February 19, 2026
Medical Device Evaluation Division
Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Human Cellular/Tissue-based Products, 4. Human Induced Pluripotent Stem Cell-processed Products
Non-proprietary Name	Human (allogeneic) iPS cell-derived cardiomyocyte sheet
Brand Name	RiHEART
Applicant	Cuorips Inc.
Date of Application	April 4, 2025 (Application for marketing approval)

Results of Deliberation

In its meeting held on February 19, 2026, the Committee on Regenerative Medicine Products and Biotechnology reached the following conclusion, and decided that this conclusion should be presented to the Pharmaceutical Affairs Council.

The product may be approved. The conditional and time-limited approval is applicable to the product. The approval conditions and the duration of approval are as follows. The product should be designated as a Designated Regenerative Medical Product.

Approval Conditions

1. The applicant is required to conduct post-marketing approval condition assessment, for example through post-marketing surveillance covering all patients treated with the product, until the submission of an application for standard marketing approval of the product to which the conditional and time-limited approval has been granted.
2. The applicant is required to take necessary measures, such as dissemination of the guideline for proper use prepared in collaboration with the relevant academic societies and provision of seminars, to ensure that physicians with adequate knowledge and experience in the treatment of severe heart failure and thoracotomy have a full understanding of relevant information, including the results of the clinical study of the product and adverse events reported, to use the product in compliance with the “Indication or Performance” and “Dosage and Administration or Method of Use” at medical institutions with an established system for treatment of severe heart failure.
3. The applicant is required to collect information about biological properties of the product that reflect the mechanism of its action and to take necessary measures, such as improvement of the quality

control strategy, until the submission of an application for standard marketing approval of the product to which the conditional and time-limited approval has been granted.

Duration of Approval

7 years

Review Report

February 10, 2026
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following regenerative medical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	RiHEART
Classification	Human Cellular/Tissue-based Products, 4. Human Induced Pluripotent Stem Cell-processed Products
Non-proprietary Name	Human (allogeneic) iPS cell-derived cardiomyocyte sheet
Applicant	Cuorips Inc.
Date of Application	April 4, 2025

Shape, Structure, Active Ingredients, Quantities, or Definition
RiHEART is presented as human (allogeneic) induced pluripotent stem (iPS) cell-derived cardiomyocyte sheets, each containing 3.3×10^7 cardiomyocytes obtained by differentiating human (allogeneic) iPS cells. The cardiomyocyte sheets are prepared in a sheet form and embedded in a gel composed of gelatin and Hank's balanced salts solution with calcium and magnesium (HBSS(+)).

Application Classification	(1-1) New regenerative medical product
Items Warranting Special Mention	Orphan Regenerative Medical Product (Orphan Regenerative Medical Product Designation No. 37 of 2025 [*R7 sai*]; PSB/MDED Notification No. 1024-3 dated October 24, 2025, by the Medical Device Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare)
Reviewing Office	Office of Cellular and Tissue-based Products

Results of Review
On the basis of the data submitted, PMDA has concluded that the product is expected to have some efficacy in the treatment of severe heart failure associated with ischemic cardiomyopathy that has an inadequate response to standard-of-care therapies, including pharmacotherapy and invasive interventions, and that the product has acceptable safety (see Attachment). However, because the available information is currently limited, the efficacy of the product should continue to be evaluated and confirmed after the marketing approval.

As a result of its review, PMDA has concluded that the product may be approved for the indication or performance and dosage and administration or method of use shown below, with the following approval conditions, and that specifically, a conditional and time-limited approval under Article 23-26 of the Act

on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices may be granted to the product.

Indication or Performance

Treatment of severe heart failure associated with ischemic cardiomyopathy that has an inadequate response to standard-of-care therapies, including pharmacotherapy and invasive interventions

Dosage and Administration or Method of Use

1 Pretreatment before transplantation of RiHEART

1.1 Melt and remove the gel surrounding a cardiomyocyte sheet, wash the cardiomyocyte sheet with a washing fluid, and immerse it in this fluid.

2 Transplantation of RiHEART

2.1 Transplant 3 cardiomyocyte sheets on the heart surface sequentially. In principle, perform a left thoracotomy for the transplantation.

3 Treatment after RiHEART transplantation

3.1 Administer 3 immunosuppressants (prednisolone, tacrolimus, and mycophenolate mofetil) according to the dosage regimen provided below for a period of 90 days, starting on the following day of transplantation of cardiomyocyte sheets (Day 1). This period includes a tapering period. The doses should be adjusted according to the symptoms.

- The usual dosage of prednisolone is 20 mg orally administered once daily. Tapering is started approximately on Day 30.
- The usual dosage of tacrolimus is 1.5 mg orally administered twice daily. The dose should be adjusted to maintain the trough blood tacrolimus level in a range of 10 to 15 ng/mL by monitoring the trough blood level. Tapering is started approximately on Day 60.
- The usual dosage of mycophenolate mofetil is 1 g orally administered twice daily. Tapering is started approximately on Day 60.

Approval Conditions

1. The applicant is required to conduct post-marketing approval condition assessment, for example through post-marketing surveillance covering all patients treated with the product, until the submission of an application for standard marketing approval of the product to which the conditional and time-limited approval has been granted.
2. The applicant is required to take necessary measures, such as dissemination of the guideline for proper use prepared in collaboration with the relevant academic societies and provision of seminars, to ensure that physicians with adequate knowledge and experience in the treatment of severe heart failure and thoracotomy have a full understanding of relevant information, including the results of the clinical study of the product and adverse events reported, to use the product in compliance with the “Indication or Performance” and “Dosage and Administration or Method of Use” at medical institutions with an established system for treatment of severe heart failure.
3. The applicant is required to collect information about biological properties of the product that reflect the mechanism of its action and to take necessary measures, such as improvement of the quality

control strategy, until the submission of an application for standard marketing approval of the product to which the conditional and time-limited approval has been granted.

Attachment

Review Report (1)

December 11, 2025

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	RiHEART
Classification	Human Cellular/Tissue-based Products, 4. Human Induced Pluripotent Stem Cell-processed Products
Non-proprietary Name	Human (allogeneic) iPS cell-derived cardiomyocyte sheet
Applicant	Cuorips Inc.
Date of Application	April 4, 2025

Shape, Structure, Active Ingredients, Quantities, or Definition

RiHEART is presented as human (allogeneic) iPS cell-derived cardiomyocyte sheets, each containing 3.3×10^7 cardiomyocytes obtained by differentiating human (allogeneic) iPS cells. The cardiomyocytes are prepared in sheet form and embedded in a gel composed of gelatin and HBSS(+).

Proposed Indication or Performance

Treatment of severe heart failure associated with ischemic cardiomyopathy that has an inadequate response to standard-of-care therapies, including pharmacotherapy and invasive interventions

Proposed Dosage and Administration or Method of Use

(1) Apply heat to melt and remove the gelatin gel surrounding a cardiomyocyte sheet, wash the cardiomyocyte sheet with the attached washing fluid, and immerse it in the attached washing fluid.
(2) Transplant 3 cardiomyocyte sheets on the heart surface sequentially. In principle, perform a left thoracotomy for the transplantation.
(3) Administer 3 immunosuppressants (prednisolone, tacrolimus, and mycophenolate mofetil) basically according to the post-heart-transplantation regimen for 90 days (including a tapering period), starting on the following day of transplantation of cardiomyocyte sheets (Day 1).

Table of Contents

List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

1.1 Outline of the proposed product

RiHEART is a regenerative medical product that consists of human (allogeneic) induced pluripotent stem (iPS) cell-derived cardiomyocyte sheets, each containing 3.3×10^7 cardiomyocytes obtained by differentiating human (allogeneic) iPS cells and Hank's balanced salts solution with calcium and magnesium (HBSS(+)), which is used as a washing fluid. The cardiomyocyte sheets are prepared in a sheet form and embedded in a gel composed of gelatin and HBSS(+). The washing fluid is used in pre-transplantation steps for melting and removing the gelatin gel as well as washing and immersing the sheets. RiHEART, directly attached to the heart surface, is expected to promote cytokine secretion that can lead to improved myocardial conditions, thereby improving and maintaining the cardiac function and exercise tolerance.

RiHEART was designated as an orphan regenerative medical product with the intended indication of "Treatment of severe heart failure associated with ischemic cardiomyopathy that has an inadequate response to standard-of-care therapies, including pharmacotherapy and invasive interventions" on October 24, 2025 (Orphan Regenerative Medical Product Designation No. 37 of 2025 [*R7 sai*]).

1.2 Development history, etc.

Ischemic cardiomyopathy is a severe ischemic heart disease that is primarily caused by chronic ischemia associated with extensive myocardial infarction and multivessel lesions, is characterized by myocardial remodeling in response to left ventricular dilatation and severely impaired ventricular wall motion, occurring secondary to chronic ischemia, and potentially results in chronic congestive heart failure.

The standard of care in patients with ischemic cardiomyopathy consists of non-invasive treatment and invasive interventions. The non-invasive treatment is basically provided as pharmacotherapy, which may be combined with cardiac rehabilitation and adaptive servo-ventilation if indicated. The invasive interventions may include coronary artery bypass graft surgery, percutaneous transluminal coronary angioplasty, and cardiac resynchronization therapy (CRT) using a pacemaker. In patients with severe ischemic cardiomyopathy, however, such standard of care often fails to improve heart failure symptoms. When the disease has had inadequate response to the conventional standard of care and is further progressed, it reaches the end stage that disables the patient from supporting life with their own heart, resulting in a condition where the patient requires heart transplantation or a ventricular assist device. Heart transplantation, however, carries issues such as lack of donors, age restrictions, and life-long use of immunosuppressants. Ventricular assist devices also have issues such as durability of the device and a risk of device-associated infections and neurologic dysfunctions. There is a need for treatment that aims at extending survival by improving or maintaining the cardiac function and exercise tolerance and thereby preventing the disease from reaching the end stage requiring heart transplantation or a ventricular assist device.

An investigator-initiated trial (Study CVSC0005) of RiHEART was conducted in Japan, starting in 2019. The application has now been submitted mainly based on the results from Study CVSC0005. Study CVSC0005 was conducted as an investigator-initiated clinical trial supported by the Program for of Research Center Network for Realization of Regenerative Medicine (Centers for Clinical Application

Research on Specific Disease/Organ) and the Research Project for Practical Applications of Regenerative Medicine of the Japan Agency for Medical Research and Development.

As of November 2025, RiHEART has not been approved or marketed in any country or region.

2. Quality and Outline of the Review Conducted by PMDA

RiHEART is a cell-based product prepared as a cell sheet containing cardiomyocytes obtained by differentiating iPS cells, which are manufactured from an iPS cell bank. The iPS cell bank was prepared from an iPS cell stock (QHJI14s04) established by transfecting episomal vectors in peripheral blood mononuclear cells donated by a healthy adult.

2.1 iPS cell bank

The iPS cell bank used in manufacture of RiHEART is prepared through the expansion culture of an iPS cell stock, which was dispensed by the Center for iPS Cell Research and Application (CiRA).

2.1.1 Establishment of iPS cell stock

The source cells used for RiHEART are iPS cells derived from peripheral blood mononuclear cells of a healthy adult donor with the human leukocyte antigen (HLA) haplotypes (HLA-A*24:02, HLA-B*52:01, HLA-C*12:02, HLA-DRB1*15:02, HLA-DQB1*06:01, and HLA-DPB1*09:01) that cover approximately 17% of the Japanese population. At the CiRA, human peripheral blood cells collected in 20[redacted], which was used as the original materials, was transfected with 5 episomal vectors [see Section 2.1.1.1]. From the cells, a clone QHJI14s04 was selected based on the results of the cell growth assay, residual plasmid assay, karyotyping, and genome analysis to establish the iPS cell stock. No regeneration of the iPS cell stock is planned.

The cell stock was characterized in terms of sterility, mycoplasma, bacterial endotoxins, viruses (hepatitis B virus [HBV], hepatitis C virus [HCV], human immunodeficiency virus [HIV]-1, HIV-2, human T-cell leukaemia virus [HTLV]-1, HTLV-2, and parvovirus [PV] B19), HLA, short tandem repeat (STR), morphological features, karyotypes, residual plasmids, genomes, clonal structure, expression of markers specific to undifferentiated state, viable cell count after thawing, proliferating cell count after thawing, and proliferation rate.

2.1.1.1 Episomal vectors

The iPS cell stock was generated using 5 episomal vectors (pCE-hSK, pCE-hUL, pCE-hOCT3/4, pCE-mp53DD, and pCXB-EBNA1). pCE-hSK contains a gene expression cassette encoding hSOX2 and human kruppel like factor 4 (hKLF4), pCE-hUL contains a gene expression cassette encoding hL-MYC and human Lin-28 homolog A (hLIN28), pCE-hOCT3/4 contains a gene expression cassette encoding hOCT3/4, and pCE-mp53DD contains a gene expression cassette encoding mp53DD, each designed to express the respective genes with EBNA-1 under the control of the CAG promoter. pCXB-EBNA1 contains a gene expression cassette encoding EBNA-1 alone under the control of the CAG promoter. All the episomal vectors were prepared at [redacted], using DNA plasmids constructed by the CiRA, as the starting materials. The control tests include description, [redacted],

[redacted], sterility, bacterial endotoxins, [redacted], [redacted], [redacted], [redacted], and [redacted].

2.1.2 Safety evaluation for adventitious agents in iPS cell bank

2.1.2.1 Human peripheral blood mononuclear cells

The human peripheral blood mononuclear cells used as the starting material for the iPS cell bank comply with the Standards for Biological Raw Materials (MHLW Public Notice No. 210 of 2003). Donor eligibility was confirmed by interview (medical history, travel history, and prior transplantation or transfusion) and by testing blood samples collected from the donor for viruses and other infectious agents (syphilis, HBV, HCV, HIV-1, HIV-2, HTLV-1, PVB19, and cytomegalovirus [CMV]).

2.1.2.2 Biological raw materials other than human peripheral blood mononuclear cells

A biological raw material other than human peripheral blood mononuclear cells used until preparation of the iPS cell bank is [redacted], which is used for establishment of the iPS cell stock and preparation of the iPS cell bank. This material has been confirmed to comply with the Standards for Biological Raw Materials (MHLW Ministerial Public Notice No. 210 of 2003).

2.1.3 Control of iPS cell bank

A master cell bank (MCB) and a working cell bank (WCB) were prepared using the iPS cell stock dispensed by the CiRA as the starting material. Table 1 shows tests performed with the MCB, WCB, and cells at the limit of in vitro cell age (LIVCA). Within the scope of tests performed for adventitious agents, neither viral nor non-viral adventitious agents were detected.

The MCB and WCB are stored in the vapor phase of liquid nitrogen. No regeneration of the MCB is planned, but new WCB will be prepared where necessary.

A genome analysis with the MCB ruled out any mutations in oncogenes.[1)]

Table 1. Characterization tests for the iPS cell bank

Bacterial endotoxins*1	
Mycoplasma*2	
Sterility*2	
Viruses	Electron microscopy*3
	Reverse transcriptase activity*3
	Infectivity (coculture with HEK293 cells)*3
	In vitro assays (MRC-5 cells, Vero cells, and HeLa cells)*3
	In vivo assays (suckling mice, adult mice, guinea pigs, and embryonated eggs)*3
	Human virus tests (nucleic acid amplification method) ([redacted])*1
Identity (STR analysis)*1	
Genome*1	

*1 Performed with the MCB
*2 Performed with the MCB and WCB
*3 Performed with the MCB and LIVCA

1) Genes included in the COSMIC census (ver. 88 or 92) and shibata list (PMDA Science Board [Cellular and Tissue-based Products Subcommittee], "Current Preparation on Evaluation of Tumorigenicity of Cellular and Tissue-based Products Derived from induced Pluripotent Stem Cells (iPSCs) and iPSCs as Their Starting Materials" (dated August 20, 2013)

2.2 Critical intermediates

Cardiomyocytes obtained by differentiating iPS cells are positioned as a critical intermediate.

2.2.1 Manufacturing process

2.2.1.1 Manufacturing process

The manufacturing process of the critical intermediate consists of the expansion culture of undifferentiated iPS cells (WCB thawing, seeding, and passage culture), induction of differentiation into cardiomyocytes, removal of undifferentiated iPS cells (treatments with [redacted]), and freezing and storage.

All the steps have been defined as critical steps.

2.2.1.2 In-process control tests

Table 2 shows in-process control tests in the manufacturing process of the critical intermediate.

Table 2. In-process control tests in the manufacturing process of the critical intermediate

Step	Test item
Expansion culture of undifferentiated iPS cells[*1]	Appearance
	Viable cell count
	Cell viability
	[redacted]
Induction of differentiation into cardiomyocytes[*2]	Identification of cardiomyocytes ([redacted])
Removal of undifferentiated iPS cells[*3]	Purity ([redacted])

*1 [redacted]

*2 [redacted]

*3 [redacted]

2.2.3 Safety evaluation for adventitious agents other than those in iPS cell bank

Table 3 shows biological raw materials used in the manufacturing process of the critical intermediate. All the materials have been confirmed to comply with the Standards for Biological Raw Materials.

Table 3. Biological raw materials used in the manufacturing process of the critical intermediate

Raw material		Animal	Part used	Process used
[redacted]		Hamster (CHO suspension cells)	-	[redacted]
FBS	Fetal bovine serum	Bovine	Blood	
[redacted]	Casein hydrolysate	Bovine	Milk	
Human serum albumin		Human	Blood	
[redacted]	Human serum albumin	Human	Blood	
[redacted]		Hamster (CHO cells)	-	
Gelatin		Porcine	Skin	

2.2.4 Manufacturing process development

Table 4 shows major changes to the manufacturing process during development.

Table 4. Major changes to manufacturing process

Process change	Description of change
From Process A to Process B	Change of manufacturing site, establishment of WCB, and change of culture scale
From Process B to Process C	Change of manufacturing site

Table 5 shows the manufacturing process of the critical intermediate used in manufacture of products subjected to non-clinical and clinical studies.

Table 5. Manufacturing process of critical intermediate used in manufacture of products evaluated in non-clinical and clinical studies

Manufacturing process	Non-clinical or clinical study using the product
Process A	Non-clinical studies, Study CVSC0005[*1]
Process B	Non-clinical studies
Process C (proposed process)	Non-clinical studies, Study CVSC0005[*1]

*1 In Study CVSC0005, 3 patients enrolled in Cohort A and 5 patients enrolled in Cohort B-I received products prepared from the critical intermediate manufactured in Processes A and C, respectively, as grafts.

In response to these process changes, quality attributes were assessed for comparability. For each of the process changes, pre- and post-change critical intermediates have been confirmed to be comparable.

2.2.5 Control of critical intermediate

Table 6 shows specifications of the critical intermediate.

Table 6. Specifications of critical intermediate

Test item		Test method
Description		Visual inspection
Identification	Identification of cardiomyocytes	Flow cytometry
	Sheet-forming ability check[*1]	Visual inspection
	Identification of cardiomyocytes after sheet formation[*1]	Flow cytometry
Purity	Cell viability	Cell counter
	[redacted]	
Bacterial endotoxin test		Turbidimetric technique (Japanese Pharmacopoeia)
Sterility test		Membrane filtration method (Japanese Pharmacopoeia)
Mycoplasma testing		Nucleic acid amplification test method (General Information in the Japanese Pharmacopoeia)
Viruses[*2]		qPCR
Viable cell count		Cell counter

*1 Specimens are cardiomyocyte sheets manufactured from the critical intermediate in the same manufacturing process as that for the final product.
*2 HIV-1, HIV-2, HTLV-1, HBV, HCV, CMV, Epstein-Barr virus (EBV), PVB19, west nile virus (WNV)-1a, and WNV-2

2.2.6 Stability of critical intermediate

Table 7 shows the outline of the main stability study of the critical intermediate.

Table 7. Outline of stability study of critical intermediate

	Number of batches	Manufacturing process	Storage condition	Study period	Storage form
Long-term testing	2	Process C (proposed process)	In vapor phase of liquid nitrogen (≤-[redacted]°C)	[redacted] months	Polypropylene vials for cryopreservation

In the long-term testing using 2 batches of the critical intermediate manufactured in the proposed process, no clear changes were observed in quality attributes throughout the study period. Currently, a long-term testing with the third batch is ongoing. The applicant explained that the shelf life of the critical intermediate will be established based on the results from this study.

2.3 Product

2.3.1 Description and composition of product and formulation development

The product consists of cardiomyocyte sheets, each containing 3.3×10^7 cardiomyocytes derived from human (allogeneic) iPS cells. The sheet is embedded in a gel comprised of gelatin and HBSS(+), which are defined as sub-ingredients. Each product consists of 4 sheets, including a spare. In addition, HBSS(+) is attached for use in pre-transplantation steps for melting and removing the gel as well as washing and immersing the sheets.

