November 19, 2010
Office of Medical Device Evaluation and Licensing
Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

[Classification]	Instrument & Apparatus 7 Organ function replacement device
[Generic name]	Implantable ventricular assist device
[Brand name]	Implantable Ventricular Assist System EVAHEART
[Applicant]	Sun Medical Technology Research Corp.
[Date of application]	January 19, 2009 (Application for marketing approval)

[Results of deliberation]
The results of deliberation of the Committee on Medical Devices and *In-vitro* Diagnostics of the Pharmaceutical Affairs and Food Sanitation Council on November 19, 2010 are as described below.
It was concluded that the results should be reported to the Pharmaceutical Affairs Department.

It is appropriate to approve the product with a re-examination period of 7 years under the following conditions for approval. The product is not classified as a biological product or a specified biological product.

[Conditions for approval]
The applicant is required to:

1. Perform a use-results survey in all patients including those who completed the extended clinical study in cooperation with related academic societies during the re-examination period. At the same time, observe the long-term prognosis of patients implanted with the assist device and report its analytical results.

2. Establish appropriate qualification criteria for medical institutions and physicians in cooperation with related academic societies, and take appropriate measures to limit the use of this product to physicians and medical institutions who/which understand its efficacy and safety and have sufficient knowledge and experience in surgical techniques, etc.

3. Provide sufficient training for healthcare professionals, patients, and caregivers to ensure the safe and smooth transition to home therapy. The safety of the product should be ensured by establishing a sufficient support system.

Review Report

October 29, 2010

Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following medical device submitted registration are as follows.

[Classification]	Instrument & Apparatus 7 Organ function replacement device
[Generic name]	Implantable ventricular assist device
[Brand name]	Implantable Ventricular Assist System EVAHEART
[Applicant]	Sun Medical Technology Research Corp.
[Date of application]	January 19, 2009
[Reviewing office]	Office of Medical Devices I

Review Results

October 29, 2010

[Classification]	Instrument & Apparatus 7 Organ function replacement device
[Generic name]	Implantable ventricular assist device
[Brand name]	Implantable Ventricular Assist System EVAHEART
[Applicant]	Sun Medical Technology Research Corp.
[Date of application]	January 19, 2009

[Review results]
Implantable Ventricular Assist System EVAHEART is an implantable left ventricular assist device intended for use to improve the blood circulation in patients with end-stage severe heart failure who require cardiac transplantation.

The data on stability and durability, and data on performance including electrical safety, biological safety, and mechanical safety were submitted as the evaluation data from the non-clinical studies. The data showed no particular problems.

The data from the Japanese pilot and pivotal studies were submitted as the evaluation data from clinical studies. Since all the 3 subjects enrolled in the pilot study have survived with the product for 3 months after implantation, the primary endpoint of efficacy was achieved. It was confirmed that the data showed no major safety problems in regard to the system. In the pivotal study with 15 subjects, the primary endpoint of efficacy, or the survival at 6 months, was achieved in 13 of 15 subjects with the product. None of them received cardiac transplantation at 6 months. The 6-month survival rate as determined by the Kaplan-Meier test was 86.7% (95% confidence interval [CI], 69.5%-100.0%). For safety, the product was clinically at least not inferior to similar devices, although it was associated with serious neurological disorder related to anticoagulant/antiplatelet therapy. The assist period as of October 19, 2010 as determined by pooling the results from the pilot, pivotal, and extended studies was 924.1 ± 526.1 days (mean ± standard deviation). The longest assist period was more than 1900 days. Based on these results from the non-clinical and clinical studies, it has been determined that the efficacy and safety of the product is assured.

Based on its regulatory reviews, the Pharmaceuticals and Medical Devices Agency has concluded that the product may be approved for the following intended use with the following conditions, taking into account that no implantable ventricular assist device is clinically available in Japan, and that this result should be deliberated at the Committee on Medical Devices and *In-vitro* Diagnostics.

[Intended use]
Implantable Ventricular Assist System EVAHEART is used to improve the blood circulation until cardiac transplantation is performed in patients who have severe heart failure for which cardiac transplantation is indicated, and show continuous decompensation in spite of drug therapy or circulation assist techniques, such as the use of an external ventricular assist device,

and whose lives cannot be saved without cardiac transplantation.

[Conditions for approval]
The applicant is required to:

1. Perform a use-results survey in all patients including those who completed the extended clinical study in cooperation with related academic societies during the re-examination period. At the same time, observe the long-term prognosis of patients implanted with the assist device and report its analytical results.

2. Establish appropriate qualification criteria for medical institutions and physicians in cooperation with related academic societies, and take appropriate measures to limit the use of this product to physicians and medical institutions who/which understand its efficacy and safety and have sufficient knowledge and experience in surgical techniques, etc.

3. Provide sufficient training for healthcare professionals, patients, and caregivers to ensure the safe and smooth transition to home therapy. The safety of the product should be ensured by establishing a sufficient support system.

Review Report

October 29, 2010

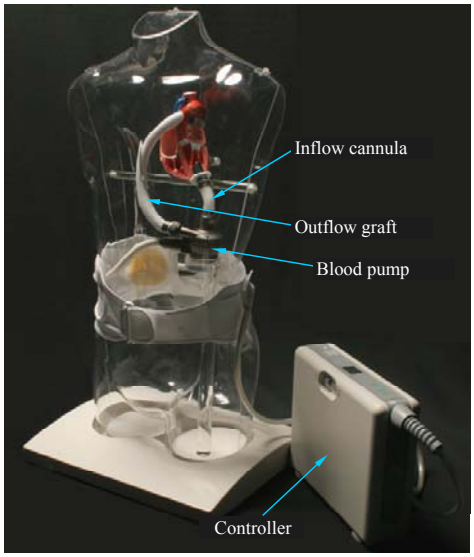
I. Product for Review

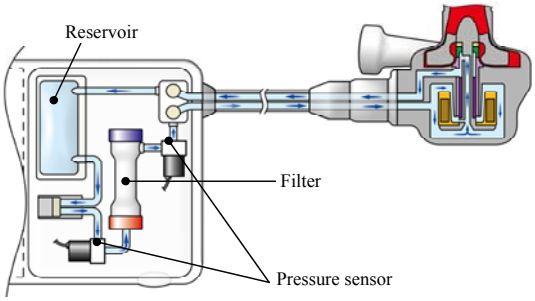
[Classification]	Instrument & Apparatus 7 Organ function replacement device
[Generic name]	Implantable ventricular assist device
[Brand name]	Implantable Ventricular Assist System EVAHEART
[Applicant]	Sun Medical Technology Research Corp.
[Date of application]	January 19, 2009
[Proposed intended use]	The product is used to improve the blood circulation in patients who have severe heart failure including dilated cardiomyopathy and ischemic heart disease, and show continuous decompensation in spite of existing therapies (drug therapy or circulation assist techniques), and whose lives cannot be saved without cardiac transplantation. The product is a left ventricle assisting ventricular bypass system consisting of internal components implanted in the body, such as the blood pump, and external components including the controller and power supply unit. The product allows patients to receive home therapy.

II. Product Overview

EVAHEART is an implantable ventricular assist device intended to improve circulation in patients with end-stage severe heart failure who require cardiac transplantation. It consists of internal components, external components, and accessories. Internal components are the centrifugal pump, inflow cannula, and outflow graft. External components are the controller, cool seal unit (CSU), controller connection kit, battery, emergency battery, and emergency controller. Accessories consist of the external monitor, external monitor connecting cable, battery charger, AC/DC adapter, car adapter, tunnelers, punchers, wrenches, and dissectors. The product creates a blood flow path through which the removed blood from the left ventricle, via the inflow cannula, is sent to the ascending aorta via the outflow graft. The external controller controls the centrifugal pump rotational speed to assist blood circulation. The controller also controls and drives the CSU and monitors and displays the status of the whole system. Two batteries for normal use and an emergency battery are connected to the controller to supply electric power. Electric power may also be supplied simultaneously from an external power supply using the AC/DC adapter or car adapter. If the controller fails, the emergency controller can control the centrifugal pumps. The centrifugal pump in this system has a simpler structure than that in pulsatile ventricular assist devices, but may cause rotation disorder by blood coagulation at the blood seal. To reduce the risk, the pump is equipped with a cool seal system. The CSU in this system supplies the cool seal fluid to the blood pump to cool the inside of the blood pump, lubricate the bearing, and maintain the blood seal.

Figure 1. System structure (left, overview; right, schematic diagram of the cool seal system)





III. Summary of the Submitted Data and the Outline of Review by the Pharmaceuticals and Medical Devices Agency

The data submitted by the applicant in the application and the applicant's responses to the inquiries from the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below.

The expert advisors of the Expert Discussion on this product declared that it does not fall under the Item 5 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. Origin or history of discovery and usage conditions in foreign countries etc.

[Origin or history of discovery]

Patients with heart failure are treated with drug therapy, although the efficacy of drug therapy is limited. The prognosis of drug therapy alone is very poor in patients with intravenous catecholamine-dependent severe chronic heart failure classified into the New York Heart Association (NYHA) functional class IV[1]. Patients with end-stage severe heart failure are therefore treated with cardiac transplantation.

On the other hand, donor hearts for cardiac transplantation are limited. The Organ Procurement and Transplantation Network (OPTN) reported that approximately 3500 patients were newly registered to the waiting list of cardiac transplantation and only about 2200 patients received cardiac transplantation in 2009 in the US where cardiac transplantation is the most common in the world. Similarly, only a small number of donor hearts are supplied in Japan: 64 patients have received cardiac transplantation as of October 2009 since the enforcement of the Act on Organ Transplant in October 1997. The mean waiting period in patients who received cardiac transplantation was as long as 883 days (29-2747 days)[2]. It is reported that 228 to 670 patients require cardiac transplantation every year in Japan[2]. The 2005 Study Report from the Active Implantable Medical Device (Advanced Ventricular Assist System) Review Guideline Working

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1 Eric A. Rose, et.al. Long-term use of a left ventricular assist device for end-stage heart failure. *N Engl J Med. 2001;*345(20):1435-1443.

2 Organ Transplantation Fact Book 2009, edited by the Public Relations Committee, the Japan Society for Transplantation

Group shows that there are about 2000 to 4000 people per year for whom cardiac transplantation or semi-permanent use of a ventricular assist device is absolutely indicated.

Novacor Left Ventricular Assist System (approval number, 21300BZY00468000, Edwards LifeScience; hereinafter referred to as Novacor) and HeartMate XVE LVAS (approval number, 22100BZY00011000, Nipro Corporation; hereinafter referred to as HeartMate XVE) were approved in 2001 and 2009, respectively. However, both of them are indicated in only a limited number of patients due to the large pumps size. Since Novacor is no longer commercially available and HeartMate XVE has not been released, no implantable ventricular assist device is currently available in Japan. Therefore, there is a strong need for circulation assist therapy using an implantable ventricular assist device that can improve and maintain blood circulation in patients with end-stage severe heart failure. Especially in Japan, high-performance implantable ventricular assist devices are required that: (a) can be used for a long waiting period for transplantation, (b) cause less complications, allow patients to be treated at home, and can maintain high quality of life (QOL) and (c): are small in size and suitable for the Japanese physical constitution. Under these situations, the applicant developed EVAHEART, small-sized and equipped with the centrifugal pump, as an implantable ventricular assist device that meets the requirements specific to Japanese patients including long-term use, less complications, use for home therapy, high QOL, and small size suitable for Japanese physical constitution, and is equipped with the cool seal system to reduce the risk of rotation disorder caused by blood coagulation at the blood seal. The applicant was financially supported by the Japan Science and Technology Corporation from 1997 and the Organization for Pharmaceutical Safety and Research from 1999.

[Usage conditions in foreign countries]
No use results in foreign countries are available for EVAHEART since it has not been approved or released in any foreign country. The results of Japanese clinical studies are described below in "8. Clinical data."

2. Setting of specifications

The specifications of EVAHEART include pressure flow characteristics for the blood pump, water entry pressure, minimum bending radius, tensile strength, and cuff tensile strength for the inflow cannula, water entry pressure, minimum bending radius, and tensile strength for the outflow graft, and cool seal fluid flow rate for the CSU. In addition, general requirements for basic safety and essential performance (electrical safety) (IEC60601-1:1988+A1:1991+ A2:1995), safety requirements for medical electrical systems (IEC60601-1-1:2000), electromagnetic compatibility (EN60601-1-2:2001), biological safety (ISO10993-1) were set. As environmental safety, use environment, blood pump surface temperature, vibration and shock resistance of the controller and emergency controller, and defibrillator protection were set. The sterility assurance level (SAL) was set at 10^{-6}. The limit value of residual ethylene oxide was set at $\leq$25 μg/g for the contact area with blood or body fluid and $\leq$250 μg/g for the other areas. Bacterial endotoxin test was also set as the specifications. Data justifying these specifications were submitted.

PMDA asked the applicant to explain the justification of the specifications for the blood pump, controller, emergency controller, CSU, battery, and durability since they have not been adequately set.

The applicant responded as follows:
The following specifications will be added: blood pump housing pressure resistance, cool seal flow path pressure resistance, mechanical seal sealing performance, pump cable tensile strength (at the fixation on the blood pump side), and pump cable collapse strength for the blood pump;

upper and lower limits of the blood pump rotational speed, anti-load torque variation, and deviation of the blood pump rotational speed for the controller; the blood pump rotational speed for the emergency controller; filtration performance for the CSU; and tensile strength of the battery connector connection for the battery. Further, the following durability specifications will be added: durability of the blood pump, inflow cannula, outflow graft, and CSU and bending durability of the pump cable and pump cable controller connection.

