July 24, 2024
Medical Device Evaluation Division
Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Human cellular/tissue-based products 2. Human somatic stem cell-processed products
Non-proprietary Name	Human (autologous) skeletal myoblast-derived cell sheet
Brand Name	HeartSheet
Applicant	Terumo Corporation
Date of Application	September 7, 2023 (Application for marketing approval)

Results of Deliberation

In its meeting held on July 19, 2024, the Committee on Regenerative Medicine Products and Biotechnology (hereinafter referred to as "the Committee") reached the conclusion shown below and decided that this conclusion should be presented to the Pharmaceutical Affairs Council.

The product proposed by the present application should not be approved for the following reasons:

1. The product was presumed to have efficacy when it was granted the conditional and time-limited approval. Although this presumption was not inappropriate, the efficacy for "Indication or Performance" was not demonstrated by the use-results survey and clinical study conducted after the conditional and time-limited approval of the product.
2. Based on 1 above, PMDA concluded that the product falls under the provision of Article 23-25, Paragraph 2, Item 3 (a) of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices.

In its meeting held on July 24, 2024, the Pharmaceutical Affairs Council supported the deliberation results of the Committee and concluded that the product should not be approved.

Reference

Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (excerpt)

Article 23-25, Paragraph 2, Item 3 (a)

when the regenerative medicine products pertaining to the application are not found to have the efficacy or effects indicated in the application.

Review Report

June 26, 2024
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	HeartSheet
Classification	Human cellular/tissue-based products 2. Human somatic stem cell-processed products
Non-proprietary Name	Human (autologous) skeletal myoblast-derived cell sheet
Applicant	Terumo Corporation
Date of Application	September 7, 2023

Shape, Structure, Active Ingredients, Quantities, or Definition

The product is a regenerative medical product intended for the treatment of patients with severe heart failure due to ischemic heart disease. Skeletal myoblasts, obtained from the patient's own skeletal muscle at a medical institution, are cultured and proliferated at a manufacturing site. The proliferated skeletal myoblasts are filled in a dedicated container and cryopreserved. Then, the cryopreserved skeletal myoblasts are prepared into cell sheets at the medical institution. Five skeletal myoblast-derived cell sheets are transplanted onto the surface of the patient's heart to treat severe heart failure.

Application Classification	(1-2) Application for a new regenerative medical product submitted within the effective period of the conditional and time-limited approval
Items Warranting Special Mention	None
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 has failed to demonstrate the efficacy for the "Proposed Indication or Performance" shown below, and that the product falls under the provisions of Article 23-25, Paragraph 2, Item 3 (a) (i.e., "when the regenerative medicine products pertaining to the application are not found to have the efficacy or effects indicated in the application") of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices.

Thus, the product should not be approved as per the provisions of Article 23-25, Paragraph 1 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices.

Proposed Indication or Performance

Treatment of patients with severe heart failure due to ischemic heart disease unresponsive to standard treatments including drug and invasive therapies who meet all of the following criteria.

Eligibility criteria:

- NYHA class III or IV heart failure; and
- Resting left ventricular ejection fraction ≤35%

Attachment

Review Report (1)

March 19, 2024

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	HeartSheet
Classification	Human cellular/tissue-based products 2. Human somatic stem cell-processed products
Non-proprietary Name	Human (autologous) skeletal myoblast-derived cell sheet
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Eligibility criteria:

- NYHA class III or IV heart failure; and
- Resting left ventricular ejection fraction ≤35%

Proposed Dosage and Administration or Method of Use

Prior to the production of skeletal myoblast-derived cell sheets

(1) Skeletal muscle is harvested from the patient. As a general procedure, the harvesting is performed according to the procedure for diagnostic muscle biopsy for neuromuscular diseases. Skeletal muscle should be harvested from the quadriceps, in principle, but may be harvested from any other appropriate site of the body depending on the patient's condition. The harvested skeletal

muscle is delivered in a dedicated container to the facility designated by the marketing authorization holder.

(2) Blood is collected from the patient to separate serum. The separated serum is delivered in a container to the facility designated by the marketing authorization holder.

Preparation and transplantation of skeletal myoblast-derived cell sheets

(1) Using the secondary constituent parts, 5 skeletal myoblast-derived cell sheets (preferably 6 sheets including 1 spare) are prepared from the cryopreserved cells. Each step is taken aseptically.

(2) Each of 5 skeletal myoblast-derived cell sheets is sequentially transplanted onto the surface of the heart. The transplantation procedure is usually performed through left thoracotomy.

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

HeartSheet is a regenerative medical product for producing cell sheets applied onto the surface of the heart through thoracotomy. HeartSheet is a combination product consisting of the primary and secondary constituent parts. The primary constituent part consists of skeletal myoblast-derived cells cryopreserved after being isolated from the skeletal muscle of patient's own quadriceps, etc., cultured *ex vivo*, and suspended in a stock solution. The secondary constituent parts include (a) a dedicated container (with a solution to keep the tissue during transportation) used to transport the skeletal muscle harvested from the patient to the manufacturing site, (b) devices used for separating patient-derived serum (patient serum) and for the delivery of the patient serum to the manufacturing site, (c) culture media etc., used to prepare skeletal myoblast-derived cell sheets from the cryopreserved cells, and (d) sheet preparation apparatuses.

1.2 Development history, etc.

The applicant's explanation about the development history of HeartSheet:

At the time point when the development of HeartSheet was initiated, patients with severe heart failure who do not respond to standard drug therapies were treated with cardiac resynchronization therapy (CRT) and surgical options such as mitral valvuloplasty and left ventricular restoration. CRT is indicated for patients with moderate or severe heart failure; however, approximately 30% of these patients are non-responders to CRT. While mitral valvuloplasty and left ventricular restoration are effective in improving the clinical condition of the patients, these surgeries are indicated for a limited number of patients and are highly invasive. An implantable ventricular assist device is effective in patients with end-stage severe heart failure, but it was approved only as a bridge to cardiac transplantation in patients scheduled to undergo the procedure. In Japan, since heart transplant donors were limited, only a small number of patients were eligible for an implantable ventricular assist device. Given these limitations in treatment methods for patients with severe heart failure who do not respond to standard drug therapies, there was a pressing need to develop new therapies, particularly because the number of such patients is expected to increase in the future.

Against the above background, the applicant submitted a marketing application for the regenerative medical product of HeartSheet. In September 2015, based on Article 23-26 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices, HeartSheet was granted a conditional and time-limited approval for the following "Indication or Performance" and the "Dosage and Administration or Method of Use," with the conditions and effective period shown below.

Indication or Performance

Treatment of patients with severe heart failure due to ischemic heart disease unresponsive to standard treatments including drug and invasive therapies who meet all of the following criteria.

Eligibility criteria:

- NYHA class III or IV heart failure; and
- Resting left ventricular ejection fraction ≤35%

Dosage and Administration or Method of Use

Prior to the production of skeletal myoblast-derived cell sheets

(1) Skeletal muscle is harvested from the patient. As a general procedure, the harvesting is performed according to the procedure for diagnostic muscle biopsy for neuromuscular diseases. Skeletal muscle should be harvested from the quadriceps, in principle, but may be harvested from any other appropriate site of the body depending on the patient's condition. The harvested skeletal muscle is delivered in a dedicated container to the facility designated by the marketing authorization holder.

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(1) Using the secondary constituent parts, 5 skeletal myoblast-derived cell sheets (preferably 6 sheets including 1 spare) are prepared from the cryopreserved cells. Each step is taken aseptically.

(2) Each of 5 skeletal myoblast-derived cell sheets is sequentially transplanted onto the surface of the heart. The transplantation procedure is usually performed through left thoracotomy.

Approval Conditions

1. The applicant is required to ensure that the product is used by physicians and surgeons with adequate knowledge and experience in severe heart failure and thoracotomy at medical institutions with capacity for emergency response under a system that ensures appropriate patient control through laboratory tests, etc.
2. The applicant is required to conduct an approval condition-based post-marketing evaluation in all patients transplanted with the product during the period between the conditional and time-limited approval and reapplication for marketing approval.

