receiving the treatment and 10 patients in the placebo group, while Cohort 2 (COVID-19–derived ARDS) included 5 patients receiving the treatment. Interim results at 90 and 180 days post-administration were announced in August and November 2021, respectively, with favorable outcomes. An associated peer-reviewed article has been published in Stem Cell Research & Therapy. (Publication of Academic Article on Clinical Trial for ARDS in Japan)

*2 MUST-ARDS study
This Phase I/II open-label, placebo-controlled trial was conducted in Europe and the United States, evaluating HLCM051 cell therapy for patients with ARDS. Detailed pharmacological analyses were performed by comparing blood cytokine levels between the treatment and placebo groups, demonstrating a significant reduction in several key proinflammatory cytokines in the treatment group. The findings of this trial have been published in the peer-reviewed journal Intensive Care Medicine (https://link.springer.com/article/10.1007/s00134-021-06570-4).

*3 REVIVE-ARDS study
A pivotal, global Phase 3 study to demonstrate and confirm the efficacy and safety of MultiStem 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.

*4 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 262,000[*c] patients in the United States, 133,000[*d] in Europe, 670,000 in China, and more than 1.1 million people worldwide are affected annually[*e].
(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

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