As a result of the review on the original and additional data, PMDA concluded that the specifications of the left ventricular assist device have been adequately set, and accepted the response.

3. Stability and durability

Stability data demonstrating that the specifications were met by the samples of the product stored for 2 years after sterilization were submitted.

Durability data including the durability test results of EVAHEART and CSU were submitted. For pump durability, the pump had a reliability of 88%, which was above the target value of at least 80% at a confidence level of 90% for 2 years of operation, specified by the American Society for Artificial Internal Organs and American Association for Thoracic Surgery.

PMDA asked the applicant to explain the following points:

(1) Adequate durability of the pump cable, inflow cannula, outflow graft, and bearing not explained in the submission.

(2) Durability of the CSU for which airtightness was reduced as a measure for the leakage inside the CSU observed in the clinical study.

The applicant responded as follows:

(1) The results of the bending durability test of the multi-lumen cable, flex resistance test of the pump cable controller connection, bending durability test of the inflow graft/outflow graft, and resistance test of the bearing were additionally submitted. Since these tests showed acceptable results, the durability of the components is assured.

(2) The durability test results of the CSU with reduced airtightness were additionally submitted. Since the test showed acceptable results, the durability of the CSU with reduced airtightness is assured.

PMDA reviewed the stability and durability data on the product and determined that the expiration period of 2 years proposed by the applicant is acceptable.

4. Conformity to the requirements specified in Paragraph 3 of Article 41 of the Pharmaceutical Affairs Act

A declaration of conformity declaring that the product meets the standards for medical devices as stipulated by the Minister of Health, Labour, and Welfare in accordance with Paragraph 3 of Article 41 of the Pharmaceutical Affairs Act (hereinafter referred to as "the Essential Principles") (MHLW Ministerial Announcement No.122, 2005) and the Ministerial Ordinance on Quality Management System for Medical Devices and *In Vitro* Diagnostics (MHLW Ministerial Ordinance No.169, 2004) was submitted.

PMDA reviewed the conformity to the standards specified in Paragraph 3 of Article 41 of the Pharmaceutical Affairs Act and accepted the declaration.

5. Performance

[Physicochemical properties]

Data on the physicochemical properties of EVAHEART including specifications as well as the results of the CSU mechanical seal washout verification and centrifugal pump flow visualization tests were submitted. The applicant explained that there were no specific concerns about physicochemical properties, except for the instantaneous stoppage followed by restart, observed in the shock resistance test of the emergency controller included in the specifications.

PMDA asked the applicant to explain whether the risk of the instantaneous stoppage followed by restart in the shock resistance test of the emergency controller was acceptable or not.

The applicant responded as follows:
The pump stopped due to disconnection of the battery connector when a shock was given, towards the same direction as which the battery connector disconnects, in the shock resistance test of the emergency controller. After the battery connector was reconnected, stoppage of the pump caused by the loosened battery connector did not recur. Therefore, this event was attributable to an insufficient lock of the battery connector. Precautions section of the instructions for use would be revised to add an instruction that the battery connector should be securely connected when using the emergency controller.

PMDA reviewed the data and above response on physicochemical properties and concluded that adding a caution statement to the instructions for use is suitable to prevent the stoppage and restart of the pump observed in the shock resistance test of the emergency controller. Therefore, PMDA accepted the applicant's view that the physicochemical properties of the product are secured.

[Electrical safety and electromagnetic compatibility]

Data on electrical safety and electromagnetic compatibility including the test results of applicable specifications were submitted. The data showed the product met all the specifications.

PMDA considered that the product should be examined for electromagnetic interference in daily life since it was expected that patients implanted with the product would be discharged and receive home therapy. Therefore, PMDA asked the applicant to explain what type of devices were tested for electromagnetic interference with the product and how the applicant would provide the information on the limitations of the test to physicians and patients.

The applicant responded as follows:
The product passed the electromagnetic interference tests with medical electrical devices in accordance with the IEC specifications or the EN specifications which includes the IEC specifications. Further, the product was tested internally for the interoperation with devices the product may encounter in daily life (including a microwave oven and IH cooker). The result showed that the product functions normally and there were no effect on the operation of the blood pump or CSU for all the devices tested. The examination of the alarm system showed no problem except for an improper operation of the E-41 alarm when the product was tested under an electric field intensity that was about 3000 times higher than the radio device (such as an amateur radio device) in normal operation (the E-41 alarm warns that the circulation function of the cool seal fluid in the cool seal system is blocked by a kink of the pump cable or obstructed cool seal fluid path, and that the cause of the block should be removed). No effect on peripheral devices was observed, except that it has been found that slight noises are superimposed on electrocardiographic waveforms on the electrocardiographic monitor, depending on the electrode position (this was not so serious as to cause misdiagnosis). The applicant therefore

considered that the product might have an improper operation in the alarm circuit under a strong electromagnetic field, but would have no effect from electric devices that the product might encounter in daily life. Based on the above results, the following caution statement on electromagnetic interference will be added to the instructions for use: "This system may have an improper operation of the alarm system under a strong electromagnetic field. Such an improper operation of the alarm does not effect the blood pump drive circuit. The healthcare professionals and patients should act calmly." Information on electrical equipment that may interfere with the product will be provided to physicians and patients as soon as it becomes clear.

PMDA reviewed the data on the electrical safety and electromagnetic compatibility of the product and determined that the product will have no problem from the electromagnetic interference the product might encounter in daily life. Therefore, PMDA accepted the applicant's view that the electrical safety and electromagnetic compatibility of the product are secured.

[Biological safety]
Biological safety test were conducted on the following product components that would be implanted in the body and come in contact with blood or tissue in accordance with ISO10993-1. That is, the region of the blood pump that would come in contact with blood and inflow cannula were tested for cytotoxicity, sensitization, intracutaneous reactivity, systemic toxicity, pyrogenicity, subacute toxicity, genotoxicity (reverse mutation), genotoxicity (chromosome aberration), and haemocompatibility (haemolysis). The blood pump cable was tested for cytotoxicity, sensitization, intracutaneous reactivity, systemic toxicity, pyrogenicity, subacute toxicity, genotoxicity (reverse mutation), genotoxicity (chromosome aberration), and implant. Data demonstrating that all the components passed all the tests were submitted. The biological safety test of the outflow graft was omitted since it was manufactured from the same raw materials as used in the inflow cannula and therefore could be evaluated with the biological safety test results of the inflow cannula.

PMDA asked the applicant to explain the necessity of performing an implant test based on ISO10993-6 for the internal components that come in contact with blood or body fluid, other than the pump cable.

The applicant responded as follows:
The pure titanium, which composes the main body of the pump, conforms to ASTM F67-95 Medical Grade 2, which is the standard specification of pure titanium for surgical implantation application. Pure titanium is known to induce minimal muscular tissue reaction. Also, no findings suggesting biological safety concerns have been observed in the biological safety tests other than the implant test. Therefore, an implant test is not necessary. An implant test is not necessary for the inflow cannula and outflow graft as well, since they are made of the same raw materials as used in approved devices.

PMDA reviewed the data on biological safety and determined that the implantability of the product can be assured without performing an implant test. Therefore, PMDA accepted the applicant's view that the biological safety of the product is assured.

[Other performance evaluations]
As other performance data on the product, results of specific tests included in the specifications were submitted, including pressure flow characteristics for the blood pump, water entry pressure, minimum bending radius, tensile strength, and cuff tensile strength for the inflow cannula; water entry pressure, minimum bending radius, and tensile strength for the outflow graft; and the cool seal fluid flow rate for the CSU. Further, the results on the pre-clinical animal safety test not included in the specifications were also submitted. The applicant explained that the submitted

data met the specifications.

The pre-clinical animal safety test was performed as an *in vivo* long-term chronic animal study intended to demonstrate the safety of the product in calves for at least 90 days. The test results were submitted for review. This study was conducted using 10 calves according to the guidelines of the American Society for Artificial Internal Organs (ASAIO) – Society of Thoracic Surgeons (STS) under GLP regulations. The product was able to be run for at least 90 days in 6 of the 10 calves. Three of the remaining 4 calves had sepsis from an unknown infection route, cannula obstruction by myocardial thickening, and postoperative accidental cardiac arrest possibly due to the implanted product component, respectively. They were attributable to the surgical procedure or anatomical characteristics of the animals, etc., and not considered to pose a risk to humans. The remaining 1 calf died of the loss of rotation control, which resulted from ringing (sucking phenomenon) between the seat ring of the blood seal (bearing on the fixation side) and seal ring. Causal analysis showed the seat ring used for the blood seal of the blood pump had a different surface texture from that of the other pumps. The surface of the seat ring had extremely low porosity. Since it was confirmed that a low-porosity sliding surface of the seat ring was more likely to cause ringing to the seal ring of the seal sliding surface, resulting in rotation disorder, the process was revised so that the surface texture of the seat ring would be inspected on the part level. Since then, no similar malfunctions have occurred.

The other observations that may be potentially problematic are as follows: (1) replacement of the CSU, which usually requires replacement every 3 months, was required in less than 90 days because of leakage, (2) white fibrin microthrombi on the outer surface of the mechanical seal (bearing), (3) kink of the outflow graft, (4) freeze of the external monitor screen, (5) wedge thrombus around the cannula at the left ventricular apex, (6) microthrombi on the uneven part between the artificial graft and metal connector in 2 cases, (7) relatively large plasma drainage, (8) contact of the cannula tip to the ventricular septum, (9) issue of the E-23 alarm (the alarm warns that the actual rotational speed is much higher than the set rotational speed), and (10) issue of the E-30 alarm (the alarm warns that the controller automatically restarted the blood pump to return the rotational speed to the set level).

PMDA asked the applicant to explain the following points:
1. The applicant added specifications of the blood pump, controller, emergency controller, CSU, and battery since they have not been adequately set. Demonstrate that the product meet the added specifications.

2. Explain the problems observed in the pre-clinical animal safety study for which the measures against them and justification of the measures have not been explained. In addition, reflect the porosity of the seat ring additionally specified as a measure against the malfunction in the raw material specifications.

The applicant responded as follows:
1. The test results of the additional specification items will be submitted. The test results met the additional specifications.

2. For the problems observed in the pre-clinical animal safety studies, not fully explained at submission, additional explanations are given below, including their details and appropriateness of the actions taken. (1) The CSU that should be changed every 3 months had to be changed in less than 90 days due to leakage. To resolve this problem, airtightness was added to the acceptance inspection items of the line block. (2) White fibrin microthrombi were observed on the outer surface of the mechanical seal (bearing) in 4 cases. The applicant considered it unnecessary to modify the device since the microthrombi might not directly cause clinical signs

of embolization according to the investigator and they were very minute. However, the operating instructions were revised to include the recommended guidelines for anticoagulant therapy since postoperative anticoagulant therapy is important in clinical settings. (3) For the kink in the outflow graft in 4 cases, the operating instructions were revised to state that the reinforcing ring should not be excessively exposed, and that intracorporeal components should be carefully positioned. Further, that the same cautions should be exercised during the implantation training. (4) The external monitor screen freeze in 6 cases can be solved by rebooting the monitor since it is an auxiliary device. However, the software was improved to reduce the risk. (5) Wedge thrombus was observed around the cannula at the left ventricular apex in 2 cases. They may occur when blood stasis is formed around the inflow cannula. Blood stasis is more likely to occur in the bovine healthy heart than in the human heart because of the smaller intracardiac cavity. To solve this problem, the operating instructions were revised to include instructions on cannula insertion direction and position. The training program was also revised to state that the postoperative anticoagulant therapy should be performed carefully, and that the pump rotational speed should be set to ensure blood flow around the apex. (6) The clinically negligible microthrombi were observed on the uneven part between the artificial blood vessel and metal connector in 2 cases. They may have resulted from a lack of proficiency in the assembling process. Since the detection of this problem, the product has been more carefully assembled in the manufacturing process and no thrombus formation has been reported. (7) The cause of the relatively large plasma drainage remains unidentified. However, the operating instructions were revised to include this event and decided to set short-term and long-term drains. (8) The contact of the cannula tip to the ventricular septum was noted in 8 cases. This may have resulted largely from inserting the cannula with its longer section placed on the ventricular septum, and from intracardiac cavity being smaller than the human intracardiac cavity, which are problems specific to animal studies. Risk of this problem in humans is considered low, in view of the fact that the cannula is inserted with its longer part placed on the free wall, and that the intracardiac cavity is round. (9) “The deviation of the blood pump rotational speed” was added to the specifications as a measure against the issuance of the E-23 alarm in 1 case. The evaluation data on the specification will be additionally submitted. No similar events occurred after the inspection of “the deviation of the blood pump rotational speed” was added to the manufacturing process. (10) The frequent issuances of the E-30 alarm in 1 case resulted from the loss of synchronism, which is caused by the inability of the driving circuit to follow the rotation of the rotor when a large instantaneous rotational resistance is applied to the rotor which delays the rotor rotation. It is mechanistically difficult to completely avoid the phenomenon. The issuance of the alarm indicates that the safety mechanism under which the controller automatically restarts the pump and returns the pump rotational speed to the set level was activated in response to the loss of synchronism, and does not indicate hazard. Since the same alarm was issued in the pivotal study described below, a “test to confirm the improved rotational speed control and followability of the controller” was performed after the function of the controller, to control the blood pump rotational speed, was modified. The results of the test are submitted. The results showed that the loss of synchronism became unlikely to occur in response to sudden load changes.

Based on the above results, the applicant considered that the safety of the product has been appropriately evaluated in the pre-clinical animal safety test, and that necessary measures were taken against the detected problems. The applicant therefore determined that the safety of the product was assured, and that the clinical use of the product was justified. The porosity of the seat ring, which was specified as a measure against the observed malfunction, will be reflected in the raw material specifications in the application.