2.3.2 Manufacturing process

The manufacturing process of the product consists of steps for thawing and sheet preparation (thawing and seeding the critical intermediate, changing the medium, detaching sheets, and embedding the sheet in a gel) as well as packaging and packing.

Thawing and sheet preparation have been defined as critical steps.

Table 8 shows in-process control tests in the manufacturing process of the product.

Table 8. In-process control tests in manufacturing process of the product

Step		Test item
Thawing and sheet preparation	Thawing and seeding the critical intermediate	Cell viability
	Detaching sheets and embedding in gels	Appearance (description)
		[redacted]

2.3.3 Safety evaluation for adventitious agents

Biological raw materials used in the manufacturing process of the product are fetal bovine serum (FBS) and gelatin, both of which are confirmed to comply with the Standards for Biological Raw Materials.

2.3.4 Manufacturing process development

Table 9 shows major changes to the manufacturing process during development.

Table 9. Major changes to the manufacturing process

Manufacturing process change	Description of change
From Process I to Process II	Change of manufacturing site, change of form of a gel embedding the final product
From Process II to Process III	Change of manufacturing site
From Process III to Process IV (proposed process)	Change of primary and secondary containers

Table 10 shows the processes of the products subjected to non-clinical and clinical studies.

Table 10. Processes of the products subjected to non-clinical and clinical studies

Manufacturing process	Non-clinical or clinical study using the product
Process I	Non-clinical studies, Study CVSC0005
Process II	Non-clinical studies
Process III	Non-clinical studies, Study CVSC0005

Process changes from Process I to Process II and from Process II to Process III were made simultaneously with the changes to the manufacturing process of the critical intermediate, from Process A to Process B and from Process B to Process C, respectively. Quality attributes of the pre- and post-change products were evaluated for comparability in coordination with evaluation of the pre- and post-change critical intermediates [see Section 2.2.4]. The pre- and post-change products have been confirmed to be comparable.

2.3.5 Characterization

2.3.5.1 Structure and characterization

The products were tested for [redacted], viable cell count, and cell viability. [redacted] were used to measure [redacted].

2.3.5.2 Process-related impurities

Process-related impurities are [redacted], gelatin, FBS, [redacted], Kenketsu Albumin 25% I.V. Injection, [redacted].

[redacted], [redacted], [redacted], and [redacted]. All the process-related impurities have been confirmed to raise no or insignificant safety concerns in humans by assessment of exposures calculated from measured or estimated residual amounts of them in the final product.

2.3.5.3 Contamination with unintended cells

Because undifferentiated iPS cells may remain as unintended cells in RiHEART, treatments with [redacted] are performed in the process for removal of undifferentiated iPS cells from the critical intermediate. To control removal of undifferentiated iPS cells, purity test is included in the in-process control tests after treatments with [redacted] as well as specification tests of the critical intermediate [see Sections 2.2.1.2 and 2.2.5]. Although the in-process control tests for and specifications of the product do not include items to control undifferentiated iPS cells, [redacted] expression level in a fresh cell suspension prepared by thawing the critical intermediate, which corresponds to a specimen subject to the specifications of the critical intermediate, has been confirmed to be comparable to that in a cell suspension prepared by re-dispersing cells from the formed sheet.

2.3.6 Control of product

Table 11 shows specifications of the product. Test cardiomyocyte sheets manufactured from the critical intermediate in the same manufacturing process as that of the final product are used as specimens for sheet-forming ability check and identification of cardiomyocytes after sheet formation, which are included in the specifications of the critical intermediate [see Section 2.2.5]. In addition, sterility test (membrane filtration method) is performed as a post-release confirmatory test using an equal-volume mixture of the culture supernatant and final washing of a cardiomyocyte sheet collected on the day of release, and the results are confirmed after transplantation.

Table 11. Specifications of product

Test item	Test method
Description	Visual inspection
Bacterial endotoxin test*1	Turbidimetric technique (Japanese Pharmacopoeia)
Mycoplasma testing*2	Nucleic acid amplification test method (General Information in the Japanese Pharmacopoeia)

*1 Test is performed using the final washing of a cardiomyocyte sheet collected on the day of release (specimen at the last point that can deliver the result before release judgement).
*2 Test is performed using the culture supernatant of a cardiomyocyte sheet collected on the day of release (specimen at the last point that can deliver the result before release judgement).

2.3.7 Stability of product

Table 12 shows the outline of the main stability studies of the product.

Table 12. Outline of stability studies of product

Study	Number of batches	Manufacturing process	Storage condition	Study period[*1]	Storage form
Long-term testing	3	Process II	15°C-23°C	66 hours	Primary container: [redacted] Secondary container: [redacted]
	1	Process IV (proposed process)	15°C-23°C	48 hours	Primary container: UpCell ADVANCE 6cm dish, [redacted] dish lid Secondary container: [redacted] dish holder, body and [redacted]

*1 Test is performed using a sample of the conditioned cardiomyocyte sheet prepared by melting and removing the gelatin gel and immersing the exposed sheet in HBSS(+) for 6 hours.

In a long-term testing using the product batches manufactured in Process II, a decrease in cell viability was observed in some of the batches stored for 66 hours. Currently, a long-term testing and a study for stability during transportation using product batches manufactured in Process IV (proposed process) are ongoing. The applicant explained that the shelf life of the product will be established based on the results from these studies.

2.4 Verification

Because it is difficult to perform prospective process validation for the manufacturing process to ensure that a product of the intended quality can be manufactured consistently, the applicant plans to conduct continuous process verification during commercial manufacturing. Through this verification consisting of the following elements, it will be confirmed for each batch that a product of the intended quality has been manufactured:

- Manufacturing process parameters
- In-process control tests (Tables 2 and 8)
- Specifications for the critical intermediate and product (Tables 6 and 11)
- Confirmatory test (sterility test [membrane filtration method], Japanese Pharmacopoeia)

2.R Outline of the review conducted by PMDA

PMDA's view on the quality of the critical intermediate and product:

For storage conditions and shelf lives of the critical intermediate and product, PMDA's conclusion in view of study results including ones to be submitted in the future will be presented in the Review Report (2). Quality control of RiHEART for the other matters is considered to have no problem at present.

Because the mechanism of action of RiHEART has not been fully elucidated [see Section 3.R.1], the applicant should continue collecting post-marketing information on RiHEART's biological attributes that reflect the mechanism of its action and should take necessary measures such as improvement of the quality control strategy of RiHEART in view of the available information including that from verifications.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

3.1 Primary pharmacodynamics or performance

The applicant submitted data supporting the primary pharmacodynamics or performance of RiHEART in the form of results from the following studies.

3.1.1 Study using myocardial infarction (coronary artery complete occlusion) nude rat model (CTD 4.2.1.1-1) (Study No. 10558)

The study used a myocardial infarction model created from immunocompromised male rats.[2)] The RiHEART group (n = 10) underwent thoracotomy and transplantation of RiHEART 2.9 × 10^6 cells (1 sheet)[3)] onto the heart surface (left ventricular anterior wall), and the graft was immobilized using a fibrinogen-aprotinin solution and a thrombin-calcium chloride solution.[4)] The sham group (n = 11) underwent thoracotomy as with the RiHEART group followed by instillation of a fibrinogen-aprotinin solution and a thrombin-calcium chloride solution onto the exposed heart surface. Over a period up to 8 weeks after the operation, cardiac function (left ventricular ejection fraction [LVEF], fractional shortening [FS], left ventricular end-diastolic dimension, left ventricular end-systolic dimension, left ventricular end-diastolic anterior wall thickness, and left ventricular end-diastolic posterior wall thickness) was evaluated by echocardiography.

Table 13 shows echocardiography results for cardiac function parameters. Results for LVEF and FS were significantly higher in the RiHEART group than in the sham group at Weeks 2, 4, 6, and 8.

Table 13. Echocardiography results for cardiac function indices

Index	Group	Before operation	Week 2	Week 4	Week 6	Week 8
LVEF (%)	Sham[*1]	53.2 ± 0.9	53.2 ± 0.7	53.3 ± 0.7	52.8 ± 0.8	52.3 ± 0.9
	RiHEART	53.5 ± 0.5	60.1 ± 0.9[*2]	60.2 ± 1.1[*2]	60.5 ± 0.9[*2]	60.5 ± 1.0[*2]
FS (%)	Sham[*1]	22.4 ± 0.5	22.3 ± 0.4	22.4 ± 0.4	22.1 ± 0.4	21.9 ± 0.5
	RiHEART	22.6 ± 0.3	26.4 ± 0.5[*2]	26.5 ± 0.7[*2]	26.7 ± 0.6[*2]	26.6 ± 0.6[*2]
Left ventricular end-diastolic dimension (mm)	Sham[*1]	7.5 ± 0.2	8.2 ± 0.2	8.4 ± 0.2	8.7 ± 0.2	8.9 ± 0.2
	RiHEART	7.4 ± 0.2	8.0 ± 0.2	8.3 ± 0.2	8.7 ± 0.2	8.9 ± 0.2
Left ventricular end-systolic dimension (mm)	Sham[*1]	5.8 ± 0.2	6.4 ± 0.2	6.5 ± 0.2	6.8 ± 0.2	7.0 ± 0.2
	RiHEART	5.7 ± 0.1	5.9 ± 0.2	6.1 ± 0.2	6.4 ± 0.2	6.5 ± 0.2
Left ventricular end-diastolic anterior wall thickness (mm)	Sham[*1]	1.1 ± 0.0	1.1 ± 0.0	1.1 ± 0.0	1.1 ± 0.0	1.0 ± 0.0
	RiHEART	1.1 ± 0.0	1.1 ± 0.0	1.1 ± 0.0	1.2 ± 0.0[*2]	1.1 ± 0.0[*2]
Left ventricular end-diastolic posterior wall thickness (mm)	Sham[*1]	1.9 ± 0.0	1.9 ± 0.0	2.0 ± 0.0	2.0 ± 0.0	2.0 ± 0.0
	RiHEART	1.9 ± 0.0	1.9 ± 0.0	2.0 ± 0.0	2.1 ± 0.0	2.1 ± 0.0

Mean ± standard error.
*1 Because 1 sham-operated animal died on the day of sham operation, 10 animals were subjected to evaluation except that before the operation.
*2 $P < 0.01$ vs. sham group (Student t test).

3.2 Secondary pharmacodynamics

3.2.1 Evaluation for cytokine secretion ability in myocardial infarction (coronary artery complete occlusion) nude rat model (CTD 3.2.S.3.1-2, reference data)

An analysis of [redacted] using Multiplex Immunoassay for a panel of [redacted] cytokines revealed that [redacted] cytokines were measurable. Of them, [redacted] cytokines ([redacted]) were identified as cytokines that expressed at relatively high levels and were expected to be produced in cardiomyocytes.

2) Male nude rats (F344/NJcl-rnu/rnu) aged 8 to 9 weeks underwent ligation of the left anterior descending coronary artery followed by echocardiography 11 and 12 days after ligation. Animals with LVEF of 30% to 55% were deemed appropriate for the myocardial infarction model.
3) The cell sheet was prepared as a sheet large enough to be transplanted onto the left ventricular anterior wall in rats. The cell count per sheet is approximately 7 times that per sheet for clinical use on the basis of body weight, which is assumed to be 60 kg for humans and 0.25 kg for rats.
4) [redacted]

To evaluate the impact of these [redacted] cytokines, produced from transplanted RiHEART, on cardiac function, sequence analyses were performed for rat and human genes using RNA extract specimens. For the analyses, RiHEART 2.9 × 10^6 cells (1 sheet)[3)] was transplanted into the myocardial infarction model created from immunocompromised male rats,[2)] and samples were collected at the transplantation site and its vicinity at Week 1 and subjected to RNA extraction.

An analysis of specimens from cardiac tissues at the transplantation site for rat genes identified the genes of which expression level changed in the RiHEART group compared with that in the sham group. An analysis of results from Causal Network Analysis (*Bioinformatics.* 2013;30:523-30) using the "Upstream Analysis" function in software for ingenuity pathway analysis (IPA) in comparison with data on the [redacted] cytokines identified by the Multiplex Immunoassay led to prediction that [redacted], [redacted], [redacted], and [redacted] would be cytokines activating expression of these genes. An analysis of specimens from tissues at the transplantation site and its vicinity for human genes was performed to check for expression of [redacted], [redacted], [redacted], and [redacted] genes derived from the transplanted RiHEART, and expression of [redacted], [redacted], and [redacted] genes was detected in specimens from cardiac tissues in 3 of 4 animals but expression of [redacted] gene was not.[5)]

3.3 Safety pharmacology

3.3.1 Study for evaluation of effects of RiHEART on cardiovascular system in miniature swine (CTD 4.2.1.3-1)

Table 14 outlines the results of a safety pharmacology study (28-day observation) in male miniature swine. Transplanted RiHEART did not affect the cardiovascular system.

Table 14. Outline of results of safety pharmacology study

Test system	Transplantation site	Observation period	Dose (cells/sheet/body)	Results	Attached document
Male miniature swine (Göttingen)	Heart surface	28 days	Sham group (n = 4)[*1]: 0 RiHEART group (n = 4): 9.9×10^7 (3 sheets, each containing 3.3×10^7 cells)	On Day 7, systolic blood pressure was higher in the RiHEART group than in the sham group, but no significant difference was observed in diastolic blood pressure or mean blood pressure between the groups. The high systolic blood pressure was considered unrelated to transplanted RiHEART. No differences were observed in the other evaluation items (clinical signs, body weight, food consumption, heart rate, electrocardiogram [QTc],[*2] oxygen saturation, and necropsy) between the RiHEART and sham groups.	4.2.1.3-1

*1 The sham group underwent thoracotomy as with the RiHEART group followed by instillation of a fibrinogen-aprotinin solution and a thrombin-calcium chloride solution.

*2 QTc was calculated from the measured RR interval, PR interval, QRS width, and QT interval.

5) No human genes were detected in specimens from 1 animal. A potential cause was that (1) transplanted cells did not survive; or (2) the system to detect trace amounts of human RNA in rat cardiac tissues had limitations even in specimens from tissues where the transplanted cells survived.

3.R Outline of the review conducted by PMDA

Based on the submitted data and the following review, PMDA accepted the applicant's explanation about non-clinical pharmacology of RiHEART.

3.R.1 Mechanism of action of RiHEART

The applicant's explanation about the mechanism of action of RiHEART:

In the study using the myocardial infarction model created from immunocompromised rats, LVEF and FS were significantly higher in the RiHEART group than in the control group, indicating that the transplanted RiHEART improved cardiac function.

Human genes of which expression was detected at the transplantation site and its vicinity in the myocardial infarction model created from immunocompromised rats were [redacted], [redacted], and [redacted] genes. These expressed products or proteins are known to have biological effects mainly on angiogenesis ([redacted]), stem cell mobilization ([redacted]), and antiinflammation ([redacted]). The cytokines produced in the transplanted RiHEART are considered to have acted on the rat heart in a paracrine manner and consequently improved the cardiac function.

As described the above, RiHEART transplanted onto the heart surface can be expected to produce various cytokines acting in a paracrine manner and thereby improve cardiac function.

Because other cytokines are potentially involved in the action of RiHEART, the applicant will continue striving to elucidate the mechanism of the action.

PMDA's view:

Results of the study using the myocardial infarction model created from immunocompromised rats suggested that transplanted RiHEART could contribute to improvement of cardiac function. However, the following issues remain unclear: whether improvement of cardiac function associated with transplantation of RiHEART can be accounted for only by the paracrine effect, as explained by the applicant; and whether cytokines contributing to the paracrine effect are only [redacted], [redacted], and [redacted]. To this end, the applicant must continue to make efforts to elucidate the mechanism of action of RiHEART even in post-marketing settings.

4. Biological Disposition and Outline of the Review Conducted by PMDA

The applicant submitted non-clinical biological disposition data for RiHEART in the form of results from single-session transplantation toxicity and *in vivo* tumorigenicity studies in NOD.Cg-PrkdcscidIl2rgtm1Sug/ShiJic (NOG) mice using RiHEART and its analog.[6)]

[6)] The test article manufactured from the critical intermediate prepared without [redacted] treatment, which was supposed to be performed in the step for removal of undifferentiated iPS cells. Although [redacted] expression level was higher than the acceptance limit for the critical intermediate, values on the other test items met the specifications of the critical intermediate.

4.1 Non-clinical biological disposition

4.1.1 Analytical methods

For evaluation of non-clinical biological disposition of RiHEART, the human Alu-quantitative polymerase chain reaction (qPCR) method was used to detect human cells in each tissue. Lamin-positive cells in the heart and chest wall were detected by immunohistochemical staining.

4.1.2 Biodistribution

Studies listed in Table 15 were conducted using RiHEART and its analog.

Table 15. Biodistribution studies of RiHEART and its analog transplanted onto the heart surface in single session

Test system	Observation period	Test article	Dose (cells/sheet/body)	Results	Attached document
Male and female NOG mice	4 weeks	RiHEART	7.5×10^5 (1 sheet)	At Week 4, human cells were detected in the heart in all of the 3 males[*1] and 4 females but were less than the lower limit of quantitation in the other tissues (lungs, liver, spleen, kidneys, bone marrow, ovaries, testes, and cerebrum). At Week 4, of 8 males,[*2] 1 and 6 were found to have Lamin-positive cells in the pericardial adipose tissue and at the thoracotomy site on the chest wall, respectively. Of 11 females,[*3] 1 and 8 were found to have Lamin-positive cells in the pericardial adipose tissue and at the thoracotomy site on the chest wall, respectively.	4.2.2.3-1
		RiHEART analog		At Week 4, human cells were detected in the heart in all of the 4 males and 4 females and in the lungs in 2 females but were less than the lower limit of quantitation in the other tissues (liver, spleen, kidneys, bone marrow, ovaries, testes, and cerebrum). At Week 4, of 9 males,[*4] 1 and 7 were found to have Lamin-positive cells in the pericardium/myocardial surface and at the thoracotomy site on the chest wall, respectively. Of 10 females,[*5] 1 and 9 were found to have Lamin-positive cells in the pericardial adipose tissue and at the thoracotomy site on the chest wall, respectively.	
Male and female NOG mice	45 weeks	RiHEART	7.5×10^5 (1 sheet)	At Week 45, of 20 males, 18 and all were found to have Lamin-positive cells in the pericardium/myocardial surface and at the thoracotomy site on the chest wall, respectively. Of 18 females, 17 and all were found to have Lamin-positive cells in the pericardium/myocardial surface and at the thoracotomy site on the chest wall, respectively.	4.2.3.4-1

*1 Of 4 males which underwent transplantation of RiHEART, 1 dropped out because of death, and 3 were subjected to the analysis.
*2 Of 10 males which underwent transplantation of RiHEART, 2 dropped out because of death, and 8 were subjected to the analysis.
*3 Of 11 females which underwent transplantation of RiHEART, 1 dropped out because of death, and a total of 11 females including 1 added later were subjected to the analysis.
*4 Of 10 males which underwent transplantation of RiHEART, 1 dropped out because of death, and 9 were subjected to the analysis.
*5 Of 11 females which underwent transplantation of RiHEART, 1 dropped out because of death, and 10 were subjected to the analysis.

4.1.3 Metabolism and excretion

Non-clinical studies to evaluate metabolism and excretion of RiHEART were not conducted.

4.2 Clinical biological disposition

Clinical biological disposition of RiHEART was not evaluated.

4.R Outline of the review conducted by PMDA

The applicant's explanation about biological disposition of RiHEART:

RiHEART transplanted onto the heart is considered to survive at the transplantation site for approximately 3 months and disappear within 6 months in view of a period of use of immunosuppressants, which is up to 90 days after transplantation of RiHEART in clinical practice [see Section 6.R.5], and the following findings:

- In NOG mice in which RiHEART was transplanted onto the heart, Lamin-positive cells were detected at the transplantation site and its vicinity at Week 45. However, because immunocompromised mice provide conditions in which transplanted cells are likely to survive, in immunocompetent conditions, transplanted allogeneic or xenogeneic cells are likely to be rapidly eliminated by immune response.
- Cardiomyocyte sheets prepared from cynomolgus monkey iPS cells were transplanted onto the heart surface in cynomolgus monkeys, and then survival of the grafts in animals receiving immunosuppressants was evaluated in a study. The transplanted cells decreased with increasing time after transplantation in this study; they were detected at up to Month 4 but no longer detected at Month 6 (*Transplantation.* 2019;103:1582-90).

In view of the following points, after transplantation of RiHEART into humans, transplanted cells are considered unlikely to distribute into the other organs.