Effective period

5 years

During the 5-year effective period of the conditional and time-limited approval, an approval condition-based post-marketing evaluation was to be conducted for all patients using HeartSheet. In order to compare data from patients using HeartSheet with those from external control patients, the applicant initiated a use-results survey covering all patients using HeartSheet and a clinical study in patients with heart failure who did not use HeartSheet. The survey started in May 2016 and the clinical study in [redacted] 20[redacted]. Subsequently, concluding contracts with study sites required more time than expected and accruing patients within the deadline was found to be difficult. Therefore, after discussions by the Pharmaceutical Affairs and Food Sanitation Council, the effective period of the conditional and time-limited approval was extended by 3 years to a total of 8 years in January 2019, based on the provisions of Article 23-26, paragraph 2 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (PSEHB Notification No. 0124-73).

Recently, based on the primary results from the use-results survey and the clinical study, the applicant submitted a reapplication for HeartSheet during the effective period of the conditional and time-limited approval (8 years) according to Article 23-26, paragraph 5 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices.

As of March 2024, HeartSheet has not been approved or marketed in any country or region.

2. Quality and Outline of the Review Conducted by PMDA

The present application is a reapplication for approval submitted within the effective period of the conditional and time-limited approval. The applicant submitted data on quality, which included data related to changes made to in-process control tests and specifications for the primary and secondary constituent parts and data related to [redacted].
No particular issues were identified after the review of the data.

3. Primary Pharmacodynamics or Performance and Outline of the Review Conducted by PMDA

The present application is a reapplication for approval submitted within the effective period of the conditional and time-limited approval. The applicant submitted data on primary pharmacodynamics or performance, which included data related to [redacted]
[see Section 2].

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

Since the present application is a reapplication for approval submitted within the effective period of the conditional and time-limited approval, data on non-clinical safety have not been submitted.

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

Since the present application is a reapplication for approval submitted within the effective period of the conditional and time-limited approval, data on biological disposition have not been submitted.

6. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted evaluation data on the efficacy and safety from a use-result survey and a clinical study shown in Table 1.

Table 1. List of efficacy and safety evaluation data

Data category	Region	Study	Phase	Patient population	No. of patients enrolled	Dosage regimen	Main endpoints
Evaluation	Japan	Use-results survey	Post-marketing	All patients who underwent skeletal muscle harvesting for transplantation of skeletal myoblast-derived cell sheets to treat severe heart failure due to ischemic heart disease unresponsive to standard treatments	67	Approved dosage and administration or method of use	Efficacy Safety
Evaluation	Japan	Prospective clinical Study	-	Patients with severe heart failure due to ischemic heart disease whose only curative treatment is cardiac transplantation.	104	-	Efficacy

6.1 Evaluation data

Table 2 below shows the primary objectives of the use-results survey and the clinical study. In order to evaluate the efficacy and safety of HeartSheet as the secondary objectives, results in patients treated with HeartSheet in the use-results survey (the HeartSheet group) were compared with those in patients enrolled in the clinical study (the control group).

Table 2. Primary objectives of the use-results survey and the clinical study

Use-results survey
To collect long-term follow-up data from all patients who underwent skeletal muscle harvesting for transplantation of skeletal myoblast-derived cell sheets to treat severe heart failure due to ischemic heart disease unresponsive to the standard treatments
Clinical study
To investigate characteristics, prognosis, and disease progression in patients with severe heart failure due to ischemic heart disease whose only curative treatment is cardiac transplantation

The use-results survey covered all patients with heart failure who underwent skeletal muscle harvesting for transplantation of skeletal myoblast-derived cell sheets.

The clinical study used the inclusion criteria shown in Table 3, with no exclusion criteria.

Table 3. Inclusion criteria for the clinical study

Patients with ischemic heart disease with no curative treatment other than cardiac transplantation who have already received optimal pharmacotherapy and other treatments, and meet the following inclusion criteria: 1) Patients with chronic ischemic heart disease 2) LVEF ≤35% (echocardiogram) 3) NYHA class III or IV 4) Patients receiving optimal drug therapy with anti-heart failure drugs including ACE inhibitors or ARB, β-blockers, and diuretics 5) Patients who have received invasive treatments (CABG, mitral valve replacement, left ventricular restoration, CRT, PCI, etc.) other than drug therapies indicated for ischemic heart disease 6) Patients who have provided written informed consent

The target sample size was 60 in the HeartSheet group and 120[1)] in the control group. Patients in the HeartSheet group were enrolled at 8 sites and those in the control group at 17 sites. The survey of the HeartSheet group began on May 30, 2016, and is still ongoing. The first 60 patients undergoing

[1)] The required sample size was calculated to be 49 patients per group using the log-rank test for the primary analysis of the primary endpoint, assuming that the expected 2-year survival for cardiac disease-related death (the primary endpoint) was 75% in the control group and 95% in the HeartSheet group, with a two-sided significance level of 5% and a power of 90%, each patient's follow-up period of ≥2 years after transplantation or enrollment, and a 1:1 ratio of patients in the control and HeartSheet groups. In order to accommodate potential dropouts, the sample size for the HeartSheet group was increased to 60 patients. The sample size for the control group was increased to 120 patients because of propensity score matching for comparison.

skeletal muscle harvesting were included in Survey Group A, and the 61st and subsequent patients in Survey Group B. The study period for the control group was from [redacted], 20[redacted] to [redacted], 20[redacted]. The observation period was from the sales launch until the completion of 2-year observation of the initial 60 patients (HeartSheet group) or until at least 2 years from the last patient enrollment (control group). The data cut-off date for the HeartSheet group was [redacted], 20[redacted].

In the HeartSheet group, 67 patients were enrolled, and 60 patients who underwent skeletal muscle harvesting for transplantation of skeletal myoblast-derived cell sheets, were included in the safety analysis population and the intention to treat (ITT) population. Of the 60 patients in the ITT population, 49 were included in the modified intention-to-treat (mITT) population, which was the efficacy analysis population. The remaining 11 patients were excluded because they did not proceed to transplantation of skeletal myoblast-derived cell sheets. The reasons for not proceeding to transplantation in 11 patients were as follows: After skeletal muscle harvesting, the cultured cells did not meet product specifications, making continuation of treatment with HeartSheet impossible (9 patients); death before transplantation (1 patient); and withdrawal from treatment due to patient's request (1 patient). As for the dosage and administration or method of use of HeartSheet, all patients received 5 skeletal myoblast-derived cell sheets that had been prepared.

In the control group, 104 patients were enrolled, and 102 patients were included in the ITT population, which was the efficacy analysis population. The remaining 2 patients were excluded for the following reasons: one patient withdrew informed consent and the other was confirmed to have died at another hospital before the enrollment form was sent.

In the HeartSheet group, the observation period was <365 days in 12 patients, ≥365 to <730 days in 13 patients, and ≥730 days in 24 patients. The mean and standard deviation (SD) of the observation period were 801.2 ± 565.61 days, with the median of 726.0 days. In the control group, the observation period was <365 days in 18 patients, ≥365 to <730 days in 19 patients, and ≥730 days in 65 patients. The mean and SD of the observation period were 835.3 ± 392.62 days, with the median of 794.0 days.

Table 4 shows patient characteristics in each group (mITT population for the HeartSheet group, ITT population for the control group).

