July 18, 2025
Medical Device Evaluation Division
Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Medical Product 4, Orthopedic Products
Term Name	Absorbable adhesion prevention dressing
Brand Name	Coseal
Applicant	Baxter Japan K.K.
Date of Application	March 31, 2023 (Application for marketing approval)

Results of Deliberation

In its meeting held on July 18, 2025, the Committee on Medical Devices and *In-vitro* Diagnostics reached the following conclusion, and decided that this conclusion should be presented to the Pharmaceutical Affairs Council.

The product should be approved with no designating as a medical device subject to a use-results survey.
The product is not classified as a biological product or a specified biological product.

Review Report

July 2, 2025
Pharmaceuticals and Medical Devices Agency

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

Classification	Medical Product 4, Orthopedic Products
Term Name	Absorbable adhesion prevention dressing
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Reviewing Office	Office of Medical Devices I

Review Results

July 2, 2025

Classification	Medical Product 4, Orthopedic Products
Term Name	Absorbable adhesion prevention dressing
Brand Name	Coseal
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Results of Review

Coseal is an absorbable adhesion barrier composed of polyethylene glycol (PEG) derivatives. Coseal consists of a Coseal Kit, which contains a PEG syringe filled with 2 types of PEG derivatives and a solution component (Solution A, PEG solvent, hydrochloric acid solution; Solution B, polymerization initiator, sodium dihydrogen phosphate/sodium carbonate solution), a Coseal Spray Set, and an EasySpray (regulator). Coseal is intended for use on the surfaces of the heart, pericardial tissues, and major blood vessels.

The applicant submitted non-clinical study data for Coseal supporting the physical and chemical properties, electrical safety and electromagnetic compatibility, biological safety, stability and durability, performance, and instructions for use for Coseal. No particular issues of concern were identified.

The applicant submitted clinical study data for Coseal, in the form of the results from an investigator-initiated clinical study (hereinafter referred to as “the study”) conducted at 3 study sites in Japan. The study enrolled a total of 30 patients aged ≥12 years who underwent implantation surgery of an extracorporeal ventricular assist device (hereinafter referred to as “extracorporeal VAD”) (16 patients in the Coseal group and 14 patients in the untreated group). The primary endpoints were established to evaluate the overall and local anti-adhesion effects of Coseal sprayed to the surgical sites, specifically (1) the “degree of adhesion between the surface of the heart/great vessels and the surrounding tissues” (total adhesion score) assessed ≥2 weeks after the initial surgery; and (2) the “number of sites where the adhesion between the surface of the heart/great vessels and the surrounding tissues was classified as Grade ≥2.” For the “degree of adhesion between the surface of the heart/great vessels and the surrounding tissues,” the mean ± standard deviation of total adhesion score was 3.5 ± 2.4 in the Coseal group and 12.1 ± 2.7 in the untreated group, demonstrating a significantly lower value in the Coseal group (Welch’s t-test, $P < 0.0001$). The “number of sites where the adhesion between the surface of the heart/great vessels and the surrounding tissues was classified as Grade ≥2” was significantly lower in the Coseal group than the untreated group (Fisher’s exact test, $P < 0.0001$). Although the number of subjects was limited, analyses of secondary and additional endpoints showed that the Coseal group required fewer transfusions due to bleeding from adhesiolysis and tended to require shorter adhesiolysis

time than that required in the untreated group, confirming the clinical usefulness of Coseal. No particular safety concerns related to Coseal were identified in the study.

On the other hand, the mean number of days from the initial surgery to the resternotomy for adhesion assessment was 31.5 days in the Coseal group and 48.0 days in the untreated group, with the maximum being 74 days in the Coseal group and 195 days in the untreated group. From the perspective of early clinical introduction of Coseal, the applicant explained the long-term anti-adhesion effect after surgery based on the study results. However, there is currently limited clinical evidence directly demonstrating that suppression of adhesion formation in the acute postoperative period leads to suppression of late postoperative adhesion formation. Sufficient clinical data on adhesion status in the late postoperative period are not available. Taking these into consideration, it is difficult to conclude from this study that Coseal has a long-term anti-adhesion effect after surgery. Taking also into account the comments from the Expert Discussion, PMDA determined that the use of Coseal should be limited to patients who are expected to undergo resternotomy during the early postoperative period, and that its indication should be restricted to patients undergoing surgery for an extracorporeal VAD, based on the results of this study.

With regard to post-marketing safety measures for Coseal, its operation is not complex and no safety concerns have been identified. Therefore sufficient risk reduction can be achieved by appropriate precautions and provision of information on its use through the instructions in the Information on Precautions, etc. Since Coseal has accumulated a certain amount of usage experience overseas and no particular safety concerns were identified in the study, a use-results survey would not be necessary.

As a result of its review, PMDA has concluded that Coseal may be approved for the intended use shown below, and that the application should be subjected to deliberation by the Committee on Medical Devices and *In-vitro* Diagnostics.

Intended Use

Coseal is applied to the surfaces of the heart, pericardial tissues, and great vessels in patients undergoing extracorporeal ventricular assist device implantation surgery, in order to reduce the frequency, extent, and severity of postoperative adhesions.

Review Report

July 2, 2025

Product for Review

Classification	Medical Product 4, Orthopedic Products
Term Name	Absorbable adhesion prevention dressing
Brand Name	Coseal
Applicant	Baxter Japan K.K.
Date of Application	March 31, 2023
Proposed Intended Use	Coseal is applied to the surfaces of the heart, pericardial tissues, and great vessels in patients aged ≥12 years undergoing cardiovascular surgery, in order to reduce the frequency, extent, and severity of postoperative adhesions.

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List of Abbreviations

BiVAD	Biventricular Assist Device
COH102	[redacted]
COH206	[redacted]
GCP	Good Clinical Practice
IABP	Intra-Aortic Balloon Pumping
ICU	Intensive Care Unit
IEC	International Electrotechnical Commission
ISO	International Organization for Standardization
jRCT	Japan Registry of Clinical Trials
LVAD	Left Ventricular Assist Device
NHS	N-Hydroxysuccinimide
PEG	Polyethylene Glycol
RVAD	Right Ventricular Assist Device
SH	Sulfhydryl (Thiol)
TCPC	Total Cavopulmonary Connection
UMIN	University Hospital Medical Information Network
VAD	Ventricular Assist Device

I. Product Overview

Coseal is an absorbable adhesion barrier composed of polyethylene glycol (PEG) derivatives, intended for use on the surfaces of the heart, pericardial tissues, and great vessels. Coseal consists of a Coseal Kit containing a PEG syringe filled with 2 types of PEG derivatives and a solution component (Solution A, PEG solvent, hydrochloric acid solution; Solution B, polymerization initiator, sodium dihydrogen phosphate/sodium carbonate solution), a Coseal Spray Set, and an EasySpray (regulator) (Figures 1 and 2). The PEG syringe is filled with 2 types of powdered PEG derivatives, i.e., one possessing N-hydroxysuccinimide (NHS) groups at the termini of a four-armed structure (designated as COH102) and the other possessing thiol (sulfhydryl [thiol], SH) groups (designated as COH206). The Coseal Kit (PEG syringe and solution component) is available in 3 fill volumes (2, 4, and 8 mL).

After the PEG derivatives are dissolved in Solution A, it is connected to Solution B via the Coseal Spray Set. The operator sprays the mixture onto the tissue surfaces of the heart/great vessels using the EasySpray. Upon spraying, the NHS and SH groups of the PEG derivatives undergo thiol–ester crosslinking at near-neutral pH, forming a hydrogel through intermolecular bonding. Simultaneously, covalent bonds form between the hydrogel and tissue-surface proteins, producing a hydrogel layer within 60 seconds of application (Figure 3). The crosslinked hydrogel layer provides tissue adherence, elasticity, and sealing properties, thereby preventing contact between the damaged surface and adjacent tissues and inhibiting adhesion formation. The hydrogel is bioabsorbable; it undergoes hydrolysis within 7 days after application and is absorbed into and excreted from the body within 30 days.

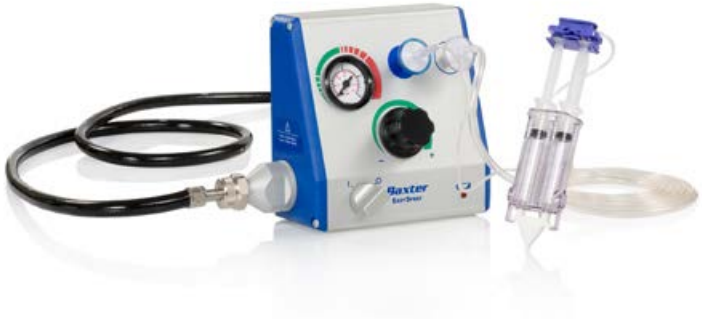


Figure 1. Overview of Coseal

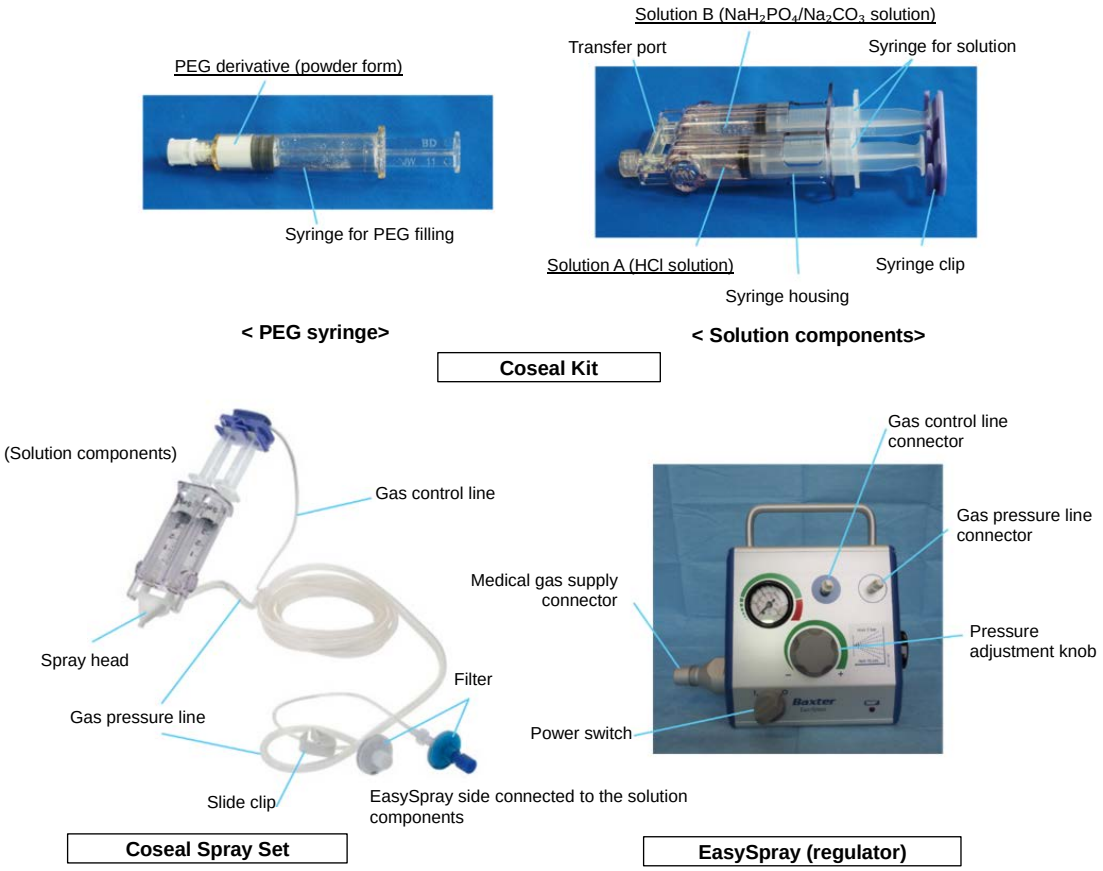
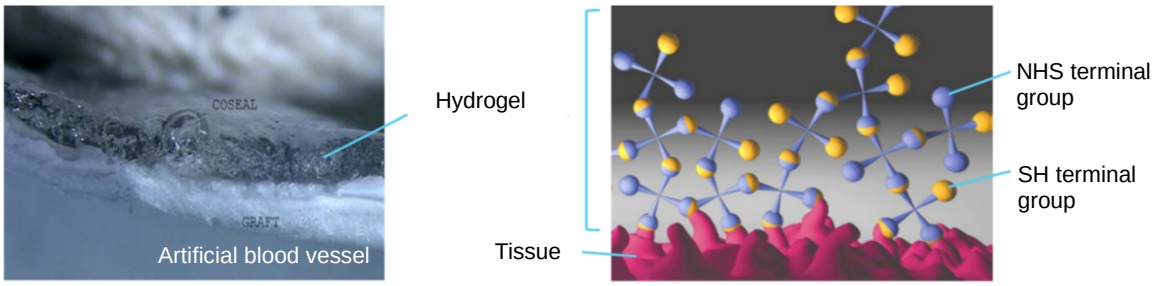


