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(TSE Growth Code: 4593)

Announcement of Subgroup Analysis Results from the MUST-ARDS Trial Regarding Kidney Dysfunction

HEALIOS K.K. ("Healios") is currently conducting a Phase II clinical trial in the United States (trial name: MATRICS-1 trial) to evaluate the safety and efficacy of our somatic stem cell regenerative medicine product, HLCM051, targeting multiple organ failure/Systemic Inflammatory Response Syndrome caused by trauma. Trauma can lead to severe kidney dysfunction due to causes such as massive blood loss leading to decreased renal blood flow, shock, and the accumulation of nephrotoxic substances caused by muscle damage. Accordingly, the MATRICS-1 trial has set the recovery from kidney dysfunction within 30 days after HLCM051 administration as its primary endpoint.

We are pleased to share the result of a subgroup analysis (20 cases) from the Phase I/II clinical trial (trial name: MUST-ARDS trial) previously conducted in Europe and the United States targeting ARDS[*1] patients. The analysis extracted patients who had concomitant severe kidney dysfunction, and the results showed an improvement trend in kidney dysfunction in the HLCM051 treatment group compared to the placebo group.

Results of MUST-ARDS Trial: Comparison of HLCM051 Treatment Group and Placebo Group 28 Days Post-Administration

	AKI[*2] or kidney low function (CC[*3]<80)	AKI Free or kidney function restore（CC≥80） 28 Days post-administration	Improvement Rate
HLCM051	13 patients	8 patients	61.5%
Placebo	7 patients	1 patient	14.3%

The improvement rate in the HLCM051 treatment group reached 61.5%, significantly exceeding the 14.3% improvement rate of the placebo group. These results suggest that the anti-inflammatory and immunomodulatory properties of HLCM051 may contribute to the improvement of kidney dysfunction.

The MUST-ARDS trial was not originally designed to evaluate the efficacy of HLCM051 against kidney dysfunction in ARDS patients. However, based on this subgroup analysis, we expect that clinical trials involving 50 cases could establish statistical significance and further validate the efficacy of HLCM051. Moving forward, we will continue to evaluate the safety and efficacy of HLCM051 through the MATRICS-1 trial, which plans to enroll 156 trauma-related kidney dysfunction patients.

Trauma is the leading cause of death for individuals under 45 years old in the United States and the third leading cause of death overall (Centers for Disease Control and Prevention). It is known to cause complications such as kidney dysfunction as part of multiple organ

failure/Systemic Inflammatory Response Syndrome. Additionally, Healios is preparing for the conditional and time-limited approval application for its investigational treatment for ARDS in Japan, and is preparing to initiate a global Phase III clinical trial (trial name: REVIVE-ARDS trial) to be run mainly in the United States. Healios will continue its product development efforts to address major causes of death in developed countries and acute inflammatory conditions (ARDS, stroke, trauma, etc.), where effective treatments are currently unavailable and new therapeutic options are eagerly awaited.

*1 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 Acute Kidney Injury (AKI)
AKI is a condition characterized by a rapid decline in kidney function, making it difficult to excrete waste products and maintain water and electrolyte balance. Trauma-related causes of AKI include massive blood loss leading to decreased renal blood flow, shock, and the accumulation of nephrotoxic substances due to muscle damage. Diagnosis is based on elevated serum creatinine levels and reduced urine output, while treatment focuses on addressing the underlying causes and supportive care. If left untreated, AKI may lead to chronic kidney disease or multiple organ failure.

*3 Creatinine Clearance (CC)
Creatinine clearance is an indicator of how much blood the kidneys can filter creatinine per minute and is used to evaluate kidney function. It is widely used in clinical settings for the rapid assessment of a patient's kidney function, particularly for the detection and monitoring of kidney disease progression, as well as for adjusting medication dosages. The following calculation formula is used: (amount of blood cleaned of creatinine by the kidneys) = [[140 - age] * weight (kg)] / [72 * serum Cr (mg/dL)]; multiply by 0.85 for females; mL/min.

About Healios:
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 ischemic stroke, ARDS, 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

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