Table 4. Patient characteristics

		HeartSheet (n = 49)	Control (n = 102)
Sex (male)		89.8% (44/49)	88.2% (90/102)
Age (years)*		60.8 ± 8.21	70.6 ± 9.80
Prior treatment of cardiac disease	CABG	36.7% (18/49)	21.6% (22/102)
	PCI	63.3% (31/49)	53.9% (55/102)
Concurrent diseases	Diabetes mellitus	53.1% (26/49)	51.0% (52/102)
	Hypertension	40.8% (20/49)	57.8% (59/102)
	Renal failure	30.6% (15/49)	18.6% (19/102)
NYHA	Class II	2.0% (1/49)	2.0% (2/102)
	Class III	93.9% (46/49)	91.2% (93/102)
	Class IV	2.0% (1/49)	4.9% (5/102)
	Not documented	2.0% (1/49)	2.0% (2/102)
SHFM-predicted 2-year survival[2)]	<70%	6.1% (3/49)	3.9% (4/102)
	≥70% to <80%	14.3% (7/49)	12.7% (13/102)
	≥80%	51.0% (25/49)	39.2% (40/102)
	Not calculable	28.6% (14/49)	44.1% (45/102)
Core laboratory-measured LVEF[3)] (%)*		28.997 ± 8.0556 (39)	25.597 ± 7.5569 (80)
Baseline core laboratory-preferred LVEF[4)] (%)*		28.243 ± 7.7120	26.148 ± 7.4413 (100)
Systolic blood pressure (mmHg)*		101.1 ± 12.48	106.9 ± 16.11 (96)
BNP (pg/mL)*		324.44 ± 370.304 (48)	498.68 ± 485.869 (99)
Hb (g/dL)*		12.97 ± 1.716	12.79 ± 1.830 (101)
Alb (g/dL)*		4.169 ± 0.3798	4.019 ± 0.4409 (91)
Na (mEq/L)*		138.92 ± 4.020	139.26 ± 3.467 (100)
K (mEq/L)*		4.33 ± 0.552	4.46 ± 0.515 (100)
Cr (mg/dL)*		1.339 ± 0.6046	1.733 ± 1.4420 (101)
Anti-heart failure drugs	ACE inhibitor	38.8% (19/49)	64.7% (66/102)
	ARB	36.7% (18/49)	21.6% (22/102)
	β-blocker	95.9% (47/49)	89.2% (91/102)
	Aldosterone antagonist	69.4% (34/49)	55.9% (57/102)
	Loop diuretics	79.6% (39/49)	83.3% (85/102)

* Mean ± SD. The number of patients in parenthesis is omitted for values calculated from data of all patients.

The primary efficacy endpoint was the time to cardiac disease-related death that meet the criteria shown in Table 5. The final determination of cardiac-related death was made by the event assessment committee.

Table 5. Primary endpoint: Cardiac disease-related death

- Sudden death
- Death from heart failure
- Death caused by myocardial infarction
- Death caused by cerebrovascular-related events
- Death associated with cardiac surgery
- Death from other events for which relationship to heart cannot be ruled out
- Death from other events for which relationship to blood vessels cannot be ruled out

2) Seattle Heart Failure Model: Prognosis prediction formula. This model predicts survival of patients with heart failure based on clinical patient characteristics, laboratory data, and drugs, devices used, etc. (*Circulation.* 2006;113:1424–33).

3) Quantitative analysis of echocardiographic images (taken at enrollment, 6 months after enrollment, and 1 year after enrollment) (central analysis) was performed.

4) Baseline core laboratory-preferred LVEF

HeartSheet group

(i) Core laboratory-measured LVEF at harvesting, if available, is used.
(ii) If core laboratory-measured LVEF at harvesting is unavailable, core laboratory-measured baseline LVEF, if available, is used.
(iii) If neither core laboratory-measured LVEF at harvesting nor at baseline is available, non-core laboratory-measured LVEF at harvesting, if available, is used.
(iv) If core laboratory-measured LVEF at harvesting, that at baseline, and non-core laboratory-measured LVEF at harvesting are all unavailable, non-core laboratory-measured baseline LVEF, if available, is used.

Control group

(i) Core laboratory-measured baseline LVEF, if available, is used.
(ii) If core laboratory-measured baseline LVEF is unavailable, non-core laboratory-measured baseline LVEF, if available, is used.

Since patient randomization was not performed in either the HeartSheet or control group, the distribution of patient characteristics was expected to be differ between the 2 groups. Therefore, the primary analysis for the primary endpoint was adjusted for difference in the distribution of patient characteristics. The propensity score was used as the adjustment method. The covariates used to estimate the propensity score, shown in Table 6, were determined using a logistic regression model. Multiple imputation was used to handle missing values of covariates when estimating the propensity score.

Table 6. Patient characteristics used for propensity score estimation

Continuous data	
Age	Years
Hb	g/dL
Alb	g/dL
Na	mEq/L
Cr	mg/dL
BNP	pg/mL
Baseline core laboratory-preferred LVEF	%
Categorical data	
Sex	Male (standard), female
NYHA class	I, II, III (standard), IV

For efficacy, the hazard ratio[5)] (95% confidence interval [CI]) (HeartSheet vs. control) for the time to cardiac disease-related death, the primary endpoint, was 1.9 [0.8, 4.4], failing to demonstrate the superiority of HeartSheet over control (two-sided *P*-value = 0.136, propensity score-weighted Cox regression model). Figure 1 shows the propensity score-weighted Kaplan-Meier curves. The unweighted percentages of all deaths were 20.4% (10 of 49 patients) in the HeartSheet group and 28.4% (29 of 102 patients) in the control group.

[5)] A hazard ratio of >1 means that the HeartSheet group had a shorter time to cardiac disease-related death than the control group. Conversely, a hazard ratio of <1 means that the HeartSheet group had a longer time to cardiac disease-related death than the control group.

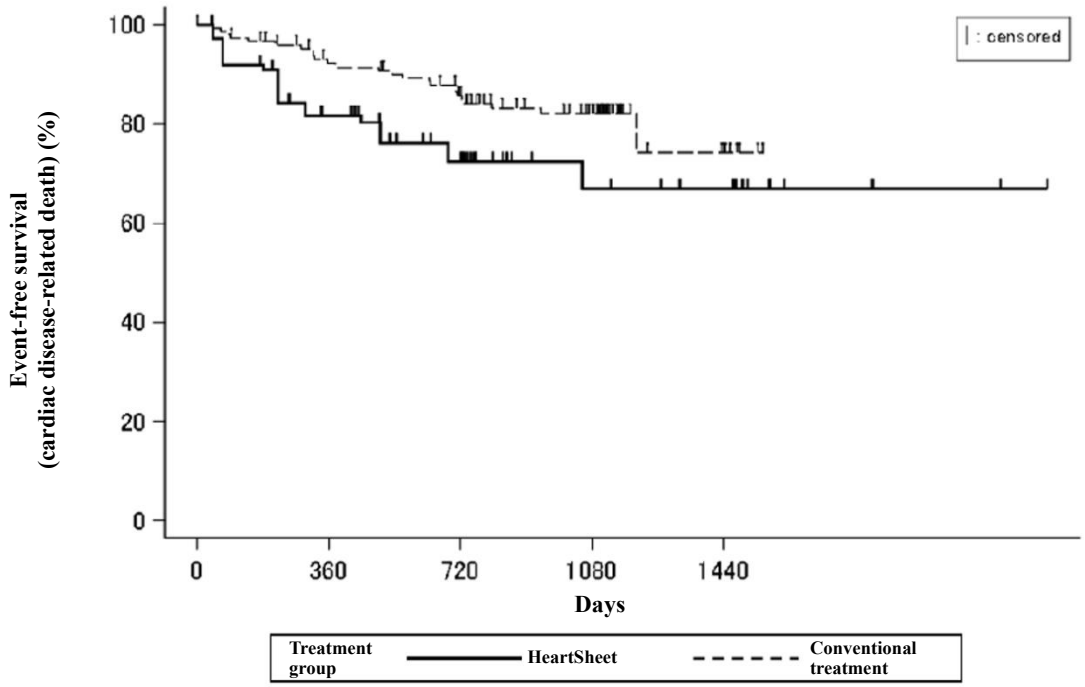

Figure 1. Kaplan-Meier curves for time to cardiac disease-related death weighted by the propensity score

The safety of HeartSheet was evaluated using data from 60 patients who underwent skeletal muscle harvesting for transplantation of skeletal myoblast-derived cell sheets (ITT population). Safety data of the control group were not collected because the objective of the control group was to collect information on the patient characteristics, prognosis, and disease progression.

In the HeartSheet group, adverse events occurred in 70.0% (42 of 60) of patients and serious adverse events in 46.7% (28 of 60) of patients (see Table 7). Among the 6 adverse events designated as safety priority items, the following serious adverse events occurred in ≥2 patients: aggravation of heart failure in 16.7% (10 of 60) of patients, arrhythmia in 13.3% (8 of 60) of patients, tumor development or recurrence in 3.3% (2 of 60) of patients. Among serious adverse events not designated as safety priority items, the following occurred in ≥2 patients: pneumonia aspiration, septic shock, and renal failure (3.3% [2 of 60] patients each).

