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Status of Conditional and Time-Limited Approval Application for ARDS in Japan

HEALIOS K.K. ("Healios") today provides an update on the status of its application for conditional and time-limited approval for ARDS[*1] in Japan, as follows.

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, Healios decided that it will submit an application for conditional and time-limited approval (hereinafter referred to as the "Application") in Japan, based on the positive results of the Phase 2 study (ONE-BRIDGE study*[2]) completed in Japan and the Phase 2 study (MUST-ARDS study) 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 MultiStem® for acute respiratory distress syndrome (ARDS), to be run mainly in the United States, would act as a confirmatory study.

Yesterday, on December 25th, Healios held a consultation with the Pharmaceuticals and Medical Devices Agency (PMDA) regarding the post approval manufacturing method and quality control of our product MultiStem®*[4] for ARDS. In this consultation, we were able to confirm the relevant manufacturing details required for the approval application package and obtained agreement with the agency regarding the Master Cell Bank to be used post launch of the product. We will proceed with various preparations, including those related to commercial manufacturing, which is required for approval.

Healios is currently discussing the manufacturing and clinical parts of the application package with the agency and has reached agreement on the manufacturing part through this consultation. We plan to consult with PMDA in mid-January regarding the clinical part of the application package. Details will be announced when they are finalized, along with those related to the start of the global Phase 3 trial in the U.S.

Future Outlook

The Company continues to plan to consult with the regulatory authorities in mid-January regarding the clinical details of the application package. 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 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.

*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 MultiStem®

MultiStem (HLCM051) is a somatic stem cell regenerative medicine product comprised of multipotent adult progenitor cells (“MAPCs”) derived from the bone marrow of healthy adult donors. MultiStem 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. MultiStem is a proprietary technology wholly owned by Healios. Healios has a long history developing MultiStem. It originally added MultiStem to its pipeline in 2016 through an exclusive license to develop and distribute the product to treat ischemic stroke in Japan. Further, in 2018 Healios expanded its license to include development and distribution to treat ARDS in Japan, and in 2023 it expanded its ARDS license to include global territories. Having acquired the full technology platform in April 2024, Healios is seeking to advance MultiStem on a global basis for ischemic stroke, ARDS, and trauma. In the U.S., MultiStem for the treatment of ischemic stroke and ARDS has received Fast Track and RMAT designation from the FDA, which allows for expedited approval of drugs that meet certain criteria for serious or life-threatening diseases or those for which no treatment is available.