PMDA reviewed the data on other performance evaluation and concluded that the added specification items are acceptable based on the additional submitted test results. PMDA also confirmed that the safety of the product has been appropriately evaluated in the pre-clinical

animal safety test, and that necessary measures were taken against the observed problems in the test. Therefore, PMDA accepted the applicant's view.

[Studies to support usage method]
The following tests/studies were performed and their results were submitted: hemolysis test, "D059 Pre-Clinical Animal Study for SunMedical LVAS" to evaluate the effect of the stoppage of the cool seal system on the blood pump, anatomical fitting test, "Controller function confirmation tests 1 and 2," "Controller operation confirmation tests 3 and 4" to confirm the detection of abnormalities by the controller and normal operation of the alarm functions, and "C01 Pump flow rate estimation formula confirmation study" to examine the difference between the measured and estimated values of the blood pump flow rate in bovines implanted with the product.

In the hemolysis test, the hemolysis level when the blood pump was driven for 6 hours to feed blood was evaluated. The result showed that the hemolysis level during normal operation was lower compared to the level observed with an approved blood pump (P = 0.0003, one-way analysis of variance). Since a mechanical seal is used as a shaft seal in EVAHEART, the effect of the leakage of the cool seal fluid to the blood circuit side by a sudden shaft seal failure was also evaluated as a potential risk. When EVAHEART had a gradual leakage of the cool seal fluid for 6 hours, the mean increase in plasma free haemoglobin was about half that of an approved product. This indicates that the hemolysis level is sufficiently low even when the potential risk is considered. Therefore, the safety of the cool seal system against hemolysis was assured.

In the study on the effect of the stoppage of the cool seal system on the blood pump, the cool seal system was continuously halted for 48 or 120 hours when EVAHEART was run in bovines. The result showed that the pump operated normally without thrombus formation in its inside for at least 48 hours after the cool seal system was halted. Therefore, the applicant considers that the stoppage of the cool seal system for any reason will have no clinical effect on the patient as long as it is repaired or replaced etc., in 48 hours.

The anatomical fitting test was performed to observe the anatomical condition of the internal components as positioned in cadavers according to the specified implantation procedure and thereby determine the appropriateness of the implantation procedure and shape/dimensions of the internal components. The result showed that the product can be implanted in patients with body surface area (BSA) of approximately 1.4 m^2, and that the product has almost no concerns in terms of anatomical fitting.

PMDA reviewed and accepted the data on the usage method.

6. Risk analysis
Documents summarizing the risk management system and its implementation status in reference to ISO14971, which is a standard on the application of risk management to medical devices, were submitted.

PMDA reviewed and accepted the risk analysis data.

7. Manufacturing process
Data on sterility assurance level, sterilization parameters, and residual ethylene oxide were submitted as sterilization method information.

PMDA reviewed and accepted the data on the manufacturing process.

8. Clinical data

The data on the pilot and pivotal study results were submitted. The data on the extended pilot and pivotal study results were also submitted as reference data.

[Pilot study]

The pilot study was designed to use the product for the first time in humans to improve and maintain the blood circulation for candidates of cardiac transplantation, and thereby confirm the safety and efficacy of the product and evaluate the feasibility of a pivotal study.

This was a single-arm, open-labeled study. Adverse events and malfunctions were evaluated for the safety of the product. The primary efficacy endpoint was the survival at 3 months with the product (survival to cardiac transplantation for subjects who received cardiac transplantation in less than 3 months after implantation). The secondary efficacy endpoints were (1) the improvement of cardiac function to the NYHA functional class I or II at 3 months after implantation, (2) maintenance of cardiac index of $\geq$2.5 L/min/m^2 at 1 week after implantation and later, (3) reduced dependence on cardiovascular agents, (4) decreased central venous pressure, (5) improved functions of major organs (the liver, kidneys, respiratory system, nervous system), and (6) improvement of QOL. Three subjects were enrolled, implanted with the product, and analyzed. This study was performed with an observation period of 3 months at 2 medical institutions in Japan.

Efficacy results are shown in Table 1. For safety, adverse events for which a causal relationship to the product cannot be denied are shown in Table 2. As for malfunctions, 1 event of fracture of the L-connector of the external monitor connecting cable and 1 event of fracture of the connecting part of the external monitor connecting cable occurred, but resulted in no trial-related injury. Mechanical device failures that affect the driving performance and function of the blood pump or complications including haemolysis, thromboembolism, infections, major organ disorder, and neurological dysfunction, which are important for the safety evaluation of the product, did not occur.

Table 1. Efficacy results (pilot study)

Endpoint	Results
Primary endpoint Survival at 3 months with EVAHEART (survival to cardiac transplantation for subjects who received cardiac transplantation in less than 3 months after implantation)	All the 3 subjects survived with EVAHEART at 3 months after implantation.
Secondary endpoint (1) Improvement of cardiac function to the NYHA functional class I or II at 3 months after implantation	All 3 subjects were classified into the NYHA functional class IV before implantation. The subjects A and B were classified into class I and the subject C into class II at 3 months after implantation.
Secondary endpoint (2) Cardiac index of not less than 2.5 L/min/m^2 at 1 week after implantation and or later	All 3 subjects had a cardiac index of 2.0 L/min/m^2 or lower before implantation and at least 2.5 L/min/m^2 after implantation.
Secondary endpoint (3) Reduced dependence on cardiovascular agents	All 3 subjects used a cardiovascular agent before implantation and discontinued it within 1 month after implantation.
Secondary endpoint (4) Decreased central venous pressure	All 3 subjects had a normal central venous pressure value before catheter removal after implantation.
Secondary endpoint (5) Improved functions of major organs (the liver, kidneys, respiratory system, nervous system)	Liver: All 3 subjects had normal T-BIL, AST, and ALT values within 3 months after implantation. Kidneys: All 3 subjects recovered normal renal function within 3 months after implantation, although 1 subject each had a creatinine or BUN value that was slightly above the normal range. Respiratory system: No abnormality was observed at 3 months after implantation. Nervous system: No abnormality was observed at 3 months after implantation.
Secondary endpoint (6) Improved QOL	Three subjects showed an improving tendency of the Minnesota cardiac failure patient questionnaire score before and after implantation: subject A, 23 → 3; subject B, 22 → 0; subject C, 64 → 30.

T-BIL: Total bilirubin, AST: Aspartate aminotransferase,
ALT: Alanine aminotransferase, BUN: Blood urea nitrogen

Table 2. Adverse events for which a causal relationship to EVAHEART cannot be denied (pilot study)

Adverse event	Number of events
Arrhythmia	1
Epistaxis	1
Lightheadedness	1
Back and low back pain by blood pump cable	2
Generalised myalgia	1

[Extended pilot study (reference data)]

All 3 subjects who participated in the pilot study and achieved the endpoint at 3 months after implantation participated in the extended pilot study scheduled to continue until the marketing approval of EVAHEART would be granted. The efficacy results as of December 9, 2009 are shown in Table 3. For safety, adverse events for which a causal relationship to the product could not be denied are presented in Table 4, and malfunctions of the product are listed in Table 5. No severe malfunction or pump replacement occurred. No event leading to trial-related injury occurred.

Table 3. Efficacy results (extended pilot study, as of December 9, 2009)

Endpoint	Results
Primary endpoints 1) Survival with EVAHEART at 6 months (or survival to cardiac transplantation for subjects who received cardiac transplantation in less than 6 months) 2) Survival with EVAHEART at 12 months (or survival to cardiac transplantation for subjects who received cardiac transplantation in less than 12 months)	All 3 subjects survived with EVAHEART at 6 and 12 months after implantation. Survival rate: 100% (3/3 subjects)
Secondary endpoint (1) Improvement of cardiac function to the NYHA functional class I or II	All 3 subjects were classified into the NYHA functional class IV before implantation. All 3 subjects were classified into class I after 6 months.
Secondary endpoint (2) Cardiac index of not less than 2.5 L/min/m^2	Cardiac index was not measured in any of the subjects since the Swan-Ganz catheter was removed during the pilot study (it was considered not necessary to measure cardiac index).
Secondary endpoint (3) Reduced dependence on cardiovascular agents	All the subjects discontinued cardiovascular agents during the pilot study and did not restart them thereafter.
Secondary endpoint (4) Decreased central venous pressure	Central venous pressure was not measured in any of the subjects since the Swan-Ganz catheter was removed during the pilot study (it was considered not necessary to measure central venous pressure).
Secondary endpoint (5) Improved functions of major organs (the liver, kidneys, respiratory system, nervous system)	Liver: The measured values of T-BIL, AST, and ALT were normal. Kidneys: The renal function was normal, although the measured values of creatinine and BUN were slightly above the normal range in some subjects. Respiratory system: Normal throughout the whole period Nervous system: Normal throughout the whole period
Secondary endpoint (6) Improved QOL	Three subjects generally showed an improving tendency of the Minnesota cardiac failure patient questionnaire score from before to 6 and 12 months after implantation: subject A, 23 → 5 → 0; subject B, 22 → 0 → 2; subject C, 64 → 28 → 46.

Table 4. Adverse events for which a causal relationship to EVAHEART could not be denied (extended pilot study, as of December 9, 2009)

Adverse event	Total
Total	37 (3)
Ventricular arrhythmia	1 (1)
Nausea	2 (1)
Implant site haemorrhage (percutaneous penetration)	3 (2)
Implant site exudation	1 (1)
Implant site pain (skin penetration)	2 (2)
Vertigo	1 (1)
Suspected bacteraemia	1 (1)
Localized infection (skin penetration)	12 (3)
Heart failure tendency	1 (1)
Sepsis	4 (1)
Extradural haematoma	1 (1)
Epilepsy	1 (1)
Loss of consciousness	1 (1)
Transient ischaemic attack	1 (1)
Hypoaesthesia	1 (1)
Cerebral haemorrhage	2 (2)
Depressive symptom	1 (1)
Orthostatic hypotension	1 (1)

The numerical values indicate the number of events (number of subjects with each event).

Table 5. Malfunctions (extended pilot study, as of December 9, 2009)

Malfunctions	Extended pilot study
	N = 3
CSU FPout pressure reduced (diaphragm pump disorder)	2 (2)
CSU FPout pressure reduced (water leakage)	2 (1)
CSU abnormal driving sound	1 (1)
Poor pump cable retention of strain relief	1 (1)
Fracture of controller housing case	1 (1)
Controller rivet cover falling off	1 (1)
Difficulty in removing the controller cover (rivet pushed too deeply, fracture)	2 (1)
Deformity of controller-power supply connector	1 (1)
Loosened battery back nut	3 (2)
Fracture of battery residual capacity check button	12 (3)
Fracture of battery by fall	2 (1)
Battery connector lock mechanism disorder	1 (1)
Loosened connector between the battery cable and main body	2 (1)
Fracture of external monitor connecting cable L-connector	4 (3)
Improper indication of external monitor	2 (1)
External monitor display troubles (no indication, freeze)	4 (1)
Rupture of carrying bag handle	2 (2)
Total	43 (3)

The numerical values indicate the number of events (number of subjects with each event).

[Pivotal study]
The pivotal study was a single-arm, open-labeled study conducted at 5 Japanese medical institutions to evaluate the efficacy and safety of EVAHEART in assisting circulation function in patients with end-stage severe heart failure for whom cardiac transplantation is indicated. The primary efficacy endpoint was survival at 6 months after implantation (or survival to cardiac transplantation for subjects who received cardiac transplantation in less than 6 months after implantation). The secondary efficacy endpoints were (1) improvement of the NYHA functional classification, (2) improvement of cardiac index from before implantation (cardiac index ≥2.5 L/min/m^2), (3) reduced dependence on cardiovascular agents, (4) no decreased function of major organs (the liver, kidneys, respiratory system, nervous system), and (5) improvement of QOL. The safety of the product was evaluated for adverse events and malfunctions. Assuming a threshold survival rate demonstrating clinical usefulness at 60% and an expected survival rate of the product at 90%, a sample size of at least 16 subjects was required to prove the statistical superiority to the threshold survival rate at α (type I error) <0.05. However, the enrollment to this study was discontinued after 15 subjects were implanted with this product.

Efficacy results are shown in Table 6. For safety, adverse events for which a causal relationship to EVAHEART could not be denied are presented in Table 7. Deaths are presented in Table 8. Malfunctions are presented in Table 9. All the malfunctions were able to be handled by replacing the defective external component or accessory or by maintenance. None of the malfunctions caused trial-related injuries to subjects. No failure of the internal component occurred at all. There was no serious device failure or pump replacement.

Table 6. Efficacy results (pivotal study)

Endpoint	Results
Primary endpoint Survival with EVAHEART at 6 months (or survival to cardiac transplantation for subjects who received cardiac transplantation in less than 6 months)	None of the subjects received cardiac transplantation before 6 months. The survival rate with EVAHEART was 86.7% (13/15 subjects). The survival rate as evaluated by the Kaplan-Meier test was also 86.7% (95% CI, 69.5%-100%).
Secondary endpoint (1) Improvement of NYHA functional classification	All 15 subjects were classified into class IV before implantation. Two subjects were classified into class I,, 6 subjects into class II, 3 subjects into class III, and 4 subjects into class IV at 1 week after implantation (P = 0.0010). Nine subjects were classified into class I and 3 subjects into class II at 6 months after implantation (one of the 13 evaluable subjects was unknown for the NYHA functional classification, P = 0.0005).
Secondary endpoint (2) Improvement of cardiac index from before implantation (cardiac index ≥2.5 L/min/m^2)	All the subjects achieved the secondary endpoint (2). The mean cardiac index was improved from 1.7 ± 0.36 L/min/m^2 to 3.2 ± 0.77 L/min/m^2 from before to 1 day after implantation (P < 0.0001). Cardiac function was sufficiently improved early after implantation and the Swan-Ganz or central venous pressure catheter was removed early. The mean measured value in 7 subjects on 5 days after implantation was 2.8 ± 0.57 L/min/m^2. The measured values in 2 subjects on 7 days after implantation were 2.6 L/min/m^2 and 2.9 L/min/m^2.
Secondary endpoint (3) Reduced dependence on cardiovascular agents	All 15 subjects received a continuous infusion of a cardiovascular agent before implantation. Six subjects continued the cardiovascular agent at 2 weeks after implantation (P = 0.0039, sign test). All the subjects discontinued the cardiovascular agent before 1 month after implantation (30 ± 14 days after implantation).