There were 13 deviations in 10 patients where the cells cultured after skeletal muscle harvesting did not meet the product specifications, and 1 deviation in 1 patient where the product specifications were met but the skeletal myoblast-derived cell sheets could not be transplanted because of a problem with detaching the cell sheets before transplantation.

Death occurred in 11 patients. Causes of death were aggravation of heart failure in 4 patients, arrhythmia in 3 patients, and aortic aneurysm rupture, cardiac arrest, septic shock, and unknown in 1 patient each. A causal relationship of the death to HeartSheet could not be ruled out in 6 patients (arrhythmia in 3 patients, aggravation of heart failure, cardiac arrest, and unknown in 1 patient each).

Among the 61st and subsequent patients who underwent skeletal muscle harvesting for transplantation of skeletal myoblast-derived cell sheets, 8 patients were enrolled by [redacted], including 7 who completed transplantation of skeletal myoblast-derived cell sheets. None of the 7 patients died or experienced serious adverse events.

Table 7. Incidence of safety priority items and other adverse events (ITT)

	HeartSheet (n = 60)
All events	70.0% (42)
Safety priority items	
Aggravation of heart failure	16.7% (10)
Arrhythmia	20.0% (12)
Events related to open-heart surgery and transplantation procedures	31.7% (19)
Tumor development or recurrence	3.3% (2)
Local infection	1.7% (1)
Adverse events caused by skeletal muscle harvesting	36.7% (22)
Adverse events other than safety priority items (incidence ≥5%)	
BNP increased	10.0% (6)
Pyrexia	8.3% (5)
Blood creatinine increased	8.3% (5)
C-reactive protein increased	8.3% (5)
White blood cell count increased	8.3% (5)
Nasopharyngitis	6.7% (4)
Constipation	6.7% (4)
Procedural pain	6.7% (4)
Anaemia	5.0% (3)
Hepatic function abnormal	5.0% (3)
Pneumonia aspiration	5.0% (3)
Alanine aminotransferase increased	5.0% (3)
Blood urea increased	5.0% (3)
Insomnia	5.0% (3)

6.R Outline of the review conducted by PMDA

6.R.1 Efficacy

PMDA concluded that the efficacy of HeartSheet for severe heart failure due to ischemic heart disease has not been demonstrated, based on the results of the following reviews.

6.R.1.1 Design of the survey and study

The design of the approval condition-based post-marketing evaluation was reviewed and accepted at the time of conditional and time-limited approval (see Review Report on HeartSheet, dated August 17, 2015). PMDA confirmed that the evaluation was conducted in accordance with the design accepted at the time of conditional and time-limited approval, including the following points:

Design consideration for conducting the evaluation using an open-label survey that compares patients using HeartSheet with external control patients

- Objective efficacy evaluation is possible to a certain extent because the primary endpoint, “cardiac disease-related death,” was reviewed and judged at regularly held meetings of the event assessment committee (composed of cardiologists and cardiovascular surgeons not participating in the use results survey or clinical study).
- Since the distribution of patient characteristics was expected to differ between the HeartSheet group in the use-results survey and the control group in the clinical study, the applicant planned to conduct a between-group comparison using a propensity score-based confounding adjustment

method. This enables an evaluation that takes into account differences in the distribution of patient characteristics between the HeartSheet and control groups.

Appropriateness of the control group

- The control group consists of patients who had ischemic heart disease with no curative treatment options other than cardiac transplantation and were already receiving optimal drug therapy and other treatments. In order to select control patients similar to the target population of HeartSheet, the inclusion criteria shown in Table 3 were established and data were collected prospectively; this ensures the comparability between patients using HeartSheet and control patients. The control group setting is thus appropriate.

Appropriateness of the primary endpoint

- Cardiac disease-related death was the primary endpoint for evaluating the efficacy of HeartSheet in patients with severe heart failure. Each cardiac disease-related death was confirmed by the event assessment committee. Hence the primary endpoint is considered appropriate.

PMDA confirmed that the approval condition-based post-marketing evaluation was implemented according to the design accepted at the time of the conditional and time-limited approval, and concluded that the efficacy of HeartSheet can be evaluated based on results of the comparison between patients using HeartSheet and control patients.

6.R.1.2 Results of the efficacy evaluation

The applicant's explanation about the efficacy of HeartSheet:

HeartSheet was not shown to be superior to control in the time to cardiac disease-related death, the primary endpoint [see Section 6.1]. The breakdown of the incidences of cardiac disease-related deaths is shown in Table 8.

Table 8. Breakdown of incidences of cardiac disease-related deaths

	HeartSheet	Control
Sudden death	7.5%	1.4%
Death from heart failure	9.2%	6.9%
Death caused by myocardial infarction	0.0%	0.0%
Death caused by cerebrovascular-related events	0.0%	0.0%
Death associated with cardiac surgery	0.0%	0.0%
Deaths from other events for which relationship to heart cannot be ruled	1.0%	8.0%
Deaths from other events for which relationship to blood vessels cannot be ruled out	8.3%	0.7%

Proportions weighted by propensity score

The results of important secondary endpoints were as follows:

1) Time to hospitalization due to any major cardiovascular event[6)]

A propensity score-weighted Cox regression model showed that the hazard ratio [95% CI] (HeartSheet vs. control) was 1.5 [0.6, 3.6]. Figure 2 shows the propensity score-weighted Kaplan-Meier curves.

6) Cardiac death, implantation of LVAD, or cardiac transplantation. Events were assessed by the event assessment committee.

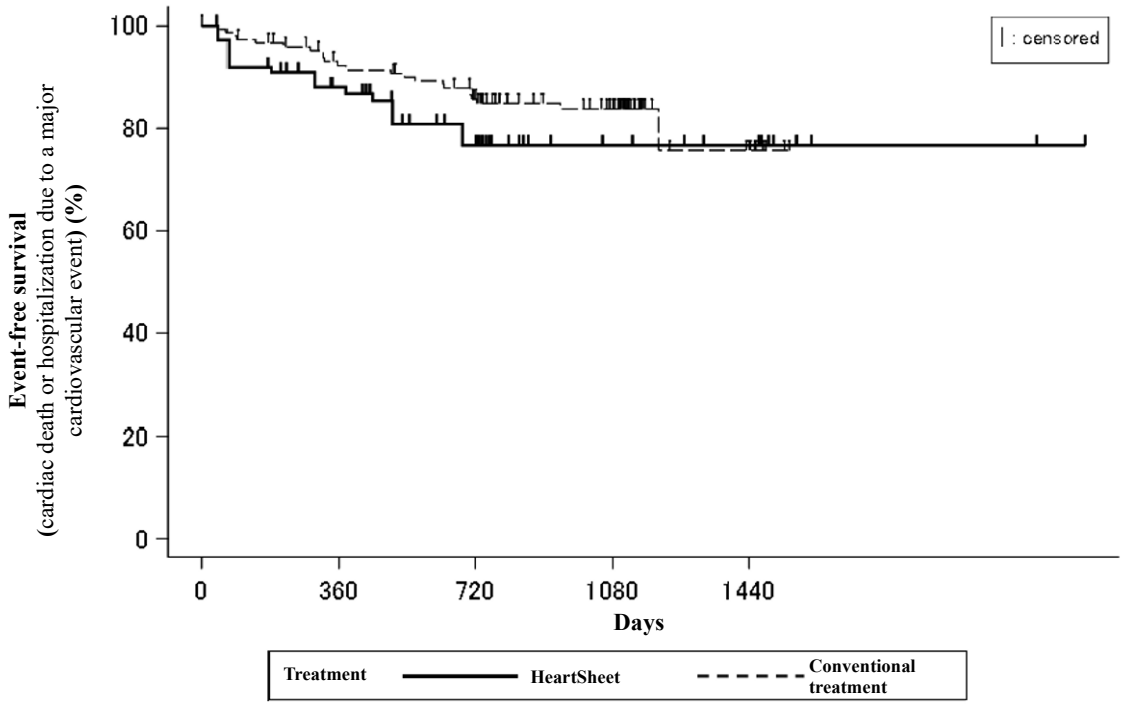

Figure 2. Propensity score-weighted Kaplan-Meier curves for time to cardiac death or hospitalization due to a major cardiovascular event

2) Proportion of patients with a ≥5% improvement in core laboratory-measured left ventricular ejection fraction (LVEF) from the time of transplantation of skeletal myoblast-derived cell sheets to 6 months post-transplantation

The propensity score-weighted proportion of patients with a ≥5% improvement was 7.9% in the HeartSheet group and 16.5% in the control group. A propensity score-weighted logistic regression model showed that the odds ratio[7)] [95% CI] for the HeartSheet group versus the control group was 0.433 [0.127, 1.480].

