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Title:

Treatment Evaluation of Acute Stroke for Using in Regenerative Cell Elements (TREASURE) Trial: Rationale and design

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Key Words:

Cell Therapy; Ischemic Stroke; Clinical trial

Word Count:

1991

Itemized list of tables and Figures:

Figure 1 (black-and-white)
Supplementary Table 1 (black-and-white)
Supplementary Table 2 (black-and-white)

Abstract

Rationale

MultiStem® (HLM051) is one of the promising allogenic cell products for acute ischemic stroke with strong evidence. A previous phase 2 randomized, double-blind, placebo-controlled, multicenter dose-escalation trial showed the safety of MultiStem® for acute ischemic stroke, with a time window beyond that of rt-PA and endovascular thrombectomy. We aim to obtain stronger evidence and to show the efficacy of the MultiStem® for treatment of ischemic stroke.

Sample size

Estimated sample size is 220 (110 patients per group), which has 90% power at the 5% significance level.

Methods and design

TREASURE is a randomized, double-blind, placebo-controlled, multicenter phase 2/3 trial. The trial will be done at 31 medical centers in Japan. Patients with acute ischemic stroke including motor or speech deficit defined by a National Institution of Health Stroke Scale (NIHSS) score of 8-20 at baseline will be randomized 1:1 to receive a single intravenous infusion of MultiStem® or placebo within 18-36 hours of stroke onset.

Study outcomes

Primary outcome in this study is the proportion of patients with an excellent outcome at day 90 defined by the functional assessment.

Trial registration

ClinicalTrials.gov (NCT02961504)

Conclusion

The TREASURE trial will provide a novel treatment option and expand the therapeutic window for patients with stroke if the results are positive.

Introduction

Stroke is one of the leading causes of death and disabilities in the world, and is one of the disorders where novel treatments are needed. Recombinant tissue plasminogen activator (rt-PA) is the well-established and widely used treatment for acute ischemic stroke, but patients who can receive benefit from thrombolytic therapy are limited because of the narrow time window in which it can be administered. In addition, endovascular thrombectomy for ischemic stroke is rapidly evolving by advances in technology of catheter-based interventions (1-5); however,

similar to rt-PA treatment, endovascular treatment is available only for patients who are transferred to hospital in a timely manner.

MultiStem® is a cell therapy medical product originating from adult adherent stem cells taken from the bone marrow of healthy, consenting, non-related donors, developed under Good Manufacturing Practice conditions. The safety of MultiStem® in patients with cortical ischemic stroke within 48 hours onset was evaluated in the previous phase 2 trial (MASTERS)(6). Overall 129 patients were randomly assigned (67 to receive MultiStem® and 62 to receive placebo) in MASTER trial.

There was no significant difference between MultiStem® and placebo in primary outcome at Day 90 defined as modified Rankin scale ≤2, NIHSS total score improvement of ≥75%, and Barthel Index ≥95 (odds ratio 1.08, 95% confidence interval 0.55–2·09], p=0.83). Post-hoc analysis of MASTER trial showed that the effectiveness of MultiStem® was detected by evaluation using excellent outcome defined as modified Rankin Scale of ≤1, NIHSS score of ≤1 and Barthel Index score of ≥95.

Furthermore, by administering MultiStem® within 36 hours onset, there was a significant improvement of an efficacy compared with placebo within 36 hours (Excellent outcome was 16.1% in MultiStem® group and 0% in Placebo group, p=0.02). Additionally, if the group using both rt-PA and endovascular thrombectomy was excluded, the effectiveness of MultiStem® compared with placebo was confirmed.

Thus, we are conducting a multicenter, randomized, double blind, placebo-controlled phase 2/3 study to further evaluate the neurological effects of MultiStem® in an earlier time window after stroke (between 18 and 36 hours).

Material and methods

Objectives

The primary objectives of the stroke clinical trial are: (1) to evaluate the efficacy of MultiStem® on functional outcome in patients with ischemic stroke; and (2) to evaluate the safety of MultiStem® in patients with ischemic stroke.

Study design

TReatment Evaluation of Acute Stroke for Using in Regenerative Cell Elements (TREASURE) is a randomized, double-blind (participant, care provider, investigator, outcomes assessor), placebo-controlled,

multicenter phase 2/3 trial to evaluate the efficacy and safety of intravenous administration of MultiStem® compared with placebo in patients with ischemic stroke.

Patients population

The target patients are individuals over 20 years old with ischemic stroke treated within 18-36 hours of onset. This time window is based on preclinical studies in a rat ischemic stroke model (7), as well as post-hoc analysis in the MASTERS (6).

Occurrence of an ischemic stroke with clear motor or speech deficit documented by National Institutes of Health Stroke Scale (NIHSS) score of 8 to 20 (at the baseline assessment) that did not change by ≥4 points from the screening to the baseline assessment.