Endpoint	Results
Secondary endpoint (4) No decreased function of major organs (the liver, kidneys, respiratory system, nervous system)	[1] Hepatic function The changes in hepatic function values from before to 6 months after implantation are shown below. • T-BIL: 0.97 ± 0.473 mg/dL → 0.65 ± 0.435 mg/dL (P = 0.0112) • AST: 36.7 ± 24.10 U/L → 22.4 ± 2.69 U/L (P = 0.0342) • ALT: 56.1 ± 77.28 U/L → 18.5 ± 8.32 U/L (P = 0.0034) [2] Renal function The changes in renal function values from before to 6 months after implantation are shown below. • BUN: 24.5 ± 14.97 mg/dL → 15.7 ± 4.37 mg/dL (P = 0.0342) • Serum creatinine: 1.3 ± 0.51 mg/dL → 1.0 ± 0.29 mg/dL (P = 0.0356) [3] Respiratory function Oxygen saturation was changed from 98.4% ± 1.50% to 97.7% ± 1.66% from before to 6 months after implantation (P = 0.4219). [4] Neurological function The changes in neurological function values from before to 6 months after implantation are shown below. • Mini-mental state examination (MMSE): 28.5 ± 1.36 points → 28.4 ± 2.75 points (P = 0.7500) • TMT-B test: 133.0 ± 85.32 sec. → 121.7 ± 85.23 sec. (P = 0.4375)
Secondary endpoint (5) Improvement of QOL	[1] SF-36 (MOS Short-Form 36-Item Health Survey) The changes in the evaluation items from before to 6 months after implantation are shown below. They tended to improve over time. a) Physical functioning: -2.1 ± 12.01 points → 32.5 ± 14.68 points (P = 0.0005) b) Role physical: 6.5 ± 8.92 points → 26.4 ± 18.84 points (P = 0.0010) c) Bodily pain: 39.3 ± 15.58 points → 40.7 ± 10.41 points (P = 0.9023) d) General health: 31.6 ± 10.79 points → 42.0 ± 11.25 points (P = 0.0151) e) Vitality: 31.6 ± 11.36 points → 47.4 ± 12.48 points (P = 0.0054) f) Social functioning: 18.5 ± 16.65 points → 31.9 ± 16.53 points (P = 0.0049) g) Role emotional: 24.0 ± 21.59 points → 38.5 ± 17.11 points (P = 0.1016) h) Mental health: 34.4 ± 10.81 points → 42.0 ± 11.78 points (P = 0.1016) [2] EuroQol The changes in the evaluation items from before to 6 months after implantation are shown below. They tended to improve over time. a) Utility value: 0.230 ± 0.2741 points → 0.730 ± 0.2064 points (P = 0.0010) b) Visual analogue scale: 29.3 ± 15.90 points → 62.1 ± 21.25 points (P = 0.0010)

Unless otherwise specified, P-values are based on the Wilcoxon signed rank test.

Table 7. Adverse events for which a causal relationship to EVAHEART could not be denied (pivotal study)

Adverse event		Total		
Total		41	(14)	5.99
Serious infections				
	Localised infection (skin penetration)	3	(2)	0.44
	Sepsis	1	(1)	0.15
Neurological dysfunction				
	Transient ischaemic attack	3	(2)	0.44
	Cerebral infarction	11	(7)	1.61
	Cerebral haemorrhage	7	(4)	1.02
Right heart failure				
	Right ventricular failure	1	(1)	0.15
Arterial thromboembolism excluding that of the central nervous system				
	Splenic infarction	1	(1)	0.15
Others		14	(5)	2.05

The numerical values indicate the number of events (number of subjects) and number of events/patient-year.

Table 8. Deaths (pivotal study)

Patient	Cause of death	Number of days after operation	Major adverse events during assist period	Causal relationship to the product as evaluated by investigator*
4[redacted]-year old [redacted] patient with ischemic cardiomyopathy who had a history of coronary artery bypass surgery	Cerebral haemorrhage	62	Cerebral infarction, cerebral haemorrhage	Cannot be denied
4[redacted]-year old [redacted] patient with end-stage severe heart failure associated with advanced cardiomegaly by severe cardiac sarcoidosis	Cerebral infarction	61	Cerebral infarction	Related

* The definitions and evaluation criteria for adverse events are as specified by INTERMACS (Interagency Registry of Mechanically Assisted Circulatory Support). A causal relationship to the product was evaluated for adverse events that commonly occur during mechanical circulatory assist.

Table 9. Malfunctions (pivotal study)

Malfunctions	Pivotal study
	N = 15
E-30 alarm	3 (3)
Abnormal noise from blood pump	1 (1)
CSU FP out pressure reduced (diaphragm pump disorder)	5 (4)
CSU abnormal driving sound	1 (1)
Difficulty in removing the controller cover (rivet pushed in too deeply, fracture)	2 (2)
Battery residual capacity alarm sound failure	1 (1)
Battery connector lock mechanism disorder	3 (2)
AC/DC adapter outlet-side pin deformity	1 (1)
Communication disorder (cause unknown)	1 (1)
Communication disorder (external monitor cable breakage)	1 (1)
External monitor improper indication	9 (4)
External monitor screen troubles (no display, freeze)	2 (1)
Battery inability charging	2 (1)
Total	32 (10)

The numerical values indicate the number of events (number of subjects).

[Extended pivotal study (reference data)]

Thirteen patients who participated in the pivotal study and achieved the endpoint at 6 months after implantation participated in the extended pivotal study scheduled to continue until the marketing approval of EVAHEART would be granted. One of them was excluded from efficacy evaluation based on the GCP on-site inspection results. Efficacy results are shown in Table 10. For safety, adverse events for which a causal relationship to the product could not be denied are shown in Table 11, and deaths are shown in Table 12. Malfunctions leading to trial-related injuries did not occur. Nine subjects experienced 27 malfunctions not leading to trial-related injuries, which are detailed in Table 13. Two subjects received cardiac transplantation as of December 9, 2009. They achieved cardiac transplantation after the assist of 848 and 829 days. The former subject had been treated at home and followed on an outpatient basis. The subject was able to walk independently when the subject received the transplant surgery. The system functioned normally throughout the whole assist period. No thrombus formation was observed in the removed pump. The latter subject received transplant surgery during hospitalization. The device functioned normally throughout the whole assist period. Since the blood pump was removed after cardiac transplant surgery because of the time of the arrival of the donor heart, blood coagulation was observed in the system components. Since the subject heart was removed after it was disconnected from the device, thrombus formation in the pump and inflow cannula at the ventricular apex could not be investigated. Both subjects recovered and were discharged after transplant surgery.

The Subject No.5 developed an adverse event of intestinal obstruction on October 7, 2010. The investigator reported that probably a part of the transverse to descending colon junction prolapsed from a small hole created on the peritoneum from the abdominal cavity for pump pocket drainage, and that the patient showed tendencies of recovery with conservative therapy. The applicant considered to give an instruction to create a minimum required hole on the peritoneum in preparing a pump pocket in patients who receive implantation surgery for the first time, in the implantation training at intended medical institutions.

Table 10. Efficacy results (extended pivotal study, as of December 9, 2009)

Endpoint	Results
Primary endpoint • Survival with EVAHEART at 12 months (or survival to cardiac transplantation for subjects who received cardiac transplantation in less than 12 months) • Survival with EVAHEART at 24 months (or survival to cardiac transplantation for subjects who received cardiac transplantation in less than 24 months)	The survival rate as determined by the Kaplan-Meier test was 79.4% at 1 year (95% CI, 58.7%-100%) and 72.2% at 2 years (95% CI, 49.0%-95.5%).
Secondary endpoint (1) Improvement of NYHA functional classification	All the subjects were classified into class IV before implantation. Ten subjects were classified into class I and 1 subject into class II at 1 year after implantation ($P = 0.0010$). Six subjects were classified into class I and 2 subjects into class II at 2 years after implantation ($P = 0.0078$).
Secondary endpoint (2) Improvement of cardiac index from before implantation (cardiac index ≥2.5 L/min/m^2)	(Results of pivotal study) The cardiac index was improved from 1.7 ± 0.36 L/min/m^2 before implantation to 3.2 ± 0.77 L/min/m^2 on Day 1 after implantation in all 15 subjects ($P < 0.0001$). The Swan-Ganz or central venous pressure catheter was removed early due to sufficient improvement of cardiac function early after implantation. The mean measured value in 7 subjects on 5 days after implantation was 2.8 ± 0.57 L/min/m^2. The measured values in 2 subjects on 7 days after implantation were 2.6 L/min/m^2 and 2.9 L/min/m^2.
Secondary endpoint (3) Reduced dependence on cardiovascular agents	(Results of pivotal study) All 15 subjects received a continuous infusion of a cardiovascular agent before implantation. Six subjects continued the cardiovascular agent at 2 weeks after implantation ($P = 0.0039$, sign test). All the subjects discontinued the cardiovascular agent before 1 month after implantation (30 ± 14 days after implantation).

Endpoint	Results
Secondary endpoint (4) No decreased function of major organs (the liver, kidneys, respiratory system, nervous system)	[1] Hepatic function The changes in laboratory test values related to hepatic function from before to 1 and 2 years after implantation are shown below. T-BIL: 0.97 ± 0.5 mg/dL → 0.55 ± 0.4 mg/dL (*P* = 0.0303) and 0.63 ± 0.2 mg/dL (*P* = 0.0313) AST: 36.7 ± 24.1 U/L → 23.9 ± 7.1 U/L (*P* = 0.0400) and 18.1 ± 4.6 U/L (*P* = 0.0078) ALT: 56.1 ± 77.3 U/L → 21.0 ± 10.0 U/L (*P* = 0.0391) and 16.0 ± 5.4 U/L (*P* = 0.0391) [2] Renal function The changes in laboratory test values related to renal function from before to 1 and 2 years after implantation are shown below. BUN: 24.5 ± 15.0 mg/dL → 14.7 ± 4.9 mg/dL (*P* = 0.0322) and 14.7 ± 2.9 mg/dL (*P* = 0.1953) Serum creatinine: 1.3 ± 0.51 mg/dL → 1.1 ± 0.29 mg/dL (*P* = 0.1475) and 1.1 ± 0.29 mg/dL (*P* = 0.6875) [3] Respiratory function Oxygen saturation was changed from before to 1 and 2 years after implantation as follows: 98.4% ± 1.50% → 97.7% ± 1.25% (*P* = 0.3750) and 97.7% ± 0.76% (*P* = 0.1406). [4] Neurological function The changes in mini-mental state examination (MMSE) and TMT-B test from before to 1 and 2 years after implantation are shown below. MMSE: 28.5 ± 1.4 points → 28.2 ± 3.8 points (*P* = 0.6797) and 24.5 ± 7.3 points (*P* = 0.2813) TMT-B: 133.0 ± 85.3 sec. → 219.3 ± 251.9 sec. (*P* = 0.4375) and 188.0 ± 195.8 sec. (*P* = 0.2500)
Secondary endpoint (5) Improvement of QOL	[1] SF-36 The changes in the evaluation items of SF-36 from before to 1 and 2 years after implantation are shown below. The evaluation items generally show improving tendency (*P*-values relative to respective preoperative values are shown). a) Physical functioning: -2.1 ± 12.01 points → 34.0 ± 16.73 points (*P* = 0.0020) → 27.4 ± 19.14 points (*P* = 0.0078) b) Role physical: 6.5 ± 8.92 points → 27.4 ± 16.09 points (*P* = 0.0039) → 20.5 ± 16.81 points (*P* = 0.0625) c) Bodily pain: 39.3 ± 15.58 points → 42.2 ± 13.36 points (*P* = 0.4238) → 39.6 ± 3.86 points (*P* = 0.4609) d) General health: 31.6 ± 10.79 points → 41.5 ± 9.11 points (*P* = 0.0098) → 44.7 ± 7.76 points (*P* = 0.0156) e) Vitality: 31.6 ± 11.36 points → 48.3 ± 13.22 points (*P* = 0.0029) → 52.6 ± 10.49 points (*P* = 0.0078) f) Social functioning: 18.5 ± 16.65 points → 33.2 ± 12.91 points (*P* = 0.0176) → 30.0 ± 17.01 points (*P* = 0.0625) g) Role emotional: 24.0 ± 21.59 points → 37.3 ± 19.60 points (*P* = 0.2656) → 29.0 ± 21.80 points (*P* = 1.0000) h) Mental health: 34.4 ± 10.81 points → 45.7 ± 13.86 points (*P* = 0.0254) → 47.8 ± 15.12 points (*P* = 0.1563) [2] EuroQol The changes in the evaluation items of EuroQol from before to 1 and 2 years after implantation are shown below. The evaluation items generally show improving tendency (*P*-values relative to respective preoperative values are shown). a) Utility value: 0.230 ± 0.2741 points → 0.719 ± 0.1874 points (*P* = 0.0020) → 0.596 ± 0.2254 points (*P* = 0.0156) b) Visual analogue scale: 29.3 ± 15.90 points → 67.8 ± 22.37 points (*P* = 0.0020) → 70.0 ± 18.26 points (*P* = 0.0156)

Unless otherwise specified, *P*-values are based on the Wilcoxon signed rank test.