- In the studies using RiHEART, human cells were less than the lower limit of quantitation in all the tissues including the lungs except for the heart in all animals. In the study using RiHEART analog, human cells were detected in the lungs in 2 females at Week 4, but the most likely potential cause is that (2) a very small number of human cells spilled during transplantation survived or (1) human cells fell off during necropsy or sampling.
- In the non-clinical studies, the thoracotomy incision was closed without suturing the pericardium incision, but in clinical transplantation of RiHEART, pericardium incision should be basically sutured before closure of the thoracotomy incision. Cells of RiHEART are considered unlikely to fall into the thoracic cavity.

PMDA has concluded that RiHEART has no particular concerns about biological disposition at present, although biological disposition of RiHEART in humans is not evaluated, and a survival period of transplanted RiHEART in humans remains unclear.

5. Non-clinical Safety and Outline of the Review Conducted by PMDA

The applicant submitted non-clinical safety data of RiHEART in the form of results from single-session transplantation general toxicity and tumorigenicity studies in immunocompromised mice.

5.1 Single-session transplantation toxicity

A single-session transplantation toxicity study using RiHEART and its analog was conducted as presented in Table 16.

Table 16. General toxicity study

Test system	Transplantation site	Observation period	Dose (cells/sheet/body)	Main findings	Attached document
Male and female mice (NOG)	Heart surface	4 weeks	Sham group*1: 0 RiHEART group: 7.5×10^5 (1 sheet) RiHEART analog group: 7.5×10^5 (1 sheet)	Death: 4 of 12 males in the sham group, 3 of 11 males in the RiHEART group, 1 of 10 males and 1 of 11 females in the RiHEART analog group Adhesion of the thoracotomy site to the heart, eosinophilic substances in the thoracotomy site, inflammatory cell infiltration and fibrogenesis in the pericardium/myocardial surface, inflammatory cell infiltration in pericardial adipose tissue, inflammatory cell infiltration and bleeding in the thoracotomy site on the chest wall, congestion of the lungs Sham group: Fibrogenesis in the left ventricular pericardium/myocardial surface, inflammatory cell infiltration in pericardial adipose tissue RiHEART group: Fibrogenesis in the left ventricular pericardium/myocardial surface RiHEART analog group: Fibrogenesis in the left ventricular pericardium/heart surface	4.2.3.1-1

*1 The sham group underwent thoracotomy as with the RiHEART group followed by instillation of a fibrinogen-aprotinin solution and a thrombin-calcium chloride solution.

Findings in these groups including dead animals were biological responses to thoracotomy and thus not considered to suggest effects of the test article.

5.2 Tumorigenicity

Soft agar colony formation assay, karyotyping, cell growth characterization, and tumorigenicity studies in NOG mice were performed. According to discussion on the results, cells constituting RiHEART and undifferentiated iPS cells potentially present in RiHEART have no tumorigenicity risk.

5.2.1 Soft agar colony formation assay (4.2.3.4-13)

Soft agar colony formation assay was performed using suspensions of cardiomyocytes prepared from RiHEART and its analog. The suspensions of cardiomyocytes prepared from RiHEART and its analog did not exhibit anchorage-independent growth.

5.2.2 Genetic stability study (4.2.3.4-14, 4.2.3.4-15)

To evaluate genetic stability, genome DNA extract samples prepared from RiHEART were subjected to array comparative genomic hybridization (CGH). Comparison of genome DNA extracted from RiHEART with that from the WCB showed no significant copy number variations (CNVs).

5.2.3 Cell growth characterization study (4.2.3.4-16)

Cells obtained by 1-passage culture of suspensions of cardiomyocytes prepared from RiHEART were subjected to cell growth characterization, and cell growth rate was measured in cultures maintained for up to 6 passages. Cardiomyocytes prepared from RiHEART in the form of suspension did not show any significant increase in cell growth rate during passage cultures.

5.2.4 Tumorigenicity studies in NOG mice

Tumorigenicity studies in NOG mice were conducted as presented in Table 17.

Table 17. Tumorigenicity

Study	Outline and results	Attached document
Male and female mice (NOG)	NOG mice aged 7 weeks underwent transplantation of RiHEART 7.5×10^5 cells/sheet (1 sheet) onto the heart surface, and necropsy was performed at Week 45. Clinical observation, measurements of body weight, food consumption, and organ weight, and histopathological and immunohistological examinations were performed. Sporadic stromal cells were observed on the pericardium, myocardial surface, and chest wall. There were no findings suggestive of tumorigenicity.	4.2.3.4-1
Male and female mice (NOG)	NOG mice aged 7 weeks underwent transplantation of RiHEART or its analog 7.5×10^5 cells/sheet (1 sheet) onto the heart surface, and necropsy was performed at Week 16. Clinical observation, body weight and organ weight measurement, and histopathological and immunohistological examinations were performed. Neither test article had findings suggestive of tumorigenicity.	4.2.3.4-2, 3, 4, 5, 6, 7 (reference)

5.3 Safety evaluation of process-related impurities

The applicant's explanation about process-related impurities of RiHEART:

Safety evaluation based on their residuals in RiHEART, published literature, and results from the single-session transplantation study of RiHEART (Process II)[7)] [see Section 5.1] indicated that impurities potentially present in the final product are unlikely to raise safety concerns in humans.

5.4 Safety evaluation of sub-ingredients

Sub-ingredients of RiHEART are gelatin and Hank's balanced salts solution (HBSS). Each of the sub-ingredients was evaluated for safety in view of their amounts in RiHEART. The applicant considered that their safety concerns in humans are limited.

5.R Outline of the review conducted by PMDA

Based on the submitted data and the following review, PMDA has concluded that RiHEART has no particular concerns about non-clinical safety.

5.R.1 Tumorigenicity risk of RiHEART

The active ingredient of RiHEART is cells obtained by differentiating iPS cells, which are undifferentiated pluripotent stem cells. In the final product, undifferentiated iPS cells may remain and, after transplantation, they may be transformed, consequently posing a tumorigenicity risk.

7) The critical intermediate manufactured in Process B was used. It was not embedded in a gel.

The applicant's explanation about the tumorigenicity of RiHEART:
Undifferentiated iPS cells are removed by treatments with [redacted] in the manufacturing process of cardiomyocytes, the critical intermediate of RiHEART, obtained by differentiating iPS cells. In addition, purity test using [redacted] is included in the in-process control tests after treatments with [redacted] as well as the specification tests of the critical intermediate, and [redacted] is controlled to [redacted] and [redacted], respectively. Such control is considered to reduce undifferentiated iPS cells in RiHEART and thereby minimize the tumorigenicity risk. Furthermore, the following findings also support the above claim that concerns about tumorigenicity attributable to presence of undifferentiated iPS cells and their transformation are limited: (1) The tumorigenicity studies of RiHEART in NOG mice had no findings suggestive of tumorigenicity [see Section 5.2.4]; and (2) results from soft agar colony formation assay, genetic stability study, and cell proliferative characterization did not suggest concerns about malignant transformation.

PMDA accepted the applicant's explanation.

6. Clinical Study Results and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data of RiHEART in the form of results from 2 Japanese clinical studies as presented in Table 18.

Table 18. List of clinical studies for efficacy and safety (evaluation data)

Phase	Study (jRCT No.)	Population	Sample size	Dosage regimen	Observation period	Endpoints
I/II	CVSC0005 (jRCT2053190081)	Patients with severe heart failure associated with chronic ischemic heart disease	8	RiHEART 1×10^8 cells (3 cell sheets, each containing 3.3×10^7 cells) transplanted onto the heart surface exposed by thoracotomy Immunosuppressants Oral administration of 3 immunosuppressants (prednisolone, tacrolimus, and mycophenolate mofetil) for 90 days (including a tapering period), starting on the following day of transplantation of RiHEART	52 weeks after transplantation of RiHEART	Efficacy Safety
I	CVSC0101 (extension study) (jRCT2053220055)	Patients who underwent transplantation of RiHEART in Study CVSC0005	3	Non-intervention	Until end of post-marketing surveillance	Safety

6.1 Study CVSC0005 (CTD 5.3.5.2-1, December 2019 to March 2024)

A Japanese multi-center, open-label, uncontrolled study (Study CVSC0005) was conducted at 5 study sites to evaluate the efficacy and safety of RiHEART in patients aged ≥20 years with severe heart failure associated with chronic ischemic heart disease (target sample size, 8 patients).

Table 19 shows the main inclusion and exclusion criteria.

Table 19. Main inclusion and exclusion criteria

Inclusion criteria	・ Patients with chronic ischemic heart disease ・ Patients with heart failure accompanied by symptoms of NYHA Functional Class* III or IV ・ Patients with heart failure despite maximum pharmacotherapy comprised of digitalis, diuretics, ACE inhibitors, ARB, β blockers, aldosterone antagonists, and/or oral cardiotonic agents ・ Patients aged ≥20 years ・ Patients with heart failure at a risk of worsening despite prior standard treatment (e.g., CABG, mitral valve repair, left ventricular reconstruction, CRT, PCI) performed ≥3 months ago ・ Patients with LVEF (echocardiography) at rest ≤35%
Exclusion criteria	・ Patients with autoimmune disease, etc. ・ Patients allergic or hypersensitive to immunosuppressants to be used ・ Patients in persistent shock due to worsening heart failure ・ Patients with severe pulmonary hypertension

* New York Heart Association (NYHA) Functional Class
Class I: No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, shortness of breath, or chest pain.
Class II: Slight limitation of physical activity. Ordinary physical activity results in fatigue, palpitation, shortness of breath, or chest pain.
Class III: Marked limitation of physical activity. Less than ordinary activity causes fatigue, palpitation, shortness of breath, or chest pain.
Class IV: Symptoms of heart failure at rest. Any physical activity causes further discomfort.

This study consisted of 3 cohorts, Cohort A, Cohort B-I/B-II, and Cohort C and was planned as follows: In Cohort A, 3 patients would undergo transplantation of RiHEART 1×10^8 cells (3 cell sheets, each containing 3.3×10^7 cells); and based on the adjudication of the Efficacy and Safety Evaluation Committee at Week 26, the study would be continued according to either of the following designs:

- Five patients would be enrolled in Cohort B-I to undergo transplantation of RiHEART 1×10^8 cells. A total of 8 patients in Cohorts A and B-I would be evaluated for safety and efficacy.
- ,Four patients would be enrolled in Cohort B-II to undergo transplantation of RiHEART 1.67 to 2×10^8 cells (5-6 cell sheets, each containing 3.3×10^7 cells). Three patients would be enrolled in Cohort C to undergo transplantation of RiHEART 1.67 to 2×10^8 cells. A total of 10 patients in Cohorts A, B-II, and C would be evaluated for safety, and a total of 7 patients in Cohorts B-II and C would be evaluated for efficacy.

Transplantation was performed in a single session; RiHEART 1×10^8 cells (3 cell sheets, each containing 3.3×10^7 cells) or 1.67 to 2×10^8 cells (5-6 cell sheets, each containing 3.3×10^7 cells) was applied onto the heart surface exposed by left thoracotomy.

To suppress rejection against RiHEART, 3 immunosuppressants (prednisolone, tacrolimus hydrate [tacrolimus], and mycophenolate mofetil) were administered basically according to the post-heart-transplantation regimen[8)] for 90 days including a tapering period (dose adjustment, interruption, or

8) Prednisolone was administered basically according to a regimen in the Guidelines for heart transplantation (JCS2016) (The Japanese Circulation Society), "The initial adult dosage is 20 to 60 mg (0.4-1.2 mg/kg) per day administered orally in 1 to 4 divided doses. The dose may be adjusted according to the patient's age or condition as appropriate."

discontinuation was allowed according to the symptoms as appropriate), starting on the following day of transplantation of RiHEART.[9)]

The observation period of this study was 52 weeks after transplantation of RiHEART.

In this study, 3 and 5 patients were enrolled in Cohort A and Cohort B-I, respectively, and a total of 8 patients underwent thoracotomy and transplantation of RiHEART. All the patients were included in the efficacy and safety analysis populations.

Table 20 shows the baseline characteristics of 8 patients who underwent transplantation of RiHEART. At the time of informed consent, patients were 61.1 ± 7.3 years of age (mean ± standard deviation [SD]), weighed 70.0 ± 11.7 kg, and had systolic blood pressure of 110.8 ± 14.2 mmHg, diastolic blood pressure of 62.5 ± 6.3 mmHg, pulse rate of 69.0 ± 8.1 beats/min, brain natriuretic peptide (BNP) of 126.5 ± 120.6 pg/mL, and LVEF of 30.5% ± 7.6%. All the 8 patients had a prior history of coronary revascularization procedure (percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]).

9) The immunosuppressants were used according to the following dosage regimens:
• Prednisolone
Oral once-daily regimen: 20 mg (Days 1-30), 15 mg (Days 31-40), 10 mg (Days 41-50), 7.5 mg (Days 51-60), 5 mg (Days 61-70), 2.5 mg (Days 71-80). At Days 81 to 90, oral every-other-day regime of 2.5 mg.
• Tacrolimus
Oral twice-daily regimen (every 12 hours): The dose should start at 1.5 mg and be then adjusted to maintain the trough blood level in a range of 10 to 15 ng/mL (Days 1-60). After Day 60, the dose should be reduced to 1/2 and 1/4 of the previously adjusted dose during periods of Days 61 to 75 and Days 76 to 90, respectively. The dose during the tapering period should be adjusted in increments of 0.5 mg, which is the minimum commercially available strength in the form of capsules.
• Mycophenolate mofetil
Oral twice-daily regimen (every 12 hours): 1 g per dose (Days 1-60), 0.5 g per dose (Days 61-75), 0.5 g per dose (Days 76-90)

Table 20. Patient characteristics

Cohort	Patient ID	Age	Sex	Time to onset of primary disease	Cardiovascular-related complications	Prior cardiac procedures	Prior medications*	NYHA Functional Class
Cohort A	[redacted]	5[redacted]	Male	20[redacted]	Hypertension Hyperuricaemia Dyslipidaemia Ventricular extrasystoles	PCI IABP PCPS Circulatory Assist Pump Catheter (IMPELLA) ICD	β blocker ACE inhibitor ARB MRA	III
	[redacted]	7[redacted]	Male	20[redacted]	Sleep apnoea syndrome Hyperuricaemia Dyslipidaemia Renal failure Diabetes mellitus Ventricular extrasystoles	PCI	β blocker MRA Loop diuretic	III
	[redacted]	6[redacted]	Male	20[redacted]	Dyslipidaemia	CABG Valvuloplasty ICD	Antiarrhythmic agent β blocker ARB	III
Cohort B-I	[redacted]	5[redacted]	Male	20[redacted]	Hypertension Dyslipidaemia Arteriosclerosis obliterans Diabetes mellitus Paroxysmal atrial fibrillation	CABG	Ca antagonist β blocker Antiarrhythmic agent ACE inhibitor MRA SGLT2 inhibitor ARNI	III
	[redacted]	6[redacted]	Male	20[redacted]	Hypertension Dyslipidaemia	PCI	ARB β blocker Loop diuretic Cardiotonic agent (dobutamine) MRA ARNI Vasopressin V_2 receptor antagonist	III
	[redacted]	5[redacted]	Male	20[redacted]	Hypertension Hyperuricaemia Diabetes mellitus Abdominal aortic aneurysm	PCI	ACE inhibitor β blocker Vasodilator Loop diuretic Ca antagonist SGLT2 inhibitor	III
	[redacted]	5[redacted]	Male	20[redacted]	Dyslipidaemia Renal failure	CABG	β blocker ACE inhibitor Loop diuretic SGLT2 inhibitor MRA ARNI	III
	[redacted]	6[redacted]	Female	20[redacted]	Hypertension Diabetes mellitus Dyslipidaemia Hyperuricaemia Renal failure Paroxysmal atrial fibrillation Obsolete anterior myocardial infarction	PCI CRT-D	β blocker ACE inhibitor SGLT inhibitor Loop diuretic Vasopressin V_2 receptor antagonist MRA Cardiotonic agent (dobutamine) Antiarrhythmic agent ARNI Oral cardiotonic agent	III

* Drugs underlined were in use at the time of transplantation of RiHEART.

Table 21 shows information about transplantation of RiHEART. Surgery for transplantation of RiHEART took 1 to 2 hours.

Table 21. Information about transplantation

Case No.	Thoracotomy site	Transplantation site	Intraoperative blood loss (mL)
[redacted]	Left fourth intercostal space	Left anterior wall, lateral wall	20
	Fifth intercostal space	Left ventricular lateral wall, anterior wall	20
	Fourth and fifth intercostal space	Left ventricular lateral wall, anterior wall	20
	Left fifth intercostal space	Left ventricular anterior lateral wall	10
	Left intercostal space	Heart surface	10
	Intercostal thoracotomy	Left ventricle surface	30
	Left fifth intercostal space	Left anterior lateral wall	24
	Left thoracotomy	Left ventricular anterior wall	5

The primary efficacy endpoint was the number of patients who were assessed to have improved LVEF, measured by echocardiography,[10)] at Week 26 compared with the pre-transplantation value. Changes in LVEF from pre-transplantation, measured by echocardiography, of "≥+5%," "≥-5% and <+5%," and "<-5%" were defined as "Improved," "Maintained," and "Worsened," respectively.

Table 22 shows changes in LVEF measured by echocardiography from pre-transplantation to Week 26 in 8 patients in the efficacy analysis population. Of the 8 patients, 2 (Patient ID Nos. [redacted] and [redacted]) presented changes in LVEF assessed as "Improved" at Week 26.

Table 22. Changes in LVEF (echocardiography) from pre-transplantation to Week 26

Patient ID	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pre-transplantation LVEF (%)	25.6	20.5	32.7	32.3	38.7	36.3	19.9	37.9
LVEF at Week 26 (%)	29.1	15.4	47.7	23.2	44.3	33.0	20.2	26.5
Change (%)	3.5	-5.1	15.0	-9.1	5.6	-3.3	0.3	-11.4

For secondary efficacy endpoints, the following items were measured/determined: (1) LVEF was measured by echocardiography and computed tomography (CT) examination to evaluate systolic function of the left ventricle overall; (2) left ventricular end-systolic volume index (LVESVI) and left ventricular end-diastolic volume index (LVEDVI) as well as cardiothoracic ratio (CTR) were measured by echocardiography and CT examination to evaluate cardiac remodeling; (3) New York Heart Association (NYHA) Functional Class, exercise tolerance (specific activity scale [SAS], 6-minute walk distance [6MWD], peak volume O_2/peak oxygen uptake [peak VO_2], anaerobic threshold [AT], and ventilatory equivalent for carbon dioxide [VE/VCO_2]), BNP, N-terminal pro-brain natriuretic peptide (NT-proBNP), etc. were determined to evaluate severity of heart failure; and (4) right arterial pressure (RAP), main pulmonary arterial pressure (PAP), and pulmonary artery wedge pressure (PAWP) were measured by cardiac catheterization to evaluate hemodynamics.

Tables 23 to 26 show results on the above items except CTR.[11)]

[10)] Images with Patient ID No. and date of imaging masked were randomly arranged and then analyzed at a facility specialized in image analyses.

[11)] The applicant considered CTR unsuitable for evaluation of cardiac remodeling because (i) quantitative evaluation of the intracardiac space is difficult, and (ii) it is susceptible to factors directly unrelated to remodeling, such as pericardial effusion and imaging conditions. One patient (Patient ID No. [redacted]) had a ≥5% decrease in CTR from pre-transplantation to Week 52, showing an improving trend, while 1 patient (Patient ID No. [redacted]) had a ≥5% increase in CTR. The other 6 patients had a <5% decrease or increase in CTR.