Results of other secondary endpoints were as follows:

1) Evaluation of cardiac function, etc.

(a) Changes in LVEF over time

[7)] An odds ratio of >1 means that the HeartSheet group has a higher proportion of patients with a ≥5% improvement in core laboratory-measured LVEF from the time of transplantation of skeletal myoblast-derived cell sheets to 6 months post-transplantation than the control group. Conversely, a odds ratio <1 means that the HeartSheet group has a lower proportion of such patients than the control group.

Table 9. Changes in core laboratory-measured LVEF

	Baseline	At 6 months	At 1 year
HeartSheet[*1]	27.922 ± 8.0304	28.502 ± 9.4274	28.364 ± 6.8763
Change from baseline[*2,*3]		−1.014 [−3.604, 1.577]	−0.980 [−2.915, 0.954]
Control[*1]	26.504 ± 7.6104	27.865 ± 7.0565	28.177 ± 8.3652
Change from baseline[*2,*3]		0.141 [−1.820, 2.103]	−0.916 [−4.600, 2.767]
Between-group difference of change from baseline[*2,*3]		−1.155 [−4.453, 2.143]	−0.064 [−4.420, 4.292]

*1 Propensity score-weighted mean ± SD (%)
*2 Least Squares Mean [95% CI]
*3 Propensity score-weighted mixed-effects model repeated model (MMRM) assuming unstructured variance-covariance structure between time points with the following covariates: treatment group, time point, interaction between time point and treatment group, baseline LVEF, and interaction between time point and baseline LVEF.

Table 10. Changes in site-measured LVEF

	Baseline	At 6 months	At 1 year	At 2 years
HeartSheet[*1]	26.93 ± 6.372	26.75 ± 8.873	29.22 ± 8.040	30.81 ± 8.267
Change from baseline[*2,*3]		−0.08 [−3.26, 3.11]	0.41 [−1.50, 2.32]	1.60 [−1.03, 4.22]
Control[*1]	28.09 ± 6.264	30.27 ± 7.892	31.37 ± 7.916	30.27 ± 9.899
Change from baseline[*2,*3]		2.35 [0.86, 3.84]	2.57 [1.13, 4.01]	1.15 [−1.50, 3.79]
Between-group difference of change from baseline[*2,*3]		−2.43 [−6.07, 1.21]	−2.16 [−4.57, 0.25]	0.45 [−3.34, 4.24]

*1 Propensity score-weighted mean ± SD
*2 Least squares mean [95% CI]
*3 Propensity score-weighted MMRM assuming unstructured variance-covariance structure between time points with the following covariates: treatment group, time point, interaction between time point and treatment group, baseline LVEF, and interaction between time point and baseline LVEF.

(b) Changes in NYHA classification category over time

Table 11. Changes in the proportion of patients by NYHA classification category

Proportion (%)[*]	I	II	III	IV
HeartSheet				
Baseline	0.0	1.4	93.5	5.1
After 6 months	20.5	46.6	32.9	0.0
After 1 year	14.0	67.8	16.4	1.7
Control				
Baseline	0.0	1.6	94.8	3.6
After 6 months	0.8	28.3	65.3	5.5
After 1 year	2.1	36.7	57.2	4.0

* Propensity score-weighted proportion

Table 12. Changes in the proportion of patients with NYHA class ≥II, ≥III or ≥IV

Proportion (%)[*]	≥II	≥III	≥IV
HeartSheet			
Baseline	99.8 [97.6, 100.0]	97.8 [79.7, 99.8]	6.1 [1.9, 18.1]
At 6 months	84.5 [70.1, 92.7]	28.5 [17.5, 42.8]	0.1 [0.0, 1.1]
At 1 year	82.9 [68.6, 91.5]	26.2 [15.7, 40.4]	0.1 [0.0, 1.2]
Control			
Baseline	99.4 [98.3, 99.8]	92.6 [86.7, 96.0]	8.0 [3.9, 15.7]
At 6 months	97.4 [93.9, 98.9]	73.1 [63.4, 81.0]	1.8 [0.5, 6.8]
At 1 year	96.2 [91.5, 98.4]	64.9 [53.9, 74.6]	1.3 [0.3, 4.9]

Least squares estimates [95% CI]
* Propensity score-weighted cumulative logistic model, assuming an exchangeable variance-covariance structure between time points, with covariates of treatment group and time point.

(c) Changes in exercise tolerance (6-minute walk distance, cardiopulmonary exercise testing)

Table 13. Changes in exercise tolerance in the HeartSheet group

	6-minute walk distance		Peak oxygen uptake		Anaerobic glycolytic threshold	
	N	Mean ± SD				
Baseline	25	413.8 ± 98.88	29	13.72 ± 4.564	23	9.97 ± 2.953
At 6 months	17	474.4 ± 114.81	21	14.46 ± 5.061	20	11.19 ± 7.612
At 1 year	15	473.2 ± 110.90	18	15.56 ± 4.864	17	10.99 ± 3.183

Exercise tolerance tests were not mandatory but optional. In the control group, the baseline 6-minute-walk was measured in only 1 patient, the baseline peak oxygen uptake in only 6 patients, and the baseline anaerobic glycolytic threshold in only 6 patients. Therefore, no quantitative comparison of exercise tolerance was made between the 2 groups.

(d) The proportion of patients with a ≥5% improvement in core laboratory-measured LVEF from the time of transplantation of skeletal myoblast-derived cell sheets to 12 months post-transplantation, and the two-sided 95% CI.

Table 14. Proportion of patients with a ≥5% improvement in core laboratory-measured LVEF from the time of transplantation of skeletal myoblast-derived cell sheets to 12 months post-transplantation

	Proportion*1	Odds ratio [95% CI]*2
HeartSheet	6.4%	0.485 [0.118, 1.991]
Control	12.3%	

*1 Propensity score-weighted proportion
*2 Propensity score-weighted logistic regression model

2) Exploratory evaluation of life expectancy

The predicted 2-year survival of patients was calculated using Seattle Heart Failure Model (SHFM) to classify them into subgroups based on the predicted 2-year survival (<70%, ≥70% and <80%, ≥80%). Hazard ratios for time to all-cause death by subgroup were as follows:

Table 15. Hazard ratios for time to all-cause death by subgroup based on SHFM-predicted 2-year survival

SHFM-predicted 2-year survival	Hazard ratio [95% CI]
<70%	3.0 [0.5, 18.3]
≥70% and <80%	0.9 [0.1, 6.5]
≥80%	0.5 [0.1, 1.8]

A hazard ratio of >1 means that the HeartSheet group had a shorter time to all-cause death than the control group. Conversely, a hazard ratio of <1 means that the HeartSheet group had a longer time to all-cause death than the control group.
* Propensity score-weighted Cox regression model with the treatment group as a covariate.

3) Details regarding death or hospitalization due to cardiovascular events

Hazard ratios for time to death or hospitalization due to cardiovascular events were as follows:

Table 16. Hazard ratios for time to death or hospitalization due to cardiovascular events

	Hazard ratio [95% CI][*1]
Time to cardiac death	1.4 [0.5, 3.5]
Time to hospitalization[*2] for additional heart failure treatment different from previous treatments for aggravation of heart failure	1.5 [0.7, 3.4]
Time to hospitalization[*3] involving additional treatment for aggravation of heart failure	0.6 [0.3, 1.2]
Time to aggravation[*4] of heart failure that led to prolongation of hospitalization (approximately ≥1 month)	1.8 [0.8, 4.4]

A hazard ratio of >1 means that the HeartSheet group had a shorter time-to-event than the control group. Conversely, a hazard ratio <1 means that the HeartSheet group had a longer time-to-event than the control group.