Table 11. Adverse events for which a causal relationship to EVAHEART could not be denied (extended pivotal study, as of December 9, 2009)

Adverse event		Total
Total		93 (13)
Serious infections		
	Localised infection (skin penetration)	19 (8)
	Suspected localised infection	3 (1)
	Sepsis	3 (3)
	Suspected cholecystitis	1 (1)
Neurological dysfunction		
	Transient ischaemic attack	3 (3)
	Suspected cerebral infarction	1 (1)
	Cerebral infarction	12 (3)
	Cerebral haemorrhage	8 (6)
Arrhythmia		
	Arrhythmia supraventricular	1 (1)
Others		42 (10)

The numerical values indicate the number of events (number of subjects).

Table 12. Deaths (extended pivotal study, as of December 9, 2009)

Patient	Cause of death	Number of days after operation	Major adverse events observed during assist period	Causal relationship to the product as evaluated by investigator*
5[redacted]-year old [redacted] patient with dilated cardiomyopathy	Cerebral haemorrhage	297	Cerebellar haemorrhage, dysphoria, queasy, vomiting, cerebral infarction	Cannot be denied
1[redacted]-year-old [redacted] patient with dilated cardiomyopathy	Sepsis	407	Acute right heart failure, cardiac arrest, cardiac tamponade, encephalopathy, multi-organ failure	Unrelated (CV catheter infection after post-resuscitation encephalopathy)
4[redacted]-year-old [redacted] patient with ischemic cardiomyopathy	Cerebral haemorrhage	561	Skin penetration infection, gastric perforation, sepsis, consciousness disturbed	Cannot be denied

* The definitions and evaluation criteria for adverse events are as specified by INTERMACS. A causal relationship to the product was evaluated for adverse events that commonly occur during mechanical circulatory assist.

Table 13. Malfunctions (extended pivotal study, as of December 9, 2009)

Malfunctions	Extended pivotal study
	N = 13
E-30 alarm frequent issuance	1 (1)
Pump cable large vibration	1 (1)
CSU FPout pressure reduced (diaphragm pump disorder)	8 (5)
CSU FPout pressure reduced (water leakage)	2 (2)
CSU abnormal driving sound	4 (2)
Controller LCD poor visibility	1 (1)
Controller emergency battery lamp failure	1 (1)
Battery connector lock mechanism disorder	3 (3)
Battery cable ID signal line breakage	1 (1)
AC/DC adapter outlet-side pin deformity	1 (1)
AC/DC adapter connector fracture	3 (3)
Carrying bag handle rupture	1 (1)
Total	27 (9)

The numerical values indicate the number of events (number of subjects).

The situations of patients including their outcome, place of stay, and transplantation waiting status as of December 9, 2009 are summarized for 18 subjects from the pilot and pivotal studies (evaluation data) and extended studies (reference data) in Table 14. The mean assist period of the product was 773.0 ± 432.1 days (mean ± standard deviation). The cumulative assist period of the product was 13,914 days. For efficacy, estimated survival rate as determined by the Kaplan-Meier test based on the data on December 9, 2009 is shown in Figure 2. The situations as of October 19, 2010 are also shown in Table 15 for reference. The mean assist period of the product was 924.1 ± 526.1 days (mean ± standard deviation). The cumulative assist period was 16,634 days. Subject No. 10 died of sepsis most likely caused by aspiration pneumonia after cerebrovascular disorder (a causal relationship to the product could not be denied).

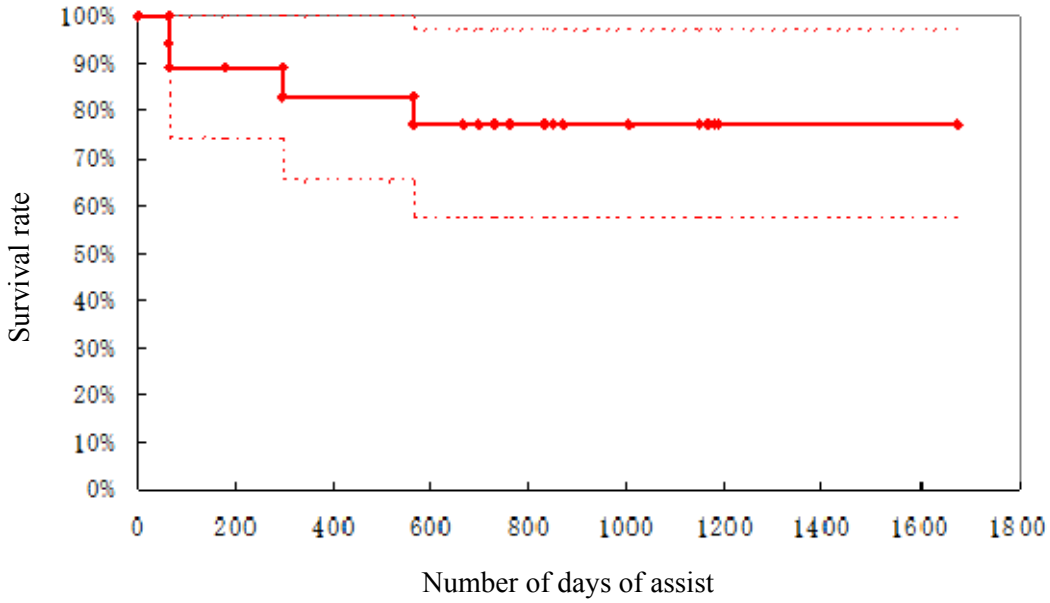
Table 14. Situations of patients from pilot, pivotal, and their extended studies (as of December 9, 2009)

No	Patient			Outcome	Number of days of assist	Place of stay	Cumulative number of days after discharge	Remarks
	Age	Sex	BSA					
1	4[redacted]	[redacted]	1.97	Being assisted	1677	Home	1382	Returned to work
2	2[redacted]	[redacted]	1.59	Transplanted	1164	Discharged after transplantation	653	
3	4[redacted]	[redacted]	1.54	Transplanted	1145	Discharged after transplantation	483	
4	5[redacted]	[redacted]	1.72	Transplanted	848	Discharged after transplantation	519	
5	3[redacted]	[redacted]	1.77	Being assisted	1188	Home	991	Returned to work, [redacted]
6	4[redacted]	[redacted]	1.45	Being assisted	1181	Rehospitalized	231	
7	4[redacted]	[redacted]	2.11	Death	62	—	0	
8	5[redacted]	[redacted]	1.46	Death	297	Returned home and died	7	
9	1[redacted]	[redacted]	2.01	During assist Death	180 407	—	0	Efficacy evaluated until the pivotal study
10	5[redacted]	[redacted]	1.63	Being assisted	1004	Rehospitalized	344	
11	4[redacted]	[redacted]	1.48	Death	561	Returned home and died	5	
12	5[redacted]	[redacted]	1.63	Being assisted	870	Home	403	Preparing for return to work
13	4[redacted]	[redacted]	1.77	Transplanted	829	Being hospitalized for transplantation	90	
14	4[redacted]	[redacted]	1.55	Death	61	—	0	
15	5[redacted]	[redacted]	1.64	Being assisted	758	Home	655	Returned to work
16	2[redacted]	[redacted]	1.57	Being assisted	726	Rehospitalized	426	Preparing for return to work
17	2[redacted]	[redacted]	1.71	Being assisted	699	Home	445	Returned to university
18	5[redacted]	[redacted]	1.76	Being assisted	664	Home	456	

Table 15. Situations of patients including pilot, pivotal, and their extended studies (as of October 19, 2010)

No	Patient			Outcome	Number of days of assist	Place of stay	Cumulative number of days after discharge	Remarks
	Age	Sex	BSA					
1	4[redacted]	[redacted]	1.97	Being assisted	1991	Home	1679	Returned to work
2	2[redacted]	[redacted]	1.59	Transplanted	1164	Discharged after transplantation	653	
3	4[redacted]	[redacted]	1.54	Transplanted	1145	Discharged after transplantation	483	
4	5[redacted]	[redacted]	1.72	Transplanted	848	Discharged after transplantation	519	
5	3[redacted]	[redacted]	1.77	Being assisted	1502	Rehospitalized	1114	Returned to work, [redacted]
6	4[redacted]	[redacted]	1.45	Being assisted	1495	Home	328	
7	4[redacted]	[redacted]	2.11	Death	62	—	0	
8	5[redacted]	[redacted]	1.46	Death	297	Returned home and died	7	
9	1[redacted]	[redacted]	2.01	During assist Death	180 407	—	0	Efficacy evaluated until the pivotal study
10	5[redacted]	[redacted]	1.63	Death	1257	Returned home and died	344	
11	4[redacted]	[redacted]	1.48	Death	561	Returned home and died	5	
12	5[redacted]	[redacted]	1.63	Being assisted	1184	Home	717	Preparing for return to work
13	4[redacted]	[redacted]	1.77	Transplanted	829	Discharged after transplantation	90	
14	4[redacted]	[redacted]	1.55	Death	61	—	0	
15	5[redacted]	[redacted]	1.64	Being assisted	1072	Home	969	Returned to work
16	2[redacted]	[redacted]	1.57	Being assisted	1040	Rehospitalized	663	Preparing for return to work
17	2[redacted]	[redacted]	1.71	Transplanted	968	Being hospitalized for transplantation	698	
18	5[redacted]	[redacted]	1.76	Being assisted	978	Home	738	

Figure 2. Estimated survival rate (as of December 9, 2009)



Time point	Survival rate	95% CI
6 months	88.89	74.37-100.0
1 year	82.96	65.37-100.0
2 years	77.04	57.23-96.84
3 years	77.04	57.23-96.84

PMDA asked the applicant to explain the following points. Since the information on the adverse event of intestinal obstruction on October 7, 2010 was limited, the applicant was instructed to continuously collect information, analyze the cause, and take necessary measures.

1. The enrollment of subjects was discontinued before the planned number of subjects was enrolled in the pivotal study. PMDA considered it inappropriate to evaluate the clinical efficacy and safety of the product using the data from this pivotal study with lower number of subjects than the initial plan. Justify the evaluation of the efficacy and safety of the product using data from the discontinued study for analysis.

2. Justify appropriateness of the evaluation at 6 months after implantation in consideration of the long waiting period for cardiac transplantation in Japan.

3. Justify the specified range of BSA for patients for whom the product is indicated.

4. Explain the causes of, and preventive measures against, neurological dysfunction.

5. Explain an appropriate home therapy program.

6. Malfunctions observed during the studies were explained, but explain what measures were taken against the malfunctions and justify the measures as well.

The applicant responded as follows:

1. It became impossible to prospectively perform the planned statistical evaluation since the enrollment in the pivotal study was discontinued after 15 subjects were enrolled. It should be noted that the number of Japanese patients for whom an implantable ventricular assist device is indicated is essentially small, and it is difficult to prove the efficacy statistically. In the pivotal study, the planned number of subjects could not be enrolled before the original enrollment deadline. Although the deadline was extended twice, one more subject was still needed to satisfy the planned number. The applicant therefore determined that, even when no statistical significance could be eventually demonstrated, "the final evaluation of the safety and efficacy of the investigational device using the clinical study data are to be performed based on the general consideration of clinical significance taking into account not only the statistical analysis data, but also comparative literature review as possible," as specified in the protocol of the pivotal study. The applicant considered that sufficient data were available for evaluating the clinical significance and usefulness of the product, based on the comprehensive evaluation of the study results from all of the 18 subjects available so far. The "Publication of Guidance for the Evaluation of Emerging Technology Medical Devices" (PFSB/ELD/OMDE Notification No. 0404002 from Office of Medical Device Evaluation, Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau dated April 4, 2008) states that "considering the past experience in Japan, the appropriate number of subjects would be around 5 for a pilot study to examine safety and 15 for a pivotal study for the time being.". The number of subjects implanted with EVAHEART in the pivotal study was 15, which agrees with the notification.

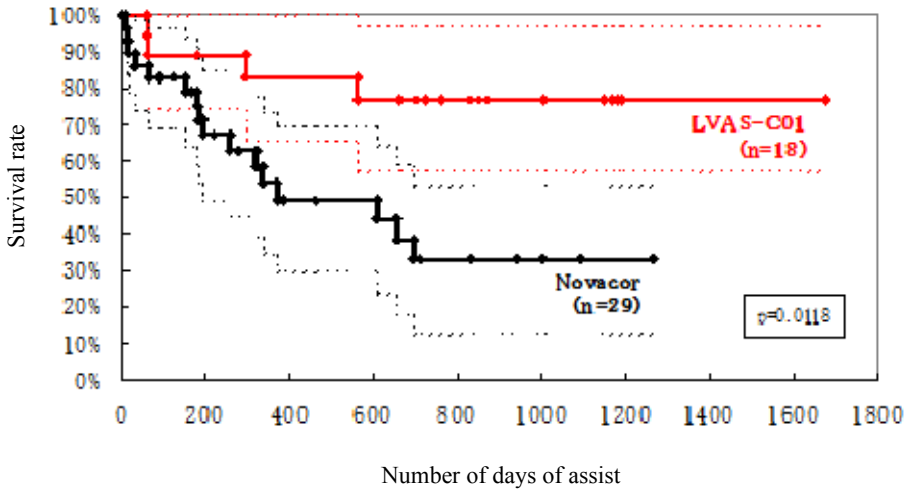
2. The ventricular assist period before cardiac transplantation is 4 to 6 months, on average, in the United States and Europe, while at least an average of 2 years of ventricular assist has to be anticipated in Japan. Therefore, the applicant considered it necessary to examine EVAHEART for not only survival up to 6 months, but also safety and usefulness for a longer term as the endpoint even if it is used as a bridge to transplantation. Although the number of subjects was small in the pilot and pivotal studies, the product provided favorable results for more than 6 months. All of the three subjects in the pilot study survived for more than 3 years under the ventricular assist with the product. The data in the US INTERMACS as of March 31, 2008 showed a 6-month survival rate of 71% and a 1-year survival rate of 56%. Although it is difficult to directly compare the results of EVAHEART with the INTERMACS data because of the differences in the indications of ventricular assist devices, the applicant determined that EVAHEART has provided favorable clinical results. Further, when the survival rate of EVAHEART as determined by the Kaplan-Meier test is compared with that of Novacor from the registry of its clinical study in Japan (the data was provided by the sponsor of Japanese clinical study of Novacor), the lower limit of the 95% confidence interval of the survival rate of EVAHEART is not lower than that of Novacor at 6 months or later (Figure 3). In addition, the lower limit of the 95% confidence interval of the survival rate of EVAHEART is not lower than that of Novacor at 6 months or later, irrespective of whether the subject who withdrew consent to the study and/or the subject who developed gastric perforation during the extended pivotal study are included in the analysis or not.

