March 20, 2023

Company Name: HEALIOS K.K.
Representative: Hardy TS Kagimoto, Chairman & CEO
(TSE Growth Code: 4593)

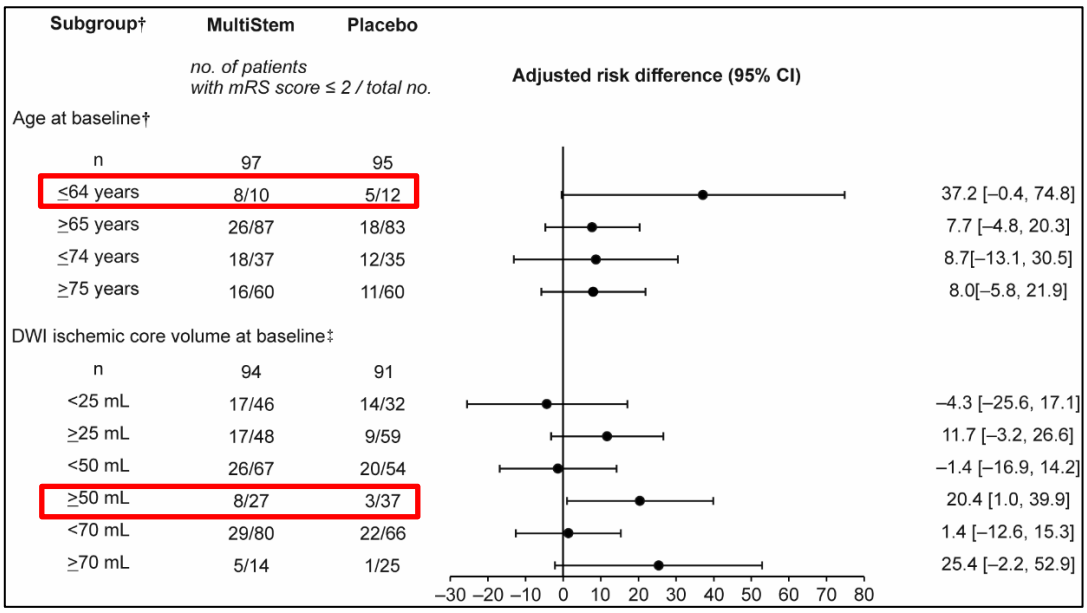
TREASURE Study subgroup analysis results
Three observations and future areas of consideration for HLCM051

HEALIOS K.K. ("Healios") conducted the TREASURE study[*1] to investigate the safety and efficacy of HLCM051[*2] (Multistem®) in patients with ischemic stroke. The results of the study were announced in May and November, 2022. We are pleased to announce that additional subgroup analysis results (mRS[*3] <=2 after 90-days of treatment) were presented by Dr. Toshiya Osanai, Hokkaido University, Department of Neurosurgery, a clinical trial investigator in this study, at the 48th Annual Meeting of the Japanese Stroke Association held on March 17, 2023.

1. Subgroup analysis results

1) The results showed a trend toward efficacy as cerebral infarct volume increased from 25 mL to 50 mL and 75 mL. The efficacy was statistically significant, especially for volumes of 50 mL or greater.

2) Though a small sample size, patients under 64 years of age appear to achieve better results.



2. Three observations

1) Effect of stroke volume on efficacy
   HLCM051 is known to suppress unwanted immune effects in the acute phase after intravenous administration. In stroke, it is known that primary damage (stroke) occurs when blood vessels are occluded, and tissue with interrupted blood flow produces cytokines that contaminate surrounding tissue, mobilizing immune cells from throughout the body to attack surrounding tissue that would not normally be attacked, causing secondary damage to a larger area (penumbra). The results of this study suggest that the effects of the drug were more readily apparent when primary damage was greater, but further verification is needed.

2) Effect of observation period on efficacy
   To evaluate efficacy in terms of neurological measures, it is necessary to wait for the recovery and elongation of nerve tissue after suppressing secondary damage with the drug. Since neurological findings improve at 7, 30 and 90 days after administration of the drug, it is likely that the effect tends to be maximized (or maintains maximization) at 365 days, the longest observation period in this trial.

3) Effect of age on efficacy
   In order to detect clinical efficacy by neurological indices, the ability of the human body to recover and elongate nerve tissue is considered important in addition to the efficacy of the drug. It is possible that neural recovery capacity in the younger age group (64 years and younger) may be higher than in the older age group, resulting in a more favorable response.