Table 23. Changes in LVEF, LVESVI, and LVEDVI over time

Patient ID	Time of evaluation	Echocardiography			CT examination		
		LVEF (%)	LVESVI (mL/m^2)	LVEDVI (mL/m^2)	LVEF (%)	LVESVI (mL/m^2)	LVEDVI (mL/m^2)
[redacted]	Pre-transplantation	25.6	92.6	124.4	35.1	90.2	139.0
	Week 26	29.1	111.2	157.4	29.2	95.7	135.1
	Week 52	21.7	90.9	116.1	32.5	76.8	113.8
[redacted]	Pre-transplantation	20.5	144.7	181.9	18.4	157.2	192.7
	Week 26	15.4	176.2	208.2	17.3	169.7	205.1
	Week 52	19.7	167.0	207.9	-	-	-
[redacted]	Pre-transplantation	32.7	57.3	85.1	36.8	58.7	92.9
	Week 26	47.7	46.5	88.9	36.7	64.1	101.1
	Week 52	43.2	50.3	88.6	41.1	56.8	96.4
[redacted]	Pre-transplantation	32.3	98.0	144.8	28.3	99.1	138.2
	Week 26	23.2	95.1	123.9	28.4	95.6	133.6
	Week 52	25.1	117.0	156.1	36.9	72.3	114.7
[redacted]	Pre-transplantation	38.7	52.4	85.5	34.9	69.3	106.6
	Week 26	44.3	72.8	130.7	33.7	50.1	75.5
	Week 52	33.2	76.4	114.4	35.1	49.1	75.6
[redacted]	Pre-transplantation	36.3	63.3	99.5	27.7	65.0	89.9
	Week 26	33.0	83.6	124.9	35.1	70.1	108.0
	Week 52	35.2	65.9	101.8	34.9	69.0	106.1
[redacted]	Pre-transplantation	19.9	116.6	145.6	20.0	146.6	183.31
	Week 26	20.2	128.9	161.6	23.6	146.5	191.9
	Week 52	31.0	126.4	183.1	20.7	152.3	191.9
[redacted]	Pre-transplantation	37.9	46.6	75.1	-	-	-
	Week 26	26.5	93.2	126.8	27.8	90.1	124.9
	Week 52	31.9	70.8	103.9	29.7	80.8	114.9

-, Not evaluable due to no data

Table 24. Changes in NYHA Functional Class and exercise tolerance over time

Patient ID	Time of evaluation	NYHA Functional Class	SAS (METs)	6MWD (m)	Peak VO_2 (mL/kg/min)	AT (mL/kg/min)	VE/VCO_2 (mL/kg/min)
[redacted]	Pre-transplantation	III	4.0	450	15.4	10.0	33.7
	Week 26	II	6.0	405	18.7	10.6	37.9
	Week 52	II	6.0	450	20.0	9.2	35.2
	Pre-transplantation	III	5.0	267	10.0	8.7	41.9
	Week 26	II	7.5	275	10.3	8.6	39.5
	Week 52	II	2.5	275	-	-	-
	Pre-transplantation	III	6.5	550	16.7	10.4	37.0
	Week 26	I	6.5	525	14.7	8.7	37.2
	Week 52	I	7.0	510	16.9	9.9	34.7
	Pre-transplantation	III	6.0	500	14.9	8.5	31.3
	Week 26	II	8.0	541	15.6	11.5	34.1
	Week 52	I	8.0	570	14.8	9.1	29.2
	Pre-transplantation	III	7.5	481	18.2	10.2	28.2
	Week 26	I	7.0	588	20.5	10.1	35.7
	Week 52	I	7.0	482	21.4	11.7	42.6
	Pre-transplantation	III	5.5	398	24.1	13.6	29.3
	Week 26	II	6.5	576	26.8	15.9	31.7
	Week 52	I	6.0	616	28.7	14.6	28.9
	Pre-transplantation	III	4.0	420	16.7	10.1	30.3
	Week 26	II	4.0	490	16.2	8.9	31.5
	Week 52	II	6.0	500	16.7	7.9	32.9
	Pre-transplantation	III	3.5	350	12.3	11.1	33.6
	Week 26	II	5.0	385	11.4	7.2	44.0
	Week 52	II	5.0	410	15	8.1	26.7

-, Not evaluable due to no data

Table 25. Changes in BNP and NT-proBNP over time

Patient ID	Time of evaluation	BNP (pg/mL)	NT-proBNP (pg/mL)
[redacted]	Pre-transplantation	76.4	288
	Week 26	239	870
	Week 52	113	538
[redacted]	Pre-transplantation	386	1,340
	Week 26	670	1,700
	Week 52	875	2,650
[redacted]	Pre-transplantation	59.8	330
	Week 26	116	415
	Week 52	175	762
[redacted]	Pre-transplantation	196	829
	Week 26	119	750
	Week 52	134	571
[redacted]	Pre-transplantation	18.2	44
	Week 26	215	211
	Week 52	39.0	60
[redacted]	Pre-transplantation	32.2	144
	Week 26	48.2	140
	Week 52	58.2	186
[redacted]	Pre-transplantation	154	870
	Week 26	35.3	456
	Week 52	88.4	433
[redacted]	Pre-transplantation	89.5	954
	Week 26	346	1,110
	Week 52	119	902

Table 26. Changes in RAP, main PAP, and PAWP over time

Patient ID	Time of evaluation	RAP (mmHg)	main PAP (mmHg)	PAWP (mmHg)
[redacted]	Pre-transplantation	4	12	6
	Week 26	5	15	11
	Week 52	1	10	3
[redacted]	Pre-transplantation	4	12	8
	Week 26	5	15	9
	Week 52	5	16	8
[redacted]	Pre-transplantation	7	19	12
	Week 26	9	19	14
	Week 52	9	25	18
[redacted]	Pre-transplantation	2	12	4
	Week 26	5	13	8
	Week 52	2	12	4
[redacted]	Pre-transplantation	5	15	8
	Week 26	5	16	11
	Week 52	6	15	8
[redacted]	Pre-transplantation	3	8	3
	Week 26	3	13	7
	Week 52	3	11	5
[redacted]	Pre-transplantation	4	14	10
	Week 26	2	16	8
	Week 52	1	19	10
[redacted]	Pre-transplantation	9	21	14
	Week 26	6	39	25
	Week 52	3	25	6

An investigator or sub-investigator at each study site performed an overall evaluation based on cardiac function,[12)] exercise tolerance,[13)] and effects on pathology of heart failure and outcome for each patient.

[12)] Cardiac function was assessed based on LVEF and left ventricular volume measured by transthoracic echocardiography as well as left ventricular volume and left ventricular wall motion measured by CT examination.

[13)] Exercise tolerance was comprehensively evaluated based on NYHA Functional Class, 6MWD, peak VO_2, SAS score, total score of the Minnesota Living with Heart Failure Questionnaire, total score of SF-36, and notable changes in other daily living activities.

This overall evaluation was reviewed for its appropriateness by the Efficacy and Safety Evaluation Committee consisting of a total of 3 specialists (1 cardiac surgeon and 2 cardiologists). The result of the final evaluation was given as one of 3 categories: “Responded,” “Not responded,” or “Not assessable.”

Table 27 shows results of the overall evaluation. At Week 26, six patients were assessed as “Responded” and 2 patients were assessed as “Not responded.” At Week 52, all the 8 patients were assessed as “Responded.”

Table 27. Results of overall evaluation

Patient ID	Date of evaluation	Evaluation by investigator or sub-investigator	Evaluation by the Efficacy and Safety Evaluation Committee
[redacted]	Week 26	Overall evaluation: Responded The patient with RiHEART transplanted was hospitalized again immediately after discharge because of chest discomfort, which resulted from a psychological factor and resolved later. The patient was assessed as “Responded” based on improvements in both cardiac function and exercise tolerance.	Appropriateness of evaluation by investigator, etc.: Appropriate Final evaluation: Responded
		(1) Cardiac function: Maintained (2) Exercise tolerance: Improved (3) Effects on pathology of heart failure and outcome: No	(1) Cardiac function: Maintained (2) Exercise tolerance: Improved (3) Effects on pathology of heart failure and outcome: No
	Week 52	Overall evaluation: Responded The patient was assessed as “Responded” based on improvements in both cardiac function and exercise tolerance.	Appropriateness of evaluation by investigator, etc.: Appropriate Final evaluation: Responded
		(1) Cardiac function: Improved (2) Exercise tolerance: Improved (3) Effects on pathology of heart failure and outcome: No	(1) Cardiac function: Maintained (2) Exercise tolerance: Improved (3) Effects on pathology of heart failure and outcome: No
[redacted]	Week 26	Overall evaluation: Not responded Cardiac function was worsened, and subjective symptoms of heart failure were improved, but improvement of exercise tolerance was not observed. Because the patient had ischemic cardiomyopathy, which is characterized by progressive pathology, he might have responded to a certain extent, but he was assessed as Not responded.	Appropriateness of evaluation by investigator, etc.: Appropriate Final evaluation: Not responded
		(1) Cardiac function: Worsened (2) Exercise tolerance: Maintained (3) Effects on pathology of heart failure and outcome: Yes	(1) Cardiac function: Worsened (2) Exercise tolerance: Maintained (3) Effects on pathology of heart failure and outcome: Yes
	Week 52	Overall evaluation: Responded Cardiac function was maintained, and subjective symptoms of heart failure were improved, but improvement of exercise tolerance was not observed. Because the patient had ischemic cardiomyopathy, which is characterized by progressive pathology, he might have responded to a certain extent and thus was assessed as Responded.	Appropriateness of evaluation by investigator, etc.: Appropriate Final evaluation: Responded
		(1) Cardiac function: Maintained (2) Exercise tolerance: Maintained (3) Effects on pathology of heart failure and outcome: Yes	(1) Cardiac function: Maintained (2) Exercise tolerance: Maintained (3) Effects on pathology of heart failure and outcome: Yes

[redacted]	Week 26	Overall evaluation: Responded The patient was assessed as “Responded” based on improvements in both cardiac function and exercise tolerance.	Appropriateness of evaluation by investigator, etc.: Appropriate Final evaluation: Responded
		(1) Cardiac function: Improved (2) Exercise tolerance: Improved (3) Effects on pathology of heart failure and outcome: Yes	(1) Cardiac function: Improved (2) Exercise tolerance: Improved (3) Effects on pathology of heart failure and outcome: Yes
	Week 52	Overall evaluation: Responded The patient was assessed as Responded based on improvements in both cardiac function and exercise tolerance.	Appropriateness of evaluation by investigator, etc.: Appropriate Final evaluation: Responded
		(1) Cardiac function: Improved (2) Exercise tolerance: Improved (3) Effects on pathology of heart failure and outcome: No	(1) Cardiac function: Improved (2) Exercise tolerance: Improved (3) Effects on pathology of heart failure and outcome: No
[redacted]	Week 26	Overall evaluation: Responded The patient was assessed as Responded based on improvements in both cardiac function and exercise tolerance.	Appropriateness of evaluation by investigator, etc.: Appropriate Final evaluation: Responded
		(1) Cardiac function: Improved (2) Exercise tolerance: Improved (3) Effects on pathology of heart failure and outcome: No	(1) Cardiac function: Maintained (2) Exercise tolerance: Improved (3) Effects on pathology of heart failure and outcome: No
	Week 52	Overall evaluation: Responded Cardiac function was improved. For exercise tolerance, the patient experienced muscle weakness potentially caused by open reduction and internal fixation to treat right patellar fracture at Week 38. At Week 52, overall improvement was observed, and rehabilitation was achieved after the surgery. He was assessed as Responded.	Appropriateness of evaluation by investigator, etc.: Appropriate Final evaluation: Responded
		(1) Cardiac function: Improved (2) Exercise tolerance: Improved (3) Effects on pathology of heart failure and outcome: No	(1) Cardiac function: Improved (2) Exercise tolerance: Improved (3) Effects on pathology of heart failure and outcome: No
[redacted]	Week 26	Overall evaluation: Responded Cardiac function was generally maintained or improved, although interpretation differed depending on indices. The patient underwent transplantation of RiHEART 7 years after onset of ischemic heart disease, and exercise tolerance showed an improving trend overall. Because he was returning to social life before surgery and had good QOL, he was assessed as Responded.	Appropriateness of evaluation by investigator, etc.: Appropriate Final evaluation: Responded
		(1) Cardiac function: Improved (2) Exercise tolerance: Improved (3) Effects on pathology of heart failure and outcome: No	(1) Cardiac function: Improved (2) Exercise tolerance: Improved (3) Effects on pathology of heart failure and outcome: No
	Week 52	Overall evaluation: Responded As with the result at Week 26	Appropriateness of evaluation by investigator, etc.: Appropriate Final evaluation: Responded
		(1) Cardiac function: Improved (2) Exercise tolerance: Improved (3) Effects on pathology of heart failure and outcome: No	(1) Cardiac function: Improved (2) Exercise tolerance: Improved (3) Effects on pathology of heart failure and outcome: No

[redacted]	Week 26	Overall evaluation: Responded Cardiac function was generally maintained or improved, although interpretation differed depending on indices. Throughout a period of 12 years after initial onset of ischemic heart disease, LVEF remained between <50% and ≥40%, but 1 year before participation in Study CVSC0005, myocardial infarction occurred, decreasing LVEF to <35% and ≥30%. After transplantation, exercise tolerance was improved, and rehabilitation was achieved. In view of these findings, the patient was assessed as Responded.	Appropriateness of evaluation by investigator, etc.: Appropriate Final evaluation: Responded
		(1) Cardiac function: Maintained (2) Exercise tolerance: Improved (3) Effects on pathology of heart failure and outcome: No	(1) Cardiac function: Maintained (2) Exercise tolerance: Improved (3) Effects on pathology of heart failure and outcome: No
	Week 52	Overall evaluation: Responded As with the result at Week 26	Appropriateness of evaluation by investigator, etc.: Appropriate Final evaluation: Responded
		(1) Cardiac function: Maintained (2) Exercise tolerance: Improved (3) Effects on pathology of heart failure and outcome: No	(1) Cardiac function: Improved Appropriateness of evaluation by investigator, etc.: Not appropriate. Because left ventricular volume was maintained as shown by both echocardiography and CT examination, and EF was improved as shown by CT examination, cardiac function was comprehensively assessed as "Improved." (2) Exercise tolerance: Improved (3) Effects on pathology of heart failure and outcome: No
[redacted]	Week 26	Overall evaluation: Responded Cardiac function was assessed as Improved based on objective findings. For exercise tolerance, subjective symptoms were improved. He had improved the quality of daily living activities such as returning to work and thus was assessed as Responded.	Appropriateness of evaluation by investigator, etc.: Appropriate Final evaluation: Responded
		(1) Cardiac function: Improved (2) Exercise tolerance: Improved (3) Effects on pathology of heart failure and outcome: No	(1) Cardiac function: Improved (2) Exercise tolerance: Improved (3) Effects on pathology of heart failure and outcome: No
	Week 52	Overall evaluation: Responded As with the result at Week 26	Appropriateness of evaluation by investigator, etc.: Appropriate Final evaluation: Responded
		(1) Cardiac function: Improved (2) Exercise tolerance: Improved (3) Effects on pathology of heart failure and outcome: No	(1) Cardiac function: Improved (2) Exercise tolerance: Improved (3) Effects on pathology of heart failure and outcome: No
[redacted]	Week 26	Overall evaluation: Not responded Although exercise tolerance was improved, cardiac function was worsened, and thus the patient was assessed as Not responded.	Appropriateness of evaluation by investigator, etc.: Appropriate Final evaluation: Not responded
		(1) Cardiac function: Worsened (2) Exercise tolerance: Improved (3) Effects on pathology of heart failure and outcome: Yes	(1) Cardiac function: Worsened (2) Exercise tolerance: Improved (3) Effects on pathology of heart failure and outcome: Yes
	Week 52	Overall evaluation: Responded Examination results on cardiac function remained unchanged, but exercise tolerance was evidently improved, and thus the patient was assessed as Responded.	Appropriateness of evaluation by investigator, etc.: Appropriate Final evaluation: Responded
		(1) Cardiac function: Maintained (2) Exercise tolerance: Improved (3) Effects on pathology of heart failure and outcome: No	(1) Cardiac function: Maintained (2) Exercise tolerance: Improved (3) Effects on pathology of heart failure and outcome: No

Furthermore, according to the assessment procedure flowchart presented in Figure 1, each patient was assessed as either “Responder” or “Non-Responder” to RiHEART based on changes from pre-transplantation to Weeks 26 and 52 in LVEF measured by echocardiography and NYHA Functional Class.

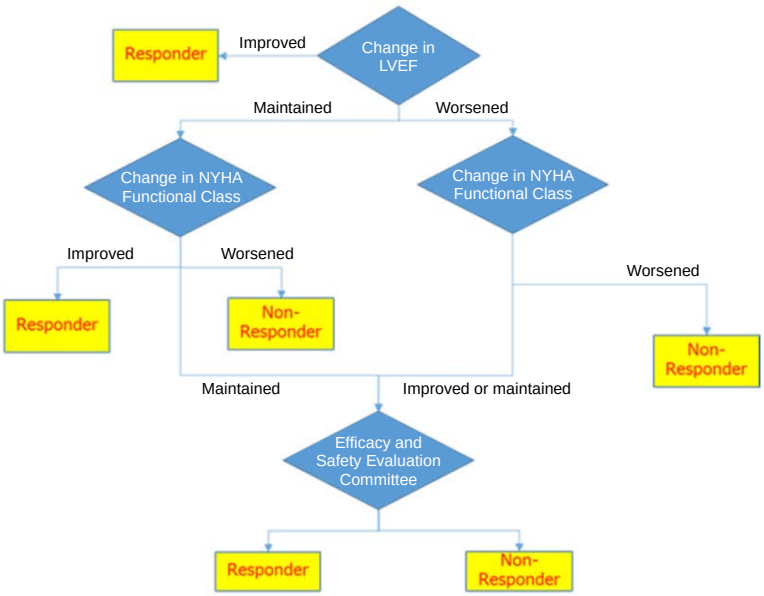

Figure 1. Assessment procedure for “Responder”

Tables 23 and 24 show changes from pre-transplantation to Weeks 26 and 52 in LVEF measured by echocardiography and NYHA Functional Class. The Efficacy and Safety Evaluation Committee assessed 3 patients (Patient ID Nos. [redacted], [redacted], and [redacted]) at Week 26 and 3 patients (Patient ID Nos. [redacted], [redacted], and [redacted]) at Week 52. At Week 26, six patients were assessed as Responder and 2 patients were assessed as Non-Responder, and at Week 52, all of them were assessed as Responder.

Table 28 shows a summary of safety in Study CVSC0005.

Table 28. Summary of safety

	Study CVSC0005 (n = 8)
	Number of patients with event (%)
All adverse events	7 (87.5)
Adverse reactions to RiHEART	0
Adverse events for which a causal relationship to the transplantation procedure cannot be ruled out	5 (62.5)
Adverse events for which a causal relationship to immunosuppressants cannot be ruled out	7 (87.5)
Severe adverse events	1 (12.5)
Adverse events leading to death	0
Serious adverse events	5 (62.5)
Serious adverse reactions	0

Adverse events occurred in 7 of 8 patients (87.5%). Of them, adverse events reported by ≥2 patients were white blood cell count increased in 4 patients (50.0%), hyperglycaemia in 3 patients (37.5%), anaemia, wound complication, and renal dysfunction in 2 patients (25.0%) each. No adverse reactions of RiHEART occurred.

Severe adverse events were large intestine perforation and colon cancer in 1 patient (12.5%), and a causal relationship to RiHEART was ruled out for both events.

A total of 10 serious adverse events occurred in 5 of 8 patients (62.5%), including chest discomfort, urinary tract infection, cardiac failure acute, amiodarone-induced pneumonia, cardiac ventricular thrombosis, enteritis infectious, colon cancer, large intestine perforation, patella fracture, and cardiac failure in 1 patient each (some patients had multiple events). All the events resolved, and a causal relationship to RiHEART was ruled out for all of them.

Adverse events for which a causal relationship to the transplantation procedure cannot be ruled out occurred in 5 of 8 patients (62.5%), and of them, those reported by ≥2 patients were anaemia and wound complication in 2 patients (25.0%) each. No serious adverse events related to the transplantation procedure occurred.

Adverse events for which a causal relationship to immunosuppressants cannot be ruled out occurred in 7 of 8 patients (87.5%), and of them, those reported by ≥2 patients were white blood cell count increased in 3 patients (37.5%), hyperglycaemia in 3 patients (37.5%), and renal dysfunction in 2 patients (25.0%). All the events were known and listed as precautions in package inserts of the immunosuppressants. They resolved after discontinuation of immunosuppressants.

6.2 Study CVSC0101 (CTD 5.3.5.2-2, ongoing since May 2022, data cut-off on [redacted], 20[redacted])

A Japanese multi-center, open-label, uncontrolled study was conducted at 4 study sites[14)] to evaluate the long-term efficacy and safety of RiHEART in patients who had undergone transplantation of RiHEART in Study CVSC0005.

At the time of data cut-off (date of end of Week [redacted] observation for the [redacted] patient, [redacted], 20[redacted]), 3 patients who had undergone transplantation of RiHEART in Cohort A in Study CVSC0005 (Patient ID Nos. [redacted], [redacted], and [redacted]) were enrolled in the study, and their follow-up period was 1,092, 1,107, and 1,120 days, respectively. All the patients survived without clinical events involving cardiac function. In Study CVSC0101, which is planned to collect only adverse events related to tumor, no such events were observed.