Figure 2. Components of Coseal



(a) Hydrogel (colorless and transparent) (b) Illustration of hydrogel layer formation

Figure 3. Formation of the hydrogel

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

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

The expert advisors present during the Expert Discussion on Coseal declared that they did not fall under Chapter 3, 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. History of Development, Use in Foreign Countries, and Other Information

1.A Summary of the data submitted

1.A.(1) History of development

In cardiovascular surgery, patients who undergo an initial procedure involving sternotomy may subsequently require reoperation with repeat sternotomy (hereinafter referred to as "resternotomy"). Planned staged surgical interventions for congenital heart diseases are widely performed in pediatric patients.[1] Resternotomy may also be required for additional treatment following cardiovascular surgery or for the management of new cardiac disorders in adult patients as well.[2] Resternotomy has been reported to be associated with an increased overall mortality compared with that of initial surgery.[3] Dense adhesions formed around the heart after the initial operation obscure anatomical landmarks, thereby increasing the technical difficulty and the risk of complications during resternotomy.[2,4,5] Complications associated with resternotomy include prolonged operative time due to meticulous sternal resection and adhesiolysis, sternal fracture, and injury to organs/blood vessels, which may lead to fatal haemorrhage.

In a retrospective study investigating the incidence and risk factors of intraoperative adverse events during resternotomy, intraoperative adverse events were observed in 7% of resternotomy cases. The timing of occurrence was 23% at the time of chest opening and 39% during adhesiolysis before the initiation of cardiopulmonary bypass. Patients who experienced intraoperative adverse events had a significantly higher risk of poor outcomes.[6] The incidence of complications in resternotomy has been reported to range from 4% to 11.3%,[3,7,8] with mortality observed in 1.6% of adult patients.[7] Other reports have described an in-hospital mortality rate (within 30 days postoperatively) of 2.9% for resternotomy.[9] In pediatric resternotomy, the in-hospital mortality rate was reported as 3.7%. Comparisons of perioperative risks between initial surgery and resternotomy demonstrated significantly longer bypass time, cross-clamp time, intensive care unit stay, and total hospitalization among patients undergoing resternotomy.[4]

As a conventional method to prevent adhesion formation, re-suturing of the pericardium at the time of closure has been attempted. However, in procedures such as implantation of a ventricular assist device (VAD), complete re-suturing of the pericardium is often not feasible. Moreover, even when re-suturing is performed, adhesions frequently form between the pericardium and adjacent tissues such as the heart and great vessels, rendering the efficacy of this method limited.

Coseal, developed by Cohesion Technologies, Inc. (US) under the name "COSEAL Surgical Sealant" (hereinafter referred to as the "previous-generation product"), was originally developed as a topical hemostatic material and has been widely used overseas in vascular surgery and other procedures. In the previous-generation product, COH102 and COH206 were separately filled into individual syringes. COH102 was dissolved in a disodium hydrogen phosphate solution (pH [redacted]), and COH206 was dissolved in a sodium dihydrogen phosphate/sodium carbonate solution. The solutions from both syringes were expelled simultaneously and mixed at the spray head, initiating the crosslinking reaction (Table 1). In Coseal, to simplify the preparation process for dissolving, powdered COH102 and COH206 are filled into a single syringe, and hydrochloric acid is used as the solvent to prevent a premature reaction of PEG derivatives during dissolution. After post-marketing use in Europe and the US, it was

found that spraying Coseal onto the surfaces of the heart and great vessels provided a secondary effect of reducing adhesion formation between these surfaces and the surrounding tissues. In Europe, it is currently used as an adhesion barrier following surgical procedures as well.

In Japan, several adhesion barriers, such as "AdSpray" (Approval number 22800BZX00234000), have been marketed; however, all approved products are indicated for patients undergoing abdominal or pelvic surgery, and none have been approved for use in cardiovascular surgery.

To facilitate the introduction of Coseal into Japan based on this background, a Japanese investigator-initiated clinical study (University Hospital Medical Information Network [UMIN]000038998) was conducted primarily in adult patients requiring implantation surgery of an extracorporeal ventricular assist device (hereinafter referred to as extracorporeal VAD). Separately, the applicant has planned and is currently conducting a Japanese company-sponsored clinical study[i] (Japan Registry of Clinical Trials [jRCT]2032220540; hereinafter referred to as the "pediatric study") in pediatric patients with congenital heart disease who undergo planned staged surgeries. To facilitate early introduction of Coseal in Japan, the applicant submitted a marketing application for use in patients aged ≥12 years undergoing cardiovascular surgery, based on the results of the Japanese investigator-initiated clinical study on extracorporeal VAD implantation surgery. Coseal was initially submitted by Baxter Limited in March 2023 and subsequently transferred to Baxter Japan K.K. in January 2024.

Table 1. Overview of differences between Coseal and the previous-generation product

		Previous-generation product	Coseal
Overseas brand name		COSEAL Surgical Sealant	COSEAL Surgical Sealant, Premixed
Coseal Kit	PEG derivatives	• COH102 • COH206	• COH102 + COH206
	Solutions	• Disodium hydrogen phosphate solution • Sodium dihydrogen phosphate/sodium carbonate solution	• Hydrochloric acid solution • Sodium dihydrogen phosphate/sodium carbonate solution
	Sterilization method	Electron beam sterilization	Gamma ray sterilization
Product generated upon application		Hydrogel	

1.A.(2) Use in foreign countries

Table 2 shows the marketing authorization status of Coseal in major foreign countries (survey period, January 2009 to December 2024). In the US, Coseal has been approved only as a local hemostatic material and has not been approved for an indication of adhesion prevention.

[i] "A multicenter, randomized, controlled clinical study to evaluate the safety and efficacy of adhesion prevision device 'BAX602,' in preventing the adhesion around great cardiac vessels in pediatric patients with congenital heart disease undergoing re-do open heart surgery" is currently being conducted at 6 study sites in Japan since September 2022. Considering the clinical practice of resternotomy in pediatric patients with congenital heart disease, subjects who underwent resternotomy at least 3 months after the initial surgery were selected for evaluation, including assessment of postoperative long-term adhesions.

Table 2. Use status in major foreign countries

Country/region	Brand name†	Date of license acquisition	Intended use	Sales volume
US	COSEAL Surgical Sealant	December 14, 2001	COSEAL is indicated for use in vascular reconstructions to achieve adjunctive hemostasis by mechanically sealing areas of leakage.	[redacted]
	COSEAL Surgical Sealant, Premixed	February 4, 2003		
Europe	COSEAL Surgical Sealant	January 2, 2004	COSEAL is a synthetic hydrogel designed to act as a sealant around suture sites and to prevent or reduce postsurgical adhesions.	
		November 3, 2005‡		
	COSEAL Surgical Sealant, Premixed	January 2, 2004		
		November 3, 2005‡		
Other*	-	-	-	

* Asia Pacific; Australia, New Zealand, South Korea, China, Taiwan, India, Singapore, Malaysia, Thailand, Hong Kong, Indonesia, and Vietnam

† "COSEAL Surgical Sealant," Previous-generation product; "COSEAL Surgical Sealant, Premixed," Coseal

‡ Expanded indication to adhesion prevention

1.A.(3) Malfunctions and adverse events reported in foreign countries

Tables 3 to 5 show the incidence of major malfunctions and serious adverse events in foreign countries (including uses other than in cardiovascular surgery or use as a local hemostatic material). Among the reported adverse events, 15 events had fatal outcomes, and in 3 of these events, a causal relationship to Coseal could not be ruled out (Table 6).

Table 3. Incidence of malfunctions in foreign countries (Coseal Kit)

(Survey period, January 2009 to December 2024)

Type of malfunction	Number of events	Incidence*
Leakage	902	[redacted]%
Difficulty in mixing	189	[redacted]%
Defect in liquid components	156	[redacted]%
Damage	77	[redacted]%
Foreign matter contamination	61	[redacted]%
Unknown	54	[redacted]%
Insufficient components	48	[redacted]%
Defect in labeling materials	15	[redacted]%
Issues during transportation or storage	14	[redacted]%
Lack of intended effect	13	[redacted]%
Discoloration	9	[redacted]%
Misuse	9	[redacted]%
Spray malfunction	1	[redacted]%
Other defects†	127	[redacted]%

* Calculated using the total number of units sold ([redacted]) during the survey period as the denominator.

† Foreign matter contamination, inability to discharge, inability to mix, suspected discoloration, fluid leakage due to component fracture, contamination, and lack of expected effect

Table 4. Incidence of malfunctions in foreign countries (Coseal Spray Set and EasySpray)

(Survey period, January 2021 to December 2024)

Types of defect events	Number of events	Incidence*
Malfunction due to battery issues (EasySpray)	6	[redacted]%
Damage (EasySpray)	4	[redacted]%
Other malfunctions (EasySpray)	2	[redacted]%
Damage (Coseal Spray Set)	3	[redacted]%

* Calculated using the total number of Coseal Spray Sets ([redacted]) and EasySpray devices ([redacted]) sold during the survey period as the denominator.

