



FOR IMMEDIATE RELEASE

Heartseed Announces Positive 26-week Data for the First Patient in the Phase 1/2 Clinical Trial (LAPiS Study) Dosed With HS-001, an Investigational Stem Cell-Derived Therapy for the Treatment of Advanced Heart Failure

TOKYO, JAPAN, July 6, 2023 – Heartseed Inc. (CEO: Keiichi Fukuda; hereinafter referred to as "Heartseed"), today announced positive 26-week data for the first patient from the Phase 1/2 clinical trial (LAPiS Study) of HS-001, a lead pipeline of Heartseed, in combination with coronary artery bypass grafting surgery for advanced heart failure.

The first patient of the LAPiS study was dosed at Tokyo Women's Medical University Hospital in December 2022, and data up to 26 weeks after administration are currently available. This patient had severe heart failure with an enlarged Left Ventricular End Diastolic Volume (LVEDV) of more than 400mL measured by MRI. Although there was no change in the first week after the procedure, there were signs of "reverse remodeling" with a decrease in LVEDV at 26-week by 27% in echocardiogram and 10% in MRI, respectively. Left ventricular ejection fraction (LVEF) improved from the baseline to 26-week by 2% points in echocardiogram and 4% points in MRI. NT-proBNP, a marker of heart failure also decreased by 50% from the baseline to 26-week, and New York Heart Association (NYHA) functional classification also improved from III at baseline to II at 26-week.

| | | Baseline | 26-week |
|---|------|-------------|------------|
| LVEF (%) | Echo | 26 | 28 |
| | MRI | 15 | 19 |
| LVEDV (mL) (): relative values with baseline as 100 | Echo | 345 (100) | 252 (73) |
| | MRI | 431 (100) | 389 (90) |
| Cardiothoracic ratio (%) | | 63.1 | 60.0 |
| NT-proBNP (pg/mL) (): relative values with baseline as 100 | | 11,471(100) | 5,733 (50) |
| NYHA functional classification | | III | II |

(All data are from the hospital)

"The first patient is now able to actively engage in rehabilitation because of the improvement in cardiac function, and I feel that the improvement in activities of daily living is greater than the improvement in numerical values", said Dr. Yuki Ichihara, Department of Cardiovascular Surgery at Tokyo Women's Medical University Hospital, who was in charge of the trial in the hospital. "I am looking forward very much to the future development of HS-001."

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For journalistic assessment and preparation before publication.

In addition, data are now available for the second and third patients up to 17 and 13 weeks, as summarized in the following table.

| | 2nd patient | | 3rd patient | |
|---|-------------|---------------|-------------|----------|
| | Baseline | 17-week | Baseline | 13-week |
| LVEF (%) | 26 | 26 | 17 | 36 |
| LVEDV (mL) (Echo) (): relative values with baseline as 100 | 324 (100) | 362 (112) | 196 (100) | 172 (88) |
| NYHA functional classification | III | III (13-week) | III | II |

(All data are from the hospitals, NYHA functional classification is measured at 13-week, not 17-week)

Regarding safety, there have been no events that would be problematic for the continuation of the clinical trial. Heartseed continues patient enrollment in the LAPiS trial and conduct an evaluation by the Safety Monitoring Committee once the data are compiled.

About the main indices and terms

- **Left Ventricular End Diastolic Volume (LVEDV):** The volume of the left ventricle when it is mostly dilated, and 102-235 mL is considered normal, depending on body weight and other factors.
- **Reverse remodeling:** In heart failure, various factors are known to cause the change of myocardial shape (ventricular remodeling), resulting in cardiac enlargement. Reverse remodeling, on the other hand, refers to the structural and functional improvement of ventricular remodeling, resulting in the reduction of left ventricular size. Reverse remodeling is associated with improved prognoses.
- **Left Ventricular Ejection Fraction (LVEF):** a measure of how efficiently the heart pumps blood; normal is 55-73%; the LAPiS study used an LVEF of 15-40% as inclusion criteria.
- **Cardiothoracic ratio:** the ratio of the width of the thorax to the width of the heart on an x-ray image. Normal values are less than 50%.
- **NT-proBNP:** A type of hormone secreted by the heart; the lower the heart function and the greater the burden on the heart, the more it is secreted into the blood and the higher the number.
- **New York Heart Association (NYHA) functional classification:** The severity of heart failure, rated on a 4-point scale from I to IV according to subjective symptoms, with I being the mildest (no limitation of physical activity) and IV being the most severe (any physical activity is restricted).

About HS-001 and LAPiS Study

HS-001, is allogeneic iPSC-derived, highly purified ventricular cardiomyocyte spheroids. By forming micro-tissue-like spheroids, retention rate and viability of cell transplant are improved. The spheroids are transplanted using a special administration needle (SEEDPLANTER®) and guide adapter developed for safe and efficient administration of the spheroids

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into the myocardial layer of the heart.

The expected mechanism of action is that the transplanted cardiomyocytes electrically couple with the patient's myocardium to improve cardiac output by remuscularization, and secretion of angiogenic factors to form new blood vessels around the transplant site (neovascularization).

LAPiS Study, a 52-week, phase 1/2, open-label, dose-escalation study in patients with advanced heart failure caused by ischaemic heart disease, is being conducted at various study sites in Japan. HS-001 will be transplanted into the diseased tissue of the heart during open-heart surgery in conjunction with a planned coronary artery bypass graft procedure. The study will enrol 10 patients in two dose cohorts of 50 million and 150 million cardiomyocytes. The primary endpoint of the study is safety at 26 weeks post-transplantation, and secondary efficacy endpoints include LVEF and myocardial wall motion.

About Heartseed

Heartseed Inc. was founded in 2015 to develop and commercialize cardiac remuscularization therapy developed by Professor Keiichi Fukuda and his group at the Department of Cardiology, Keio University, Tokyo, Japan. Heartseed has proprietary technologies throughout the entire manufacturing process of the cardiomyocyte-cell product, including purification, cell delivery and iPSC production.

Heartseed announced the global collaboration and license agreement with Novo Nordisk A/S for HS-001 in June 2021. Heartseed received "Minister of Science and Technology Policy Award" at Japan Venture Awards 2021 and "Ministry of Education, Culture, Sports, Science and Technology Award" at Academic Startups 2021, and "Most Promising Pipelines Awards (iPSC)" at Asia Pacific Cell & Gene Therapy Excellence Awards 2022. For more information, visit heartseed.jp, [LinkedIn](#) and [YouTube](#).

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