6.R Outline of the review conducted by PMDA

6.R.1 Efficacy

6.R.1.1 Data for review of efficacy evaluation

The applicant's explanation about efficacy evaluation for RiHEART based on the results from Study CVSC0005:

Expansion of options for treatment of severe heart failure is an urgent issue in clinical practice. For the efficacy of RiHEART, desirable evaluation is based on long-term mortality, but a clinical study using

14) The number of study sites planned to be included in the study. At the time of data cut-off, [redacted] site was included.

long-term mortality as an outcome measure would take time. Considering that improved LVEF is a prognostic factor of decreased mortality (*Circulation.* 1993;87:VI17-23), the number of patients who were assessed to have improved LVEF measured by echocardiogr aphy from pre-transplantation to Week 26 was selected as the primary endpoint to evaluate the efficacy of RiHEART in an exploratory manner. However, a clinical study of CABG for treatment of ischemic cardiomyopathy showed that survival was better in the operation group than in the control group, but no difference was observed in improvement of LVEF between the groups (*N Engl J Med.* 2019;381:739-48). The applicant considers that RiHEART may not improve all efficacy outcome measures uniformly, but improvement or maintenance of any of cardiac function measures (e.g., LVEF, LVESVI, PAWP) or interactions of effects on the measures would improve or maintain clinical symptoms of heart failure (NYHA Functional Class) and exercise tolerance (e.g., peak VO_2), leading to improved survival. When the efficacy of RiHEART is explained based on the results from Study CVSC0005, comprehensive evaluation must be performed, covering not only results of LVEF but also those of secondary endpoints such as LVESVI, LVEDVI, NYHA Functional Class, and exercise tolerance and examinations in individual patients.

PMDA's view:
Because Study CVSC0005 was conducted in a small number of patients in an exploratory, open-label, uncontrolled manner, evaluation of the efficacy of RiHEART based on the results from Study CVSC0005 has limitations. However, patients enrolled in Study CVSC0005 cannot be expected to restore once-necrotized myocardium spontaneously and thereby improve cardiac function measures. With this matter considered, the efficacy of RiHEART can be evaluated. As explained by the applicant, there is a demand for development of treatment that aims at extending survival by improving or maintaining the cardiac function and exercise tolerance and thereby preventing the disease from reaching the end stage requiring heart transplantation or a ventricular assist device. With such demand considered, PMDA decided to evaluate the efficacy of RiHEART based on not only results of LVEF but also those for other endpoints comprehensively.

6.R.1.2 Main results on efficacy in Study CVSC0005

(a) LVEF

The applicant's explanation about results of LVEF:
Generally, CT examination is reported to deliver more precise data on left ventricular function such as LVEF than echocardiography (*J Am Coll Cardiol.* 2012;59:1897-907, *European heart journal-Cardiovascular Imaging.* 2015;16:848-52). In Study CVSC0005, results of LVEF measured by echocardiography and CT examination in individual patients at each timepoint were compared. Comparisons were performed on not only changes but also results of assessment using definitions of "Improved," "Maintained," and "Worsened" for LVEF measured by echocardiography.

Table 29 shows comparison of LVEF measured by echocardiography and CT examination. Agreement of the assessment results was found only at Week 52 in Patient ID No. [redacted] and at Week 26 in Patient ID No. [redacted]. In 2 patients (Patient ID Nos. [redacted] and [redacted]), changes in LVEF measured by echocardiography from pre-transplantation to Week 26 were assessed as "Improved," but changes in LVEF measured by CT examination were both assessed as "Maintained."

Table 29. Changes in LVEF (echocardiography and CT examination)

Patient ID	Time of evaluation	Echocardiography			CT examination		
		LVEF (%)	Change (%)	Assessed as	LVEF (%)	Change (%)	Assessed as
[redacted]	Pre-transplantation	25.6			35.1		
	Week 26	29.1	3.5	Maintained	29.2	-5.9	Worsened
	Week 52	21.7	-3.9	Maintained	32.5	-2.6	Maintained
[redacted]	Pre-transplantation	20.5			18.4		
	Week 26	15.4	-5.1	Worsened	17.3	-1.1	Maintained
	Week 52	19.7	-0.8	Maintained	-	-	-
[redacted]	Pre-transplantation	32.7			36.8		
	Week 26	47.7	15.0	Improved	36.7	-0.1	Maintained
	Week 52	43.2	10.5	Improved	41.1	4.3	Maintained
[redacted]	Pre-transplantation	32.3			28.3		
	Week 26	23.2	-9.1	Worsened	28.4	0.1	Maintained
	Week 52	25.1	-7.2	Worsened	36.9	8.7	Improved
[redacted]	Pre-transplantation	38.7			34.9		
	Week 26	44.3	5.6	Improved	33.7	-1.2	Maintained
	Week 52	33.2	-5.5	Worsened	35.1	0.2	Maintained
[redacted]	Pre-transplantation	36.3			27.7		
	Week 26	33.0	-3.3	Maintained	35.1	7.4	Improved
	Week 52	35.2	-1.1	Maintained	34.9	7.2	Improved
[redacted]	Pre-transplantation	19.9			20.0		
	Week 26	20.2	0.3	Maintained	23.6	3.6	Maintained
	Week 52	31.0	11.1	Improved	20.7	0.6	Maintained
[redacted]	Pre-transplantation	37.9			-	-	
	Week 26	26.5	-11.4	Worsened	27.8	-	-
	Week 52	31.9	-6.0	Worsened	29.7	-	-

In Study CVSC0005, videos of echocardiography were assessed for image quality on a 4-level scale of "Excellent" (border between left ventricular endocardium and cavity clearly identified in all of the 16 sections of the left ventricle), "Good" (border between left ventricular endocardium and cavity clearly identified in 14 or 15 of 16 sections of the left ventricle), "Fair" (border between left ventricular endocardium and cavity clearly identified in 11 to 13 of 16 sections of the left ventricle), and "Poor" (border between left ventricular endocardium and cavity clearly identified in <11 of 16 sections of the left ventricle), and the image quality was rated as "Good" for 1 video, "Fair" for 8 videos, and "Poor" for 15 videos. The disagreement of results of LVEF measured by echocardiography with those measured by CT examination was caused by poor image quality of echocardiography, which compromised assessment.

(b) LVESVI and LVEDVI

The applicant's explanation about results of LVESVI and LVEDVI:

In patients with heart failure, 10 mL decreases in left ventricular end-systolic volume (LVESV) and left ventricular end-diastolic volume (LVEDV) had odds ratios for death [95% CI] of 0.96 [0.93, 0.98] and 0.95 [0.94, 0.97], respectively, corresponding to a statistically significant decrease of mortality risk (*J Am Coll Cardiol.* 2010;56:392-406). Evaluation of changes in LVESV and LVEDV is considered clinically significant. Patients with heart failure who had a ≥10% decrease in LVESV after CRT and those who had a <10% decrease in LVESV after CRT had all-cause mortality of 6.9% and 30.6%, respectively at 1 year after transplantation (*Circulation.* 2005;112:1580-6). Thus, a ≥10% decrease in LVESV (or 10 mL decrease in LVESV) and a ≥10 mL decrease in LVEDV are considered clinically meaningful.

In Study CVSC0005, LVESVI and LVEDVI, which are indices determined by dividing LVESV and LVEDV by body surface area, respectively, were evaluated as the secondary outcome measures. Patients enrolled in Study CVSC0005 had the median body surface area [range] of 1.7 [1.4, 2.0], and thus LVESVI and LVEDVI are smaller than LVESV and LVEDV. Accordingly, LVESVI and LVEDVI were evaluated based on clinically meaningful changes in LVESV and LVEDV.

Table 23 shows results of LVESVI and LVEDVI. Table 30 shows changes from pre-transplantation based on data from CT examination.

For LVESVI, 3 patients (37.5%) had a ≥10 mL/m^2 or ≥10% decrease from pre-transplantation to Week 52. For LVEDVI, 3 patients (37.5%) had a ≥10 mL/m^2 decrease from pre-transplantation to Week 52.

Table 30. Changes in LVESVI and LVEDVI (CT examination)

Patient ID	Time of evaluation	LVESVI			LVEDVI		
		Measured value (mL/m^2)	Change (mL/m^2)	Change (%)	Measured value (mL/m^2)	Change (mL/m^2)	Change (%)
[redacted]	Pre-transplantation	90.2			139.0		
	Week 26	95.7	5.5	6.1	135.1	-3.9	-2.8
	Week 52	76.8	-13.4	-14.8	113.8	-25.3	-18.1
[redacted]	Pre-transplantation	157.2			192.7		
	Week 26	169.7	12.5	8.0	205.1	12.4	6.5
	Week 52	-	-	-	-	-	
[redacted]	Pre-transplantation	58.7			92.9		
	Week 26	64.1	5.4	9.1	101.1	8.2	8.9
	Week 52	56.8	-1.9	-3.2	96.4	3.5	3.8
[redacted]	Pre-transplantation	99.1			138.2		
	Week 26	95.6	-3.5	-3.5	133.6	-4.6	-3.3
	Week 52	72.3	-26.8	-27.0	114.7	-23.5	-17.0
[redacted]	Pre-transplantation	69.3			106.6		
	Week 26	50.1	-19.2	-27.8	75.5	-31.1	-29.2
	Week 52	49.1	-20.2	-29.2	75.6	-31	-29.0
[redacted]	Pre-transplantation	65			89.9		
	Week 26	70.1	5.1	7.9	108	18.1	20.1
	Week 52	69	4	6.2	106.1	16.2	18.0
[redacted]	Pre-transplantation	146.6			183.3		
	Week 26	146.5	-0.1	0.0	191.9	8.6	4.7
	Week 52	152.3	5.7	3.9	191.9	8.6	4.7
[redacted]	Pre-transplantation	-			-		
	Week 26	90.1	-	-	124.9	-	-
	Week 52	80.8	-	-	114.9	-	-

(c) NYHA Functional Class

The applicant's explanation about results of NYHA Functional Class:

Although NYHA Functional Class is a measure potentially affected by the subjective view of the patient and rater, it directly reflects clinical symptoms, and 1-level improvement is a clinically meaningful change.

Table 24 shows results of NYHA Functional Class. For NYHA Functional Class, all the patients were assessed as Class III at pre-transplantation, but 6 patients (75%) were Class II and 2 patients (25%) were Class I at Week 26, and 4 patients (50%) were Class II and 4 patients (50%) were Class I at Week 52.

(d) SAS score

The applicant's explanation about results of SAS score:

Each 1-metabolic equivalent of task (MET) increase in patients with cardiovascular disease conferred a 12% improvement in survival (*N Engl J Med.* 2002;346:793-801). One MET is defined as exercise equivalent to a body oxygen consumption of 3.5 mL/kg/min, and a ≥1-MET increase is considered clinically meaningful.

Table 24 shows results of SAS score. In Study CVSC0005, a ≥1-MET increase from pre-transplantation was observed in 5 patients (62.5%) at Week 26 and 4 patients (50%) at Week 52. However, a ≥1-MET decrease from pre-transplantation was observed only in 1 patient (12.5%) at Week 52.

(e) 6MWD

The applicant's explanation about results of 6MWD:

A 50-m increase in 6MWD conferred a 23% improvement in survival (*JAMA Cardiol.* 2021;6:522-31). Changes of 40 to 45 m are accompanied by moderate improvement in peak VO_2 or quality of life (QOL) index (*Cardiopulm Phys Ther J.* 2012;23:5-15). A ≥45-m increase is considered a clinically meaningful change.

Table 24 shows results of 6MWD. In Study CVSC0005, a ≥45-m increase from pre-transplantation was observed in 3 patients (38%) at Week 26 and 4 patients (50%) at Week 52.

(f) Peak VO_2

The applicant's explanation about results of peak VO_2:

Peak VO_2 is measured in a cardiopulmonary exercise test, widely used as a measure of exercise tolerance in patients with heart failure, and important for prognosis prediction. Peak VO_2 of ≤14 mL/kg/min increased mortality risk approximately 3 fold in patients with heart failure (*Circulation.* 2002;106:3079-84). In Study HF-ACTION in patients with chronic heart failure, a 6% improvement in peak VO_2 led to a 5% decrease in mortality or hospitalization and an 8% decrease in cardiovascular mortality or hospitalization due to heart failure, suggesting that improved peak VO_2 was associated with better outcome (*Circ Heart Fail.* 2012;5:579-85). Thus, a ≥10% increase in peak VO_2 is considered a clinically meaningful change.

Table 24 shows results of peak VO_2. In Study CVSC0005, a ≥10% increase in peak VO_2 from pre-transplantation was observed in 3 patients (37.5%) at Week 26 and 4 patients (50%) at Week 52. There are some patients who had increased peak VO_2 but decreased AT. Peak VO_2 largely depends on cardiac output, ventilation, and oxygen-carrying capacity, while AT largely depends on peripheral factors and metabolic factors such as oxygen utilization in skeletal muscles, density of capillary vessels, and lactic acid clearance capacity. In these patients, cardiopulmonary function was improved, but oxygen utilization in skeletal muscles and metabolic efficiency were not, possibly resulting in such disagreement.

PMDA's evaluation on main efficacy results in Study CVSC0005 is presented in Section 6.R.1.4.

6.R.1.3 Effects of concomitant medications (except immunosuppressants)

Before evaluating the efficacy of RiHEART, PMDA considered that effects of concomitant medications (except immunosuppressants) on the improvement of conditions associated with heart failure needed to be reviewed. Use of concomitant medications for treatment of primary disease in each patient was reviewed (Table 31).

Table 31. Use of concomitant medications for treatment of primary disease

Patient ID	Drug[*1] (non-proprietary name)	Dose[*2]		Clinical course or reason for change
		Pre-transplantation	Post-transplantation	
[redacted]	Carvedilol	20 mg	20 mg	After perioperative management, oral use at the same dose as at pre-transplantation was re-started on Day 14.
	Clopidogrel sulfate	75 mg	75 mg	Its oral use was re-started at the same dose as that before transplantation on Day 1.
	Aspirin	100 mg	100 mg	Its oral use was re-started at the same dose as that before transplantation on Day 1.
	Candesartan cilexetil	8 mg	12 mg	After transplantation, it was discontinued because of concern for hypotension, but no problems such as hypotension occurred. It was re-started at 4 mg on Day 237 followed by a dose increase to 8 mg on Day 272. Blood pressure was mildly elevated, and the dose was increased to 12 mg on Day 321.
	Spironolactone	25 mg	25 mg	Its oral use was re-started at the same dose as that before transplantation on Day 2.
[redacted]	Clopidogrel sulfate	75 mg	-	It was used as an oral antiplatelet drug for treatment of ischemic cardiomyopathy but discontinued 10 days before transplantation. It was changed to aspirin.
	Aspirin	-	100 mg	Clopidogrel sulfate was changed to aspirin 100 mg on Day 1 because of concern for post-transplantation bleeding.
	Ethyl icosapentate	1,800 mg	1,800 mg	Its oral use was re-started at the same dose as that before transplantation on Day 2.
	Eplerenone	-	50 mg	It was used as an oral drug for treatment of heart failure before transplantation. On Day 161, a mineralocorticoid receptor antagonist (spironolactone), which had been discontinued after transplantation, was changed to eplerenone 25 mg to prevent adverse reactions such as gynaecomastia. The dose was increased to 50 mg on Day 273, and oral use was continued.
	Carvedilol	5 mg	5 mg	Its oral use was re-started at the same dose as that before transplantation on Day 2.
	Cilostazol	50 mg	50 mg	Its oral use was re-started at the same dose as that before transplantation on Day 2.
	Spironolactone	25 mg	25 mg	Its oral use was re-started at the same dose as that before transplantation on Day 2. It was discontinued on Day 5.
	Torasemide	4 mg	4 mg	Its oral use was re-started at the same dose as that before transplantation on Day 2, and the dose was reduced to 2 mg on Day 27 and then increased to 4 mg on Day 143. Its oral use was continued.
	Dapagliflozin propylene glycolate hydrate	-	10 mg	To control the primary disease, it was started at 10 mg on Day 147 but discontinued on Day 153.
	Valsartan	-	40 mg	To control the primary disease, it was started at 20 mg on Day 182 followed by the dose increase to 40 mg on Day 210. Its oral use was continued.
	Furosemide	-	20 mg	While visiting as an outpatient, the patient experienced weight increased, which was suspected to be a consequence of fluid retention. It was started as a diuretic at 20 mg on Day 266.

	Rosuvastatin calcium	2.5 mg	2.5 mg	Its oral use was re-started at the same dose as that before transplantation on Day 2.
	Isosorbide dinitrate	-	20 mg	The patient was hospitalized because of heart failure on Day 131. The condition was improved with a sedative, an antihypertensive, and a cardiotonic. The patient had no evident chest symptoms but had discomfort with the throat, which is an anginal symptom. On Day 139, Myocor spray, which had been used preventively from a point before transplantation, was changed to isosorbide dinitrate.
	Aspirin	100 mg	100 mg	Its oral use was re-started at the same dose as that before transplantation on Day 1.
	Amiodarone hydrochloride	200 mg	200 mg	Its oral use was re-started at the same dose as that before transplantation on Day 1. It was discontinued on Day 128.
	Carvedilol	5 mg	10 mg	Its oral use was re-started at the same dose as that before transplantation on Day 1. Oral amiodarone was used for treatment of ventricular extrasystoles, but discontinued because of onset of pneumonia. The condition was indicated for an increased dose of the β blocker, and thus the dose was increased to 7.5 mg on Day 342 and then to 10 mg on Day 346.
	Telmisartan	20 mg	20 mg	Its oral use was re-started at the same dose as that before transplantation on Day 1.
	Sotalol hydrochloride	-	80 mg	Because of the onset of amiodarone-induced pneumonia, amiodarone was changed to this drug, and its oral use was started at 80 mg on Day 129.
[redacted]	Spironolactone	-	25 mg	For treatment of hypertension occurring during a hospital stay due to amiodarone-induced pneumonia, spironolactone was started at 25 mg on Day 210. After discharge, blood pressure decreased occurred, and it was discontinued on Day 287. Right heart catheterization performed during a hospital stay for examinations at Week 52 revealed that pulmonary capillary wedge pressure was 18 mmHg, indicating use of a diuretic. It was re-started at 25 mg on Day 344, being expected to act as a diuretic.
	Furosemide	-	20 mg	On Day 1, weight increased caused by fluid retention associated with fluid replacement occurred, and it was started at 20 mg. While visiting as an outpatient, the patient was found recovering from weight increased, and it was reduced to 10 mg on Day 288. Right heart catheterization performed during a hospital stay for examinations at Week 52 revealed that pulmonary capillary wedge pressure was 18 mmHg, which was slightly higher, and thus it was increased to 20 mg.
	Aspirin	100 mg	100 mg	It had been discontinued from a point after transplantation, but its oral use was re-started at the same dose as that before transplantation on Day 28.
	Amiodarone hydrochloride	100 mg	100 mg	Its oral use was continued without interruption associated with transplantation.
[redacted]	Edoxaban tosilate hydrate	60 mg	60 mg	It had been discontinued from a point after transplantation, but its oral use was re-started at 60 mg on Day 93. It was discontinued on Day 166. Its oral use was re-started at 60 mg on Day 176 and continued.
	Carvedilol	15 mg	15 mg	Its oral use was continued without interruption associated with transplantation.
	Sacubitril valsartan sodium hydrate	100 mg	100 mg	Its oral use was continued without interruption associated with transplantation.
	Spironolactone	25 mg	25 mg	Its oral use was continued without interruption associated with transplantation.
	Dapagliflozin propylene glycolate hydrate	10 mg	10 mg	Its oral use was continued without interruption associated with transplantation.