To be enrolled, patients need to have confirmation of hemispheric cortical infarct with brain magnetic resonance imaging (MRI) including diffusion-weighted imaging demonstrating an acute lesion measuring ≥ 2.0 cm of longest diameter.

Patients are eligible if they receive rt-PA or endovascular thrombectomy. However we exclude the patients who received both therapy.

The inclusion and exclusion criteria are in Supplementary Table 1.

Procedure

This study consists of three phases, screening, baseline (Day 0: before and after treatment), and post-treatment. Patients will be evaluated at screening, baseline, Day 1 through Day 365, or early termination visit. The detail of procedure is shown on figure 1.

Randomization and blinding

A total of 220 patients will be randomly assigned to receive MultiStem® or placebo in a 1:1 ratio by using an Interactive Web Response System (IWRS). At each site, designated staff at a pharmacy or equivalent facility will be unblinded to ~~subject~~ treatment assignments.

Treatment and intervention

Patients will receive a single dose of 1.2 billion MultiStem® cells or placebo within 18 to 36 hours after the onset of ischemic stroke. Infusion was performed at the rate of up to 10 mL/minute over a period of 30 to 60 minutes.

Primary outcome

The proportion of patients with an excellent outcome at Day 90 defined by the functional assessment as follows: modified Rankin Scale of ≤1, NIHSS score of ≤1 and Barthel Index score of ≥95.

Safety outcomes

The safety endpoints include adverse events and changes in laboratory parameters, vital signs, ECG, and incidence of infection (local and systemic).

Data monitoring

Protocol stopping rules will be in place (Supplementary Table 2), with an independent Data Safety Monitoring Board (DSMB) assembled if serious safety events, including infusion reactions, occur related to investigational product. In addition, the DSMB will meet twice or more during the subject enrollment period to examine the unblinded safety data.

Sample size determination

According to the results of the MASTERS in which 27 patients in the MultiStem® group treated within 36 hours after onset of stroke and 52 patients in the placebo group treated within 48 hours after onset of stroke, excluding all patients treated with rt-PA and endovascular thrombectomy, the proportion of subject with an excellent outcome at day 90 were 18.5% in the MultiStem® group and 3.8% in the placebo group, respectively (6). Under the setting that the results of this trial are the same as those observed in the MASTERS, the number of patients is calculated as 100 per group with a 90% power at the 5% significance level. After considering that there may be some patients to be excluded/dropouts, 110 patients per group will be enrolled in the trial.

Statistical analysis

The primary efficacy outcome will be analyzed via a Cochran-Mantel-Haenszel test, stratified by baseline NIHSS score (≤12

vs ≥13), age (<65 vs ≥65), use of concomitant reperfusion therapy (Yes or No).

Funding: HEALIOS K.K.

Discussion

MultiStem® is considered to provide benefit through various mechanisms of action such as reduction of inflammation, control of immune function, protection of damaged or injured cells and tissues, promotion of angiogenesis, and promotion of healing (8). The hypothesis supporting MultiStem® treatment for ischemic stroke is based on the improvement of motor function observed when MultiStem® was directly transplanted into the adult rat brains(9) or into the hippocampus of newborn rats(10-12) following the induction of hypoxic-ischemic injury. Intravenous administration of allogeneic rat or xenogeneic human MultiStem® (without immunosuppressant drugs) in rat models of ischemic stroke resulted in statistically significant and continuous effects in a dose-dependent manner(13, 14). The data suggests that MultiStem® provides benefit through various biological mechanisms, such as prevention of apoptosis, inhibition of inflammatory injury, and production of homing factors that recruit endogenous stem cells or progenitor cells followed by further improvement of central nervous system functions and recovery. Therefore, the effects of MultiStem® has been examined in patients with ischemic stroke.

The initiation time of treatment is considerably important in the clinical trial for ischemic stroke. Intravenous thrombolysis with alteplase is an approved treatment for acute ischemic stroke, but it needs to be administered within 3-4.5 hours of onset in certain eligible stroke patients (2-5). Treatment using endovascular thrombectomy is similar. Many clinical trials of endovascular treatment for acute ischemic stroke did not show efficacy because of the delay of the recanalization (15). Therefore, new therapies are anticipated with a time window beyond that of existing treatment. MultiStem® was safe and well tolerated after a one time intravenous infusion in patients with acute ischemic stroke in the MASTERS study (6). Although no significant improvement was observed

at 90 days in neurological outcomes, post-hoc analyses showed consistent evidence that early MultiStem® treatment, within 36 hours following ischemic stroke onset, can provide substantial benefits to patients. Thus, we will implement a confirmatory clinical trial in an earlier time window (within 36 hours) after stroke onset.

Conclusion

MultiStem® will provide the novel treatment option and expand the therapeutic window for stroke if the TREASURE trial shows the efficacy and the safety for the patients with acute phase stroke.