For safety, the information on adverse events in 6 subjects in the Japanese clinical study of Novacor was able to be obtained. The mean implantation period was 232.5 ± 127.3 days (65-392 days). A total of 16 adverse events occurred during the period, including 2 events of haemorrhage (reoperation) in 2 subjects, 9 neurological events in 4 subjects (6 events of cerebral infarction by thromboembolism, 3 events of cerebral haemorrhage), 3 events of infection in 3 subjects, 1 event of function kidney decreased in 1 subject, and 1 event of ileus adhesive in 1 subject. Classifying the adverse events by causes showed that 4 adverse events were related to patients (not related to the device, surgical procedures, or postoperative management) and 12 adverse events were related to the surgical procedures or postoperative management. None of the adverse events (malfunctions) were related to the device. Three

subjects died from thromboembolism, intra-cerebral haemorrhage, and necrotizing cholecystitis and sepsis (1 subject each). These deaths were judged not related to the device. In addition, 1 subject died of the aggravation of pocket infection after the device was removed. Although it is difficult to compare such adverse events occurred for Novacor to EVAHEART due to the differences in the number of subjects, definitions of adverse events, and evaluation for causal relationship to devices etc., it should be noted that EVAHEART functioned normally at the specified pump rotational speed in all the subjects throughout the study period without causing any severe malfunction and pump replacement or trial-related injury by mechanical failure.

Based on these results, the applicant considered that EVAHEART was not inferior to the approved product.

Figure 3. Comparison of results of EVAHEART (as of December 9, 2009) and those of Novacor in Japan



Solid lines: survival rate, Dash lines: 95% confidence interval, *P*-value: Log-Rank test
LVAS-C01 in this figure refers to EVAHEART.

3. An exclusion criterion of BSA <1.4 m^2 was specified since the anatomical fitting test before the clinical studies confirmed that EVAHEART is able to be smoothly implanted in cadavers with a height of 157 to 160 cm and a weight of 43 to 45 kg (corresponding to BSA of 1.4 m^2) (the results of the test are submitted in "Studies to support usage method"). For an information, the same exclusion criterion of BSA <1.4 m^2 was used in the Japanese clinical study of Novacor, which has about 3 times as large volume as EVAHEART. BSA serves as a guide for selecting patients who have a sufficient insertion space for such an implantable medical device as EVAHEART. However, the application of an implantable medical device cannot be decided by BSA alone. It is possible that an appropriate implantation space can not be secured in a patient with BSA of above 1.4 m^2 and vice versa. In the clinical study, a subject with BSA of about 1.4 m^2 developed gastric perforation, which might have resulted from the combination of the continuous compression of a specific site in the stomach, thin peritoneal and diaphragmatic tissue, and being in a supine position for a long time. Before the product is implanted, the sufficiency of the implantation space should be determined based on the general consideration of physical constitution and BSA. In addition, the applicability of the product should be carefully considered. Therefore, the following statement was added to Contraindications section of the instructions for use: "Patients considered not suitable for implantation by the general decision of an experienced physician on the basis of patient's

physical constitution, BSA, and anatomical conditions of the intended implantation site." The subject died of cerebral haemorrhage, and the applicant considered it to be an effect of anticoagulant therapy or secondary hemorrhage to thromboembolism and not directly related to gastric perforation.

4. Appropriate anticoagulant/antiplatelet therapy is essential during the use of EVAHEART, but excessive or insufficient anticoagulant/antiplatelet therapy may cause cerebrovascular disorder including cerebral infarction and cerebral haemorrhage or neurological dysfunction including transient ischemic attack. At the beginning of the clinical study, anticoagulant/antiplatelet therapy in accordance with that for patients with an artificial mechanical heart valve was recommended as a reference prescription and the actual prescription was to be prescribed depending on each study institution. However, since a subject died of cerebral haemorrhage possibly resulting from a different prescription from the reference prescription, a prescription for anticoagulant/antiplatelet therapy was established according to the recommendations of the Efficacy and Safety Assessment Committee on January 5, 2007. Table 16 shows the incidence of neurological dysfunction in 5 and 10 subjects implanted with the product before and after January 5, 2007 in the pivotal study, respectively. Table 17 shows the comparison of neurological dysfunction excluding 11 subjects who had no functional sequelae. These results indicate that the incidence of neurological dysfunction was reduced after the establishment of the prescription.

Table 16. Comparison of neurological dysfunction before and after establishment of anticoagulant/antiplatelet therapy prescription (1) (pivotal study)

Symptom		**Before establishing prescription** (5 subjects)			**After establishing prescription** (10 subjects)			**Total** (15 subjects)		
		2.17 patient-years			4.67 patient-years			6.84 patient-years		
Neurological dysfunction		15	(5)	6.91	6	(4)	1.28	21	(9)	3.07
	Transient ischaemic attack	2	(1)	0.92	1	(1)	0.21	3	(2)	0.44
	Cerebral embolism	7	(4)	3.22	4	(3)	0.86	11	(7)	1.61
	Cerebral haemorrhage	6	(3)	2.76	1	(1)	0.21	7	(4)	1.02

The numerical values indicate the number of events (number of subjects), and number of events/patient-year.

Table 17. Comparison of neurological dysfunction before and after establishment of anticoagulant/antiplatelet therapy prescription (2) (excluding events not associated with functional sequelae) (pivotal study)

Symptom		**Before establishing prescription** (5 subjects)			**After establishing prescription** (10 subjects)			**Total** (15 subjects)		
		2.17 patient-years			4.67 patient-years			6.84 patient-years		
Neurological dysfunction		9	(2)	4.14	1	(1)	0.21	10	(3)	1.46
	Transient ischaemic attack	0	(0)	0.00	0	(0)	0.00	0	(0)	0.00
	Cerebral embolism	4	(2)	1.84	1	(1)	0.21	5	(3)	0.73
	Cerebral haemorrhage	5	(2)	2.30	0	(0)	0.00	5	(2)	0.73

The numerical values indicate the number of events (number of subjects), and number of events/patient-year.

The possible effect of the blood pump rotational speed on the development of neurological dysfunction was examined by investigating the relationship between the blood pump rotational speed and development of cerebrovascular disorder in 2 years after implantation. Although no

deviation from the specified anticoagulant/antiplatelet therapy occurred after the prescription was established, one subject died of sepsis after repeated cerebral infarctions. The autopsy of the subject showed circumferential thrombi around the intraventricular portion of the inflow cannula. Based on the autopsy results, the applicant estimated that the tip of the expanded thrombus might have been drawn into the cannula. In an autopsy of another subject who died of multiple cerebral infarctions, the thrombus formed around the cannula (wedge thrombus) overrode the cannula. Histopathological examination to identify the source of the emboli detected at cerebral infarctions showed that cerebral infarctions were likely resulted from the thrombi formed in the left ventricle.

Thus, the possibility should be considered that the formation of the wedge thrombus around the inflow cannula in the left ventricle may be promoted by an unknown factor, and the thrombus may be drawn into the cannula, resulting in cerebrovascular disorder in subjects who were considered well-controlled by appropriate anticoagulant/antiplatelet therapy. The factors promoting the formation of the wedge thrombus around the cannula may include not only the predisposition to thrombus formation and poor control of anticoagulant/antiplatelet therapy, but also the congestion of blood flow at the root of the inflow cannula in the ventricle. An investigator reported that varying the pump rotational speed did not result in a large difference in the blood flow rate of the pump, but that setting the rotational speed at a high level increased the strength to draw blood flow in the pump, leading the blood to congest at the root of the cannula in the ventricle. The optimum rotational speed of the blood pump may depend on the shape of the heart, physical constitution, hemodynamics, primary disease, and severity of heart valve insufficiency etc. Therefore, the applicant discussed the frequency of cerebrovascular disorder in case of rotation of ≥2000 rpm and <2000 rpm for convenience. A COX regression analysis including the time to the development of cerebrovascular disorder was performed using adjustment factors including sex, age, primary disease, and number of subjects in whom anticoagulant/antiplatelet therapy was poorly controlled at the beginning of the study. The result showed the frequency of cerebrovascular disorder was higher at ≥2000 rpm compared to <2000 rpm (Table 18). The applicant therefore planned to notify at the time of post-marketing, in the operating instructions and during training that increasing the pump rotational speed to an unnecessarily high level may cause blood flow congestion at the root of the inflow cannula to stimulate wedge thrombus formation.

Table 18. Analysis on development of cerebrovascular accidents (CVA) (COX regression analysis) (Analytical results at 2 years after implantation in all 18 subjects)

Pump rotational speed [rpm]	**Subjects with CVA** (N)	**Subjects without CVA** (N)	**Before adjustment**		**After adjustment**	
			***P*-value**	**Hazard ratio**	***P*-value**	**Hazard ratio**
< 2000	7	5	0.3138	1.811	0.0250	6.128
≥ 2000	5	1				

5. Appropriate home therapy program

The home therapy program employed in the clinical studies is described below. To ensure the smooth transition to home therapy, trained healthcare professionals provided patients and their families (caregivers) with in-hospital and out-of-hospital trainings before home therapy (discharge). In the in-hospital training, patients and caregivers were trained to appropriately handle the device, care for the skin penetration site, shower, actions taken in case of emergency, and other necessary things during home therapy. The effect of the training was evaluated using paper and practical tests. In the out-of-hospital training, they were trained to deepen the understanding on precautions for daily life activities during home therapy by a step-by-step

approach; going out with a healthcare professional (Step A), going out without a healthcare professional (Step B), returning home for a brief visit with a healthcare professional (Step C), and staying out of hospital on a trial basis without a healthcare professional (Step D). The effect of the training was evaluated by healthcare professionals.

Since EVAHEART is used on a 24-hour basis, there is no major problem with maintaining the educational effect of the training for activities performed every day, such as power supply control and care for the skin penetration site. Healthcare professionals have opportunities to give necessary guidance related to the use of the device during home therapy by observing the skin penetration site, inspecting the appearance of the device components including fracture, and checking the event and trend data stored in the controller at the clinical visits of patients. The investigators have to comprehensively evaluate the condition of life, compliance with rules, and physical condition of patients during home therapy to determine whether home therapy can be continued or not. They also have to maintain the educational effect of the training by re-hospitalizing patients for re-training, as required. The applicant planned that patients and caregivers will be trained for the actions to be taken in case of emergency at periodic clinical visits at necessary intervals (at least once a year) depending on their understanding on the actions since they may forget the actions if no alarm or malfunction occurs for a long period of time. Patients discharged for home therapy have experienced no serious malfunction or accident by the improper use of the device. In addition, patients who experienced sudden change in the condition have been successfully taken to the hospital by ambulance, and these results demonstrate the effectiveness of the training of the home therapy program used in the clinical studies.

The following problems were observed during the home therapy in the clinical studies. (1) The initial response to the development of symptoms was delayed in 1 subject. Although the emergency contact at the hospital was established and the subject was instructed on the actions to be taken in case of emergency, the subject failed to report subjective symptoms of cerebrovascular disorder to the hospital. It was possible that cerebral haemorrhage might have constituted the prognosis exacerbating factor. The report to the hospital may have delayed since the subject/caregiver did not recognize the symptoms as a sign of cerebrovascular disorder and they decided to wait since it occurred at night. For prevention, a sticker listing the symptoms of neurological dysfunction in simple words was distributed, and patients were instructed to immediately call the hospital at any time if any symptom in the list occurred. (2) Patients were not sufficiently supported at the workplace or school. The home therapy program was intended to support the return home from the hospital. In reality, however, some patients returned to work or school. Although it was specified that a family member should serve as a caregiver, it was practically impossible for the caregiver to always accompany the patient at the workplace or school. Therefore, the investigator visited the workplace or school to instruct their colleagues or friends on how to take actions against emergencies including the issuance of alarms and stoppage of the blood pump. The applicant plans that, after the marketing of the product, physicians will not be required to accompany patients at the workplace or school, and that the home therapy program will be performed at the discretion of each medical institution, considering the personnel and financial burdens of the medical institution and patient safety. (3) The home therapy program imposed a burden on healthcare professionals. The home therapy program required healthcare professionals to accompany patients while they went out of the hospital or returned home for a brief visit during the out-of-hospital training before discharge. Healthcare professionals checked the compliance with the requirements for home therapy during the return home. Therefore, the program imposed a strong burden on healthcare professionals due to various reasons including the trips to and from the patient house, compliance check at the patient's house, and long on-duty hours. The applicant plans that, after the marketing of the product, the home therapy program will be performed at the discretion of each medical institution considering the personnel and financial burdens of the medical

institution and patient safety by, for example, allowing the medical institution to contract out non-medical tasks except for medical tasks by healthcare professionals to third parties or patient family members.