*1 Propensity score-weighted Cox regression model with the treatment group as a covariate.

*2 Day of the following events: (a) Hospitalization for additional heart failure treatment different from previous treatments for aggravation of heart failure (hospitalization date); (b) hospitalization due to a major cardiovascular event (hospitalization date [or onset date of a major cardiovascular event if the event occurred during hospitalization and the hospitalization was determined due to the event]); or (c) cardiac death (date of death)

*3 Day of the following events: (a) Inpatient treatment involving additional treatment for aggravation of heart failure (hospitalization date); (b) hospitalization due to a major cardiovascular event (hospitalization date [or onset date of a major cardiovascular event if the event occurred during hospitalization and the hospitalization was determined due to the event]); or (c) cardiac death (date of death)

*4 (a) Distinct prolongation of hospitalization due to aggravation of heart failure (onset date of aggravation of heart failure); (b) hospitalization due to a major cardiovascular event (hospitalization date [or onset date of a major cardiovascular event if the event occurred during hospitalization and the hospitalization was determined due to the event]); or (c) cardiac death (date of death)

4) Details and incidence of all-cause death or hospitalization involving treatment

Table 17. Incidence of all-cause death or hospitalization involving treatment

	HeartSheet	Control
Death	26.1%	21.6%
Hospitalization involving treatment	50.4%	54.4%
Hospitalization for reasons other than cardiovascular events (as judged by the event assessment committee)	4.7%	7.0%
Hospitalization for reasons other than cardiovascular events (case report form)[*1]	27.4%	29.2%
Hospitalization due to cardiovascular events (as judged by event assessment committee)	28.3%	42.7%
Hospitalization due to cardiovascular events (case report form)[*1]	21.1%	41.6%

*1 Events were collected based on the description in the case report from, not according to judgment by the event assessment committee.

*2 Cardiac death, hospitalization for additional heart failure treatment different from previous treatments for aggravation of heart failure, inpatient treatment involving additional treatment for aggravation of heart failure, or distinct prolongation of hospitalization (approximately ≥1 month) due to aggravation of heart failure

Propensity score-weighted proportion

The applicant's explanation about the efficacy of HeartSheet:

The primary analysis for the primary endpoint did not demonstrate the superiority of HeartSheet over the control. However, the applicant considers that the efficacy of HeartSheet was confirmed by a comprehensive consideration of the following reasons:

(a) In the subgroup of "SHFM-predicted 2-year survival of ≥80%," the propensity score-weighted Cox regression model showed a hazard ratio [95% CI] of 0.5 [0.1, 1.8] (HeartSheet vs. control) for all-cause death, suggesting a trend toward longer time to all-cause death in the HeartSheet group than in the control group (Table 15).

(b) The propensity score-weighted Cox regression model showed a hazard ratio [95% CI] of 0.6 [0.3, 1.2] (HeartSheet vs. control) for the time to hospitalization involving additional treatment for aggravation of heart failure. This suggests that the HeartSheet group tended to have a longer time to hospitalization involving additional treatment for aggravation of heart failure than the control group (Table 16).

(c) The incidence of "hospitalization due to cardiovascular events," weighted by the propensity score (events were collected based on the description in the case report from, not according to judgment

by the event assessment committee), was lower in the HeartSheet group (21.1%) than in the control group (41.6%) (Table 17).

(d) The following are the changes in the proportion of patients with New York Heart Association (NYHA) class III or higher, calculated using a propensity score-weighted cumulative logistic model:

The HeartSheet group: 97.8% at baseline, 28.5% at 6 months, and 26.2% at 1 year

The control group: 92.6% at baseline, 73.1% at 6 months, and 64.9% at 1 year

These results suggest a trend toward a greater improvement in the HeartSheet group than in the control group (Table 12).

(e) The following are the least squares means of propensity score-weighted mixed-effects model repeated model (MMRM) regarding changes in site-measured LVEF:

The HeartSheet group: 0.41 at 1 year and 1.60 at 2 years

The control group: 2.57 at 1 year and 1.15 at 2 years

These results suggested that the HeartSheet group tended to achieve a greater recovery in LVEF at 2 years than the control group (Table 10).

Examining the above results comprehensively, the applicant considers that HeartSheet can suppress disease progression and prevent hospitalization for heart failure-related events, provided that eligible patients for treatment with HeartSheet are selected based on the severity of heart failure and the status of treatment for heart failure.

PMDA's view on the efficacy of HeartSheet:

The hazard ratio [95% CI] (HeartSheet vs. control) for the time to cardiac disease-related death, the primary endpoint, was 1.9 [0.8, 4.4], failing to show the superiority of HeartSheet over the control (two-sided *P*-value = 0.136, using a propensity score-weighted Cox regression model).

The propensity score-weighted Cox regression analysis showed that the hazard ratio [95% CI] (HeartSheet vs. control) for time to hospitalization due to any major cardiovascular event, an important secondary endpoint, was 1.5 [0.6, 3.6]; the propensity score-weighted Kaplan-Meier curves are shown in Figure 2. Furthermore, HeartSheet did not show superior results over the control in other secondary endpoints, such as changes in core laboratory-measured LVEF, which allows more objective evaluation than site-measured LVEF.

Additionally, the reasons (a) to (e) provided by the applicant for claiming the efficacy of HeartSheet do not support its efficacy, for the following grounds:

(a) The SHFM-predicted 2-year survival could not be calculated in 28.6% of patients in the HeartSheet group and 44.1% of patients in the control group. Therefore, there are limitations to evaluating the analysis results of the time to all-cause death in the subgroup "SHFM-predicted 2-year survival of ≥80%" (Table 4).

(b) Table 16 suggested that the HeartSheet group tended to have a longer time to hospitalization involving additional treatment for aggravation of heart failure than the control group, but conversely suggested a shorter time-to-events in the HeartSheet group than in the control group for the other 3 categories. The results shown in Table 16 are thus inconsistent.

(c) The incidence of "hospitalizations due to cardiovascular events" was lower in the HeartSheet group than in the control group. However, the efficacy of HeartSheet was not suggested by the results of "time to hospitalization due to any major cardiovascular event" (an important secondary endpoint [Figure 2]) or "time to cardiovascular-related events" (Table 16). The presented results are thus inconsistent.

(d) NYHA is an index that may reflect the subjective opinion of the attending physician, and the use-results survey and the clinical study were conducted in an open-label fashion. This means that the presented results of NYHA classification may be biased, limiting the interpretation of the results.

(e) Since evaluator bias can arise in LVEF evaluation by ultrasound, the changes in core laboratory-measured LVEF should be prioritized over those in site-measured LVEF. Additionally, the HeartSheet group showed no greater improvement in either core laboratory-measured LVEF (Table 9) or site-measured LVEF (Table 10) than the control group at either 6 months or 1 year. The presented results are thus inconsistent.

As shown the above, the results from the use-result survey and the clinical study do not demonstrate the efficacy of HeartSheet in terms of Indication or Performance.

6.R.2 Safety

The applicant's explanation about the safety of HeartSheet:

Table 18 shows the incidence of 6 events designated as safety priority items in the use-results survey.

Table 18. Incidence of safety priority items (safety analysis population [60 patients])

	All events	Serious events[*1]	Events for which a causal relationship to HeartSheet could not be ruled out[*1]
Aggravation of heart failure	16.7% (10)	16.7% (10)	10.0% (6)
Arrhythmia	20.0% (12)	13.3% (8)	10.0% (6)
Events related to open-heart surgery and transplantation procedures	31.7% (19)	1.7% (1)	6.7% (4)
Tumor development or recurrence	3.3% (2)	3.3% (2)	1.7% (1)
Local infection	1.7% (1)	1.7% (1)	0.0% (0)
Adverse events caused by skeletal muscle harvesting	36.7% (22)	0.0% (0)	1.7% (1)

*1 Assessment by the applicant

- Aggravation of heart failure occurred in 16.7% (10 of 60 patients, 16 events). Among the 4 patients with a fatal outcome, 1 patient (5[redacted]-year-old man) experienced aggravation of heart failure before the transplantation of skeletal myoblast-derived cell sheets, 1 patient (6[redacted]-year-old woman) at 2 days post-transplantation (the event was assumed to be associated with surgical stress-induced microcirculation disturbances of the heart and accompanying blood pressure fluctuations, and was thus causally unrelated to HeartSheet itself), and the other 2 patients in the late phase (at 343 days [4[redacted] year-old man] and 354 days [6[redacted]-year-old man] post-transplantation of skeletal myoblast-derived cell sheets). The only case of aggravation of heart failure occurring within 30 days post-transplantation was the above-mentioned fatal case in 6[redacted]-year-old woman. No patients experienced rapid aggravations of heart failure attributable to HeartSheet. In view of these results and the pathophysiology of patients with severe heart failure, these events (aggravation of heart failure) are deemed acceptable from a safety perspective.

