April 23, 2025

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Completion of Formal Regulatory Consultation for ARDS and Agreement on the Global Phase 3 Trial (REVIVE-ARDS Study)

HEALIOS K.K. ("Healios") has completed regulatory consultations for the conditional and time-limited approval application in Japan for its investigational treatment for Acute Respiratory Distress Syndrome (ARDS*[1]), and is proceeding with preparations toward the submission. We are pleased to announce that, following a formal consultation with the Pharmaceuticals and Medical Devices Agency (PMDA) that took place this week regarding the post-approval confirmatory study, we have reached an agreement regarding the inclusion of Japanese patients in the upcoming global Phase 3 trial (REVIVE-ARDS study*[2]) to be run mainly in the United States.

By way of background, and as disclosed in our press release "Decision to Apply for Conditional and Time-Limited Approval for ARDS in Japan and ARDS Development Strategy Update" on October 2, 2024, the clinical trial design of the REVIVE-ARDS study has been the subject of multiple consultations with the U.S. Food and Drug Administration (FDA), and we have reached agreement on its framework. The REVIVE-ARDS study is designed to include interim analyses after enrollment of 300 and 400 patients, respectively, and will be completed at either of those points if statistical significance in efficacy is demonstrated. The maximum number of patients to be enrolled is set at 550.

With the framework for the inclusion of Japanese patients now concluded, we believe that we can accelerate the advancement of the REVIVE-ARDS global Phase 3 trial, including in Japan, in collaboration with the clinical trial sites that participated in the previously completed domestic Phase 2 study (the ONE-BRIDGE study*[3]).

Future Outlook

This matter has no impact on our consolidated financial results of the fiscal year ending December 31, 2025. We will promptly announce any matters that should be disclosed in the future.

*1 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

*2 REVIVE-ARDS study

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.

*3 ONE-BRIDGE Study

A Phase 2 clinical trial that tested MultiStem 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.