Table 5. Incidence of serious adverse events in foreign countries

(Survey period, January 2009 to December 2024)

Type of adverse event	Number of events	Incidence*
Surgical site infection	13	[redacted]%
Postoperative haematoma	10	[redacted]%
Adhesion formation	8	[redacted]%
Inflammatory reaction	7	[redacted]%
Infection	6	[redacted]%
Cerebral infarction	5	[redacted]%
Anastomotic leak	4	[redacted]%
Pericarditis	4	[redacted]%
Ventricular assist device obstruction	4	[redacted]%
Ventricular assist device thrombosis	4	[redacted]%
Cardiac tamponade	4	[redacted]%
Abdominal distension	4	[redacted]%
Nerve paralysis	3	[redacted]%
Cardiac failure	3	[redacted]%
Pyrexia	3	[redacted]%
Allergy/anaphylactic reaction	3	[redacted]%
Pneumonia	3	[redacted]%
Postoperative mediastinitis	3	[redacted]%

* Calculated using the total number of units sold during the survey period ([redacted]) as the denominator. Events with an incidence of ≥0.0003% are listed.

Table 6. Serious adverse events related to Coseal or serious adverse events for which a causal relationship to Coseal could not be ruled out reported in foreign countries

Type of adverse event	Details
Ventricular assist device obstruction	After Coseal was used for vascular sealing, obstruction of the inflow cannula of an implanted left ventricular assist device (LVAD) occurred. The patient died because the family refused LVAD replacement. At autopsy, collapse of the lumen of the vascular graft in the inflow cannula was confirmed, suggesting that Coseal occluded the vascular graft and reduced inflow. The reason why Coseal entered the lumina of the inflow cannula and vascular graft was unknown. However, the use of an excessive amount (32 mL) of Coseal was considered a potential contributing factor.
Post-procedural haemorrhage	In a patient who underwent emergency laparotomy for an aortic aneurysm, Coseal was used as a local hemostatic material. The patient died during reoperation for postoperative haemorrhage. The surgeon had not received training on Coseal, and it was used in an area of active bleeding. The death was considered unrelated to Coseal itself but due to inappropriate use, improper application method, and the patient's condition.
Cardiac tamponade	Coseal was used at an anastomotic site during surgery several years earlier. It was reported that swelling of Coseal might have caused compression leading to the patient's death. Detailed information was unavailable, but given that the event occurred several years earlier, it was considered that a causal relationship could not be established.

1.B Outline of the review conducted by PMDA

PMDA asked the applicant to explain the risk reduction measures for an event in which the inflow cannula of an implanted left ventricular assist device (LVAD) became obstructed.

The applicant's explanation:

When Coseal adheres to artificial materials such as patches or artificial vessels, a hydrogel layer covalently bound to tissue components present on the surface of the artificial material is formed within 60 seconds after spraying, similar to its mechanism of action on tissue surfaces. The degradation mechanism of Coseal involves protease-mediated hydrolysis. Even when Coseal adheres to artificial materials, it undergoes hydrolysis in the same manner as on tissue surfaces and is primarily excreted in the urine. The foreign manufacturer analyzed that one of the contributing factors to the obstruction of the inflow cannula in the patient with implantable LVAD was the use of 32 mL of Coseal, which exceeded the maximum safe dose of 24 mL. Based on the above, the following precautions will be included in the package insert and other documents as risk reduction measures for this event.

- To prevent adhesion of Coseal or the heart surface to devices that are to be removed soon after surgery (e.g., tubes, catheters, pacing wires), either place these devices after spraying Coseal or temporarily move them so that Coseal can be sprayed directly onto the tissue surface. If devices are to be placed on top of Coseal, do so 60 seconds after spraying.
- Spray the recommended dose (1 mL/10 cm^2) while maintaining the recommended spray pressure and distance, ensuring that the hydrogel forms a uniform layer throughout.
- Minimize the amount of Coseal sprayed and avoid excessive application.

PMDA accepted the applicant's explanation and decided to evaluate this matter in conjunction with the assessment described later in Section 6.

2. Design and Development

2.(1) Performance and safety specifications

2.(1).A Summary of the data submitted

As specifications for the performance and safety of Coseal, the following parameters were established for the PEG syringe: The NHS substitution rate of COH102, the SH substitution rate of COH206, the pH of Solutions A and B, and PEG syringe performance (climbing resistance, positive pressure leakage, and amount of lubricant).

For the solution components and the Coseal Spray Set, specifications were established for airtightness, flow rate, pressure resistance, functionality, amount of lubricant, and residuals from ethylene oxide sterilization (for the Coseal Spray Set).

As system-wide specifications, biological safety and bacterial endotoxin were established.

2.(1).B Outline of the review conducted by PMDA

Coseal is required to meet the specifications necessary for clinical use in terms of the gelation time and swelling characteristics of the hydrogel formed, as well as to possess sufficient strength as a physical barrier. PMDA requested that the applicant include the characteristics and strength of the hydrogel in the specifications for performance and safety. To ensure the performance and safety of the EasySpray device, PMDA requested that the applicant include specifications for electrical safety, electromagnetic compatibility, pressure adjustment range, and overpressure protection as part of the performance and safety standards.

The applicant's response:
Specifications for the hydrogel will include gelation time, swelling, tensile strength, and burst strength. Specifications for the EasySpray device will include electrical safety, electromagnetic compatibility, pressure adjustment range, and overpressure protection.

PMDA considered the applicant's response to be appropriate. PMDA reviewed the submitted materials concerning the performance and safety specifications, including the selected parameters, evaluation methods, and specification values, and concluded that there were no particular issues.

2.(2) Physical and chemical properties

2.(2).A Summary of the data submitted

The applicant submitted data concerning the physical and chemical properties of Coseal, such as test results for the NHS and SH substitution rates of PEG derivatives, the pH of Solutions A and B, the functionality of the solution syringe, and the mechanical properties of the PEG-filled syringe.

2.(2).B Outline of the review conducted by PMDA

PMDA reviewed the documents concerning the physical and chemical properties and concluded that there were no particular issues.

2.(3) Electrical safety and electromagnetic compatibility

2.(3).A Summary of the data submitted

The applicant submitted data concerning the electrical safety and electromagnetic compatibility of the EasySpray device, demonstrating conformity with the standard that specifies general requirements for basic safety and essential performance of medical electrical equipment (International Electrotechnical Commission [IEC] 60601-1:2005/AMD1:2012 1/AMD2:2020, and with the standard that specifies electromagnetic compatibility requirements for medical electrical equipment (IEC 60601-1-2:2014).

2.(3).B Outline of the review conducted by PMDA

PMDA reviewed the documents concerning electrical safety and electromagnetic compatibility and concluded that there were no particular issues.

2.(4) Biological safety

2.(4).A Summary of the data submitted

2.(4).A.1) Biological safety

Regarding the biological safety of Coseal, the applicant submitted test results for biological safety studies conducted in accordance with the “Revision of Basic Principles of Biological Safety Evaluation Required for Application for Market Approval of Medical Devices” (PSEHB/MDED Notification No. 0106-1 dated January 6, 2020) and International Organization for Standardization (ISO) 10993-1.

The following studies were conducted for the hydrogel: Cytotoxicity, sensitization, intracutaneous reactivity, material-mediated pyrogenicity, acute systemic toxicity, subacute systemic toxicity (including evaluation of implantation), hemocompatibility (material-mediated hemolysis, coagulation, hematology, and complement activation), and genotoxicity (bacterial reverse mutation and chromosomal aberration). No findings of concern were observed in any of the studies.

For the PEG-filled syringe, cytotoxicity, sensitization, intracutaneous reactivity, material-mediated pyrogenicity, and acute systemic toxicity studies were conducted. No findings of concern were observed in any of the study results.

For the solution components, using a test article differing from Coseal in the raw material of the transfer port, cytotoxicity, sensitization, intracutaneous reactivity, material-mediated pyrogenicity, and acute systemic toxicity studies were conducted. No findings of concern were observed in any of the studies.

Regarding the difference in raw materials of the transfer port between Coseal and the test article, chemical characterization and toxicological risk assessments were performed. Based on the analytical results, the applicant explained that the toxicological risk of the transfer port material of Coseal does not exceed that of the test article.

For the spray head of the Coseal Spray Set, cytotoxicity, sensitization, intracutaneous reactivity, material-mediated pyrogenicity, acute systemic toxicity, and hemocompatibility (material-mediated hemolysis) studies were conducted using Duplocath,[ii] an unapproved product in Japan that uses the same raw materials as Coseal, as the test article. No findings of concern were observed in any of the study results.

2.(4).A.2) Pharmacokinetics

Regarding the pharmacokinetics of the hydrogel, a bioabsorbable material, the applicant submitted test results for pharmacokinetic studies evaluating PEG, the main component of the hydrogel, and NHS, which is released during hydrogel formation, based on the reaction mechanisms described below.

- When 2 types of PEG derivatives (COH102 and COH206) are dissolved in Solution A (hydrochloric acid solution) and then mixed with Solution B (sodium dihydrogen phosphate/sodium carbonate solution), crosslinking between COH102 and COH206 begins, releasing NHS in the process. Subsequently, COH102 molecules react with amine groups in tissues and covalently bind to the surface of 4-armed COH206 PEG molecules and their reactive SH termini, resulting in the formation of the hydrogel.
- In the formed hydrogel, the ester bond within the amide/thioester portion of COH102 is hydrolyzed by proteases, generating free-OH-terminated 4-armed [redacted] Da PEG molecules. These free-OH-terminated 4-arm [redacted] Da PEG molecules are further degraded by proteases into glutaric acid and COH206.

A pharmacokinetic study of PEG was conducted in rats using ^{14}C-labeled COH102 and COH206. Using a previous-generation product as the test article, the formed hydrogel was implanted intraperitoneally, and plasma radioactivity concentration, tissue distribution, and excretion/mass balance were evaluated. Results showed that PEG was rapidly absorbed from the peritoneal cavity, with a maximum plasma concentration (C_{max}) of 693 µg/g at 36 hours post-implantation (T_{max}) and a half-life ($t_{1/2}$) of 197 hours. In most tissues, concentrations peaked at 36 hours post-implantation. At 24 to 48 hours post-implantation, the highest tissue radioactivity concentrations were as follows: Adipose tissue (reproductive) 1830 µg/g, pancreas 1120 µg/g, urinary bladder (urine) 946 µg/g, kidney 530 µg/g, spleen 327 µg/g, prostate 243 µg/g, lymph node (mesenteric) 240 µg/g, liver 219 µg/g, and adrenal gland 210 µg/g. Approximately 72% of the administered radioactivity was excreted in urine within 72 hours. At 672 hours post-implantation, 84.7% and 6.25% of the administered radioactivity were recovered in urine and feces, respectively, for a mean total recovery of 98.6%. The applicant explained that the results were considered extrapolatable to Coseal because the hydrogel formed from the previous-generation product, which is used as the test article, is identical to that formed from Coseal.

[ii] Duplocath, A catheter component of a spray-type sealing material used as an adjunct to hemostasis or for tissue closure in surgical procedures, applied to administer the sealing material intraperitoneally or in similar settings.