	Warfarin potassium	-	2.5 mg	Echocardiography on Week 4 revealed a thrombus in the left ventricle, and thus it was started. Echocardiography on Day 59 revealed the thrombus in the left ventricle disappeared, and thus it was discontinued on Day 91. It was changed to edoxaban tosilate hydrate, which had been orally used for treatment of paroxysmal atrial fibrillation.
[redacted]	Sacubitril valsartan sodium hydrate	200 mg	200 mg	Its oral use was continued without interruption associated with transplantation.
	Bisoprolol fumarate	5 mg	5 mg	Its oral use was continued without interruption associated with transplantation.
	Febuxostat	20 mg	20 mg	Its oral use was continued without interruption associated with transplantation.
	Prasugrel hydrochloride	3.75 mg	3.75 mg	Its oral use was continued without interruption associated with transplantation.
	Spironolactone	25 mg	25 mg	No interruption associated with transplantation occurred. It was discontinued on Day 13. Its oral use was re-started at 25 mg 154 days later and continued.
	Rosuvastatin calcium	10 mg	10 mg	Its oral use was continued without interruption associated with transplantation.
[redacted]	Aspirin	100 mg	100 mg	No interruption associated with transplantation occurred. It was discontinued on Day 177.
	Ezetimibe/atorvastatin calcium hydrate fixed dose combination	1 tablet	1 tablet	Its oral use was continued without interruption associated with transplantation.
	Enalapril maleate	2.5 mg	2.5 mg	Its oral use was continued without interruption associated with transplantation.
	Carvedilol	15 mg	20 mg	To prevent paroxysmal atrial fibrillation, it was increased to 20 mg on Day 119. It was discontinued 265 days later.
	Clopidogrel sulfate	75 mg	75 mg	Its oral use was continued without interruption associated with transplantation.
	Dapagliflozin propylene glycolate hydrate	10 mg	10 mg	Its oral use was continued without interruption associated with transplantation.
	Bisoprolol fumarate	-	2.5 mg	It was changed from carvedilol because of a sign of orthostatic dizziness at discretion of the attending physician. Its oral use was started at 2.5 mg on Day 266.
	Febuxostat	20 mg	20 mg	Its oral use was continued without interruption associated with transplantation.
[redacted]	Aspirin	100 mg	100 mg	Its oral use was re-started at the same dose as that before transplantation on Day 1.
	Empagliflozin	10 mg	10 mg	Its oral use was re-started at the same dose as that before transplantation on Day 2.
	Carvedilol	15 mg	15 mg	Its oral use was re-started at the same dose as that before transplantation on Day 3.
	Spironolactone	25 mg	25 mg	Its oral use was re-started at the same dose as that before transplantation on Day 2.
	Sacubitril valsartan sodium hydrate	100 mg	100 mg	Its oral use was re-started at the same dose as that before transplantation on Day 2.
[redacted] *3	Carvedilol	5 mg	5 mg	Its oral use was re-started at the same dose as that before transplantation on Day 1.
	Spironolactone	25 mg	-	It was discontinued because of elevated Cr and K values 3 days before transplantation. After transplantation, drugs potentially worsening renal function such as tacrolimus were added, and thus it was not re-started.
	Trichlormethiazide	-	0.5 mg	Its oral use was started at 0.5 mg on Day 366 according to the decision that diuretics should be continued to keep BNP low.
	Tolvaptan	7.5 mg	7.5 mg	Its oral use was re-started at the same dose as that before transplantation on Day 3. It was discontinued 169 days later.

	Pimobendan	5 mg	5 mg	It was interrupted before transplantation and re-started at the same dose on Day 2.
	Furosemide	20 mg	20 mg	Its oral use was re-started at the same dose as that before transplantation on Day 3. The dose was reduced to 10 mg on Day 23, and it was discontinued 141 days later. It was re-started at 40 mg on Day 366.
	Sacubitril valsartan sodium hydrate	200 mg	200 mg	Its oral use was re-started at the same dose as that before transplantation on Day 1.

*1 Except drugs/products used for perioperative management, used for control/treatment of transient changes of the pathological condition for <1 week, undergoing dose changes, and used for electrolyte supplementation
*2 Total daily dose
*3 For treatment of diabetes mellitus, ipragliflozin was orally used, but it was changed to dapagliflozin propylene glycolate hydrate on Day 3.

PMDA's view on effects of concomitant medications:
Some patients who were taking drugs affecting heart failure underwent dose adjustments, switching to other drugs, or addition of another drug. They were [redacted] (a sodium glucose transporter 2 [SGLT2] inhibitor and an angiotensin II receptor blocker [ARB] were added), [redacted] (dose increase of a β blocker; amiodarone hydrochloride was switched to sotalol hydrochloride; a diuretic was added), [redacted] (a drug was switched because of an adverse reaction associated with a dose increase of a β blocker), and [redacted] (for treatment of diabetes mellitus, an SGLT2 inhibitor was switched to another SGLT2 inhibitor). These medication alterations can be made in routine clinical practice to manage adverse reactions, fluid retention, hypertension, etc. It should be noted that a possibility of concomitant medications having effects on efficacy results cannot be ruled out. There are limitations in evaluation using data only from Study CVSC0005, which included the limited number of patients, and thus the efficacy of RiHEART should be evaluated again in use-results survey, etc. to be implemented in post-marketing settings.

6.R.1.4 PMDA's conclusion on the efficacy of RiHEART

The applicant's explanation about the expected efficacy of RiHEART:
RiHEART is intended to treat patients with severe ischemic cardiomyopathy inadequately responding to standard of care, and aims at extending survival by improving or maintaining the cardiac function and thereby preventing the disease from reaching the end stage requiring heart transplantation or a ventricular assist device. RiHEART transplanted onto the heart surface is expected to improve microcirculation by inducing microvascularization, enhance cardiac function by alleviating fibrogenesis in the myocardial tissues, and relieve the heart from remodeling or the lungs from congestion. Combinations of these expected effects of RiHEART are expected to improve clinical symptoms and exercise tolerance, thereby extending survival.

PMDA's view on efficacy results of RiHEART:
For patients with ischemic cardiomyopathy, extended survival is meaningful. In view of the mechanism of action of RiHEART, whether it can be expected to extend survival is considered important in evaluating efficacy. LVEF is suggested to be a prognostic factor for long-term mortality in patients with heart failure. In Study CVSC0005 conducted in an open-label manner, LVEF, an objective measure, was employed as the primary endpoint. However, a clinical study of CABG for treatment of ischemic cardiomyopathy showed that CABG improved survival, but no difference was observed in improvement of LVEF (*N Engl J Med.* 2019;381:739-48); and RiHEART may not improve all efficacy outcome measures, but improvement or maintenance of any of cardiac function measures or interactions of effects

on the measures would improve or maintain clinical symptoms of heart failure and exercise tolerance, leading to improved survival. The following applicant's explanation, therefore, is understandable: Based on such finding and view, to explain the efficacy of RiHEART, comprehensive evaluation must be performed, covering not only results of LVEF but also those of secondary endpoints such as LVESVI, LVEDVI, NYHA Functional Class, and exercise tolerance and examinations in individual patients.

In view of the applicant's explanation about the mechanism of action expected for RiHEART and clinical meaningful changes [see Section 6.R.1.2], PMDA evaluated the efficacy of RiHEART mainly based on the results of (a) LVEF, (b) LVESVI and LVEDVI, (c) NYHA Functional Class, and (d) SAS score, 6MWD, and peak VO_2, which were selected as the primary and secondary outcome measures in Study CVSC0005. To confirm long-term efficacy, PMDA decided to use results at Week 52 for evaluation but not at Week 26.

Table 32 shows evaluation results.

Table 32. Efficacy of RiHEART (changes from pre-transplantation to Week 52)

Patient ID	Echocardiography	CT examination			NYHA Functional Class	SAS	6MWD	Peak VO_2
	LVEF	LVEF	LVESVI	LVEDVI				
[redacted]	△	△	○	○	○	○	△	○
[redacted]	△	-	-	-	○	×	△	-
[redacted]	○	△	△	△	○	△	△	△
[redacted]	×	○	○	○	○	○	○	△
[redacted]	×	△	○	○	○	△	△	○
[redacted]	△	○	△	×	○	△	○	○
[redacted]	○	△	△	△	○	○	○	△
[redacted]	×	-	-	-	○	○	○	○
Proportion of patients with improvement	2/8 (25.0%)	2/8 (25.0%)	3/8 (37.5%)	3/8 (37.5%)	8/8 (100%)	4/8 (50.0%)	4/8 (50.0%)	4/8 (50.0%)

-, Not evaluable due to no data
○, Improved (LVEF ≥+5%, LVESVI ≤-10%, LVEDVI ≤-10 mL/m^2, NYHA ≥1-level improvement, SAS ≥1 MET, 6MWD ≥+45 m, peak VO_2 ≥+10%)
△, Maintained (other than ○ and ×)
×, Worsened (LVEF <-5%, LVESVI ≥+10%, LVEDVI ≥+10 mL/m^2, NYHA ≥1-level worsening, SAS ≤-1 MET, 6MWD ≤-45 m, peak VO_2 ≤-10%)

(a) LVEF

Generally, CT examination is reported to deliver more precise data on left ventricular function such as LVEF than echocardiography (*J Am Coll Cardiol.* 2012;59:1897-907, *European heart journal-Cardiovascular Imaging.* 2015;16:848-52). Results measured by CT examination but not echocardiography should be used for evaluation. For CT examination, results were not available in 2 patients, but of 6 patients with results available, 2 patients (25.0%) showed improvement.

(b) LVESVI and LVEDVI

Changes over time for each patient are as shown in Table 23. For evaluation of cardiac remodeling, results measured by CT examination but not echocardiography should be used as done for LVEF, in view of technical problems in image analysis, etc. Based on CT examination results, 3 patients (37.5%) showed improvement for both LVESVI and LVEDVI.

(c) NYHA Functional Class

Because Study CVSC0005 was conducted in an open-label manner, a psychological effect on assessment for NYHA Functional Class cannot be ruled out, potentially limiting the evaluation. However, 4 patients (50.0%) showed 2-level improvement from Class III to I.

(d) SAS score, 6MWD, and peak VO_2

Although the effect of patient's motivation for exercising at the time of measurement cannot be ruled out, at Week 52, four patients (50%) showed improvement for each of SAS score, 6MWD, and peak VO_2. However, the effects of cardiac rehabilitation and concomitant medications cannot be ruled out, and the study was conducted not only in an open-label manner but also in the very limited number of patients eligible for RiHEART, precluding conclusion on the efficacy of RiHEART at present. Despites the circumstances, the efficacy of RiHEART may be expected because published literature has reported that a 6% improvement in peak VO_2 led to a 5% decrease in mortality or hospitalization and an 8% decrease in cardiovascular mortality or hospitalization due to heart failure, suggesting improved peak VO_2 was associated with better outcome (*Circ Heart Fail.* 2012;5:579-85).

(e) Other endpoints

Results of the overall evaluation (Table 27) showed that many patients achieved improvement of symptoms and increased physical activity in daily living. Increases in BNP and NT-pro BNP were observed, although they might reflect increased physical activity. In view of all the patients achieving improvement in NYHA Functional Class, increases in BNP and NT-pro BNP are considered as clinically minor changes.

For assessment of Responder to RiHEART (Figure 1), all the patients were assessed as Responder, and the Efficacy and Safety Evaluation Committee gave all of them Responded as a conclusion. However, results of some objective outcome measures showed worsening, limiting the Responded conclusion based on improvement of symptoms. The assessment of Responder to RiHEART warrants caution in drawing conclusions.

For NYHA Functional Class, 2-level and 1-level improvements were observed in 4 and 4 patients, respectively; all the patients' achieving improvement is considered clinically meaningful. However, Study CVSC0005 was conducted in an open-label manner, and a psychological effect on the assessment cannot be ruled out, limiting the evaluation. For hemodynamic measures (RAP, main PAP, and PAWP), most of the patients enrolled in Study CVSC0005 had values within a normal range (Table 26). PMDA thus considered it difficult to evaluate the efficacy of RiHEART using data on hemodynamic measures.

Results on the primary and secondary efficacy endpoints in Study CVSC0005 are as described above. Of the primary and secondary outcome measures, peak VO_2 is a measure that reflects clinical efficacy, is used to represent exercise tolerance, and is important to determining prognosis prediction. Although effects of cardiac rehabilitation and patient's motivation for exercising at the time of measurement cannot be ruled out, a $\geq$10% increase in peak VO_2 which is deemed as a clinically meaningful change was observed in 4 patients at Week 52, suggesting the efficacy of RiHEART. Some of the patients had results assessed as Worsening for some outcome measures but results assessed as Improved for the others,

which were comprehensively assessed as Maintained or Improved. PMDA considers that transplantation of RiHEART did not evidently worsen the condition in any patient.

Based on the above, RiHEART can be expected to have some efficacy in patients with ischemic cardiomyopathy inadequately responding to the conventional standard of care. However, the efficacy of RiHEART should be evaluated again in post-marketing settings because evaluation of the efficacy of RiHEART based on the results from Study CVSC0005 has limitations, and investigations of the efficacy of RiHEART are very limited at present.

6.R.2 Safety

Results on the safety of RiHEART in Study CVSC0005 are as described in Section 6.1.

No adverse reactions to RiHEART occurred in Study CVSC0005, and PMDA decided to review each of the serious adverse events carefully. In addition, a tumorigenicity risk, arrhythmia, and adverse reactions associated with use of immunosuppressants were reviewed as concerns associated with transplantation of RiHEART.

(a) Serious adverse events in Study CVSC0005

In Study CVSC0005, 10 serious adverse events occurred in 5 of 8 patients (62.5%) (Table 33).

Table 33. Information about serious adverse events

Patient ID Age Sex	MedDRA PT or name of adverse event	Severity	Time to onset (Day)[*1]	Duration (days)[*2]	Outcome	Causal relationship	Course	Reason for assessment result for a relationship to RiHEART
[redacted] 5[redacted] years Male	Chest discomfort	Mild	37	2	Resolved	No	He subjectively noticed chest discomfort and was hospitalized for workup. Electrocardiography, echocardiography, and blood collection were performed. No particular abnormalities were observed, and he was placed in follow-up.	The event was deemed accidental, and thus was assessed as unrelated.
[redacted] 7[redacted] years Male	Urinary tract infection	Moderate	97	19	Resolved	No	Urinalysis indicated urinary tract infection. It was alleviated with antibiotics.	Not related
	Cardiac failure acute	Moderate	132	15	Resolved	No	He subjectively noticed shortness of breath during the daytime, experienced intensified feeling of dyspnoea, and was urgently hospitalized. An antihypertensive was started. In response to EF of 18.6% indicated in echocardiography, dobutamine was	A potential cause was increased afterload on the left ventricle due to hypertensive surge in response to rapid temperature drop. The event was assessed as unrelated.

							started. X-ray and CT examinations revealed pulmonary congestion and pleural effusion, and the symptoms were alleviated after the start of a diuretic.	
[redacted] years Male	Amiodarone -induced pneumonia	Mild	121	229	Resolved	No	Infection was ruled out by results of various examinations, and amiodarone-induced pneumonia was suspected, resulting in discontinuation of amiodarone. Then, pneumonia was alleviated.	Amiodarone was considered responsible.
[redacted] years Male	Cardiac ventricular thrombosis	Moderate	29	32	Resolved	No	Echocardiography at Week 4 revealed a thrombus in the left ventricle, and thus anticoagulant drugs (heparin, bayaspirin, and warfarin) were administered. The patient was placed in follow-up. Echocardiography showed that the thrombus in the left ventricle gradually decreased in size and then disappeared. As scheduled, immunosuppressants were continued and discontinued 1 month after disappearance of the thrombus.	The thrombus disappeared with anticoagulant therapy. It was potentially caused by impaired left ventricular function as generally observed in clinical settings, and there was poor evidence supporting that it was caused by the study product.
	Enteritis infectious	Moderate	113	6	Resolved	No	Blood test and imaging indicated inflammation, and CF was performed. Diagnoses of enteritis infectious and large intestine polyp were given. Enteritis infectious was alleviated.	It occurred on Day 112 or 22 days after the end of immunosuppressants. Based on time to onset, the event was assessed as causally unrelated.
	Colon cancer	Severe	117	63	Resolved	No	In response to enteritis infectious, CF was performed, indicating large intestine polyp. ESD was performed, resulting in a diagnosis of colon cancer.	Colon cancer was found 6 months after transplantation, and thus relationships to the study product and procedure were ruled out.
	Large intestine perforation	Severe	170	30	Resolved	No	Colon ESD was performed. During the procedure, microperforation partially occurred, and the wound underwent clip closure. After resection of the lesion, perforating wound dehiscence occurred, and the wound underwent additional clip closure. Complete closure was	Because large intestine perforation was a complication of ESD procedure, and the event was assessed as causally unrelated.

							achieved, resulting in recovery.	
	Patella fracture	Moderate	270	106	Resolved	No	Fall caused a right knee bruise. The injury was diagnosed as a right patella fracture at a nearby clinic and underwent right patellar surgery, resulting in recovery.	Because the cause was an accidental fall, the event was assessed as causally unrelated.
[redacted] 6[redacted] years Female	Heart failure	Moderate	170	197	Resolved	No	Examination at Week 26 showed that BNP was increased to 1010.9 pg/mL. Chest X-ray examination revealed increased CTR and image indicative of mild congestion. The condition was deemed as worsened heart failure. After hospitalization, a diuretic was administered.	After transplantation, BNP remained within a range from 100 to 200 pg/mL but increased at Week 26, and thus the condition was deemed as worsened heart failure. Potential causes for worsened heart failure were overactive life at home and intensified activity of living. Echocardiography showed a decrease in EF, but BNP and EF were improved with a diuretic and resting. Because the event occurred 6 months after transplantation, the direct effect of transplantation was ruled out.

*1 Number of days after transplantation of RiHEART
*2 Number of days equivalent to duration of the adverse event

PMDA reviewed clinical courses in patients with serious adverse events and considers that for the following events, a causal relationship to RiHEART cannot be ruled out.

- Cardiac ventricular thrombosis (Patient ID No. [redacted])

The thrombus disappeared with anticoagulant therapy. It was potentially caused by impaired left ventricular function as generally observed in clinical settings, and a causal relationship to RiHEART was ruled out. Based on the clinical course, the thrombus was formed during transplantation of RiHEART, and thus an effect of RiHEART cannot be ruled out, although an effect of the transplantation procedure or concomitant medications may have been responsible.

- Urinary tract infection (Patient ID No. [redacted]) and enteritis infectious (Patient ID No. [redacted])

A possibility of effects of immunosuppressants or impaired immunocompetence by physical burden associated with transplantation of RiHEART cannot be ruled out. However, both patients had improved NYHA Functional Class at Week 26, indicating that physical burden associated with the transplantation procedure did not involve the heart, although the physical burden would have affected the condition to a certain extent. Both events resolved with symptomatic treatment and thus are considered manageable and tolerable.

(b) Risk of neoplastic transformation

Because undifferentiated cells present in transplanted cells may lead to tumorigenesis (*Stem Cells Dev.* 2016;25:815-25), a risk of neoplastic transformation associated with transplantation of RiHEART was reviewed.

At present, no tumor development associated with transplantation of RiHEART has occurred in Study CVSC0101, which is conducted for long-term follow-up of patients with RiHEART transplanted in Study CVSC0005.

Although colon cancer was observed in 1 patient ([redacted]) in Study CVSC0005, the patient had been found to have a large intestine polyp by colonoscopy before transplantation of RiHEART and was scheduled to be followed up periodically. Because colon cancer was found as short as approximately 6 months (178 days) after transplantation of RiHEART, causal relationships to RiHEART and the transplantation procedure were ruled out. The patient underwent endoscopic submucosal dissection and recovered.

(c) Arrhythmia

In Study CVSC0005, an adverse event of atrial fibrillation occurred in 1 patient. Although its causal relationship to RiHEART was ruled out, use of RiHEART may lead to the risk of arrhythmia attributable to the transplantation procedure or primary disease. Recipients of RiHEART should undergo adequate examination and observation for arrhythmia, and arrhythmia, if any, should be appropriately managed.

(d) Adverse reactions associated with use of immunosuppressants

RiHEART is manufactured from allogeneic cells, and use of concomitant immunosuppressants is required. Attention should be paid to adverse reactions of immunosuppressants. In Study CVSC0005, serious adverse events of infections potentially attributable to immunosuppressants used after transplantation of RiHEART occurred in 2 patients. Both events resolved, and they are considered manageable. Immunosuppressants are used according to the same dosage regimen as that for heart transplantation, and a period of their use is 90 days. In view of such use status, adverse reactions associated with use of immunosuppressants are considered tolerable.

Based on the above, PMDA has concluded that RiHEART can be tolerated if physicians with adequate knowledge and experience in treatment of severe heart failure caused by ischemic cardiomyopathy take necessary measures during transplantation of RiHEART, and select patients eligible for RiHEART as well as manage recipients of RiHEART appropriately. However, because safety information of RiHEART is very limited, the applicant is required to continue collecting safety information of RiHEART even in post-marketing settings and to provide obtained information to healthcare professionals appropriately.

6.R.3 Clinical positioning

The applicant's explanation about clinical positioning of RiHEART:

The standard of care for ischemic cardiomyopathy combines non-invasive treatment and invasive interventions. The non-invasive treatment is provided mainly as pharmacotherapy in which nitrate, Ca

antagonists, angiotensin converting enzyme (ACE) inhibitors, ivabradine, digitalis, oral cardiotonic agents, diuretics, and antiplatelet drugs are widely used. Some recently introduced non-invasive treatments use, in addition to conventional β blockers, mineralocorticoid receptor antagonists (MRAs), angiotensin receptor-neprilysin inhibitors (ARNIs), and/or SGLT2 inhibitors, and cardiac rehabilitation is also concomitantly used. The invasive interventions are provided as coronary artery bypass graft surgery, percutaneous transluminal coronary angioplasty, etc., ≥75% of patients eligible for invasive interventions achieved improved cardiac function with an intervention (*Thorac Caridiovasc Surg.* 2022;70:544-8, *Heart Vessels.* 2024;39:571-81). However, in some patients with severe ischemic cardiomyopathy, symptoms of heart failure are not improved by the above standard of care. When patients whose disease has inadequately responded to the conventional standard of care and the disease is further progressed, it reaches the end stage that disables the patient from supporting life with their own heart and is indicated for heart transplantation or a ventricular assist device. Heart transplantation, however, has issues such as lack of donors, age restrictions, and life-long use of immunosuppressants. Ventricular assist devices also have issues such as durability of the device and a risk of device-associated infections and neurologic dysfunctions. There is a need for treatment that aims at extending survival by improving or maintaining the cardiac function and exercise tolerance and thereby preventing the disease from reaching the end stage requiring heart transplantation or a ventricular assist device.