Authors' contributions

All authors were involved in the study design, protocol preparation, and acquisition of funding. TO was responsible for first draft and final revision. All authors have reviewed and approved the final manuscript.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Expert Witness from HEALIOS K.K. (TO, KH, SU, AT). The other authors report no conflicts.

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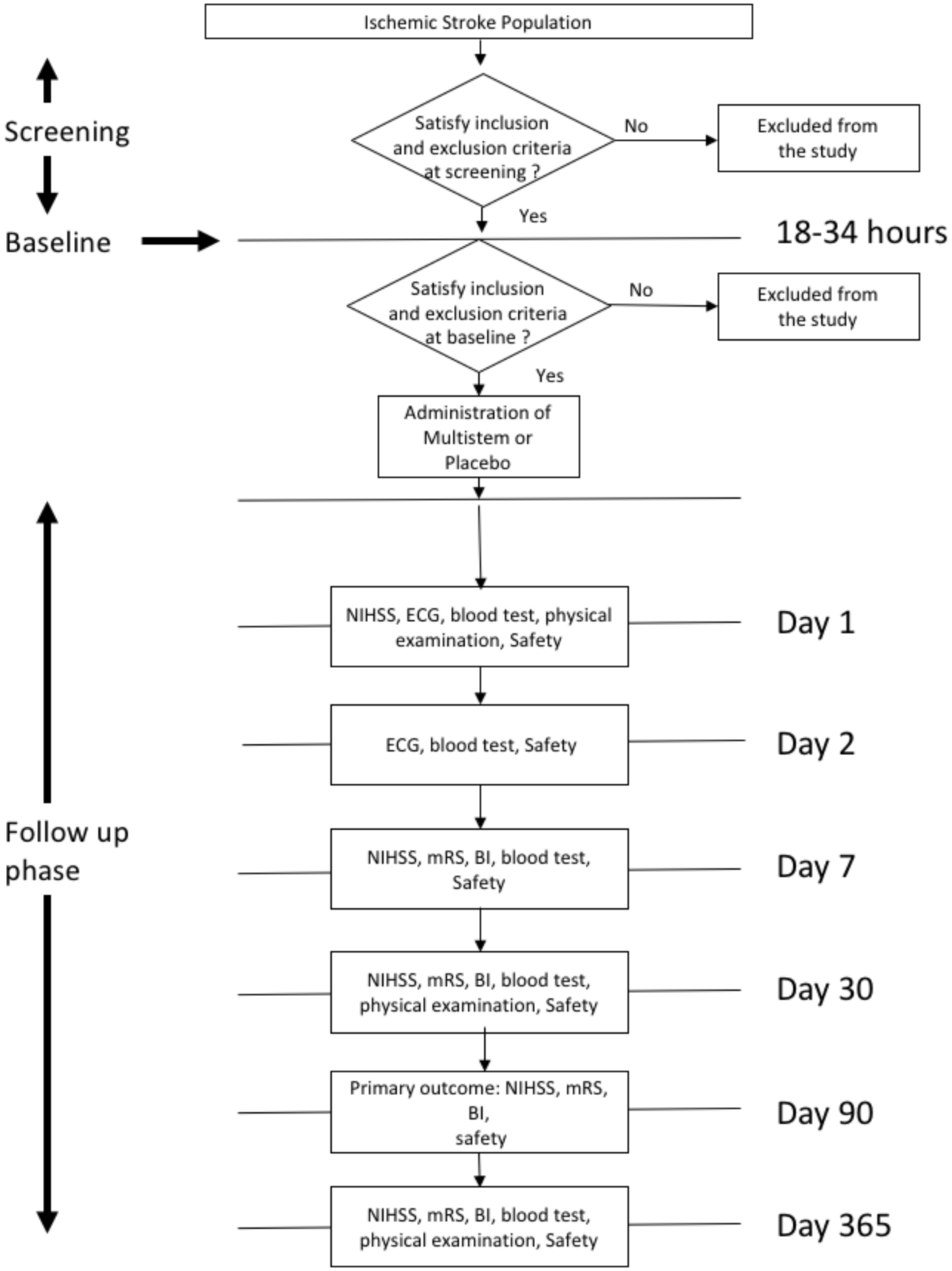
Figure legends

Figure 1 Study design diagram for the study of Efficacy and Safety Trial of MultiStem®.


Ischemic Stroke Population
Screening
Satisfy inclusion and exclusion criteria at screening ?
No
Excluded from the study
Yes
Baseline
18-34 hours
Satisfy inclusion and exclusion criteria at baseline ?
No
Excluded from the study
Yes
Administration of Multistem or Placebo
Follow up phase
NIHSS, ECG, blood test, physical examination, Safety
Day 1
ECG, blood test, Safety
Day 2
NIHSS, mRS, BI, blood test, Safety
Day 7
NIHSS, mRS, BI, blood test, physical examination, Safety
Day 30
Primary outcome: NIHSS, mRS, BI, safety
Day 90
NIHSS, mRS, BI, blood test, physical examination, Safety
Day 365