A pharmacokinetic study of the NHS was conducted using ^{14}C-labeled COH102 in a rat renal abrasion model. An unapproved absorbable local hemostatic material in Japan, Hemopatch,[iii] containing the same NHS raw material as Coseal, was used as the test article. After application to the bleeding surface of a superficial lesion created in the left kidney of rats, followed by abdominal closure, the blood radioactivity concentration, tissue distribution, metabolic profile, and excretion/mass balance were evaluated. The results showed that NHS was rapidly absorbed after application, with a C_{max} of 46,100 ng eq/g at 0.5 hours (T_{max}), α distribution-phase half-life ($t_{1/2, \alpha}$) of 15.2 hours, and β elimination-phase half-life ($t_{1/2, \beta}$) of 98.6 hours. In most tissues, radioactivity concentrations peaked at 0.5 hours after implantation. High radioactivity concentrations were observed in renal medulla (left/right), kidney (left), renal cortex (left), liver, small intestinal contents, kidney (right), renal cortex (right), and seminal vesicles. Within 24 hours, approximately 84% of the administered radioactivity was excreted mainly in urine and exhaled air, including metabolites. Although nearly 30% of the administered dose (181 components) remained unidentified in the metabolic profile, approximately 27% of radioactivity was excreted in exhaled air, suggesting possible hydrolysis and oxidation. The applicant explained as follows: Since the decomposition products (NHS, PEG, and glutaric acid) generated from Hemopatch (used as the test article) and Coseal are equivalent and the dose in the study was specified considering the clinical dose of Coseal, extrapolation of the results was considered justified; unreacted COH102, when present in excess during hydrogel formation, is expected to react with tissue surface proteins or undergo hydrolysis in interstitial fluid. Because reports show that PEGs larger than 5 kDa are scarcely metabolized and PEGs primarily excreted via urine, the same is considered applicable to COH102, whose backbone structure is based on [redacted] Da PEG.

The applicant's explanation about the potential effects of different application sites on systemic exposure and metabolism:

When Coseal is applied to the heart, its degradation products are also primarily excreted in urine, as in intraperitoneal application, without any increase in systemic exposure or change in metabolic pathway that would raise safety concerns. This was supported by the following considerations:

- On the surface of the tissue or organ at the application site, the degradation products are released into the interstitial fluid within the applied organ and into the ascites or pleural fluid. Degradation products of larger molecular weight are considered to ultimately be collected by the lymphatic system and enter the blood circulation.
- The major elimination pathway for PEG is reported to be renal excretion,[10,11,12,13] and NHS is also primarily excreted in urine after intraperitoneal application, with low tissue permeability.[14] In the pharmacokinetic studies of hydrogel and NHS, PEG and NHS were confirmed to be largely excreted in urine within 72 hours.
- In an adhesion prevention study using a rabbit cardiac abrasion model with a previous-generation product described later, no residual hydrogel was observed 20 to 21 days after treatment.

[iii] Hemopatch, An absorbable local hemostatic patch made of bovine dermal microfibrillar collagen, coated with COH102 on the tissue-adhesive surface.

The applicant's explanation about the pharmacokinetics of glutaric acid, which is a degradation product of the hydrogel, based on existing information concerning glutaric acid:
Glutaric acid is an endogenous metabolite generated in amino acid metabolism processes, expected to be widely distributed in body fluids due to its hydrophilicity and low molecular weight, and not to accumulate in tissues. In rat metabolism studies of glutaric acid, its main metabolic pathway *in vivo* involves formation of acetate and acetoacetate, with α-ketoglutaric acid as a secondary pathway.[15,16] For adipic acid, a structural analog of glutaric acid, rat metabolism study identified carbon dioxide, urea, glutamic acid, lactic acid, citric acid, and keto-adipic acid as metabolites.[17] Assuming glutaric acid shares a similar metabolic profile, except for forming keto-glutaric acid instead of keto-adipic acid, it is presumed to be extensively metabolized and eliminated via urine and exhalation.

The tolerable intake and toxicological risk of PEG, NHS, and glutaric acid were evaluated based on the results of biological safety and existing data. The maximum clinical dose of Coseal is 24 mL per patient, and tolerability has been demonstrated in clinical experience. Considering the anticipated patient population for Coseal, the tolerable intake of each degradation product of Coseal under a worst-case scenario (assuming a maximum dose of 24 mL for a body weight of 20 kg) was calculated based on available information. Based on the daily exposures of each degradation product released over 7 days after the application of Coseal under the aforementioned worst-case scenario, the toxicological risk of each degradation product was assessed using available information together with the results of biological safety studies conducted on the hydrogel. The applicant explained that no toxicological concerns were anticipated for any of the degradation products.

2.(4).B Outline of the review conducted by PMDA

PMDA comprehensively reviewed the data related to the biological safety of Coseal and concluded that there were no particular issues.

2.(5) Stability and durability

2.(5).A Summary of the data submitted

The applicant submitted the stability data of PEG derivatives for NHS substitution rate of COH102 and SH substitution rate of COH206 after 25 months of storage after manufacture. Additionally, for material degradation caused by radiation sterilization, the applicant submitted test results of NHS and SH substitution rates after irradiation at a dose higher than the maximum sterilization dose (45 ± 4.5 kGy) and 6 months of storage after sterilization.

The applicant omitted the submission of the stability data of the PEG-filled syringe, solution components, and Coseal Spray Set and instead submitted a self-declaration stating that the shelf-life was determined based on the results of necessary stability evaluation in accordance with "Handling of Stability Studies Related to the Determination of the Shelf Life in the Application for Marketing Approvals (Certifications) of Medical Devices (in Japanese)" (PFSB/ELD/OMDE Notification No. 1227-5 dated December 27, 2012). The applicant also omitted the submission of the data on material degradation due to radiation sterilization in accordance with "Partial Revision of the 'Points to Consider in Preparing Summary Technical Documentation Submitted in Applications for Marketing Approval for Medical Devices (in Japanese)'" (PSEHB/MDED Notification No. 0228-7 dated February 28, 2018). Material

degradation was tested using appropriate test samples taking into consideration the maximum possible dose estimated from the dose distribution described in the data on manufacturing process. Based on the results of the test, the applicant submitted a self-declaration assuring the product performance of Coseal.

2.(5).B Outline of the review conducted by PMDA

PMDA asked the applicant to explain the rationale for the acceptance criteria and the appropriateness of evaluating the stability of PEG derivatives and the material degradation due to radiation sterilization solely on the basis of the NHS substitution rate of COH102 and the SH substitution rate of COH206.

The applicant's response:

The NHS substitution degree of PEG derivatives decreases due to hydrolysis of the glutarate ester linking NHS groups to PEG under environmental humidity. Non-clinical studies confirmed that hydrogel formation does not occur below a certain NHS substitution threshold ([redacted]%), while above [redacted]%, the formed hydrogel achieves the required mechanical strength of Coseal.[18] Based on the above findings, the acceptance criteria were established.

The SH substitution degree of PEG derivatives decreases over time due to oxidation of thiol groups. The applicant evaluated the mechanical properties of hydrogels using COH206 samples prepared at different SH substitution rates and established acceptance criteria based on the results.

The acceptance criteria for NHS and SH substitution rates of PEG derivatives were specified considering time-dependent decreases and their impact on hydrogel performance, ensuring that compliance with these criteria guarantees the specifications of the hydrogel.

PMDA accepted the applicant's explanation and concluded that there were no particular issues regarding the submitted data on stability and durability.

2.(6) Performance

2.(6).A Summary of the data submitted

The applicant submitted the supporting data for the performance of Coseal, including performance tests of the hydrogel, performance tests of the Coseal Spray Set, design verification tests of the EasySpray, and animal studies.

The applicant submitted the test results supporting the performance of the hydrogel, including tensile strength, mixing properties, gelation time, swelling, burst strength, and degradation characteristics. For the performance of the Coseal Spray Set, the applicant submitted test results for airtightness, flow rate, pressure resistance, filter performance, compatibility with the solution components, and leakage of the spray head. As design verification tests of the EasySpray, the applicant also submitted test results for overpressure protection and pressure adjustment range. The results of these tests demonstrated that Coseal conformed to the established specifications and exhibited the intended performance.

Animal studies shown in Table 7 were conducted to evaluate the anti-adhesion effect and biodegradability of Coseal.

Regarding the animal studies evaluating the anti-adhesion effect of Coseal, the applicant explained that conducting the evaluation in the abdominal cavity, rather than at the intended cardiac site, was appropriate based on the following considerations:

- The mechanism of action of Coseal involves 2 types of PEG derivatives forming a hydrogel through thioester bonding while covalently binding to tissue. There is no difference between the abdominal cavity and the heart in this mechanism.
- The anti-adhesion effect of Coseal is exerted through the hydrogel functioning as a physical barrier against tissue adhesion, and it is considered unlikely that the application site would influence this effect.
- As described in Section "2.(4) Biological safety," no major concerns were identified regarding the effect of application site differences on systemic exposure or metabolic pathways, and a similar anti-adhesion effect of Coseal was confirmed in the rabbit cardiac abrasion model described later, consistent with that observed in the abdominal models in the animal studies.

Table 7. Summary of animal studies

Study title	Test articles/No. of animals	Study objective
Evaluation of anti-adhesion effect of Coseal in a rabbit peritoneal injury adhesion model	Study device: Coseal Control group: (i) TISSEEL† (ii) Adept‡ (iii) TISSEEL + Adept (iv) Coseal + Adept (v) Lactated Ringer's solution No. of animals: 10 per group	Using a rabbit peritoneal injury adhesion model, the anti-adhesion effect of Coseal on the prevention of diffuse and localized re-adhesion at the site of adhesiolysis was evaluated in comparison with similar adhesion barriers (unapproved in Japan) and with lactated Ringer's solution.
Evaluation of anti-adhesion effect and degradability of Coseal in a rabbit peritoneal injury model	Study device: Coseal (i) Low-dose group (0.05 mL/cm^2) (ii) Medium-dose group (0.1 mL/cm^2) (iii) High-dose group (0.2 mL/cm^2) Control group: Untreated No. of animals: 10 per group	Coseal was sprayed at each dose in a rabbit peritoneal injury model, and its *in vivo* degradation characteristics and anti-adhesion effect were macroscopically evaluated
Evaluation of anti-adhesion effect of Coseal in a rabbit cardiac abrasion model (reference data)	Study device: Previous-generation product Control groups: (i) TISSEEL (ii) Untreated No. of animals: 6 per group	Using a rabbit cardiac abrasion model, the safety and anti-adhesion effects of the previous-generation product were compared with those of the untreated group.

† TISSEEL: A spray-type surgical sealant used for assist of hemostasis or tissue sealing (Approval No. 63E-Import-644; approval cancelled).
‡ Adept: A solution-type adhesion barrier used for laparoscopic adhesiolysis in gynecology (unapproved in Japan).