Study CVSC0005 has shown that RiHEART can be expected to have some efficacy in patients with ischemic cardiomyopathy inadequately responding to the conventional standard of care. RiHEART is expected to offer a new treatment option for such patients.

PMDA accepted the above applicant's explanation.

6.R.4 Indication or performance

For RiHEART, "Indication or Performance" and "Precautions Concerning Indication or Performance" were proposed as follows:

Indication or Performance

Treatment of severe heart failure associated with ischemic cardiomyopathy that has an inadequate response to standard-of-care therapies, including pharmacotherapy and invasive interventions

Precautions Concerning Indication or Performance

- RiHEART should be used in patients with left ventricular ejection fraction (LVEF) at rest ≤35%.
- Patients with serious heart failure subject to consideration for eligibility for LVAD are not indicated. Eligible patients must be selected by physicians with a full understanding of the information on characteristics of patients included in the clinical studies (e.g., LVEF, prior treatments, NYHA Functional Class), presented in the "17. Clinical Studies" section, and of the efficacy and safety of RiHEART and after carefully weighing its benefits and risks.

As a result of Sections "6.R.1 Efficacy," "6.R.2 Safety," and the review presented below, PMDA has concluded that the "Indication or Performance" of RiHEART as proposed by the applicant is acceptable. In addition, the "Precautions Concerning Indication or Performance" should be specified as follows:

Precautions Concerning Indication or Performance (Underline denotes additions or corrections. Strikethrough denotes deletions.)

- RiHEART should be used in patients with left ventricular ejection fraction (LVEF) at rest ≤35%.
- Patients with serious heart failure subject to consideration for eligibility for LVAD are not indicated.
- Eligible patients must be selected by physicians with a full understanding of the information on characteristics of patients included in the clinical studies (e.g., ~~LVEF, prior treatments,~~ NYHA Functional Class, prior treatments), presented in the "17. Clinical Studies" section, and of the efficacy and safety of RiHEART and after carefully weighing its benefits and risks.

6.R.4.1 Patient population eligible for RiHEART

The applicant's explanation about the rationale for proposed "Indication or Performance":
Indication or Performance was selected based on the findings that Study CVSC0005 in 8 patients with ischemic cardiomyopathy inadequately responding to standard-of-care therapies, including pharmacotherapy and invasive interventions has shown that RiHEART can be expected to have some efficacy; and that RiHEART was well tolerated in this study.

For Study CVSC0005, patients with LVEF at rest (echocardiography) ≤35% were selected based on the results of echocardiography performed at screening sites. Based on the inclusion criterion in Study CVSC0005, the "Precautions Concerning Indication or Performance" section defines patients eligible for RiHEART as those with LVEF ≤35%. However, values can differ between screening and last pre-transplantation time points or between a study site and a facility specialized in image analyses. LVEF ≥35% just before transplantation was observed in 3 patients (Patient ID Nos. [redacted], [redacted], and [redacted]) when measured by echocardiography and in 2 patients (Patient ID Nos. [redacted] and [redacted]) when measured by CT examination. Variations and errors can usually occur in measurement of LVEF, and patients with LVEF ≤40% are uniformly defined as those with heart failure with reduced ejection fraction (HFrEF) in medical guidelines, and thus pathological conditions of such patients do not substantially differ if their LVEF is approximately 40% or less. Patients with LVEF ≤35% at screening but slightly exceeding 35% at the last pre-transplantation time point may be deemed eligible for the use of RiHEART as long as other eligibility criteria are met (e.g., the conditions remain unchanged despite maximum pharmacotherapy).

The precaution that "RiHEART is not indicated for use in patients with serious heart failure subject to consideration for eligibility for left ventricular assist device (LVAD)" is provided to clarify the clinical positioning of RiHEART and to avoid giving physicians and patients unrealistic expectations, because RiHEART does not function as a substitute for the heart. In view of the limited number of patients included in Study CVSC0005, the applicant considered that eligible patients must be selected by physicians with a full understanding of the efficacy and safety of RiHEART.

PMDA's view:
The indication included "patients with severe heart failure associated with ischemic cardiomyopathy who has an inadequate response to standard-of-care therapies, including pharmacotherapy and invasive

interventions," which were the study population in Study CVSC0005. The applicant's proposal is appropriate.

Although patients with symptoms of NYHA Functional Class III or IV were eligible for Study CVSC0005, actually enrolled patients had symptoms of NYHA Functional Class III only. Eligible patients are defined as those with LVEF ≤35% and the disease that has an inadequate response to standard-of-care therapies, including pharmacotherapy and invasive interventions, and thus little need can be found for separately defining the criterion about NYHA Functional Class. It is sufficient to provide information about NYHA Functional Class in patients included in Study CVSC0005 in the "Clinical Studies" section.

Some of the patients included in Study CVSC0005 had LVEF ≤35% at the time of enrollment but >35% just before transplantation. In view of this, information about changes in LVEF over time should be provided in the "Clinical Studies" section. In addition, the applicant's explanation about LVAD is acceptable.

6.R.5 Dosage and administration or method of use

For RiHEART, the "Dosage and Administration or Method of Use" and "Precautions Concerning Dosage and Administration or Method of Use" were proposed as follows:

Dosage and Administration or Method of Use

(1) Apply heat to melt and remove the gelatin gel surrounding a cardiomyocyte sheet, wash the cardiomyocyte sheet with the attached washing fluid, and immerse it in the attached washing fluid.
(2) Transplant 3 cardiomyocyte sheets on the heart surface sequentially. In principle, perform a left thoracotomy for the transplantation.
(3) Administer 3 immunosuppressants (prednisolone, tacrolimus, and mycophenolate mofetil) basically according to the post-heart-transplantation regimen for 90 days (including a tapering period), starting on the following day of transplantation of cardiomyocyte sheets (Day 1).

Precautions Concerning Dosage and Administration or Method of Use

1 Precautions during transplantation of RiHEART
1.1 Consider application sites carefully because a cardiomyocyte sheet, once applied to the heart surface, is difficult to detach and apply again.
1.2 If bleeding is observed on the heart surface, hemostasis should be adequately achieved to ensure that no blood matters remain between the cardiomyocyte sheet and heart surface.
1.3 Blood matters should be suctioned, if any, with caution to avoid aspirating a cardiomyocyte sheet.
1.4 When applied to the heart surface, a cardiomyocyte sheet may slip and fall. Especially when a cardiomyocyte sheet is applied to a steep part, measures such as securing the sheet with stay sutures should be taken to prevent it from slipping and falling.
1.5 A spare cardiomyocyte sheet should be used only when its use is inevitable, for example, because of breakage of another sheet. Any unused cardiomyocyte sheet should be disposed of in accordance with relevant institutional procedures.
2 Precautions concerning treatment after transplantation of RiHEART

2.1 Each immunosuppressant should be used in accordance with the Dosage and Administration and Precautions sections in its electronic package insert.

As a result of reviews in Sections "6.R.1 Efficacy," "6.R.2 Safety," and the review presented below, PMDA has concluded that the "Dosage and Administration or Method of Use" and "Precautions Concerning Dosage and Administration or Method of Use" of RiHEART should be specified based on the protocol of Study CVSC0005 with modifications as presented below.

Dosage and Administration or Method of Use (Underline denotes additions or corrections. Strikethrough denotes deletions.)

1 Pretreatment before transplantation of RiHEART

1.1 ~~Apply heat to m~~Melt and remove the ~~gelatin~~ gel surrounding a cardiomyocyte sheet, wash the cardiomyocyte sheet with ~~the attached~~ a washing fluid, and immerse it in this fluid ~~in the attached washing fluid~~.

2 Transplantation of RiHEART

2.1 Transplant 3 cardiomyocyte sheets on the heart surface sequentially. In principle, perform a left thoracotomy for the transplantation.

3 Treatment after RiHEART transplantation

3.1 Administer 3 immunosuppressants (prednisolone, tacrolimus, and mycophenolate mofetil) ~~basically~~ according to the ~~post-heart transplantation~~ dosage regimen provided below for a period of 90 days ~~(including a tapering period)~~, starting on the following day of transplantation of cardiomyocyte sheets (Day 1). This period includes a tapering period. The doses should be adjusted according to the symptoms.

- The usual dosage of prednisolone is 20 mg orally administered once daily. Tapering is started approximately on Day 30.
- The usual dosage of tacrolimus is 1.5 mg orally administered twice daily. The dose should be adjusted to maintain the trough blood tacrolimus level in a range of 10 to 15 ng/mL by monitoring the trough blood level. Tapering is started approximately on Day 60.
- The usual dosage of mycophenolate mofetil is 1 g orally administered twice daily. Tapering is started approximately on Day 60.

Precautions Concerning Dosage and Administration or Method of Use (Underline denotes additions. Strikethrough denotes deletions.)

1 Precautions during transplantation of RiHEART

1.1 Consider application sites carefully because a cardiomyocyte sheet, once applied to the heart surface, is difficult to detach and apply again.

1.2 If bleeding is observed on the heart surface, hemostasis should be adequately achieved to ensure that no blood matters remain between the cardiomyocyte sheet and heart surface.

1.3 Blood matters should be suctioned, if any, with caution to avoid aspirating a cardiomyocyte sheet.

1.4 When applied to the heart surface, a cardiomyocyte sheet may slip and fall. Especially when a cardiomyocyte sheet is applied to a steep part, measures such as securing the sheet with stay sutures should be taken to prevent it from slipping and falling.

1.5 A spare cardiomyocyte sheet should be used only when its use is inevitable, for example, because of breakage of another sheet. Any unused cardiomyocyte sheet should be disposed of in accordance with relevant institutional procedures.

2 Precautions concerning treatment after transplantation of RiHEART

2.1 Each immunosuppressant should be used in accordance with the Dosage and Administration and Precautions sections in its electronic package insert.

2.2 Physicians should attend seminars and training sessions before using RiHEART.

2.3 Because transplantation of cardiomyocyte sheets involves thoracotomy, patients should have only a single chance to undergo transplantation of RiHEART.

6.R.5.1 Use of immunosuppressants associated with transplantation of RiHEART

The applicant's explanation about use of immunosuppressants associated with transplantation of RiHEART:

Choice of immunosuppressants was based on a protocol for use of immunosuppressants applied to patients undergoing heart transplantation at the Department of Cardiovascular Surgery, the University of Osaka Hospital [see Section 6.1]. The administration period of 90 days was determined based on investigation of the administration period in an ischemic cardiomyopathy model in cynomolgus monkeys which had undergone allogeneic transplantation of cynomolgus monkey iPS cell-derived cardiomyocytes (*Transplantation.* 2019;103:1582-90) and in view of the risk of prolonged use of immunosuppressants.

PMDA's view:

There are no data from clinical studies assessing the efficacy and safety of RiHEART with and without immunosuppressants, and rejection to RiHEART in patients without immunosuppressants remains unknown. However, at present, Study CVSC0005 has not suggest any particular concern about the safety of immunosuppressants, which were well tolerated. In view of the above, immunosuppressants should be used according to the same regimen as that employed in Study CVSC0005 for transplantation of RiHEART, and dosage regimens of immunosuppressants should also be included in the "Dosage and Administration or Method of Use" section of RiHEART.

6.R.5.2 RiHEART transplantation method

The applicant's explanation about the RiHEART transplantation method:

RiHEART is supposed to be used at an institution where a heart team comprised of departments of cardiovascular medicine and cardiovascular surgery is formed to allow comprehensive management and treatment of heart failure as well as cardiovascular surgery. Eligibility for use of RiHEART will be considered for a patient who has been assessed to have no other options for treatment because of persistent symptoms of heart failure despite maximum conventional treatment provided by the heart team. More specifically, the ischemic site should be examined by echocardiography, magnetic resonance imaging (MRI), or by other means to assess the heart condition before surgery. During surgery, the heart surface should be further examined to identify irreversible fibrotic areas with myocardial scar and living myocardial areas potentially eligible for use of RiHEART before a decision is made about the patient's eligibility. Although minor adjustments were made for each patient in view of the above examination results, in principle, RiHEART was applied to accessible areas in Study CVSC0005 because areas

accessible with left intercostal space thoracotomy (area from the left ventricular anterior wall to the lateral wall) were limited. Patients with ischemic cardiomyopathy accompanied by decreased LVEF, including 8 patients in Study CVSC0005, generally have ischemia in an area from the left ventricular anterior wall to the lateral wall.

PMDA's view:
Although whether or how differences in procedures for transplantation of RiHEART among medical institutions would impact the efficacy and safety of RiHEART remains unclear, the applicant is required to take measures such as standardization of procedures used in Study CVSC0005, preparation of training materials, and implementation of training sessions to ensure that transplantation techniques do not differ among medical institutions and that RiHEART is transplanted via appropriate standardized procedures. PMDA has concluded that the package insert of RiHEART should include a statement "Physicians should attend seminars and training sessions before using RiHEART" and that detailed information should be separately provided through materials.

7. Risk Analysis and Outline of the Review Conducted by PMDA

7.1 Post-marketing investigations

The applicant's explanation about plan for post-marketing surveillance, which is implemented to confirm the efficacy of RiHEART continuously and collect further safety information in post-marketing settings until a specified time limit:
Efficacy evaluation based on the results from Study CVSC0005, which was conducted in an exploratory manner, has limitations, and investigations of the efficacy of RiHEART are very limited at present. For these reasons, the applicant plans use-results survey covering all recipients of RiHEART to evaluate the efficacy of RiHEART in post-marketing clinical settings in Japan in a confirmatory manner (Table 34).

Table 34. Outline of use-results survey (draft)

Objective	To verify the efficacy of RiHEART in clinical settings and evaluate its safety, using external control of patients with severe heart failure associated with ischemic cardiomyopathy who has an inadequate response to the standard of care in separately conducted prospective clinical research.
Survey method	All-case surveillance method
Population	All patients with ischemic cardiomyopathy who have undergone transplantation of RiHEART
Registration and survey periods	Until a decision is made on an application for standard marketing approval, which is supposed to be submitted within the specified period of the conditional and time-limited approval
Observation period	From the day of transplantation of RiHEART to the day when a decision is made on an application for standard marketing approval, which is supposed to be submitted within the specified period of the conditional and time-limited approval
Target sample size	75 patients[*1]
Number of medical institutions	■ medical institutions
Primary efficacy endpoint	Proportion of patients with improvement of peak VO_2 (≥10% increase) from baseline[*2] to Week 52 and improvement or maintenance of LVESVI (CT or MRI examination) from baseline to Week 52 (decrease, unchanged, or <10% increase)
Analysis method of primary endpoint	Propensity score[*3] matching is performed and a difference in the proportions of matched patients who met the specified requirements, the primary endpoint, between the RiHEART and control groups is subjected to Wald test (2-sided significance level of 10%). For missing data, in patients who have died, undergone heart transplantation, or undergone implantation of a ventricular assist device, the result of the primary endpoint should be "Worsened." Missing data caused by other reasons should be addressed by multiple imputation.
Efficacy secondary endpoints	Hospitalization due to heart failure Survival (cardiovascular mortality, all-cause mortality) Cardiopulmonary exercise test (peak VO_2) (change from baseline) 6-minute walk distance test (change from baseline) NYHA Functional Class Cardiac function indices (LVEF, LVESVI, LVEDVI measured by CT or MRI examination or echocardiography) Cardiac function evaluation by right ventricular catheterization (e.g., PAWP, CI, CO) (limited to patients available for measurement)
Safety endpoints	Hospitalization due to heart failure Survival (cardiovascular mortality, all-cause mortality) Adverse events (events for which a causal relationship to RiHEART cannot be ruled out and events for which a causal relationship to surgery during transplantation of RiHEART cannot be ruled out) Adverse reactions associated with use of immunosuppressants after transplantation of RiHEART Tumor development at the site of transplantation of RiHEART and its vicinity

*1 Until 5 years have passed since the day of conditional and time-limited approval or the target sample size is reached, whichever comes first, recipients of RiHEART will be included in the full analysis set for efficacy and safety analysis population. Since then, all recipients of RiHEART will be included only in the safety analysis population until a decision is made on an application for standard marketing approval, which is supposed to be submitted within a validity period of the conditional and time-limited approval.

*2 Baseline should be an examination value before surgery (within 35 days before transplantation)

*3 Estimated by logistic regression model using 6 covariates of age, estimated glomerular filtration rate (eGFR), baseline peak VO_2, guideline-directed medical therapy (GDMT) score, presence or absence of prior hospitalization due to heart failure, and duration of ischemic heart disease as independent variables and group (transplantation or control group) as a dependent variable. Missing data on a covariate should be addressed by multiple imputation to estimate propensity score.

The use-results survey was planned on the following ground.

Study design

Transplantation of RiHEART involves thoracotomy, and the conduct of a randomized controlled study is ethically infeasible. The applicant planned to evaluate the efficacy of RiHEART and confirm its safety by comparing recipients of RiHEART in the use-results survey with external control of patients with severe heart failure associated with ischemic cardiomyopathy who has an inadequate response to the standard of care in separately conducted prospective clinical research. The clinical research to be used as the control group is planned to include approximately ■ medical institutions.

Primary endpoint

The primary endpoint was the proportion of patients with improvement of peak VO_2 (≥10% increase) from baseline to Week 52 and improvement or maintenance of LVESVI from baseline to Week 52 (decrease, unchanged, or <10% increase).

Peak VO_2 is measured in a cardiopulmonary exercise test, widely used as a measure of exercise tolerance in patients with heart failure, and important for prognosis prediction. In Study HF-ACTION in patients with chronic heart failure, a 6% improvement in peak VO_2 led to a 5% decrease in mortality or hospitalization and an 8% decrease in cardiovascular mortality or hospitalization due to heart failure, suggesting that improved peak VO_2 was associated with better outcome (*Circ Heart Fail.* 2012;5:579-85). A ≥10% increase in peak VO_2 is considered clinically meaningful, and thus "≥10% increase from baseline" is defined as "Improved." This definition is included in the criteria.

For evaluation of peak VO_2 in the use-results survey, LVESVI which is unsusceptible to the patient's motivation for exercising was also included as an outcome measure, taking into account that effects of patient's motivation for exercising at the time of measurement or other factors cannot be ruled out; and that LVESV is shown to be a stronger predictive factor than LVEF (*Circulation.* 2005;112:1580-6). For LVESVI, cardiac function gradually deteriorates with aging and/or comorbidity, and patients eligible for transplantation of RiHEART would have difficulty in maintaining the current cardiac function without treatment. Considering the above and information about clinically meaningful changes in LVESVI [see Section 6.R.1.2], "Decrease, unchanged, or <10% increase from baseline" is defined as "Improved or maintained" in view of the following understanding, and this definition is included in the criteria.

Target sample size

Based on the results from Study CVSC0005, the sample size was determined to be 75 patients in the RiHEART group and 150 patients in the control group on the following assumptions: (1) The expected value of the above primary endpoint at Week 52 is 0.4 in the RiHEART group and 0.2 in the control group; (2) the sample size ratio of the RiHEART to control groups is 1:2; and (3) it is calculated to provide 90% power at a significance level of 0.1. For the first 5 years of the survey, approximately 88 recipients of RiHEART are estimated to be registered. The use-results survey is planned to cover all patients, but patients who have undergone transplantation of RiHEART by 6 months after transplantation of RiHEART in the patient counted last to meet the target sample size will be included in the full analysis set and safety analysis population (up to 110 patients). Subsequent patients will be included only in the safety analysis population to collect safety information.

Safety specification

Table 35 shows potential risks that may occur after the market launch of RiHEART in view of neoplastic transformation at the transplantation site and its vicinity as well as hazards that may occur during manufacture and transplantation of RiHEART.