3. Future considerations

The above discussion is the effect of the drug derived from the results to date and requires further scientific verification. Athersys Inc., which is conducting a clinical trial (trial name: MASTERS-2 study) in the U.S. and Europe using the same drug for ischemic stroke, will discuss with the FDA (Food and Drug Administration) in March 2023 to change certain endpoints based on the TREASURE study results. Following the new agreement with the FDA, we plan to consult further with the PMDA, including with regards to the use of U.S. data.

In response to these results, Tadahisa “Hardy” Kagimoto, MD, CEO and Representative Executive Officer of Healios, stated the following.

“Cell therapy is an area in which therapeutic effects are achieved through the interaction between cells and the human body, so nonclinical trials and clinical trials on a small number of subjects may not fully determine the efficacy of a drug in humans. By conducting a large-scale double-blind study like this one, it is possible to obtain scientific knowledge that is sufficient for objective evaluation. We believe that the scientific clarification of the clinical efficacy profile through the TREASURE study opens up the possibility of HLCM051 in the future. We will continue to make contributions to patients and to science, and will make management efforts to realize our mission, to foster a life explosion that enriches the lives of people around the world.”

*1 TREASURE study
The TREASURE study was conducted to investigate the safety and efficacy of HLCM051 (Multistem®) 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 1836 hours from stroke onset. The trial was conducted at 48 sites in Japan and enrolled 206 patients. HLCM051 is an off-the-shelf, somatic stem cell regenerative medicine product that Healios is developing for both ischemic stroke and acute respiratory distress syndrome in Japan.

*2 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.
The followings are summary of the results of the TREASURE study that have been published to date.

- No significant difference was demonstrated in the primary endpoint of Excellent Outcome*5 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 are able to live independently without the need for nursing care, as indicated by BI*6 and Global Recovery*7 after one year, was statistically significant.
- Although the placebo group tended to be slightly larger in the distribution of subjects' stroke volume, compared to no effect for stroke volumes of less than 25 mL, there was a trend toward a stronger drug effect for larger volumes of 25, 50 and 75 mL, with a statistically significant difference, especially for volumes of 50 mL or larger.
- It was suggested that the drug was more effective in patients under 64 years of age.

*3 mRS
The mRS measures the degree of disability or dependence in the activities of daily living of people who have had a stroke or have a neurological disability due to other reasons. It is used to categorize the level of functional independence with reference to pre-stroke activities. The scale includes scores from 0 to 6, ranging from perfect health without symptoms of disability (i.e., a score of 0) to death (a score of 6). A lower score indicates a lower degree of disability. In this study, mRS was set as a secondary evaluation item.

*4 NIHSS
The NIHSS is a systematic assessment tool that provides a quantitative measure of stroke-related neurologic deficit. A higher score on the NIHSS indicates a higher degree of neurological impairment in a stroke patient. The score for each function ranges from 0 to 4, the total NIHSS score of the patient is calculated by adding the score for each element on the scale, and 42 is the highest possible score, which reflects the maximum disability of the patient in each category. In this study, NIHSS was set as a secondary evaluation item.

*[5] Excellent Outcome
Functional and neurological deficit and recovery following ischemic stroke are evaluated using three standard methods: the modified Rankin scale (mRS), the NIH stroke scale (NIHSS), and the Barthel Index (BI). “Excellent Outcome” is defined as achieving scores ≤1 on the mRS and on the NIHSS and a score ≥95 on the BI. In this study, Excellent Outcome was set as the primary evaluation item.

*[6] Barthel Index
The BI is a 100-point scale that is used to assess the ability of the patient to independently perform activities of daily living and to evaluate a range of different functions. These include the ability of the patient to walk, dress, feed, bathe, climb stairs, use a toilet, self-groom, and certain other metrics. The patient is evaluated for each activity to assess for independence, partial dependence, or complete dependence, and then, a score between 0 and 10 is assigned (10 points = independence, 5 points = partially dependent, and 0 points = completely dependent). The BI score ranges from 0 to 100; a score of 100 indicates no dependence on any activity, and a lower score indicates a greater need for assistance. In this study, BI was set as a secondary evaluation item.

*[7] Global Recovery
Functional and neurological deficit and recovery following ischemic stroke are evaluated using three standard methods: the modified Rankin scale (mRS), the NIH stroke scale (NIHSS), and the Barthel Index (BI). “Global Recovery” is defined as achieving scores ≤2 on the mRS, NIHSS improvement >=75% and a score ≥95 on the BI. A Global Recovery assessment using multivariate, correlation adjustment, was the primary endpoint in Athersys’s Phase 2 MASTERS-1 study run in the United States and Europe, and in this study, Global Recovery was set as a secondary evaluation item.

(Source) Prepared by Healios on the basis of materials provided by The Japan Stroke Society.

Contact:
IR, Finance and Accounting Division, HEALIOS K.K.
E-mail: ir@healios.jp