Evaluation of anti-adhesion effect of Coseal in the rabbit peritoneal injury adhesion model

This study was conducted to evaluate the anti-adhesion effect of Coseal on diffuse and localized re-adhesion at the adhesion detachment site of adhesiolysis. Approximately 30 cm^2 of the rabbit serosal surface was abraded with gauze until petechiae was observed, followed by induction of subserosal haemorrhage by applying pressure to the cecal surface. A portion of the abdominal wall peritoneum and transverse muscle (4.5 × 3 cm) corresponding to the cecal site was excised, and the incision was closed. The abdomen was reopened 14 days after the procedure, and the adhesion area was measured. After adhesiolysis, both lesion sites were treated with each adhesion barrier. Necropsy was performed 14 days after treatment with the adhesion barriers, and adhesion formation (adhesion area of the lesion/non-lesion sites and adhesion strength) was evaluated.

At 14 days after treatment with the adhesion barriers, the adhesion area of the lesion sites was reduced by 90% in the Coseal group compared with before treatment, and adhesion strength was markedly decreased. Favorable results were also observed compared with the lactated Ringer's solution group.

Evaluation of anti-adhesion effect and degradability of Coseal in the rabbit peritoneal injury model

This study was conducted to macroscopsically evaluate the *in vivo* degradation characteristics and anti-adhesion effect of Coseal, with sequential necropsies performed to assess degradation characteristics (time-dependent changes). Approximately 30 cm^2 of the rabbit cecum was abraded, and a 15 cm^2 injury was created by separating the transverse abdominal muscle on the right lateral wall. The lesion on the abdominal wall was then sprayed with Coseal at each dose. On Days 2, 4, 6, 7, and 8 after spraying (2 animals/group; 6 animals/day in total), visual evaluation of the presence or absence of Coseal and adhesion formation (adhesion area and adhesion strength of the lesion sites) was conducted.

As a result, adhesions were observed in 3 animals in the Coseal groups (1 in the low-dose group on Day 2, 1 in the high-dose group on Day 2, and 1 in the low-dose group on Day 8), with adhesion areas ranging from 0.28 cm^2 to 0.81 cm^2. In the untreated group, adhesions were observed in 7 animals, with adhesion areas ranging from 0.25 cm^2 to 19.9 cm^2. Adhesion strength was comparable between the untreated and Coseal groups. Residual Coseal at the treated site was observed in 5 animals on Day 2, 4 animals on Day 4, and 1 animal on Day 6, appearing as a transparent gelatinous material. No residual Coseal was observed on Days 7 and 8, confirming that Coseal degraded within 7 days in the peritoneal cavity. No dose-dependent effect was observed within the dose range (0.05-0.2 mL/cm^2). Considering complete tissue coverage and swelling characteristics, the recommended dose was set as 1 mL/10 cm^2.

As reference data, the applicant submitted an adhesion prevention study using the previous-generation product in a rabbit cardiac abrasion model. After median sternotomy in rabbits, the anterior pericardium was incised (4-5 cm), and the surface of the left ventricular epicardium was abraded with dry gauze for 5 minutes to induce petechial haemorrhage. The abraded epicardial area and pericardial incision site were treated with each adhesion barrier (2-3 mL). At 20 to 21 days after treatment, histopathological examination and assessment of adhesion formation (adhesion area ratio of lesion site to heart and adhesion strength) were performed. In the Coseal group, no adhesion was observed in 50% (3 of 6) of animals, and both the adhesion area ratio and adhesion strength were significantly lower than in the untreated group (P = 0.015 and P = 0.022, respectively). No residual hydrogel was observed in the Coseal group.

2.(6).B Outline of the review conducted by PMDA

PMDA asked the applicant to explain the evaluation of hydrogel adhesive performance, given that adhesion of the hydrogel to tissue at the time of formation is essential for exerting Coseal's anti-adhesion effect as a physical barrier.

The applicant's response:

The adhesive performance of the hydrogel was evaluated using rabbit peritoneal tissue in a hydrogel adhesion test, and the results of this study were additionally submitted. In this test, to assess the adhesive

characteristics according to the degree of hydrogel curing, Coseal was sprayed onto peritoneal tissue and left for 0, 60, 120, or 180 seconds before overlaying with another peritoneal tissue piece to measure the peel strength. Compared with the cured hydrogel, the uncured hydrogel showed stronger tissue adhesion, and a stable adhesion strength was achieved at 60 seconds after spraying.

PMDA comprehensively reviewed the performance of Coseal in the submitted and additional data, and concluded that there were no particular issues.

2.(7) Usability

2.(7).A Summary of the data submitted

The applicant submitted document for Coseal demonstrating conformity to the international standard specifying the usability engineering process for medical devices (IEC 62366-1:2015).

2.(7).B Outline of the review conducted by PMDA

PMDA reviewed the document on conformity to IEC 62366-1 and concluded that there were no particular issues.

2.(8) Method of use

2.(8).A Summary of the data submitted

The applicant submitted data regarding mixing characteristics, gelation time, swelling, tensile strength, and burst strength of the hydrogel prepared 2 hours after dissolution of the PEG derivatives as document on instructions for use of Coseal.

2.(8).B Outline of the review conducted by PMDA

PMDA reviewed the document on the method for use and concluded that there were no particular issues.

3. Conformity to the Requirements Specified in Paragraph 3 of Article 41 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices

3.A Summary of the data submitted

The applicant submitted a declaration of conformity declaring that Coseal 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 Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (hereinafter referred to as "the Essential Principles") (MHLW Public Notice No. 122, 2005).

3.B Outline of the review conducted by PMDA

PMDA reviewed the conformity of Coseal to the Essential Principles.

(1) PMDA's view on the conformity of Coseal to Article 3, which specifies requirements for the performance and function of medical devices, and to Article 6, which specifies the efficacy of medical devices:

As described in Section "6.B Outline of the review conducted by PMDA" below, the submitted clinical study results did not demonstrate the anti-adhesion effect of Coseal in late postoperative phase. Consequently, regardless of whether resternotomy surgery was anticipated, the clinical

significance and utility of using Coseal for general cardiovascular surgery could not be confirmed. Based on the clinical study results, Coseal was used only to patients undergoing extracorporeal VAD implantation surgery. Coseal conforms to Articles 3 and 6.

(2) PMDA's view on the conformity of Coseal to Article 17, which specifies requirements for publicizing information including precautions or the communication of information to users via instructions for use, etc. (hereinafter referred to as "Information on Precautions, etc."):
As described in Section "1.B Outline of the review conducted by PMDA" above and in Section "6.B Outline of the review conducted by PMDA" below, compliance with the specified instructions for use is critical to maintaining an appropriate risk-benefit balance for Coseal. Adequate information should be provided to users through Information on Precautions, etc.

PMDA comprehensively reviewed the conformity of Coseal to the Essential Principles and concluded that there were no particular issues.

4. Risk Management

4.A Summary of the data submitted

The applicant submitted a summary of risk management, the risk management system, and its progress in accordance with ISO 14971:2019 "Medical devices – Application of risk management to medical devices."

4.B Outline of the review conducted by PMDA

PMDA comprehensively reviewed the document on risk management taking into account the discussion presented above in Section "3.B Outline of the review conducted by PMDA" and concluded that there was no particular problem.

5. Manufacturing Process

5.A Summary of the data submitted

The applicant submitted data on the sterilization method of Coseal, including sterilization validation, residual ethylene oxide gas (for the Coseal Spray Set), and bacterial endotoxin testing.

5.B Outline of the review conducted by PMDA

PMDA reviewed the data related to the manufacturing methods and concluded that there were no particular issues.

6. Clinical Data or Alternative Data Accepted by the Minister of Health, Labour and Welfare

6.A Summary of the data submitted

As the clinical study results for evaluating the efficacy and safety of Coseal, the applicant submitted data from a multicenter, prospective, randomized, investigator-initiated clinical study conducted at 3 study sites in Japan (hereinafter referred to as "this clinical study"). This clinical study was conducted with the objective of facilitating the early introduction of Coseal in Japan. The study enrolled patients aged ≥12 years who underwent implantation surgery for an extracorporeal VAD. A total of 30 patients were enrolled and randomized to either the Coseal group or the untreated group. In the initial

implantation surgery for an extracorporeal VAD (the first surgery, assuming the possibility of multiple surgeries), patients assigned to the Coseal group received spray application of Coseal over the surface of the heart and great vessels prior to chest closure, following the extracorporeal VAD implantation. During subsequent resternotomy procedures for extracorporeal VAD explantation or transition to other treatments, the degree of adhesion was assessed and that between the 2 groups was compared.

Table 8 shows an outline of this clinical study.

Table 8. Outline of this clinical study

<table>
<tr><th>Item</th><th>Outline</th></tr>
<tr><td>Study objective</td><td>To evaluate the efficacy of Coseal in preventing postoperative adhesions when sprayed over the surface of the heart/great vessels, and to assess its safety, in patients undergoing open-chest implantation surgery for an extracorporeal VAD to treat cardiogenic circulatory failure.</td></tr>
<tr><td>Study design</td><td>Multicenter, prospective, open-label, randomized, parallel-group study (Coseal group: Untreated group = 1:1)</td></tr>
<tr><td>Target patients</td><td>Patients undergoing open-chest implantation surgery for an extracorporeal VAD due to acute circulatory failure</td></tr>
<tr><td>Inclusion criteria</td><td>(1) Patients aged ≥12 years and <80 years at the time of obtaining consent
(2) Patients requiring extracorporeal VAD implantation due to acute congestive heart failure
(3) Patients who provided written informed consent, either personally or through a legally acceptable representative or close relative</td></tr>
<tr><td>Exclusion criteria</td><td>(1) Patients with a prior cardiac or great vessel surgery
(2) Patients currently participating in another clinical study or scheduled to participate during this study period
(3) Patients deemed unsuitable by the investigator or sub-investigator for participation in this clinical study for any other reason</td></tr>
<tr><td>Sample size</td><td>Total of 30 enrolled patients (16 in the Coseal group and 14 in the untreated group)</td></tr>
<tr><td colspan="2">Efficacy endpoints</td></tr>
<tr><td>Primary endpoints</td><td>(1) Degree of adhesion between the surface of the heart/ great vessels and surrounding tissues (≥2 weeks after the initial surgery)
(2) Number of sites where the adhesion between the surface of the heart/great vessels and the surrounding tissues was classified as Grade ≥2 (≥2 weeks after the initial surgery)

Assessment of adhesion
<u>Evaluators of adhesion</u>
Adhesion was assessed by 2 evaluators, i.e., the operating surgeon at the time of resternotomy and an independent third-party evaluator (a cardiovascular surgeon who was not involved in either the initial or the resternotomy surgery in this clinical study and who had been designated in advance by the investigator for each study site). The third-party evaluator attended the resternotomy surgery and assessed the adhesions at each evaluation site. In cases of disagreement between the 2 evaluators, the final assessment was determined through discussion until consensus was reached.