- Arrhythmias (including suspected arrhythmias) occurred in 20.0% (12 of 60 patients, 18 events). All events occurring within 30 days post-transplantation were non-serious. Among the 3 patients with a fatal outcome, 1 patient (6[redacted]-year-old man) was found unconscious at home at 296 days post-transplantation and quickly transported to a hospital but died (ventricular tachycardia was confirmed in cardiac resynchronization therapy-defibrillator [CRT-D] records). Another patient (5[redacted]-year-old man) experienced ventricular fibrillation and lost consciousness at 69 days post-transplantation and, despite cardiopulmonary resuscitation, died. The remaining patient (4[redacted]-year-old man) was found collapsed on a street at 181 days post-transplantation and quickly transported to a hospital but died. Other than the 3 patients who died, 4 patients experienced serious arrhythmias after transplantation of skeletal myoblast-derived cell sheets. Two of the 4 patients experienced the event in the late phase (at 175 and 826 days post-transplantation in 1 patient each); the event in one patient was considered related to discontinuation of anti-arrhythmic drugs and the event in the other patient to electrolyte imbalance. Based on these observations, it is unlikely that the use of HeartSheet led to the onset or exacerbation of arrhythmias.
- Events related to open-heart surgery and transplantation procedures (including diastolic dysfunction caused by constrictive pericarditis, local inflammation and associated pericardial effusion, effects on coronary arteries, and adhesions) occurred in 31.7% (19 of 60 patients, 132 events). Events with an incidence of >10% were laboratory abnormalities in 28.6% (14 of 49 patients, 101 events), “injuries, poisoning and procedural complications” in 26.5% (13 of 49 patients, 13 events), and “respiratory, thoracic and mediastinal disorders” in 16.3% (8 of 49 patients, 8 events). There were no events related to diastolic dysfunction caused by constrictive pericarditis, inflammation-induced pericardial effusion, effects on coronary arteries, or adhesions. The following events occurred in ≥2 patients: wound complications, increased blood creatine phosphokinase, and decreased lymphocyte percentage in 26.5% (13 of 49 patients, 13 events) each; increased C-reactive protein in 24.5% (12 of 49 patients, 12 events); decreased platelet count and increased neutrophil percentage in 12.2% (6 of 49 patients, 6 events) each; increased blood urea, increased white blood cell count, increased eosinophil percentage, and pleural effusion in 10.2% (5 of 49 patients, 5 events) each; increased brain natriuretic peptide (BNP) in 8.2% (4 of 49 patients, 4 events); anaemia (including anemia requiring transfusion), decreased blood albumin, and increased blood creatinine in 6.1% (3 of 49 patients, 3 events) each; and increased alanine aminotransferase, increased blood lactate dehydrogenase, increased blood pressure, decreased hematocrit, decreased haemoglobin, increased platelet count, and decreased urine output in 4.1% (2 of 49 patients, 2 events) each. A fatal outcome was reported in 1 patient (7[redacted]-year-old man) who showed laboratory abnormalities (increased CRP, increased BNP, and increased eosinophil count) at 2 to 6 days post-transplantation. These abnormal laboratory changes were considered to fall within the range of fluctuations associated with surgical stress, and the patient was discharged. However, the patient was reported dead at home at 2 months post-transplantation. In addition, a serious event (intrapleural haematoma) occurred in 2.0% (1 of 49 patients, 1 event). These events were considered attributable to the effects of left thoracotomy under general anesthesia performed for transplantation of skeletal myoblast-derived cell sheets, and were deemed acceptable from a safety perspective.
- Tumors occurred or recurred in 3.3% (2 of 60 patients, 2 events): Pancreatic cancer was identified at 1,009 days post-transplantation in one patient (6[redacted]-year-old man) and lung cancer at 1,204 days

post-transplantation in the other patient (5[redacted]-year-old man). The tumors in both patients were considered causally unrelated to HeartSheet by their attending physicians.

- Local infection occurred in 1.7% (1 of 60 patients, 1 event). This was an infection of the pacemaker lead, manifesting 57 days post-transplantation. The infection improved following antibiotic administration and lead removal.
- Adverse events caused by skeletal muscle harvesting (wound complications, post-procedural swelling, etc.) occurred in 36.7% (22 of 60 patients, 73 events). Common events were laboratory abnormalities in 26.7% (16 of 60 patients, 50 events) and wound complications in 26.7% (16 of 60 patients, 18 events). Additionally, anaemia occurred in 2 patients (2 events), and pyrexia, incision site haemorrhage, and arthralgia occurred in 1 patient (1 event) each. All events were non-serious. In all of these patients, skeletal muscle was harvested from the thigh, with the harvesting procedure taking 21 minutes on average (47 minutes at maximum, 8 minutes at minimum).

The mortality rate was 18.3% (11 of 60) of patients using HeartSheet in the use-results survey and 28.4% (29 of 102) of control patients in the clinical study. The evaluation results of post-transplantation mortality (including cardiac disease-related death) in patients using HeartSheet versus control patients, are presented in Section 6.R.1.2.

Other than the safety priority items, no adverse events were considered to pose significant problems in terms of seriousness, incidence, etc.

As shown above, the use-results survey revealed no new safety concerns regarding HeartSheet. Therefore, no additional safety measures are required other than providing safety information obtained from the survey to healthcare professionals through the instructions for use.

Ten patients had at least 1 deviation from the product specifications after harvesting of skeletal muscle, the raw material (13 deviations in total). In 4 of the 10 patients, skeletal muscle was re-harvested and cells from the re-harvested muscle were cultured. In 3 of the 4 patients, the cells cultured after re-harvesting did not meet the product specifications. In the remaining 1 patient, the cells cultured after re-harvesting met the product specifications and then the cell sheets were transplanted. In 9 patients, cells cultured from harvested skeletal muscle did not meet the product specifications and thus could not be shipped. In 1 patient, after the shipment of cultured cells, there was a deviation associated with preparation of skeletal myoblast-derived cell sheets (i.e., a problem with detaching the cell sheets) and therefore the cell sheets could not be transplanted; subsequently, skeletal muscle was re-harvested, cells from the re-harvested muscle were cultured and shipped again, and then skeletal myoblast-derived cell sheets were prepared without deviations and transplanted in this patient.

The test items that failed to meet the specifications at least twice (i.e., ≥2 events) were flow cytometry analysis ([redacted]) and cell count verification. These deviations in both test items were suspected to have originated from the skeletal muscle tissue, the patient-derived raw material. To address the deviations, improvements were made (e.g., improvement in the processing amount of skeletal muscle used for manufacturing), but such deviations have still occurred. The investigation into the causes and potential solutions is ongoing.

PMDA's view:
The safety evaluation of HeartSheet must include assessments of raw material harvesting and transplantation procedure. Skeletal myoblast-derived cell sheets are transplanted under general anesthesia, imposing a significant burden on patients with severe heart failure.

The use-results survey revealed that adverse events necessitating intervention occurred post-surgery, including anaemia requiring transfusion, arrhythmias requiring intervention, decreased urine output, and inflammatory responses, all of which could potentially worsen heart failure. Although no new safety concerns have been identified with HeartSheet, its safety cannot be deemed acceptable from a benefit-risk perspective because its efficacy has not been demonstrated [see Section 6.R.1].

6.R.3 Indication or performance

The proposed Indication or Performance of HeartSheet in the present application is the same as that established at the time of conditional and time-limited approval.