6. The following measures were taken against all the malfunctions that occurred during the clinical studies. The malfunctions were classified into categories such as those for which measures to reduce recurrence risk including design change were taken and those for which risk reduction measures were taken by modifying Precautions. No similar malfunction recurred after the following measures were taken. Hence, the applicant considered that the measures taken were appropriate.

Table 19. Malfunctions for which measures to reduce recurrence risk were taken by design change

Malfunction	Description	Measures taken etc.
Controller rivet cover falling off	A rivet cover fell off the controller case.	An adhesive was added to fix a rivet cover to the controller case.
Difficulty in removing the controller cover (rivet pushed in too deeply, fracture)	Since a rivet was pushed in too deeply, the controller cover could not be removed.	A dedicated tool (maintenance part) to manipulate the rivet to open the controller cover was developed. A caution about this malfunction was included in the instructions for use to call attention to this.
Battery residual capacity alarm sound failure	The controller issued an alarm to warn that the battery connected to Battery 2 was running out. The controller then automatically switched power supply from Battery 2 to 1. After this switch, the controller no longer generated any audible sound of the alarm to warn that Battery 2 was running out.	Software bugs were corrected. The controller functions to detect abnormality and issue alarms were verified (controller function confirmation test) to confirm the effectiveness of the measure.
Controller emergency battery lamp failure	Because of the poor contact between the part and base plate, the emergency battery lamp was not activated even when the button was pushed.	The materials of the contact part were changed.
Battery back nut loosening	A back nut of the battery connector (L-connector) was loosened.	An adhesive was added to fix the back nut, thereby preventing loosening. The same measure was taken to the cool seal cable connector of the controller, which uses the same L-connector.
Battery residual capacity check button fracture	The repeated stress on the residual capacity check button produced a folding line on the button cover seat, resulting in a fracture.	The material for the residual capacity check button sheet was changed.
Loosened connector connecting battery cable and main body	The connector connecting the battery cable and battery main body was loosened.	An adhesive was added to fix the connector, thereby preventing the loosening.
External monitor cable L-connector fracture	A force applied to the external monitor cable L-connector on the controller side damaged the connector.	Connector shape was changed. The lock mechanism was removed.
External monitor cable connector fracture on the external monitor side	The fixation screw of the external monitor cable connector on the external monitor side was fractured since it was tightened too much with a screwdriver.	The screw fixation for the connector was removed.
Communication failure (external monitor cable breakage)	The communication between the external monitor and controller failed because of poor soldering in the external monitor cable connector on the external monitor side.	Check steps were added in the manufacturing process.

Malfunction	Description	Measures taken etc.
Frequent issuances of E-30 alarm	The E-30 alarm warns that the automatic restoration mechanism has been activated to automatically restart the blood pump and return the pump rotational speed to the preset level in case of the loss of synchronism phenomenon. Therefore, the alarm does not indicate any hazard. This event was the frequent issuances of the alarm in a certain period (3 events in 3 subjects).	Appropriate maintenance was performed including the cleaning of the cool seal fluid path as needed. The device has been operating stably without recurrence of the malfunction in all the subjects since the last issuance of the E-30 alarm. To reduce the frequency of the loss of synchronism, preventive measures were taken to the blood pump and controller by the revision of the magnetic flux density specifications of the magnet in the blood pump rotor case and the improvement of the ability to follow the rotation of the rotor by changing the constant of the control of the blood pump rotational speed by the controller.
CSU FPout pressure reduced (diaphragm pump disorder)	A CSU had to be replaced before the periodic replacement at intervals of 3 months since the disorder of the diaphragm pump reduced the FPout pressure.	A preventive measure against excessive stress to the diaphragm pump during the manufacturing process was taken.
CSU FPout pressure reduced (water leakage)	Water leakage occurred from a crack produced when force was applied to the conduit connecting the collection port and reservoir of the CSU, and from a urethane molded part of the filter.	Preventive measures against water leakage were taken including the increased thickness of the conduit connecting the collection port and reservoir and addition of a process in which the urethane molded part of the filter is repeatedly coated with urethane.
Controller liquid crystal display (LCD) poor visibility	The LCD of the controller indicating the pump rotational speed and event code in case of alarm issuance had scratches due to the friction with the carrying bag for the controller (not included in the present submission), resulting in poor visibility.	A preventive measure against poor visibility was taken by applying a protective film to the LCD.
External monitor improper indication	The external monitor indicated improper signals including an alarm not issued actually due to transient communication failures between the external monitor and controller (the possible cause is the poor contact at the connector due to the disconnection/reinsertion, vibrations, and pulling of the external monitor cable.).	Software was improved to prevent improper indications in case of communication failures and was validated. This event was a communication failure between the external monitor and controller and did not affect other functions.
External monitor screen trouble	The external monitor screen was frozen.	Software was modified so that it would warn on the monitor screen that the communication from the controller was stopped. Software was also modified by adding functions to detect double activation and shut down the controller without causing double activation.

Table 20. Malfunctions for which risk reduction measures were taken by modifying Precautions

Malfunctions	Description	Measures taken
Strain relief pump cable retention failure	The strain relief of the controller connection kit that connects and fixes the pump cable to the controller was loosened, resulting in a pump cable kink.	The instructions for use were revised to include the caution to check the strain relief for loosening as a routine check and tighten the strain relief, as required.
Controller exterior case fracture	A crack occurred at the bottom of the controller exterior case.	The instructions for use were revised to include cautions not to give any strong impact or vibration to the controller and replace the controller with a new one as early as possible if any damage, such as a crack, was detected.
Controller power supply connector deformity	Since the connector was not inserted straight, the resin part of the controller power supply connector was partially deformed.	The instructions for use were revised to include cautions on how to handle connectors including the power supply connector.
Battery fracture by drop	The battery was dropped several times and the battery case was damaged, although the battery function was not affected at all.	The instructions for use were revised to include a caution not to give any strong impact to each component of the device, such as dropping it.
Battery connector lock mechanism failure	After the battery connector was repeatedly inserted and removed, the lock mechanism of the battery connector failed due to deformity of the part involved in the mechanism.	The instructions for use were revised to include cautions on how to handle connectors including the power supply connector.
Battery cable ID signal line breakage	When a battery that had been used for a long time was fully charged and lifted while it was connected to the charger, the flashing of the charge lamp indicating the completion of the charge was stopped.	The instructions for use were revised to include cautions on how to handle the battery cable.
AC/DC adapter connector fracture	The AC/DC adapter connector had not been inserted and removed straight while it was repeatedly used for a long time. As a result, the connector had fractures, such as deformity of the pin.	The instructions for use were revised to include cautions on how to handle connectors including the power supply connector.
Charger charge failure	A diode element in a charger failed, resulting in the inability to charge a battery.	The instructions for use were revised to include a caution not to place the controller, battery, AC/DC adapter, charger, or pump cable near heating appliances or other devices that generate heat.

Table 21. Other malfunctions

Malfunctions	Description	Measures taken
Abnormal noise from blood pump	The blood pump produced an intermittent abnormal noise for a certain period.	Subsequently, the blood pump operated in a stable manner without producing any abnormal noise. Although the abnormal noise might be generated at the mechanical seal or bearing, the quality data of the pump parts showed no abnormality and the cause of the noise could not be identified. This event was considered to be a malfunction since the subject complained of it. However, the applicant now considers that this event was not a failure or a predictor of a failure.
Increased vibration of pump cable	The pulsation of the cool seal fluid is inevitable since the CSU uses the pulsatile diaphragm pump to circulate the cool seal fluid. The subject felt that the vibration of the pump cable by the pulsation was too large.	This event occurred once in a specific subject and was handled by replacing the CSU. Other subjects reported that they felt the vibration, but were not concerned by it. Therefore, it seemed that the individual difference in the CSU or perception of the subjects might be related to this event. This event was considered to be a malfunction since the subject complained of discomfort. However, it raises no safety concerns.
Abnormal operating noise from the CSU	The operating sound of the CSU is structurally inevitable since it uses the pulsatile diaphragm pump to circulate the cool seal fluid. The operating sound was considered abnormal since the subject felt it to be too loud or noisy.	Although there is an individual difference in the perception of the operating sound by subject, a sound pressure specification was set for the diaphragm pump operating sound as a measure to reduce it, and the pump producing sound pressure below the specification limit was used. The operating sound of the CSU may become too loud when the controller is placed on a table or floor that may reflect the sound. However, the sound can be reduced by placing the controller in the carrying bag, away from the head while sleeping, or on a soft pad such as a cushion. This event was considered to be a malfunction since the subject complained of discomfort. However, it raises no safety concerns.
AC/DC adapter pin deformity on the outlet side	Two events of pin deformity occurred. One event occurred when the plug head of the AC/DC adapter was caught in the power-assisted bed. The other event occurred similarly when the subject applied a strong force to the pin.	These events can be handled by replacing the AC/DC adapter.
Communication failure (by unknown cause)	Although the controller operated normally, the data stored in the controller could not be downloaded to the external monitor.	The cause of this event could not be identified. It was a mere communication failure between the external monitor and controller, and did not have any effect on other functions. Therefore, it raised no safety concerns.
Carrying bag (not included in the submission) handle rupture	The repeated use of the controller carrying bag deteriorated and ruptured the handle surface cover.	The handle material was changed to increase the resistance to rupture.

Taking account of the above responses, PMDA concluded, as follows:
1. The target sample size for the pivotal study (16 subjects) was calculated as the minimum required number to statistically demonstrate the superiority of EVAHEART, assuming that a survival rate of at least 60% was required to regard the product as clinically useful, and that an expected survival rate for the product was 90% at α (type I error) <0.05. Therefore, the prospective evaluation of the superiority based on the above assumption could not be made with the actual number of subjects (15 subjects). Further, discontinuing the open-labeled study before completion might have produced bias. The applicant quoted the following statement in the protocol to claim the justification: "the final evaluation of the safety and efficacy of the investigational device using the clinical study data are to be performed based on the general consideration of clinical significance taking into account not only the statistical analysis data, but also comparative literature review as possible." However, this is meant to indicate that literature review should be performed in addition to the analysis of study data and does not justify the discontinuation of the entry to the study before completion. Therefore, the discontinuation of the enrollment of patients before completion is not justified.

2. PMDA's view is as described in 1, but PMDA considered that comparing the results from the clinical studies of EVAHEART with the data from the registry of the approved product, Novacor, submitted by the applicant, serves as one of the important evaluations for the usefulness of EVAHEART, considering that EVAHEART is an orphan medical device, and that no ventricular assist device used as a bridge to cardiac transplantation is available in Japan, although it should be noted that the two types of data cannot be strictly compared since studies were not carried out under the same conditions. The comparison showed no statistical superiority of EVAHEART over Novacor in the survival, obtained in the clinical studies. However, the lower limit of the 95% confidence interval for the survival rate with EVAHEART after 6 months was not lower than Novacor. Further, the data for more than 3 years from the extended study were not inferior to the data from the U.S. INTERMACS registry. As for safety of EVAHEART, serious adverse events occurred, such as infections and neurological dysfunction. Although it is difficult to determine whether they are specific to EVAHEART due to the small number of subjects, the incidence of adverse events was not higher with EVAHEART than the approved product. Based on these, PMDA concluded as follows: The applicant's view that the efficacy and safety of EVAHEART are assured is appropriate; the usefulness of EVAHEART as an implantable ventricular assist device used as a bridge to cardiac transplantation is not inferior to that of the approved product; Making this product clinically available as an option is important also from the view point of transplantation therapy, based on the current situation that no implantable ventricular assist device as a bridge to cardiac transplantation is available in Japan; However, because of the small number of subjects in the pilot and pivotal studies and for the necessity of assuring safety during long-term assist, post-marketing clinical data should be collected from as many patients as possible together with the long-term prognostic data to further ensure the efficacy and safety of EVAHEART; Therefore, including the collection of these data as a condition for approval is appropriate.

The prolonged ventricular assist period before cardiac transplantation in Japan constitutes a discrepancy that should not be overlooked in the medical environment between Japan and foreign countries. It is therefore important to assure the efficacy and safety of the long-term use of EVAHEART before introducing it into Japan. When the results of the pilot, pivotal, and their extended studies were pooled, the mean assist period as of October 19, 2010 was 924.1 ± 526.1 days (mean ± standard deviation) and the product was used for more than 1900 days in the longest case. PMDA considered that these results support the durability of the product for long-term use.

3. The criteria for selecting patients to be implanted with the product include BSA of, in principle, at least 1.4 m^2, which was based on the results tested in cadavers. The subject who

had gastric perforation during the clinical study had BSA of approximately 1.4 m^2. It was estimated that the subject had continuous organ compression. Based on the comments raised in the Expert Discussion, a causal relationship between cerebral haemorrhage, the cause of death of the subject, and the product cannot be denied. However, cerebral haemorrhage is one of the generally expected adverse events of implantable ventricular assist devices. The subject discontinued aspirin and warfarin before receiving the surgical repair of gastric perforation and resumed warfarin at an increased dose after operation. Therefore, gastric perforation was not the direct cause of cerebral haemorrhage, although there may be a possibility that cerebral haemorrhage could have been triggered by gastric perforation. Gastric perforation is one of the expected adverse events in patients implanted with an implantable ventricular assist device and not specific to the product. BSA is a guide for selecting patients suitable for implantation, though it should be noted that it is not appropriate to select patients solely by the BSA. The application of the product may be carefully considered even in patients with BSA of less than 1.4 m^2 when the product is especially required and a sufficient implantation space can be secured. It is also possible that the product cannot be implanted in patients with BSA of 1.4 m^2 or larger when a sufficient implantation space cannot be secured, depending on the physical constitution. Therefore, PMDA concluded that it is appropriate to include following statement in Contraindications section of the instructions for use: "Patients considered not suitable for the implantation of EVAHEART by the general judgment of an experienced physician, considering patient's physical constitution, body surface area, and anatomical conditions of the intended implantation site."