<u>Evaluation criteria</u>
The extent of adhesion was quantified using a grade scoring system defined below. When the macroscopic and surgical assessments differed, the surgical grade was prioritized. During adhesiolysis, blunt dissection was always performed first, followed by sharp dissection if necessary, based on the feasibility of blunt dissection.
<table>
<tr><th>Grade</th><th>Definition</th><th colspan="2">Detailed description</th></tr>
<tr><td rowspan="2">0</td><td rowspan="2">No adhesion</td><td>Macroscopic</td><td>No visible adhesion</td></tr>
<tr><td>Surgical</td><td>Neither blunt nor sharp dissection required.</td></tr>
<tr><td rowspan="2">1</td><td rowspan="2">Membranous adhesion without neovascularization</td><td>Macroscopic</td><td>Partial adhesion visible</td></tr>
<tr><td>Surgical</td><td>All adhesions can be separated by blunt (manual) dissection, and no hemostatic procedure is required.</td></tr>
<tr><td rowspan="2">2</td><td rowspan="2">Moderate-thickness adhesion with partial neovascularization</td><td>Macroscopic</td><td>Adhesion visible</td></tr>
<tr><td>Surgical</td><td>A mixture of areas that can be separated by blunt dissection and areas requiring sharp dissection and hemostasis (intermediate between Grade 1 and Grade 3).</td></tr>
<tr><td rowspan="2">3</td><td rowspan="2">Dense adhesion with marked neovascularization</td><td>Macroscopic</td><td>Adhesion visible; boundaries of adhesions difficult to identify (adhered surfaces inseparable or not visually distinguishable).</td></tr>
<tr><td>Surgical</td><td>Sharp dissection and hemostatic procedures required for nearly all areas of adhesion.</td></tr>
</table>
<u>Sites for evaluation</u>
Adhesion Grade (adhesion score) was assessed for each of the following 5 sites:
(a) Anterior surface of the right ventricle
(b) Right atrial lateral wall
(c) Diaphragmatic surface
(d) Left ventricular lateral wall
(e) Periaortic region</td></tr>
</table>

	Evaluation method For each subject, both the "total adhesion score across 5 sites" and "number of sites with adhesion Grade ≥2 among 5 sites" were calculated, and the adhesion status between the 2 groups was compared.
Secondary endpoints	(1) Degree of adhesion between the surface of the heart/ great vessels and surrounding tissues (≥1 week after the initial surgery) (2) Number of sites where the adhesion between the surface of the heart/ great vessels and the surrounding tissues was classified as Grade ≥2 (≥1 week after the initial surgery) (3) Survival (avoidance of death) (4) Performance of resternotomy for hemostasis (5) Blood transfusion volume during resternotomy surgery (6) Avoidance of mediastinitis requiring surgical intervention
Additional analyses	• Blood transfusion volume during resternotomy categorized by reason for transfusion • Time required for adhesiolysis during resternotomy
Safety endpoints	(4 weeks after the initial surgery)
	• Adverse events • Device malfunctions
Observation period	For each subject, the observation period continued until either resternotomy surgery or completion of safety assessment (4 weeks after the initial surgery), whichever occurred later. However, after the target number of subjects for efficacy evaluation had been achieved, the observation period for the final enrolled subject was extended to 12 weeks after the initial surgery, at which point the study was concluded for all subjects under observation.
Method of use	After implantation of the extracorporeal VAD and before chest closure, the entire amount of Coseal (8 mL per subject) was sprayed uniformly over the surface of the heart and great vessels.
Concomitant therapy	"Gore-Tex EPTFE Patch II" (Approval number: 16000BZY00180000) In principle, concomitant use was not permitted. Concomitant use for pericardial reinforcement was allowed only in patients for whom tissue or graft damage due to sternal reentry during resternotomy was anticipated.
Study sites	3 sites
Study period	January 2020 to August 2021

For the primary endpoint of this clinical study, the anti-adhesion effect of Coseal was evaluated in terms of both overall and local adhesion at the application sites. Specifically, the primary endpoints were the "degree of adhesion between the surface of the heart/great vessels and the surrounding tissues" (total adhesion score) and the "number of sites where the adhesion between the surface of the heart/great vessels and the surrounding tissues was classified as Grade ≥2," assessed at ≥2 weeks after the initial surgery. Basic research on adhesion formation mechanisms reported that adhesion formation occurs within 1 to 2 weeks postoperatively. Most patients with an extracorporeal VAD tend to be weaned within approximately 1 month in clinical practice. Taken these into consideration, patients undergoing resternotomy ≥2 weeks after the initial surgery were defined as appropriate for evaluation of the primary endpoints. The timing and procedures of resternotomy were determined through discussion by the heart team during clinical practice, and adhesion assessments were conducted at the time of resternotomy when intervention at the evaluation sites occurred.

The required number of subjects for the evaluation of the primary endpoints was determined by taking into account an adjustment for multiplicity of statistical testing. Based on the assumptions and considerations described below, and assuming a dropout rate of up to approximately 30%, the total sample size was 30 subjects.

- Based on an observational study[19] of Coseal in pediatric patients with congenital heart disease, the mean difference in the "total adhesion score across 5 sites" between the 2 groups was assumed to be 5 (5 in the Coseal group and 10 in the untreated group), with a score range of 10 and an assumed standard deviation (SD) of 3.5 for the total adhesion score in each group.

- With a two-sided significance level of 5% equally allocated (2.5% each) to the 2 primary endpoints, the required sample size for detecting a difference in the “total adhesion score across 5 sites” with 85% power at a 2.5% significance level was calculated to be 24 subjects.
- When the sample size was 24 subjects, the statistical power for comparing the “number of sites with adhesion Grade ≥2 among 5 sites” between the 2 groups was estimated by simulation to be approximately 80% to 90%.

Figure 4 shows the breakdown of the analysis population in this clinical study. Among the 31 subjects who provided informed consent, 30 subjects were enrolled. The remaining 1 subject who did not meet the inclusion criteria was excluded. The enrolled subjects were randomized to the Coseal group (16 subjects) or the untreated group (14 subjects), and underwent implantation of the extracorporeal VAD. Among them, resternotomy with adhesion assessment was performed in 28 subjects (14 in the Coseal group, 14 in the untreated group). The remaining 2 subjects in the Coseal group whose observations were incomplete were excluded. Of the 2 incomplete cases, 1 subject was discontinued because the underlying disease was deemed irreversible and resternotomy was not expected, and 1 subject died (cerebral infarction) during the study period. Protocol deviation was identified in 1 subject in the Coseal group. The deviation pertained to the method of application, i.e., due to a malfunction of the EasySpray device, Coseal was applied manually rather than by spray administration, constituting a deviation from the prescribed method of use.

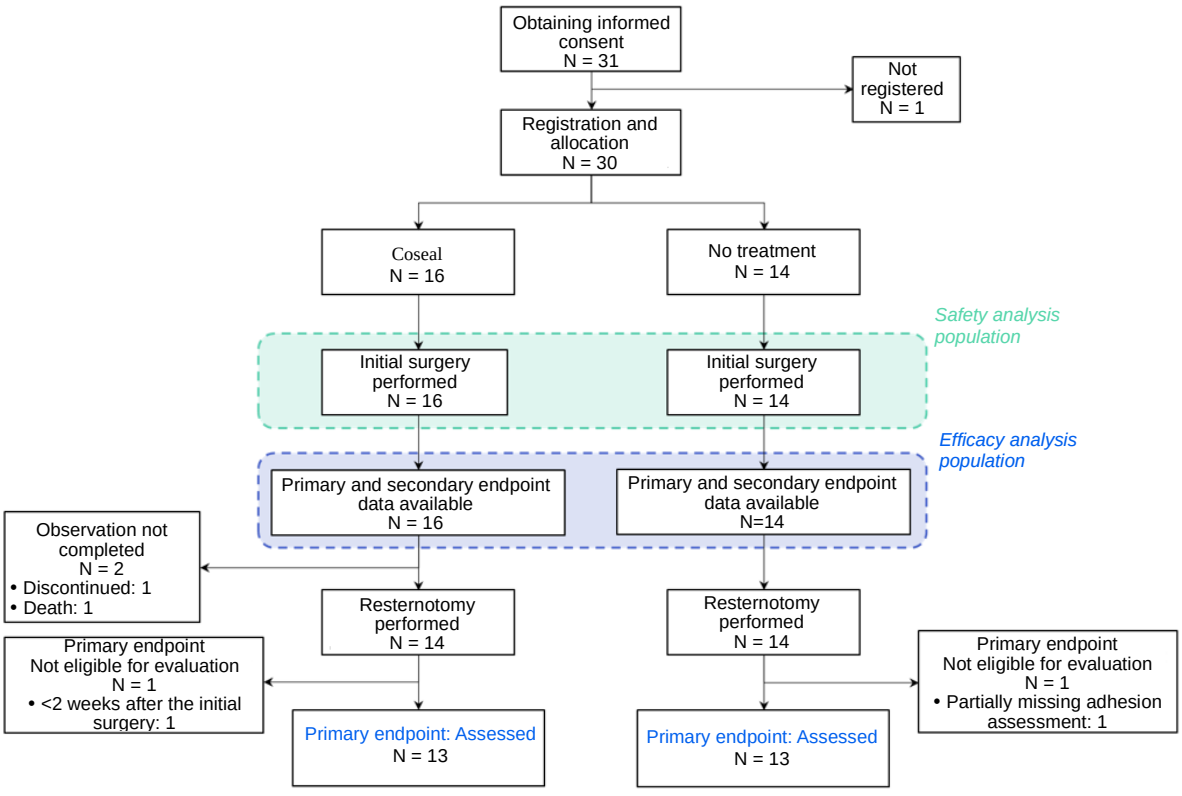


Figure 4. Breakdown of the analysis population

6.A.(1) Patient characteristics

Table 9 presents the demographic and baseline characteristics of the safety analysis population. The median (minimum, maximum) age of the subjects was 49.5 years (31, 62) in the Coseal group and 38.5

years (17, 78) in the untreated group. Although the untreated group included younger subjects, no notable differences were observed between the 2 groups in other baseline characteristics.