Given the review in Section "6.R.1 Efficacy," PMDA considers that no discussion can be made regarding the Indication or Performance since the efficacy of HeartSheet has not been demonstrated.

6.R.4 Dosage and administration or method of use

The proposed Dosage and Administration or Method of Use of HeartSheet in the present application is the same as that established at the time of conditional and time-limited approval.

Given the review in Section "6.R.1 Efficacy," PMDA considers that no discussion can be made regarding the Dosage and Administration or Method of Use since the efficacy of HeartSheet has not been demonstrated by the experience with HeartSheet used according to the proposed "Dosage and Administration or Method of Use."

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

The applicant's explanation about the plan for the post-marketing surveillance on HeartSheet:
There is no specific plan for post-marketing surveillance after the decision on the disposition of the present application.

PMDA considers that no discussion can be made regarding post-marketing surveillance since the efficacy of HeartSheet has not been demonstrated, as per the review in Section "6.R.1 Efficacy."

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 submitted after the conditional and time-limited approval 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. Overall, the collection of data and preparation of the application documents were conducted in accordance with the data integrity standards for product application. PMDA therefore 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 GPSP inspection

The new regenerative medical product application data submitted after the conditional and time-limited approval (7. Data of clinical studies) were subjected to an on-site GPSP inspection on regenerative medical products, 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. However, the inspection revealed the following finding requiring corrective action by the marketing authorization holder, although it had no significant impact on the review of the use-results survey and clinical study overall. PMDA notified the marketing authorization holder of the finding.

Finding requiring corrective action

Marketing authorization holder

- [redacted]

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

On the basis of the data submitted, PMDA has concluded that HeartSheet has no efficacy in patients with severe heart failure, and falls under the provisions of Article 23-25, Paragraph 2, Item 3 (a) (i.e., "when the regenerative medicine products pertaining to the application are not found to have the efficacy or effects indicated in the application") of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. Furthermore, the safety of HeartSheet is not acceptable from a benefit-risk perspective. PMDA has therefore concluded that HeartSheet has no clinical significance as a treatment option for patients with severe heart failure.

Thus, PMDA considers that HeartSheet should not be approved as per the provisions of Article 23-25, Paragraph 1 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices, but will make the final decision taking account of comments from the Expert Discussion.

Review Report (2)

June 25, 2024

Product Submitted for Approval

Brand Name	HeartSheet
Applicant	Terumo Corporation
Date of Application	September 7, 2023

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

PMDA concluded that the efficacy of HeartSheet for patients with severe heart failure was not demonstrate because of the following results presented in Section "6.R.1 Efficacy" of the Review Report (1):

(a) A between-group comparison using a propensity score-confounding adjustment method showed that the hazard ratio[8)] [95% CI] (HeartSheet vs. control) for the time to cardiac disease-related death, the primary endpoint, was 1.9 [0.8, 4.4], failing to demonstrate the superiority of HeartSheet over the control.

(b) HeartSheet did not show superior results over the control in time to hospitalization due to any major cardiovascular event, an important secondary endpoint, or in other secondary endpoints including changes in the core laboratory-measured LVEF.

The expert advisors supported the above PMDA's conclusion, and some of them made the following comments:

- The applicant presented the analysis results for time to all-cause death in the subgroup of "SHFM-predicted 2-year survival of ≥80%" as a reason for claiming the efficacy of HeartSheet. It is unclear whether the distribution imbalance of patient characteristics between patients using

8) A hazard ratio of >1 means that the HeartSheet group had a shorter time to cardiac disease-related death than the control group. Conversely, a hazard ratio of <1 means that the HeartSheet group had a longer time to cardiac disease-related death than the control group.

HeartSheet and control patients in the subgroup can be adjusted using the propensity score estimated from the overall population; this point should be verified.

- The discussion about the appropriateness of the propensity score should be included in the Review Report.

PMDA's view:

In response to the comments from the expert advisors, PMDA asked the applicant for an explanation.

The applicant's response:

The distribution of patient characteristics in the subgroup of "SHFM-predicted 2-year survival of ≥80%" was adjusted using the propensity score estimated from the overall population; the adjusted distribution did not significantly differ between patients using HeartSheet and control patients.

PMDA accepted the applicant's explanation.

The appropriateness of the propensity score is not mentioned in the Review Report (1), but it was discussed during the review process. The 9 patient characteristics presented in Table 6 of the Review Report (1), used for propensity score estimation, comprehensively covered characteristics that may have a significant impact on the results. Therefore the PMDA's conclusion presented above is appropriate. Other than the 9 patient characteristics, the following 3 characteristics also differed between the HeartSheet and control groups:

- Proportion of patients with eGFR <30 mL/min/1.73 m² (renal failure): 40.3% in the HeartSheet group vs. 15.6% in the control group
- Proportion of patients with prior angiotensin converting enzyme (ACE) inhibitor therapy: 38.9% in the HeartSheet group vs. 70.7% in the control group
- Proportion of patients with prior angiotensin receptor blocker (ARB) therapy: 37.4% in the HeartSheet group vs. 19.5% in the control group

Therefore, a propensity score was calculated using these 12 factors (i.e., 9 characteristics in Table 6 of the Review Report (1) and the additional 3 characteristics), and a weighted Cox regression model analysis was conducted using the propensity score. The analysis showed a hazard ratio[8)] of 2.3 [95% CI, 1.0, 5.5] (HeartSheet vs. control) for the time to cardiac disease-related death, the primary endpoint.

Based on the above discussions, PMDA concluded that the efficacy of HeartSheet has not been demonstrated for patients with severe heart failure.

1.2 Safety

PMDA's conclusion as a result of the review in Section "6.R.2 Safety" of the Review Report (1):

Although no new concerns were identified from the use-results survey, the safety of HeartSheet is not acceptable from a benefit-risk perspective because its efficacy has not been demonstrated [see Section 1.1], in view of the following points:

- The harvesting of skeletal muscle, the raw material of skeletal myoblast-derived cell sheets, is itself an invasive procedure, and adverse events occurred in patients undergoing the procedure.
- The transplantation of skeletal myoblast-derived cell sheets involves surgery under general anesthesia, which is a strenuous procedure for patients with severe heart failure. Indeed, adverse

events requiring intervention occurred after the transplantation surgery, including anaemia requiring transfusion, arrhythmias needing treatment, decreased urine output, inflammatory reactions, and other events that could lead to aggravation of heart failure.

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

2. Overall Evaluation

PMDA's conclusion based on the above review:

The product was presumed to have efficacy when it was granted the conditional and time-limited approval. Although this presumption was not inappropriate, the efficacy for the "Indication or Performance" shown below was not demonstrated by the use-results survey and clinical study conducted after the conditional and time-limited approval of the product. The product therefore falls under the provisions of Article 23-25, Paragraph 2, Item 3 (a) (i.e., "when the regenerative medicine products pertaining to the application are not found to have the efficacy or effects indicated in the application") of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. Thus, the product should not be approved as per the provisions of Article 23-25, Paragraph 1 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Device.

Proposed Indication or Performance

Treatment of patients with severe heart failure due to ischemic heart disease unresponsive to standard treatments including drug and invasive therapies who meet all of the following criteria.

Eligibility criteria:

- NYHA class III or IV heart failure; and
- Resting left ventricular ejection fraction ≤35%

Appendix

List of Abbreviations

ACE	Angiotensin converting enzyme
Alb	Albumin
Application	Application for marketing approval
ARB	Angiotensin receptor blocker
ATE	Average treatment effect
BNP	Brain natriuretic peptide
CABG	Coronary artery bypass graft
CD	Cluster of differentiation
CRT	Cardiac resynchronization therapy
CRT-D	Cardiac resynchronization therapy-defibrillator
Hb	Hemoglobin
[redacted]	[redacted]
ITT	Intention To Treat
LVEF	Left ventricular ejection fraction
mITT	modified Intention To Treat
MMRM	Mixed-effects model repeated model
NYHA	New York Heart Association
PCI	Percutaneous coronary intervention
PMDA	Pharmaceuticals and Medical Devices Agency
PT	Preferred terms
[redacted]	[redacted]
SHFM	Seattle Heart Failure Model
[redacted]	[redacted]