4. Since appropriate anticoagulant/antiplatelet therapy assures the safety of the product, PMDA directed the applicant to describe the importance of the therapy in the instructions for use. Considering that there is a risk that the excessive use of an anticoagulant/antiplatelet drug may increase haemorrhagic complications, and that no anticoagulant/antiplatelet therapy has been established for implantable ventricular assist devices both in Japan and overseas, PMDA determined, based on the comments raised in the Expert Discussion, that appropriate anticoagulant/antiplatelet therapy should be performed at medical institutions with reference to the basic anticoagulant/antiplatelet therapy given during the clinical studies, and that the information on the therapy including the possible relationship between the pump rotational speed and frequency of cerebrovascular disorder should be provided in the operating instructions etc. To secure the efficacy and safety of the product, it is essential to ensure the full understanding of the product by physicians and medical institutions. PMDA therefore concluded that the following conditions for approval should be imposed: EVAHEART should be used only by physicians and medical institutions that fully understand the efficacy and safety of EVAHEART and have sufficient knowledge and experience in surgical techniques, etc.

5. The product is directly related to patient life support and intended to be used outside medical institutions. Therefore, healthcare professionals, patients, and their caregivers have to be thoroughly trained and a sufficient support system should be established so that appropriate emergency actions can be taken even when patients and their caregivers are outside medical institutions. Since there is no established home therapy program for patients implanted with a ventricular assist device, PMDA considered, based on the comments raised in the Expert Discussion, that the introduction of the home therapy program used in the clinical studies was acceptable at the present after taking the problems detected in the studies into account. Therefore, PMDA determined that the following conditions for approval should be imposed: The applicant is required to secure safety by thoroughly training healthcare professionals, patients, and their caregivers and establishing a sufficient support system.

6. PMDA confirmed that appropriate measures were taken against all the malfunctions reported in the clinical studies. Since the risk of malfunctions cannot be eliminated, it is important to use the product carefully in consideration of its characteristics.

PMDA reviewed and accepted the clinical data and the above responses.

IV. Results of Compliance Assessment by PMDA Concerning the Data Submitted in the New Medical Device Application

[PMDA's conclusion on the results of document-based compliance assessment]

A document-based inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new medical device application. As a result, there were no particular problems. Thus, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted product application documents.

[PMDA's conclusion on the results of GCP on-site inspection]

A GCP on-site inspection was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new medical device application (pilot, extended pilot, pivotal, and extended pivotal studies). The Expert Discussion meeting was held to hear the opinions of external expert advisors, such as medical regulation experts and experts involved in clinical practice, about major issues.

In the extended pivotal study at a medical institution, a legally acceptable representative of a subject submitted a document that declared the will to continuously participate in the study based on the new safety information provided[3]. Based on the examination of the document including the date, signature of the legally acceptable representative, and comment of the representative, PMDA considered it questionable whether the representative gave consent to the participation in the study under the full understanding of the written information. Therefore, PMDA concluded that the consent from the subject was invalid, and that part of the data from the subject in the extended pivotal study was not compliant with GCP. The consent of the subject to participate in the pivotal study was appropriately obtained in light of applicable GCP provisions. An Expert Discussion meeting with external expert advisors was held on the above conclusion. When the issues of noncompliant with GCP and applicable articles of GCP were presented to the applicant, the study institution in which the subject was enrolled submitted a written opinion. Therefore, an additional Expert Discussion meeting was held to hear their opinions.

In addition, the following cases were observed. PMDA concluded that there should be no problem with conducting a regulatory review after appropriate measures were taken, such as removing data considered as non-GCP-compliant from the application data.

1. There was a protocol deviation to protect a subject from an immediate danger at the above study institution (use of chest compression massage). The investigator failed to submit a document reporting the description and reason of the deviation to the sponsor and head of the medical institution.

2. At another medical institution, the investigator failed to report the completion and summary results of the study to the head of the medical institution since the investigator transferred during the study. The investigator failed to check and write a signature on the

[3] It is specified in the GCP provisions that, when any new information that may influence the will of subjects to participate in the study is obtained during the study, the investigator shall revise the written information for the patient, submit it to the Institutional Review Board for review and approval, and obtain the consent of subjects to continue to participate in the study again.

corrections of case report forms made by subinvestigators. The head of the medical institution failed to take necessary measures related to the transfer of the investigator (change of the investigator).

3. At another medical institution, the appropriateness to continue the study was reviewed at the IRB in consideration of adverse events reported from the sponsor. However, it was performed as an expedited review which did not comply with the applicable operating procedures.

4. Considering that the sponsor had the knowledge of 1 and 2 above, it is reasonable to consider that the sponsor failed to appropriately monitor the studies according to applicable operating procedures.

Based on the comments raised in the Expert Discussion, PMDA concluded that there are no particular problems with the following points in light of applicable GCP provisions.

a. Consent to participate in extended studies

It is specified in the protocol that "a written consent to voluntarily participate in the clinical study should be obtained from the subject and his/her family." No provisions are specified in the protocol for the consent of the representative of the subject when the subject is incapable of giving his/her consent.

One subject was unable to submit consent to participate in the extended study. The subject's legally acceptable representative (the subject's mother) provided the written consent according to Article 70, Paragraph 2 of GCP. No objection was expressed at the Expert Discussion meeting. PMDA concluded that there are no particular problems in light of applicable GCP provisions.

b. Conformance to exclusion criterion of the protocol

The protocol includes an exclusion criterion of "patients with BSA of <1.4 m^2." It is specified in the protocol that "the latest measured values or measured values on admission may be used for body height and weight" for the baseline examination.

One patient whose BSA was ≥ 1.4 m^2 on admission and <1.4 m^2 immediately before implantation was included as a subject. The patient was not considered to meet the exclusion criterion of the protocol at the Expert Discussion. PMDA also concluded that there are no particular problems in light of applicable GCP provisions.

c. Process to obtain informed consent

It is specified in the protocol that the physician who developed the investigational device and is related to the executive officer of the sponsor should not participate in any evaluation/decision process including the preparation/entry of case report forms even as a subinvestigator of the study. The GCP inspection by PMDA revealed no record indicating that the physician prepared a case report form. It was recorded that the physician gave explanations on the disease and the investigational device to subjects and their families before they provided their consent, and that another subinvestigator explained the study to them and confirmed their will when they provided the consent.

Based on the comments raised in the Expert Discussion, PMDA concluded that there are no particular problems with the process to obtain the consent of subjects to participate in the study at the medical institution in light of applicable GCP provisions.

d. Videotaping

It is specified in the protocol that the entire surgical process from thoracotomy for implantation to chest closure should be recorded with a video camera for all the subjects implanted with the product at the medical institutions, and that the video should be kept as source material and a copy of the video provided to the sponsor.

The surgical process of 1 subject at a medical institution was not videotaped. Since this deviation from the protocol was reported from the investigator to the sponsor in writing, the deviation was appropriately handled according to applicable GCP provisions. The sponsor's monitor recorded the absence of videotaping as a protocol deviation in the monitoring report on the day of operation. Based on these results and comments raised in the Expert Discussion, PMDA concluded that there are no particular problems in light of applicable GCP provisions.

[PMDA's conclusion on the results of the QMS document-based and on-site inspection]

A compliance review was conducted in accordance with the provision of paragraph 6 of Article 14 of the Pharmaceutical Affairs Act. As a result, PMDA concluded that there were no particular problems.

V. Overall Evaluation

Implantable Ventricular Assist System EVAHEART is an implantable ventricular assist device intended for use to improve the blood circulation in patients with end-stage severe heart failure who require cardiac transplantation.

The issues in the regulatory review of EVAHEART were as follows: (1) assurance of the clinical efficacy and safety of the product by the results of the pilot and pivotal studies, (2) appropriate evaluation of malfunctions and adverse events observed during the use of the product to take appropriate post-marketing safety measures, and (3) assurance of efficacy and safety of the product for a long-term use.

PMDA's conclusions, taking account of comments raised in the Expert Discussion, are as follows:

1. Since the enrollment of patients was discontinued before the target sample size was achieved in the pivotal study, it is impossible to prospectively evaluate the hypothesis with the clinical study results. The discontinued enrollment of patients is not justified. However, considering that the number of candidate patients for the product is limited since it is an orphan medical device and that no ventricular assist device as a bridge to cardiac transplantation is available in Japan, PMDA concluded that EVAHEART was not inferior to the approved product when the results of the pilot and pivotal studies of EVAHEART were compared with clinical results of the approved product in Japan.

2. Important measures to ensure the safety of the product include appropriate anticoagulant/antiplatelet therapy, use of the product only by physicians/medical institutions that have met predetermined standards, and establishment and maintenance of an appropriate training and support system. Considering the seriousness of the target disease and device characteristics, implantable ventricular assist devices inevitably cause adverse events. Particularly, appropriate measures against thromboembolism have to be taken since, once it becomes serious, its prognosis may become poor. Appropriate anticoagulant/antiplatelet therapy is important to prevent thromboembolism. Since excessive use of an anticoagulant/antiplatelet drug may increase haemorrhagic complications, appropriate anticoagulant/antiplatelet therapy should be performed at each medical institution in reference to the basic anticoagulant/antiplatelet therapy prescription used in the clinical studies. PMDA therefore determined that the appropriate use of anticoagulant/antiplatelet therapy should be specified in

the instructions for use, and that the basic anticoagulant/antiplatelet therapy prescription used in the clinical studies should be described in the operating instructions etc. to provide information.

To ensure the effective and safe use of the product, it is important to appropriately handle any malfunction or adverse event of the product that occurred after the market launch before it becomes serious. Therefore, the product should be used only by physicians and medical institutions that fully understand the product and immediate measures should be taken against malfunctions. Furthermore, patients implanted with the product and their caregivers have to fully understand the product and take appropriate actions at home. Therefore, PMDA determined that the following statement should be imposed as a Condition for Approval 2: The product should be used only by physicians and medical institutions that fully understand the product.

Since the product is intended to be used outside medical institutions, PMDA determined that the following statement should be imposed as a Condition for Approval 3: The full training of healthcare professionals, patients, and their caregivers in the home-therapy program and the establishment of a sufficient support system are necessary.

3. Taking account of the current status of cardiac transplantation in Japan, it is concerned that the product will be used to assist cardiac function for a long time. Considering that the durability of the product for 2 years was confirmed in the non-clinical study, that the mean assist period as determined by pooling the results from the pilot, pivotal, and extended studies was 924.1 ± 526.1 days (mean ± standard deviation) as of October 19, 2010, and that the product was used for more than 1900 days in the longest case, the product is likely to provide efficacy and safety to an extent, when it is used for a long time. It is expected that the risk of thromboembolism will be reduced by promoting appropriate patient management and providing sufficient information to healthcare professionals and patients. Thus, although it is expected that the product will be used for a long time before cardiac transplantation in Japan, PMDA determined that, by the use of the product as a bridge, the product may increase the possibility of cardiac transplantation for patients with end-stage severe heart failure who cannot survive without cardiac transplantation, considering that no left ventricular assist device is currently available in Japan. Considering no sufficient long-term results of the product are available in Japan, the Condition for Approval 1 described below should be imposed to carefully monitor long-term prognosis.

Based on the above discussion, PMDA considered that EVAHEART would be beneficial for the Japanese clinical environment since it is not inferior to Novacor or HeartMate XVE approved in Japan in the usefulness as the implantable ventricular assist device used for the bridge to cardiac transplantation. PMDA therefore concluded that the product may be approved after modifying the intended use of the "Intended Use, Indications" in the submitted application form as shown below, with following conditions for approval.

[Intended use]
Implantable Ventricular Assist System EVAHEART is used to improve the blood circulation until cardiac transplantation is performed in patients who have severe heart failure for which cardiac transplantation is indicated, and show continuous decompensation in spite of drug therapy or circulation assist techniques, such as the use of an external ventricular assist device, and whose lives cannot be saved without cardiac transplantation.

[Conditions for approval]
The applicant is required to:

1. Perform a use-results survey in all patients including those who completed the extended

clinical study in cooperation with related academic societies during the re-examination period. At the same time, observe the long-term prognosis of patients implanted with the assist device and report its analytical results.

2. Establish appropriate qualification criteria for medical institutions and physicians in cooperation with related academic societies, and take appropriate measures to limit the use of this product to physicians and medical institutions who/which understand its efficacy and safety and have sufficient knowledge and experience in surgical techniques, etc.

3. Provide sufficient training for healthcare professionals, patients, and caregivers to ensure the safe and smooth transition to home therapy. The safety of the product should be ensured by establishing a sufficient support system.

Implantable Ventricular Assist System EVAHEART is a new performance medical device and designated as an orphan medical device. The re-examination period should be 7 years and a use-results survey for all the patients implanted with the product should be performed. The product is not classified as a biological product or a specified biological product. In addition, the product should be designated as a specially designated medical device and be tracked since it is assumed that patients implanted with the product will be discharged.

The application should be deliberated at the Committee on Medical Devices and *In-vitro* Diagnostics.

[Instructions]

1. Continuously collect information, analyze the cause, and take appropriate measures for adverse events of intestinal obstruction that occurred on October 7, 2010.