Table 9. Demographic and baseline characteristics (safety analysis population)

Parameter		Coseal (N = 16)	Untreated (N = 14)
Sex	Male	7 (43.8)	11 (78.6)
	Female	9 (56.2)	3 (21.4)
Age [years]	Mean ± SD	50.5 ± 9.1	39.2 ± 17.8
	Median (Min, Max)	49.5 (31, 62)	38.5 (17, 78)
Height [cm]	Mean ± SD	162.05 ± 6.89	164.01 ± 9.97
	Median (Min, Max)	163.00 (148.0, 175.0)	163.50 (141.5, 180.0)
Body weight [kg]	Mean ± SD	61.21 ± 14.48	62.58 ± 13.09
	Median (Min, Max)	60.55 (40.0, 85.0)	63.50 (27.8, 80.0)
Underlying disease	Acute myocardial infarction	3 (18.8%)	4 (28.6%)
	Fulminant myocarditis	5 (31.2%)	5 (35.7%)
	Dilated cardiomyopathy	6 (37.5%)	3 (21.4%)
	Other cardiogenic circulatory failure	2 (12.5%)	2 (14.3%)
Comorbidities	None	1 (6.3%)	1 (7.1%)
	Yes	15 (93.8%)	13 (92.9%)
Alcohol consumption	None	10 (62.5%)	8 (57.1%)
	Yes	6 (37.5%)	6 (42.9%)
Smoking history	Current smoker	3 (18.8%)	3 (21.4%)
	Former smoker	2 (12.5%)	0 (0.0%)
	Never smoked	11 (68.8%)	11 (78.6%)
Systolic blood pressure [mmHg]	Mean ± SD	98.4 ± 23.3	101.8 ±18.4
Diastolic blood pressure [mmHg]	Mean ± SD	64.8 ± 17.1	63.2 ± 17.1
Pulse rate [bpm]	Mean ± SD	88.9 ± 21.5	98.1 ± 21.7
Abnormal chest X-ray findings	None	1 (6.3%)	0 (0.0%)
	Yes	14 (87.5%)	14 (100.0%)
	Not performed	1 (6.3%)	0 (0.0%)
Mitral regurgitation	Trivial	4 (25.0%)	7 (50.0%)
	Mild	6 (37.5%)	3 (21.4%)
	Moderate	3 (18.8%)	0 (0.0%)
	Severe	1 (6.2%)	2 (14.3%)
	None	2 (12.5%)	2 (14.3%)
Left ventricular ejection fraction [%]	Mean ± SD	15.9 ± 7.4	14.6 ± 11.7
Left ventricular end-diastolic diameter [mm]	Mean ± SD	56.9 ± 16.5	51.6 ± 14.8
Left ventricular end-systolic diameter [mm]	Mean ± SD	51.5 ± 16.0	46.9 ± 15.4

* Categorical variables are presented as n (%).

6.A.(2) Status of initial surgery

Table 10 shows the status of extracorporeal VAD implantation and surgical procedures during the initial surgery. Table 11 shows the usage status of device components comprising the extracorporeal VAD system. Use of the “Gore-Tex EPTFE Patch II” for pericardial repair was reported in 1 patient in the Coseal group and 1 patient in the untreated group. In the Coseal group, Coseal was administered at the specified dose of 8 mL in all patients.

Table 10. Status of extracorporeal VAD implantation and surgical procedures at the time of initial surgery

Parameter	Status	Coseal (N = 16)	Untreated (N = 14)
Purpose of treatment	LVAD only	13 (81.2%)	9 (64.3%)
	RVAD* only	0 (0.0%)	0 (0.0%)
	BiVAD†	3 (18.8%)	5 (35.7%)
LVAD			
Drainage site	Left ventricle	16 (100.0%)	14 (100.0%)
Return site	Ascending aorta	16 (100.0%)	14 (100.0%)
Artificial lung	None	7 (43.7%)	8 (57.1%)
	Yes	9 (56.3%)	6 (42.9%)
RVAD			
Drainage site	Right ventricle	0 (0.0%)	1 (20.0%)
	Right atrium	2 (66.7%)	2 (40.0%)
	Femoral vein	1 (33.3%)	2 (40.0%)
Return site	Ascending aorta	1 (33.3%)	0 (0.0%)
	Pulmonary artery	2 (66.7%)	5 (100.0%)
Artificial lung	None	0 (0.0%)	2 (40.0%)
	Yes	3 (100.0%)	3 (60.0%)
Pericardial repair			
Patch	None	15 (93.8%)	13 (92.9%)
	Gore-Tex EPTFE Patch II	1 (6.2%)	1 (7.1%)

* RVAD: Right ventricular assist device, †BiVAD: Biventricular assist device

Table 11. Use of components comprising the extracorporeal VAD system

Type	Device name*	Coseal (N = 16)	Untreated (N = 14)
LVAD		N = 16	N = 14
Blood pump	Single-use extracorporeal assistant artificial cardiac pump	0 (0.0%)	1 (7.1%)
	Nipro ventricular assist device set	0 (0.0%)	1 (7.1%)
	Single-use centrifugal pump	16 (100.0%)	13 (92.9%)
	Biofloat	12 (75.0%)	12 (85.7%)
	Mera centrifugal pump	1 (6.3%)	0 (0.0%)
	Terumo Capiox EBS	3 (18.8%)	0 (0.0%)
	Terumo Capiox FX	0 (0.0%)	1 (7.1%)
Drainage cannula	Nipro ventricular assist device set (drainage cannula)	14 (87.5%)	14 (100.0%)
	Extracorporeal circulation cannula Flexmate	1 (6.3%)	0 (0.0%)
	Malleable cannula	1 (6.3%)	0 (0.0%)
Return cannula	Nipro ventricular assist device set (return cannula)	7 (43.8%)	3 (21.4%)
	Gelweave	6 (37.5%)	9 (64.3%)
	J Graft Shield	3 (18.8%)	2 (14.3%)
Artificial lung	None	7 (43.8%)	8 (57.1%)
	Biofloat	1 (6.3%)	0 (0.0%)
	Biocube	4 (25.0%)	5 (35.7%)
	Mera NHP Excelung NSH-R	1 (6.3%)	0 (0.0%)
	Terumo Capiox EBS	3 (18.8%)	0 (0.0%)
	Terumo Capiox FX	0 (0.0%)	1 (7.1%)
RVAD		N = 3	N = 5
Blood pump	Single-use extracorporeal assistant artificial cardiac pump	0 (0.0%)	0 (0.0%)
	Single-use centrifugal pump	3 (100.0%)	5 (100.0%)
	Biofloat	0 (0.0%)	1 (20.0%)
	Mera centrifugal pump	1 (33.3%)	0 (0.0%)
	ROTAFLOW	0 (0.0%)	1 (20.0%)
	Terumo Capiox EBS	2 (66.7%)	3 (60.0%)
Drainage cannula	Nipro ventricular assist device set (drainage cannula)	0 (0.0%)	1 (20.0%)
	BioMedicus	2 (66.7%)	3 (60.0%)
	Edwards extracorporeal circulation cannula NC	1 (33.3%)	1 (20.0%)
Return cannula	Nipro ventricular assist device set (return cannula)	1 (33.3%)	1 (20.0%)
	BioMedicus	2 (66.7%)	2 (40.0%)
	Gelweave	0 (0.0%)	1 (20.0%)
	Extracorporeal circulation cannula Flexmate	0 (0.0%)	1 (20.0%)
Artificial lung	None	0 (0.0%)	2 (40.0%)
	Biocube	0 (0.0%)	1 (20.0%)
	Mera NHP Excelung NSH-R	1 (33.3%)	0 (0.0%)
	Terumo Capiox EBS	2 (66.7%)	2 (40.0%)

* Device names are presented as reported by the clinical study sites.

6.A.(3) Status of resternotomy

Table 12 shows the number and reasons for thoracotomies during the observation period prior to the resternotomy for assessment in the 28 patients who underwent resternotomy and adhesion assessment. In both groups, thoracotomy for hemostasis was performed in more than half of the patients during the observation period. Table 13 presents the reasons for resternotomy in which adhesion assessment was performed. Table 14 presents the number of days from the initial surgery to the resternotomy for assessment. The median (minimum, maximum) number of days from the initial surgery to the resternotomy for adhesion assessment was 23.0 days (15, 74) in the Coseal group and 35.0 days (15, 195) in the untreated group, showing a tendency toward a longer duration in the untreated group.

Table 12. Number and reasons for thoracotomies performed during the observation period until the resternotomy for adhesion assessment

Number and reason	Coseal (N = 14)	Untreated (N = 14)
0	5 (35.8%)	5 (35.8%)
1 For hemostasis Blood pump replacement	7 (50.0%) 6 cases 1 case	6 (42.9%) 6 cases 0 cases
2 For hemostasis	1 (7.1%) 2 cases	1 (7.1%) 2 cases
3 For hemostasis	1 (7.1%) 3 cases	2 (14.3%) 6 cases
Mean ± SD	0.86 ± 0.83	1.0 ± 1.0

Table 13. Reasons for resternotomy in which adhesion assessment was performed

Reason	Coseal (N = 14)	Untreated (N = 14)
Mediastinitis treatment	0 (0.0%)	1 (7.1%)
Hemostasis	0 (0.0%)	1 (7.1%)
VAD weaning*	14 (100.0%)	8 (57.1%)
RVAD implantation	0 (0.0%)	3 (21.4%)
Other	0 (0.0%)	1† (7.1%)

* Including transition to implanted LVAD or intra-aortic balloon pumping (IABP).
† Case of organ harvesting and VAD removal following legal determination of brain death

Table 14. Days from the initial surgery to the resternotomy for adhesion assessment*

Days [day]	Coseal (N = 13)	Untreated (N = 13)
Mean ± SD	31.5 ± 20.5	48.0 ± 49.2
Median (Min, Max)	23.0 (15, 74)	35.0 (15, 195)

* Among 28 subjects who underwent resternotomy and adhesion assessment, the number of days was calculated for 26 subjects included in the analysis of the primary endpoint, with the date of thoracotomy defined as Day 1.

6.A.(4) Results of the primary endpoint

Among the 28 subjects who underwent resternotomy and adhesion assessment, 26 subjects (13 in the Coseal group and 13 in the untreated group) were included in the analysis. The remaining 2 subjects were excluded: One subject who did not undergo assessment on the left ventricular lateral wall due to safety considerations during withdrawal from a biventricular assist device (BiVAD) to a right ventricular assist device (RVAD) and 1 subject who underwent resternotomy and adhesion assessment within 2 weeks after the initial surgery. Table 15 shows the adhesion scores for each assessment site.

Table 15. Adhesion scores at each assessment site

Assessment site		Coseal (N = 13)	Untreated (N = 13)
(a) Right ventricular anterior surface	Mean ± SD	0.8 ± 0.9	2.3 ± 0.9
	Median (Min, Max)	1.0 (0, 2)	3.0 (1, 3)
(b) Right atrial lateral surface	Mean ± SD	0.5 ± 0.5	2.2 ± 0.8
	Median (Min, Max)	1.0 (0, 1)	2.0 (1, 3)
(c) Diaphragmatic surface	Mean ± SD	0.8 ± 0.6	2.5 ± 0.5
	Median (Min, Max)	1.0 (0, 2)	3.0 (2, 3)
(d) Ventricular lateral surface	Mean ± SD	0.7 ± 0.6	2.4 ± 0.5
	Median (Min, Max)	1.0 (0, 2)	2.0 (2, 3)
(e) Periaortic area	Mean ± SD	0.7 ± 0.6	2.7 ± 0.5
	Median (Min, Max)	1.0 (0, 2)	3.0 (2, 3)

6.A.(4).1) Degree of adhesion between the surface of the heart/great vessels and the surrounding tissues (≥2 weeks after the initial surgery)

Table 16 shows the results for "degree of adhesion between the surface of the heart/great vessels and the surrounding tissues (≥2 weeks after the initial surgery)" (calculated as the total adhesion score across 5 sites). The mean ± SD values were 3.5 ± 2.4 in the Coseal group and 12.1 ± 2.7 in the untreated group. The adhesion score was significantly lower in the Coseal group than in the untreated group (Welch's t-test, $P < 0.0001$).

