

To our shareholders and investors,

Thank you sincerely for your ongoing support of Heartseed Inc. I am Keiichi Fukuda, President and CEO. In this TOP MESSAGE, I would like to share with you about our presentations on the final results of the LAPiS study, which were delivered at the European Society of Cardiology (ESC) Congress held in Munich, Germany, from August 28, and at the Japanese College of Cardiology annual meeting held in Nagasaki, Japan, from September 11.

■ European Society of Cardiology (ESC)

The ESC is the world's largest cardiology congress, gathering over 35,000 physicians, researchers, and company representatives each year to present cutting-edge research findings. Since my youth, presenting at the ESC and the American Heart Association (AHA) has been a driving force for my work. I felt extremely honored to present the results of our clinical trial at this opportunity. During the afternoon symposium on Saturday, August 29, four speakers gave presentations on cardiac regenerative medicine, and I had the privilege of serving as the final speaker.



In my presentation, I began by comparing the disease severity of patients in the LAPiS study with those in a past large-scale clinical trial, the STICH trial. The STICH trial evaluated patients with severe heart failure due to ischemic heart disease who had a left ventricular ejection fraction (LVEF)—a key indicator of heart failure severity—of 30% or lower. They were divided into two groups based on whether coronary artery bypass grafting (CABG) was performed, and their 10-year mortality rates were compared. The results were sobering, showing that over 60% of patients died after 10 years, regardless of whether CABG was performed. Comparing our LAPiS study patients with the STICH trial, although the average age was comparable, our patients presented with lower cardiac function (lower LVEF values) and greater heart enlargement (higher LVEDVI [Left Ventricular End-Diastolic Volume Index] values). This demonstrated that the LAPiS study enrolled patients with even higher disease severity.

I then explained the 1-year data for all 10 patients. As previously disclosed in our corporate IR announcements, mean LVEF showed an increase in both the low-dose and

high-dose cohorts. This trend was particularly pronounced in the high-dose cohort, suggesting a potential dose-dependent effect. Furthermore, left ventricular size (LVEDVI) showed a significant mean decrease in both groups, yielding favorable results. A reduction in left ventricular size signifies the relief of cardiac congestion, leading to improvements in pleural effusion, ascites, and lower limb edema. For patients, this translates into a substantial improvement in subjective symptoms.

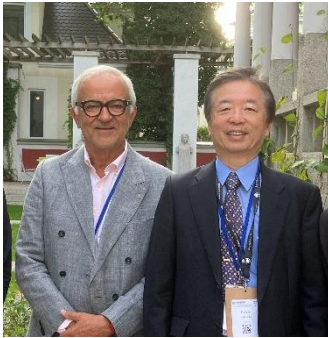
Regarding the KCCQ index, which measures subjective symptoms, the average score in the low-dose cohort remained unchanged due to a case influenced by non-cardiac factors (blockage of lower extremity blood vessels). However, an increase was observed in the high-dose cohort, where maintenance or improvement was confirmed in all 5 patients. In terms of the NYHA functional classification for heart failure severity (Class I: no symptoms; Class II: shortness of breath during uphill walking; Class III: shortness of breath on level walking; Class IV: distress even at rest), among the LAPiS study patients who were Class II (4 patients) or Class III (6 patients) pre-transplantation, 7 out of 10 patients improved to Class I at 1 year post-transplantation.

Transplantation of regenerated cardiomyocytes is expected to improve contractility at the transplantation site. In this presentation, I highlighted a case where cardiomyocytes were transplanted into an area that had lost muscle tissue and formed an aneurysm due to myocardial infarction, resulting in the re-observation of myocardial contraction. It is widely understood that such areas do not regain contractility even if blood flow is improved via CABG because the heart muscle cells are absent. Therefore, the findings in this case represent a phenomenon unique to cardiac cell therapy.

Regarding safety, no ventricular arrhythmias or serious adverse events that would impede the continuation of the trial were observed. Although instances of herpes zoster and mild pneumonia associated with immunosuppressive therapy occurred, I reported that, overall, there were no major issues. Given that arrhythmia issues had been occurred in non-clinical and/or clinical trials by other groups, we received numerous questions during the Q&A session asking why such problems did not occur in our LAPiS study. I thoroughly addressed these questions by explaining our technical advantages.

At the end of the lecture, I announced the initiation of a clinical trial for catheter-based cardiomyocyte transplantation. I presented detailed information on the specific characteristics of our catheter system used and the transplantation sites in severe heart

failure cases due to dilated cardiomyopathy. Showing a procedural and imaging videos of the first case performed at Shinshu University Hospital drew a significant response. The fact that half of the questions in the session were concentrated on our presentation underscored the high level of global interest in this field.



Professor Faiez Zannad (left)



Professor Javed Butler (left)

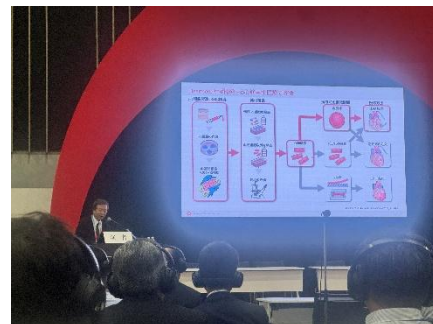
During the ESC, I also attended a meeting bringing together core members of CVCT (Cardiovascular Clinical Trialists), a U.S. organization focusing on cardiovascular clinical trials. Companies conducting high-profile clinical trials in this field are invited to this meeting, which is held

annually in Washington, D.C., in December. I met with Chairman Prof. Faiez Zannad (Professor Emeritus at Nancy University Hospital, France) and Co-chair Prof. Javed Butler (President of Baylor Scott & White Research Institute, U.S.), engaging in fruitful discussions regarding our role at the upcoming December congress.

■ Japanese College of Cardiology

On September 12, during the President's Special Session titled *"Where Is Japanese Cardiovascular Medicine Heading? — Future Strategies Connecting Basic Science, Clinical Practice, and Social Implementation,"* chaired by Congress President Prof. Tohru Minamino (Juntendo University) and Prof. Koji Maemura (Nagasaki University), I delivered a lecture similar to the one at ESC, covering the final results of the LAPiS study and initial progress of the EMERALD study based on catheter-based

administration. During the Q&A session and after the event, many physicians shared feedback such as, "I not only gained a clear understanding of the safety and efficacy of cardiac regenerative medicine, but I also held high expectations for the future development of this treatment." I would like to express my heartfelt gratitude to Prof. Minamino for providing such a special opportunity to present.



■ Closing Remarks

Previously, my international speaking engagements had mostly been at academic conferences specializing in regenerative medicine or biotechnology. However, this ESC congress was an international conference attended by many practicing physicians, and the Japanese College of Cardiology also boasts a high proportion of practicing physicians attendees. Now that the LAPiS study is complete and the EMERALD study is underway, I strongly felt firsthand that academic interest is shifting from "validating research outcomes" to a more practical phase: "how to bring this therapy to clinical practice."

Heartseed Inc. President and CEO Keiichi Fukuda



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