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Decision Regarding Policy to File for Conditional and Time-Limited Approval of Ischemic Stroke Treatment in Japan and Development Strategy Overview

HEALIOS K.K. ("Healios") has conducted a placebo-controlled, double-blind Phase II/III clinical study (TREASURE study[*1]) in Japan to evaluate the efficacy and safety of HLCM051 (invimestrocel), a somatic stem cell regenerative medicine product, for the treatment of acute ischemic stroke. We have been in ongoing discussions with regulatory authorities regarding the direction of data collection and our application strategy. We further made an announcement today in our release titled "Notice of Selection for NEDO Public Call Project: 'Verification and Validation of Safety Toward Social Implementation of Japanese Medical-Specialized LLM' - Pilot Program for Post-Marketing Study of a Treatment for Acute Ischemic Stroke –". In line with the plan for this project, we hereby announce that we have decided on a policy to target a conditional and time-limited approval application (hereinafter, the "Application") for acute ischemic stroke in Japan.

In the TREASURE study, as announced in May 2022 in the "HEALIOS K.K. REPORTS TOP-LINE RESULTS FROM TREASURE STUDY FOR ISCHEMIC STROKE" the primary endpoint—set based on clinical results from the U.S.—was not met in approximately 200 patients in Japan. However, the study demonstrated statistically significant improvements in multiple established efficacy measures reflecting patients' activities of daily living and functional independence, suggesting clinical benefits one year after treatment.

Furthermore, in March 2024, Japan's Ministry of Health, Labour and Welfare issued guidance titled "Guidance on Conditional and Time-Limited Approval and Post-Marketing Efficacy Evaluation Plans for Regenerative Medical Products." This guidance emphasizes the importance of rational and feasible designs for post-marketing surveillance studies, which may include post-marketing use-result surveys or clinical studies (hereinafter, "Post-Marketing Studies").

In this context, we plan to use a registry system linked with electronic medical records powered by the LLM developed through this project. We believe this will enable the registration of several hundred cases annually for the Post-Marketing Study. The registry will be modeled on the Fukuoka Stroke Registry (hereinafter, "FSR"), a multi-institutional stroke database that has already accumulated clinical data on stroke patients. With respect to the development and regulatory filing strategy for our acute ischemic stroke treatment, we do not intend to conduct an additional Phase 3 trial; instead, the efficacy of the product will be evaluated through Post-Marketing Studies.

Several organizations are scheduled to participate in the project as co-implementing partners, including Kyushu University and The University of Tokyo, along with multiple medical institutions, research organizations, and companies. Kyushu University has long maintained FSR, a multi-institutional stroke database collecting clinical data on stroke patients with over 1,000 cases registered annually and a cumulative total exceeding 17,000 cases. Drawing on this experience, Kyushu University will propose survey items and assist in designing the automated data collection system for post-marketed drugs. The Matsuo and Iwasawa Laboratory at The University of Tokyo will be responsible for developing and examining methods for extracting medical data using the LLM. Healios will focus primarily on the development of regenerative medicine products and the implementation of Post-Marketing Studies, specifically targeting acute ischemic stroke.

By presenting this rational and feasible Post-Marketing Study design, we believe that the path toward filing for conditional and time-limited approval—and ultimately full approval—for ischemic stroke has become clear. We will continue discussions with stakeholders, including regulatory authorities, to ensure that the registry using the LLM is appropriately designed and operated, and will then proceed with the Application, focusing particularly on confirming whether statistically defined efficacy thresholds can be established.

HLCM051 for acute ischemic stroke was designated under the SAKIGAKE designation system[*2] in February 2017. Given the lack of effective treatments and the shortage of caregiving resources, we hope to deliver this therapy to patients as soon as possible, alleviating the burden on patients and their families and addressing a pressing societal issue.

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 TREASURE study

The TREASURE study was conducted to investigate the safety and efficacy of HLCM051 in patients with ischemic stroke. The study targeted patients with moderate to moderate-severe strokes (baseline NIHSS score 8-20), with administration of a single dose of HLCM051 intravenously within 18-36 hours from stroke onset. The trial was conducted at 48 sites in Japan and enrolled 206 patients. HLCM051 (invimestrocel) is an off-the-shelf, somatic stem cell regenerative medicine product that Healios is developing for both ischemic stroke and acute respiratory distress syndrome (ARDS) in Japan, as well as for ARDS and trauma in the United States. The following is a summary of the results of the TREASURE study that has been published to date.

- No significant difference was demonstrated in the primary endpoint of Excellent Outcome after 90 days of treatment.
- The drug effect was stronger as time passed from 7, 30, 90 and 365 days after administration of the drug compared to the placebo group. In particular, the increase in the percentage of patients who were able to live independently without the need for nursing care, as indicated by BI and Global Recovery after one year, was statistically significant.

*2 SAKIGAKE Designation System

This system is designed to promote the early practical application in Japan of innovative pharmaceuticals, medical devices, and regenerative medical products that are being developed

ahead of the rest of the world and are expected to demonstrate significant efficacy in the early stages of clinical trials. The program aims to accelerate their implementation through various forms of support, including prioritized consultation and review processes for regulatory approval.