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Protocol change for ischemic stroke trial in the U.S. and Europe
Primary endpoint observation period extended to 365 days following TREASURE study results

HEALIOS K.K. ("Healios") conducted the TREASURE study*1 to investigate the safety and efficacy of HLCM051*2 (Multistem®) in patients with ischemic stroke. Healios is continuing discussions with the regulatory authority (PMDA) regarding future data acquisition and submission policies.

Athersys is conducting a clinical trial (trial name: MASTERS-2 study) in the U.S. and Europe using the same drug for ischemic stroke. The results of the TREASURE study announced by Healios in May 2022 showed an overall positive trend in the evaluation after 365 days of administration, suggesting a long-term improvement in independence in daily living. Therefore, Athersys has discussed with the U.S. Food and Drug Administration (FDA) to change the timing of the primary endpoint of the MASTERS-2 study (shift analysis in mRS*3 score) from 90 days to 365 days after administration. This and other requests have been accepted by the FDA. The main changes are as follows:

1. Athersys will change the timing of the primary endpoint assessed by shift analysis in modified Rankin Scale (mRS) score to day 365, from day 90 previously.
2. Athersys will retain shift analysis in mRS score at day 90 as a key secondary endpoint, along with other revised secondary endpoints.
3. Athersys will remove eligibility caps on concomitant reperfusion therapy (e.g., tPA, MR or tPA+MR) to ensure the final study population is reflective of current standard of care in the population eligible for this therapy.
4. Athersys may elect to have an independent statistician conduct an interim analysis to assess potential sample size adjustment. MASTERS-2 currently plans to enroll 300 patients and enrollment, as previously communicated, is >50% complete.

Please refer to the press release from Athersys for more information.

Based on this new agreement with the FDA, Healios plans to discuss with the PMDA the future direction of HLCM051 development for ischemic stroke in Japan, including the use of clinical trial data from the U.S.

This matter has no impact on our business performance for the fiscal year ending December 2023 at this time. Healios shall promptly announce all future matters that require

disclosure, including any potential impact on expenses associated with launching this clinical trial.

*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 following is a 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 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 and Global Recovery 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.
- Though a small sample size, patients under 64 years of age appear to achieve better results.

*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 the TREASURE study, mRS was set as a secondary evaluation item.

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

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