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Top Line Results of the ONE-BRIDGE Study in Patients with ARDS

HEALIOS K.K. ("Healios") announces that the top line data for the primary and secondary endpoints of its ONE-BRIDGE clinical trial conducted to examine the safety and efficacy of HLCM051[*1] in patients with acute respiratory distress syndrome (ARDS)[*2] in Japan were analyzed and showed positive safety and efficacy.

Healios will continue to analyze the data from this clinical trial and continue ongoing consultations with the regulatory authorities to prepare for the application for manufacturing and marketing approval.

Top Line Results

Cohort 1

	HLCM051	Standard therapy
Primary Endpoint		
Ventilator-free days (VFD; the number of days out of 28 during which a ventilator was not used for the patient)	20 days	11 days
Secondary Endpoint		
Mortality (90 days after administration)	26.3%	42.9%

・Enrollment, N = 30 (HLCM051, n = 20; Standard therapy, n = 10)

Cohort 2

	HLCM051
Primary Endpoint	
Safety	No safety issues found
Secondary Endpoint	
VFD	25 days
Mortality (90 days after administration)	0%

・Enrollment, N = 5

Note: The above data is top line data based on the current results and will be finalized after the follow-up period of 180 days.

Based on these top line results, Dr. Kazuya Ichikado, Director, Department of Respiratory Medicine, Kumamoto Hospital, the lead investigator in this clinical trial, commented that "Since the start of the novel coronavirus (COVID-19) pandemic, pneumonia-induced ARDS has become a global medical issue. Of the various causes, pneumonia is seen to be the most common cause of ARDS in patients

with COVID-19 infection. In addition, no medicine available to date has been able to decrease the mortality associated with ARDS or decrease the number of days of ventilator use. The top line results obtained from this trial, as described above, showed that compared with standard therapy, HLCM051 increased the number of ventilator-free days (VFD) and decreased the mortality. Furthermore, in this trial, we enrolled patients with severe pneumonia-induced ARDS who are predicted to have a mortality rate of 60% with conventional treatment. Therefore, the results from this trial are expected to provide insights into future treatment options for patients with a poor prognosis. Despite the small number of patients enrolled in this trial, the results indicate that this investigational drug can be safely used in patients with severe COVID-19 infection. We believe that the approval of this investigational drug and the confirmation of its efficacy and safety in post-marketing surveillance studies will be good news for patients with ARDS."

In addition, Dr. Hardy TS Kagimoto, Chairman and CEO of Healios, commented that "We are thrilled to report positive results for our ONE-BRIDGE study. HLCM051 demonstrated an approximately 39% reduction in mortality relative to the standard therapy group, giving us further confidence in its efficacy to save the lives of patients who would otherwise die from pneumonia-induced ARDS. These results are consistent with those obtained in the double-blind study conducted by our partner Athersys in the United States (Please refer to our announcement dated January 24, 2019). Further, with respect to the five patients with severe COVID-19 who were included in this study, no deaths were reported, and all five patients were taken off the ventilator within 28 days after administration. Three of these COVID-19-induced ARDS patients were able to have the ventilator removed within three days of intubation. This result has the potential to be of great importance in light of the scarce medical resources in hospitals and the relative ease of administration of HLCM051 which requires only a single intravenous infusion. Further, this investigational agent has received orphan regenerative medicine designation for ARDS providing a supportive regulatory pathway for our efforts going forward. We will continue with our regulatory consultations and work towards a regulatory submission and ultimately delivery of this therapeutic medicine to patients as soon as possible. These positive developments bring us another step closer to achieving our mission of "Life Explosion!" by delivering cures for patients with unmet medical needs."

ONE-BRIDGE is an open-label clinical study, the main cohort of which enrolled patients with pneumonia-induced ARDS treated with either HLCM051 or standard therapy. For an overview of the trial with regards to Cohort 1, please refer to our company's press release dated April 22, 2019. In addition to the main cohort, a second cohort was included to test the safety of HLCM051 in patients with COVID-19-induced ARDS. The enrollment of Cohort 2 was completed in August 2020. For more information regarding the second cohort, Cohort 2, please refer to our company's press release dated April 13, 2020.

The primary endpoint in Cohort 1 was the number of days without a ventilator (VFD) out of the 28 days after administration of the treatment. A median difference of 9 days was observed in the VFD between the HLCM051 and standard therapy groups, and the mortality was approximately 39% lower in the HLCM051 group than in the standard therapy group. In Cohort 2, all patients who received HLCM051 were discharged without any particular safety concerns.

Currently, no direct treatment is available for ARDS. The available management approaches include coping therapy such as respiratory management using a ventilator in the intensive care unit (ICU). Thus, HLCM051 has the potential to be the first drug utilized for the treatment for ARDS. This drug will be manufactured in Japan by Nikon CeLL Innovation Co., Ltd., a wholly owned subsidiary of Nikon Corporation.

If matters to be disclosed arise in the future that would impact the financial performance of fiscal year 2021, Healios will make an announcement without delay.

Overview of ONE-BRIDGE study

	Cohort 1	Cohort 2
Enrollment	From April 2019 to March 2021	From April 2020 to August 2020
Subjects	Patients with pneumonia-induced ARDS	Patients with pneumonia-induced ARDS caused by COVID-19
Number of Enrollment	30 (HLCM051, n = 20; Standard therapy, n = 10)	5 (HLCM051, n = 5)
Objective	Efficacy and safety evaluation	Safety evaluation
Primary Endpoint	VFD (the number of days out of 28 during which a ventilator was not used for the patient)	Safety
Secondary Endpoint (Excerpt)	Mortality (28, 60, 90, and 180 days after administration)	1) VFD 2) Mortality
Follow-up period	180 days after administration	

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*1 HLCM051

HLCM051 is a somatic stem cell regenerative medicine product. Healios added it to its pipeline by signing an exclusive licensing agreement with the United States-based Athersys, Inc. ("Athersys") in January 2016, whereby Healios acquired rights to develop and distribute Athersys' proprietary stem cell product MultiStem® to treat ischemic stroke in Japan. Further, in June 2018, Healios and Athersys expanded their collaboration broadly, and as part of this expansion Healios acquired the development and distribution licenses to use MultiStem to treat ARDS in Japan.

*2 ARDS

ARDS is a general term for the symptoms of acute respiratory failure suddenly occurring in seriously ill patients. The major causes of ARDS are severe pneumonia, septicemia, and trauma. Inflammatory cells are activated in response to these diseases or injuries and cause damage to lung tissue. Thus, water accumulates in the lungs, leading to acute respiratory failure. According to the ARDS treatment guidelines 2016, the mortality rate of patients is approximately 30% to 58%. Artificial respiration using an endotracheal tube or mask is used to treat respiratory failure in an ICU.