Table 35. Potential risks that may occur after market launch of RiHEART

Important identified risks	• Defects, adverse reactions, complications, and adverse events (adverse events for which a causal relationship to RiHEART cannot be ruled out) • Risks attributable to use of immunosuppressants associated with transplantation (non-adherence to immunosuppressant medication, adverse reactions associated with use of immunosuppressants) • Risks attributable to the transplantation procedure (adverse events for which a causal relationship to surgery for transplantation of RiHEART cannot be ruled out)
Important potential risks	• Defects, adverse reactions, complications, and adverse events (neoplastic transformation at the transplantation site and its vicinity) • Hazards attributable to raw materials and excipients (immune reactions and infections caused by raw materials and excipients used in RiHEART as well as residual process-related impurities [e.g., FBS]) • Hazards attributable to manufacturing and quality control processes (transplantation of RiHEART exposed to excursed temperature during transportation, sterility test performed as specification test for post-release assessment indicates contamination) • Risks associated with preparation of RiHEART (transplantation of RiHEART contaminated or damaged at a medical facility for some reasons) • Risks attributable to operations for transplantation of RiHEART (overdose caused by application of a spare sheet)

Missing information of RiHEART is specified as follows: “Effects of use of RiHEART in children, pregnant women, parturient women, patients with malignant tumor, patients with autoimmune disease, patients with acute heart failure, and patients with active infection” and “Adverse events associated with use of RiHEART not occurring in clinical studies.” Efficacy specification is defined as “Long-term efficacy” evaluated based on hospitalization due to heart failure, cardiovascular mortality, and all-cause mortality.

The observation period of 1 year from registration of the last registered patient is specified in view of the primary endpoint, but to evaluate each specification (e.g., all-cause mortality) in this survey, observation will be continued for at least 2 years after transplantation of RiHEART.

After registration of the first patient, data cut-off accompanied by meeting of the Clinical Event Evaluation Committee will be performed every 6 months to evaluate data from both RiHEART and control groups.

7.R Outline of the review conducted by PMDA

PMDA’s view on the use-results survey plan (draft) proposed by the applicant:

The applicant plans to re-evaluate the efficacy of RiHEART in post-marketing settings because efficacy evaluation based on the results from Study CVSC0005, which was conducted in an exploratory manner, has limitations, and investigations of the efficacy of RiHEART are very limited at present. PMDA considers the applicant’s plan appropriate.

The use-results survey is planned to evaluate the efficacy of RiHEART in comparison with external control in a confirmatory manner. PMDA considers such survey design inevitable from a viewpoint of feasibility.

Efficacy evaluation of RiHEART is planned to employ peak VO_2 and its criterion defining “≥10% increase from baseline” as “Improved.” In view of the applicant’s explanation, the proposed evaluation plan is acceptable. The primary endpoint is planned to be evaluated using outcome measures of exercise tolerance (peak VO_2) and cardiac function. PMDA considers the proposed endpoint appropriate from

viewpoints of not only employing an outcome measure unsusceptible to the patient's motivation for exercising for the endpoint but also putting a focus on evaluation of cardiac function at rest. Evaluation of cardiac function is planned to employ LVESVI and its criterion defining "Decrease, unchanged, or <10% increase from baseline" as "Improved or maintained" based on currently available information. The proposed evaluation plan is understandable, although the mechanism of action of RiHEART has not been fully elucidated. Of note, results on the specified secondary efficacy endpoints should also be assessed to determine the efficacy of RiHEART.

Since experience with transplantation of RiHEART is limited, the applicant is required to collect safety information from all recipients of RiHEART after the market launch of RiHEART and promptly provide obtained safety information to healthcare professionals. Furthermore, importance should be placed on extensive collection of information about the safety and efficacy of RiHEART, and the applicant plans to implement a use-results survey involving all recipients of RiHEART by registering every recipient even after the target sample size is reached. PMDA considers the applicant's plan appropriate. In the use-results survey, the long-term safety and efficacy of RiHEART should also be evaluated, and thus the observation period proposed by the applicant is acceptable.

Details of the use-results survey will be finalized, taking account of comments on efficacy and safety evaluation of RiHEART raised at the Expert Discussion.

8. Results of Compliance Assessment Concerning the New Regenerative Medical Product Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new regenerative medical product application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new regenerative medical product application data (CTD 5.3.5.2-1, CTD 5.3.5.2-2) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that RiHEART has some efficacy in the "treatment of severe heart failure associated with ischemic cardiomyopathy that has an inadequate response to standard-of-care therapies, including pharmacotherapy and invasive interventions," and that RiHEART has acceptable safety in view of its benefits. Although information about the efficacy and safety of RiHEART is currently limited, making RiHEART available for use in clinical practice is

meaningful because it offers a new treatment option for patients with severe heart failure associated with ischemic cardiomyopathy who has an inadequate response to standard-of-care therapies, including pharmacotherapy and invasive interventions.

PMDA has concluded that if no particular concerns about the efficacy or safety of RiHEART are raised by the Expert Discussion, RiHEART may be approved with the conditions and time limit under Article 23-26 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices, which will require continued efficacy assessment and safety data collection in a specified time period after marketing. The time limit as stipulated in this article will be determined with consideration of the post-marketing surveillance plan (e.g., preparation period for marketing, patient enrollment period, observation period for each patient, and preparation period for regulatory submission), as well as the outcomes of the Expert Discussion.

Review Report (2)

February 10, 2026

Product Submitted for Approval

Brand Name	RiHEART
Non-proprietary Name	Human (allogeneic) iPS cell-derived cardiomyocyte sheet
Applicant	Cuorips Inc.
Date of Application	April 4, 2025

List of Abbreviations
See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations, etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions, etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy

As a result of the review in Section "6.R.1 Efficacy" of the Review Report (1), PMDA has concluded that RiHEART can be expected to have some efficacy in patients with severe heart failure associated with ischemic cardiomyopathy who has an inadequate response to standard-of-care therapies, including pharmacotherapy and invasive interventions.

Since efficacy information of RiHEART is very limited, PMDA has concluded that the applicant should continue to evaluate the efficacy of RiHEART even in post-marketing settings.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

The following comments were raised from the expert advisors:

- In view of results on outcome measures (SAS, 6MWD, and BNP) other than NYHA Functional Class in individual patients in Study CVSC0005, some patients might have had symptoms of NYHA Functional Class II at pre-transplantation. Results on NYHA Functional Class warrant careful interpretation.

PMDA's view with the expert advisor's comment considered:
In addition to the expert advisor's comment, as described in Section 6.R.1.2, a psychological effect on assessment for NYHA Functional Class cannot be ruled out, potentially limiting the assessment because of design of Study CVSC0005, which was conducted in an open-label manner. The results on NYHA

Functional Class in Study CVSC0005 warrant careful interpretation. However, NYHA Functional Class is widely used as a measure allowing simple classification of heart failure by severity, and thus results on NYHA Functional Class are considered informative to a certain extent. The information concerned should be included in the package insert, etc.

Based on the above, PMDA instructed the applicant to include information about NYHA Functional Class in Study CVSC0005 in the "Clinical Studies" section of the package insert and to provide detailed information using materials. The applicant appropriately responded, and PMDA accepted their response.

1.2 Safety

As a result of the review in Section "6.R.2 Safety" of the Review Report (1), no clinically significant adverse events for which a causal relationship to RiHEART cannot be ruled out have occurred throughout the clinical study. Based on the above, PMDA has concluded that RiHEART can be tolerated if physicians with adequate knowledge and experience in treatment of severe heart failure associated with ischemic cardiomyopathy take necessary measures during transplantation of RiHEART, and if such physicians select patients eligible for use of RiHEART as well as manage recipients of RiHEART appropriately.

The above conclusion of PMDA was supported by the expert advisors at the Expert Discussion.

The expert advisors commented that the serious adverse events in Study CVSC0005 for which a causal relationship to RiHEART may not be ruled out, such as cardiac ventricular thrombosis, should be addressed as a risk associated with RiHEART.

PMDA instructed the applicant to appropriately collect information about specific serious adverse events, including cardiac ventricular thrombosis, in the post-marketing surveillance. The applicant appropriately responded, and PMDA accepted their response.

1.3 Indication or performance

As a result of the review in Section "6.R.4 Indication or performance" of the Review Report (1), the "Indication or Performance" and "Precautions Concerning Indication or Performance" sections should be specified as described in the above-mentioned section of the Review Report (1).

At the Expert Discussion, the conclusion of PMDA on the "Indication or Performance" section was generally supported by the expert advisors, but the following comment was raised from some of the expert advisors:

- Since data showing that RiHEART improves survival are limited, the "Indication or Performance" section should explain the expected effects of RiHEART more specifically, such as improved exercise tolerance observed in Study CVSC0005.

For the "Precautions Concerning Indication or Performance" section, the expert advisors commented as follows:

- Information about the characteristics of the patients included in the clinical study should additionally include information on exercise tolerance.

PMDA's view with the expert advisor's comment considered:
As described in Section 6.R.1.2, favorable results were obtained for peak VO_2, which is widely used as a measure representative of exercise tolerance and important in predicting prognosis. Such results are considered meaningful, suggesting the efficacy of RiHEART. However, the mechanism of action of RiHEART has not been clearly elucidated at present, and thus PMDA considers that the "Indication or Performance" of RiHEART may be specified as described in Section "6.R.4 Indication or performance" of the Review Report (1), but the statement of the "Indication or Performance" should be discussed again based on the results from efficacy evaluation of RiHEART used in clinical practice in Japan, which will be performed in post-marketing settings. Currently available information about the efficacy of RiHEART should be included in the package insert and other materials for appropriate provision of information. In view of comments raised from the expert advisors, the "Precautions Concerning Indication or Performance" section should be specified as follows:

Precautions Concerning Indication or Performance (Underline denotes additions to the Review Report [1])
- RiHEART should be used in patients with left ventricular ejection fraction (LVEF) at rest ≤35%.
- Patients with serious heart failure subject to consideration for eligibility for LVAD are not indicated.
- Eligible patients must be selected by physicians with a full understanding of the information on characteristics of patients included in the clinical studies (e.g., NYHA Functional Class, <u>exercise tolerance,</u> prior treatments), presented in the "17. Clinical Studies" section, and of the efficacy and safety of RiHEART and after carefully weighing its benefits and risks.

PMDA instructed the applicant to include currently available information about the efficacy of RiHEART, including data on survival after transplantation of RiHEART, in the package insert and other materials for appropriate provision of information, and to modify the "Precautions Concerning Indication or Performance" section. The applicant responded appropriately, and PMDA accepted their response.

1.4 Dosage and administration or method of use

As a result of the review in Section "6.R.5 Dosage and administration or method of use" of the Review Report (1), PMDA has concluded that the "Dosage and Administration or Method of Use" and "Precautions Concerning Dosage and Administration or Method of Use" sections for RiHEART should be specified as described in the above-mentioned section of the Review Report (1).

At the Expert Discussion, the expert advisors supported the above conclusion of PMDA and also made the following comments:
- For use of RiHEART, participation in seminars and training sessions is critical.
- Regarding the method of use of RiHEART such as transplantation method and number of transplantation sessions, more specific information should be provided.

In view of expert advisors' comments, PMDA has concluded that "Dosage and Administration or Method of Use" should be specified as described in Section "6.R.5 Dosage and administration or method

of use" of the Review Report (1), and the "Precautions Concerning Dosage and Administration or Method of Use" should be specified as presented below. Description about immunosuppressants was modified to clarify that for tacrolimus, immediate-release dosage forms should be used as done in Study CVSC0005. PMDA instructed the applicant to provide detailed information about the method of use of RiHEART to healthcare professionals through materials such as data for seminars and a proper use guide for healthcare professionals. The applicant appropriately responded, and PMDA accepted their response.

Precautions Concerning Dosage and Administration or Method of Use (Underline denotes additions to or correction on the Review Report [1]. Strikethrough denotes deletions from the Review Report [1])

1 Precautions during transplantation of RiHEART

1.1 Consider application sites carefully because a cardiomyocyte sheet, once applied to the heart surface, is difficult to detach and apply again. (See Section 14.1.1.)

1.2 If bleeding is observed on the heart surface, hemostasis should be adequately achieved to ensure that no blood matters remain between the cardiomyocyte sheet and heart surface.

1.3 Blood matters should be suctioned, if any, with caution to avoid aspirating a cardiomyocyte sheet.

1.4 When applied to the heart surface, a cardiomyocyte sheet may slip and fall. Especially when a cardiomyocyte sheet is applied to a steep part, measures such as securing the sheet with stay sutures should be taken to prevent it from slipping and falling.

1.5 A spare cardiomyocyte sheet should be used only when its use is inevitable, for example, because of breakage of another sheet. Any unused cardiomyocyte sheet should be disposed of in accordance with relevant institutional procedures.

2 Precautions concerning treatment after transplantation of RiHEART

2.1 For administration of tacrolimus after transplantation of RiHEART, use immediate-release dosage forms only, but not extended-release dosage forms.
~~Each immunosuppressant should be used in accordance with the Dosage and Administration and Precautions sections in its electronic package insert.~~

2.2 Physicians should attend seminars and training sessions before using RiHEART.

2.3 Because transplantation of cardiomyocyte sheets involves thoracotomy, patients should have only a single chance to undergo transplantation of RiHEART.

PMDA instructed the applicant to modify the "Precautions Concerning Dosage and Administration or Method of Use" section as above. The applicant appropriately responded, and PMDA accepted their response.

1.5 Post-marketing surveillance plan (draft)

As a result of the review in Section "7. Risk Analysis and Outline of the Review Conducted by PMDA" of the Review Report (1), PMDA has concluded that the use-results survey should be specified as described in the concerned section of the Review Report (1).

At the Expert Discussion, the expert advisors supported the above conclusion of PMDA and also made comments mainly presented below.

- To monitor a recipient of RiHEART for arrhythmia, 1-week ambulatory electrocardiography should be performed for a certain period after the transplantation of RiHEART.

- Measures to assess QOL and health status of patients should be added.
- Cardiac rehabilitation to be provided to patients in the RiHEART and control groups should be standardized wherever possible to minimize the impact of differences, if any, on evaluation of the efficacy of RiHEART.

In view of results at the Expert Discussion, PMDA instructed the applicant to add 1-week ambulatory electrocardiography and QOL assessment using Kansas City Cardiomyopathy Questionnaire (KCCQ). PMDA also instructed the applicant to add the content of the rehabilitation to endpoints to enable evaluation for an effect of the rehabilitation. The applicant appropriately responded to the above instructions, and PMDA accepted their response.

1.6 Others

1.6.1 Designation of Designated Regenerative Medical Product

On the basis of "Principles for Designation of Biological Products, Specified Biological Products, and Designated Regenerative Medical Products" (PFSB/ELD Notifications No. 1105-1 and 1105-2 dated November 5, 2014, by the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare), PMDA has concluded that RiHEART should be designated as a Designated Regenerative Medical Product because it is a regenerative medical product manufactured using allogeneic cells as the starting material.

1.6.2 Storage conditions and shelf lives of critical intermediate and product

The applicant submitted results with the third batch of the critical intermediate from the long-term testing up to Month [redacted], which was ongoing at the time of initial submission, as well as results with the second batch of the product manufactured in Process IV (proposed process) from the 48-hour long-term testing and results from study for stability during transportation.

The applicant explained that no clear changes were observed in quality attributes throughout the study period in any study, and thus shelf lives of the critical intermediate and product will be specified as presented below. PMDA accepted their explanation.

- Critical intermediate: [redacted] months when stored in polypropylene vials for cryopreservation, placed in a vapor phase of liquid nitrogen (≤-[redacted]°C)
- Product: 48 hours when stored at 15°C to 23°C using the primary container (UpCell ADVANCE 6cm dish and [redacted] dish lid) and secondary container ([redacted] dish holder, body and [redacted])

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the proposed indication or performance and dosage and administration or method of use as shown below, with the following approval conditions, and that specifically, a conditional and time-limit approval under Article 23-26 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices may be granted to the product, provided that a cautionary statement is given in the package insert, and information on proper use is disseminated after the market launch. The time limit

under the above article should be 7 years, and the product should be designated as a Designated Regenerative Medical Product.

Indication or Performance

Treatment of severe heart failure associated with ischemic cardiomyopathy that has an inadequate response to standard-of-care therapies, including pharmacotherapy and invasive interventions

Dosage and Administration or Method of Use

1 Pretreatment before transplantation of RiHEART

1.1 Melt and remove the gel surrounding a cardiomyocyte sheet, wash the cardiomyocyte sheet with a washing fluid, and immerse it in this fluid.

2 Transplantation of RiHEART

2.1 Transplant 3 cardiomyocyte sheets on the heart surface sequentially. In principle, perform a left thoracotomy for the transplantation.

3 Treatment after RiHEART transplantation

3.1 Administer 3 immunosuppressants (prednisolone, tacrolimus, and mycophenolate mofetil) according to the dosage regimen provided below for a period of 90 days, starting on the following day of transplantation of cardiomyocyte sheets (Day 1). This period includes a tapering period. The doses should be adjusted according to the symptoms.

- The usual dosage of prednisolone is 20 mg orally administered once daily. Tapering is started approximately on Day 30.
- The usual dosage of tacrolimus is 1.5 mg orally administered twice daily. The dose should be adjusted to maintain the trough blood tacrolimus level in a range of 10 to 15 ng/mL by monitoring the trough blood level. Tapering is started approximately on Day 60.
- The usual dosage of mycophenolate mofetil is 1 g orally administered twice daily. Tapering is started approximately on Day 60.

Approval Conditions

1. The applicant is required to conduct post-marketing approval condition assessment, for example through post-marketing surveillance covering all patients treated with the product, until the submission of an application for standard marketing approval of the product, to which the conditional and time-limited approval has been granted.
2. The applicant is required to take necessary measures, such as dissemination of the guideline for proper use prepared in collaboration with the relevant academic societies and provision of seminars, to ensure that physicians with adequate knowledge and experience in the treatment of severe heart failure and thoracotomy have a full understanding of relevant information, including the results of the clinical study of the product and adverse events reported, to use the product in compliance with the “Indication or Performance” and “Dosage and Administration or Method of Use” at medical institutions with an established system for treatment of severe heart failure.
3. The applicant is required to collect information about biological properties of the product that reflect the mechanism of its action and to take necessary measures, such as improvement of the quality control strategy, until the submission of an application for standard marketing approval of the product to which the conditional and time-limited approval has been granted.

List of Abbreviations

6MWD	6-minute walk distance
ACE	angiotensin converting enzyme
Application	Application for marketing approval
ARB	angiotensin II receptor blocker
ARNI	angiotensin receptor-neprilysin inhibitor
AT	anaerobic threshold
BNP	brain natriuretic peptide
CABG	coronary artery bypass grafting
CGH	comparative genomic hybridization
CHO	chinese hamster ovary
CI	confidence interval
CiRA	Center for iPS Cell Research and Application
CMV	cytomegalovirus
CNV	copy number variation
CO	cardiac output
CRT	cardiac resynchronization therapy
CRT-D	cardiac resynchronization therapy defibrillator
CT	computed tomography
CTR	cardiothoracic ratio
EBV	Epstein-Barr virus
EF	ejection fraction
eGFR	estimated glomerular filtration rate
ESD	endoscopic submucosal dissection
FBS	fetal bovine serum
FS	fractional shortening
GDMT	guideline-directed medical therapy
HBSS	Hank’s balanced salts solution
HBSS(+)	Hank’s balanced salts solution (with calcium and magnesium)
HBV	hepatitis B virus
HCV	hepatitis C virus
HFrEF	heart failure with reduced ejection fraction
HEK293 cells	human embryonic kidney 293
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HTLV	human T-cell leukemia virus
IABP	intra-aortic balloon pumping
ICD	implantable cardioverter defibrillator
IPA	ingenuity pathway analysis
iPS	induced pluripotent stem cells

KCCQ	Kansas City Cardiomyopathy Questionnaire
KLF4	kruppel like factor 4
LIN28	Lin-28 homolog A
LIVCA	limit of in vitro cell age
LVAD	left ventricular assist device
LVEDV	left ventricular end-diastolic volume
LVEDVI	left ventricular end-diastolic volume index
LVEF	left ventricular ejection fraction
LVESV	left ventricular end-systolic volume
LVESVI	left ventricular end-systolic volume index
MCB	master cell bank
MedDRA	Medical Dictionary for Regulatory Activities Japanese version
METs	metabolic equivalent of task
MRA	mineralocorticoid receptor antagonists
MRC-5 cells	Human fetal lung fibroblast
MRI	magnetic resonance imaging
NOG	NOD.Cg-PrkdcscidIl2rgtm1Sug/ShiJic
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
PAP	pulmonary arterial pressure
PAWP	pulmonary artery wedge pressure
PBMC	peripheral blood mononuclear cell
PCI	percutaneous coronary intervention
PCPS	percutaneous cardiopulmonary support
Peak VO_2	peak volume O_2/ peak oxygen uptake
PMDA	Pharmaceuticals and Medical Devices Agency
PT	preferred term
PVB19	parvovirus B19
QOL	quality of life
qPCR	quantitative polymerase chain reaction
RAP	right arterial pressure
RiHEART	RiHEART
RNA	ribonucleic acid
SAS	specific activity scale
SGLT2	sodium glucose transporter 2
STR	short tandem repeat
Tacrolimus	tacrolimus hydrate
Vero cells	African green monkey kidney epithelial cells
VE/VCO_2	ventilatory equivalent for carbon dioxide
WCB	working cell bank

WNV	west nile virus