Table 16. Results for the primary endpoint "degree of adhesion between the surface of the heart/great vessels and the surrounding tissues (≥2 weeks after the initial surgery)"

Total adhesion score across 5 sites	Coseal (N = 13)	Untreated (N = 13)
Mean ± SD	3.5 ± 2.4	12.1 ± 2.7
Median (Min, Max)	4.0 (0, 7)	12.0 (8, 15)
[95% CI for mean]	[2.1, 5.0]	[10.5, 13.7]
Welch's t-test	$P < 0.0001$	
Difference in means	-8.5	
[95% CI for difference in means]	[-10.6, -6.5]	

In order to examine the relationship between the degree of adhesion and the interval until the resternotomy, an analysis of covariance of "total adhesion score across 5 sites" was performed using the "number of days from the initial surgery to the resternotomy for adhesion assessment" as a covariate. Figure 5 and Table 17 show results. The mean ± standard error for each group was 3.8 ± 0.6 in the Coseal group and 11.8 ± 0.6 in the untreated group, with a mean difference of –8.0 (95% confidence interval [CI], –9.9, –6.1). Furthermore, the "number of days from the initial surgery to the resternotomy for adhesion assessment" was divided into the following 4 categories: "2 to 4 weeks after the initial surgery," "4 to 6 weeks after the initial surgery," "6 to 8 weeks after the initial surgery," and "≥8 weeks after the initial surgery." Table 18 shows the results of the comparison of adhesion scores between the 2 groups in each category. In all time periods, the adhesion scores were lower (indicating improvement) in the Coseal group than in the untreated group.

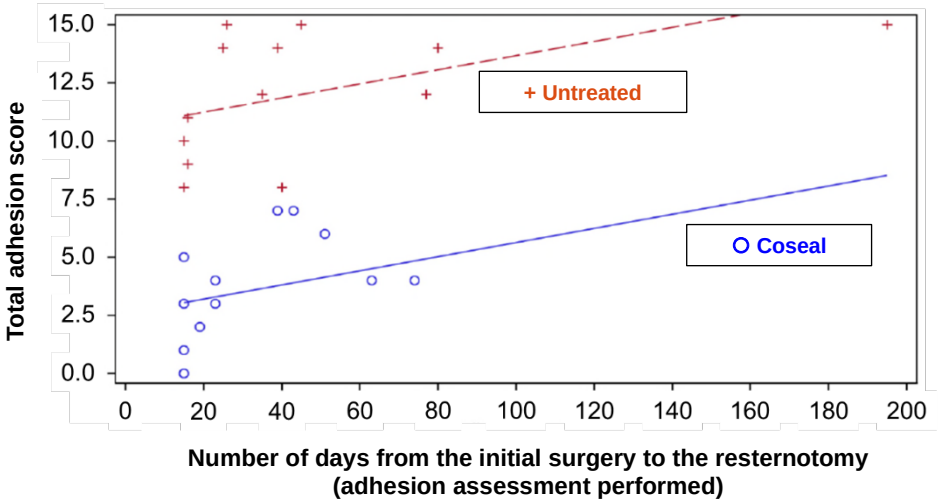


Figure 5. Comparison of the total adhesion scores by analysis of covariance

Table 17. Comparison of total adhesion scores (mean ± standard error) by analysis of covariance

	Untreated (N = 13)	Coseal (N = 13)	Difference [95% CI]
Adhesion score	12.1 ± 0.7	3.5 ± 0.7	-8.5 [-10.6, -6.5]
Adhesion score by analysis of covariance	11.8 ± 0.6	3.8 ± 0.6	-8.0 [-9.9, -6.1]

Table 18. Distribution of the total adhesion scores by timing of resternotomy for adhesion assessment

Period from initial surgery to resternotomy	2-4 weeks		4-6 weeks		6-8 weeks		≥8 weeks	
	Coseal	Untreated	Coseal	Untreated	Coseal	Untreated	Coseal	Untreated
Number of subjects	8	6	1	3	2	1	2	3
Mean ± SD	2.3 ± 1.8	11.2 ± 2.8	7.0	11.3 ± 3.1	6.5 ± 0.7	15.0	4.0 ± 0.0	13.7 ± 1.5
Median (min, max)	2.5 (0, 5)	10.5 (8, 15)	7.0 (-, -)	12.0 (8, 14)	6.5 (6, 7)	15.0 (-, -)	4.0 (4, 4)	14.0 (12, 15)
[95% CI for Mean]	[0.7, 3.8]	[8.2, 14.1]	[-, -]	[3.7, 18.9]	[0.1, 12.9]	[-, -]	[4.0, 4.0]	[9.9, 17.5]
Difference in means	-8.9		-4.3		-8.5		-9.7	
[95% CI for difference in means]	[-11.9, -5.9]		[-, -]		[-, -]		[-13.5, -5.9]	

6.A.(4).2) Number of sites with adhesion Grade ≥2 between the surface of the heart/great vessels and the surrounding tissues (≥2 weeks after the initial surgery)

Table 19 shows the results for the "number of sites with adhesion Grade ≥2 between the surface of the heart/great vessels and the surrounding tissues (≥2 weeks after the initial surgery)" (defined as the number of sites with adhesion Grade ≥2 among 5 sites). The number of sites with adhesion Grade ≥2 was significantly lower in the Coseal group than in the untreated group (Fisher's exact test, $P < 0.0001$).

Table 19. Results for the primary endpoint "number of sites with adhesion Grade ≥2 between the surface of the heart/great vessels and the surrounding tissues (≥2 weeks after the initial surgery)"

Number of sites with adhesion Grade ≥2 among 5 sites	Coseal (N = 13)	Untreated (N = 13)
0	9 (69.2%)	0 (0.0%)
1	2 (15.4%)	0 (0.0%)
2	1 (7.7%)	0 (0.0%)
3	1 (7.7%)	2 (15.4%)
4	0 (0.0%)	3 (23.1%)
5	0 (0.0%)	8 (61.5%)
Fisher's exact test	$P < 0.0001$	

As part of the analysis of the relationship between adhesion status and the interval until resternotomy, Table 20 shows the results by the timing of resternotomy for adhesion assessment. In the Coseal group, 1 subject had 2 sites with adhesion Grade ≥2 at 4 to 6 weeks after the initial surgery, and 1 subject had 3 sites with adhesion Grade ≥2 at 6 to 8 weeks after the initial surgery. However, no subject had ≥2 sites with adhesion Grade ≥2 at ≥8 weeks after the initial surgery. No temporal trend toward an increase in the number of sites with adhesion Grade ≥2 was observed in the Coseal group.

Table 20. Distribution of the "number of sites with adhesion Grade ≥2" by timing of resternotomy for adhesion assessment

Period from initial surgery to resternotomy	2-4 weeks		4-6 weeks		6-8 weeks		≥8 weeks	
	Coseal	Untreated	Coseal	Untreated	Coseal	Untreated	Coseal	Untreated
Number of patients	8	6	1	3	2	1	2	3
0	8 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)
1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)	1 (50.0%)	0 (0.0%)
2	0 (0.0%)	0 (0.0%)	1 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
3	0 (0.0%)	1 (16.7%)	0 (0.0%)	1 (33.3%)	1 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
4	0 (0.0%)	3 (50.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
5	0 (0.0%)	2 (33.3%)	0 (0.0%)	2 (66.7%)	0 (0.0%)	1 (100.0%)	0 (0.0%)	3 (100.0%)

6.A.(5) Results of secondary and additional analyses

6.A.(5).1) Degree of adhesion between the surface of the heart/great vessels and the surrounding tissues (≥1 week after the initial surgery)

Of the 28 subjects who underwent resternotomy and adhesion assessment, 27 subjects (14 in the Coseal group and 13 in the untreated group) were included in the analysis. The remaining 1 subject in the untreated group was excluded from the analysis because assessment of the left ventricular lateral wall was not performed for safety reasons during weaning from a BiVAD to an RVAD.

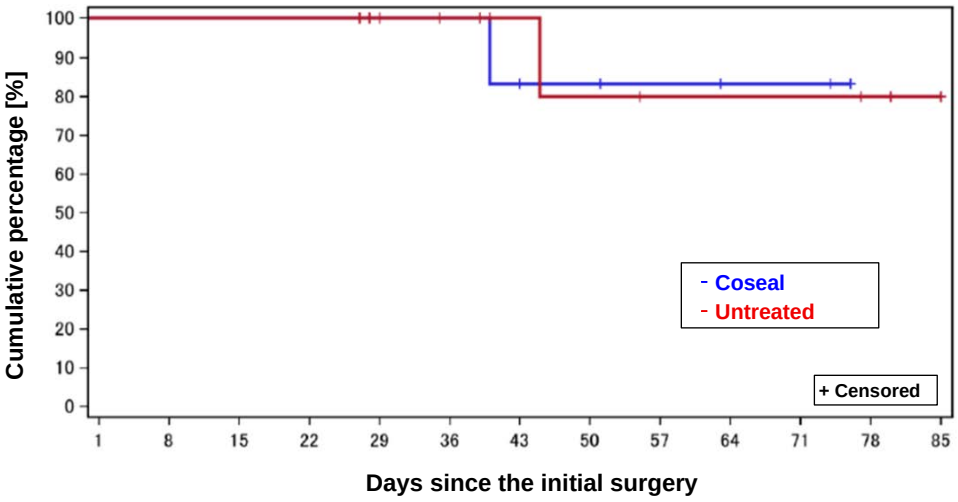
The total adhesion score (sum of scores for 5 sites) for "degree of adhesion between the surface of the heart/great vessels and the surrounding tissues (≥1 week after the initial surgery)" was 3.3 ± 2.5 in the Coseal group and 12.1 ± 2.7 in the untreated group. Consistent with the primary endpoint (≥2 weeks after the initial surgery), the degree of adhesion was significantly lower in the Coseal group than in the untreated group (Welch's t-test, $P < 0.0001$).

6.A.(5).2) Number of sites with adhesion Grade ≥2 between the surface of the heart/great vessels and the surrounding tissues (≥1 week after the initial surgery)

The "number of sites with adhesion Grade ≥2 between the surface of the heart/great vessels and the surrounding tissues (≥1 week after the initial surgery)" (defined as the number of sites with adhesion Grade ≥2 among 5 sites) was as follows in the Coseal group: 0 sites in 10 subjects (71.4%), 1 site in 2 subjects (14.3%), and 2 and 3 sites in 1 subject (7.1%) each. Consistent with the results of primary endpoint (≥2 weeks after the initial surgery), the number of sites with adhesion Grade ≥2 was significantly lower in the Coseal group than in the untreated group (Fisher's exact test, $P < 0.0001$).

6.A.(5).3) Avoidance of death

Figure 6 shows the Kaplan–Meier curve for survival up to 12 weeks after the initial surgery in the efficacy analysis population. During the adverse event observation period, death (cerebral infarction) occurred in 1 subject in the Coseal group, and during the efficacy evaluation period outside the adverse event observation period, death (cerebral haemorrhage) occurred in 1 subject in the untreated group. No significant difference was observed between the 2 groups (log-rank test [exact method], $P = 0.9372$).



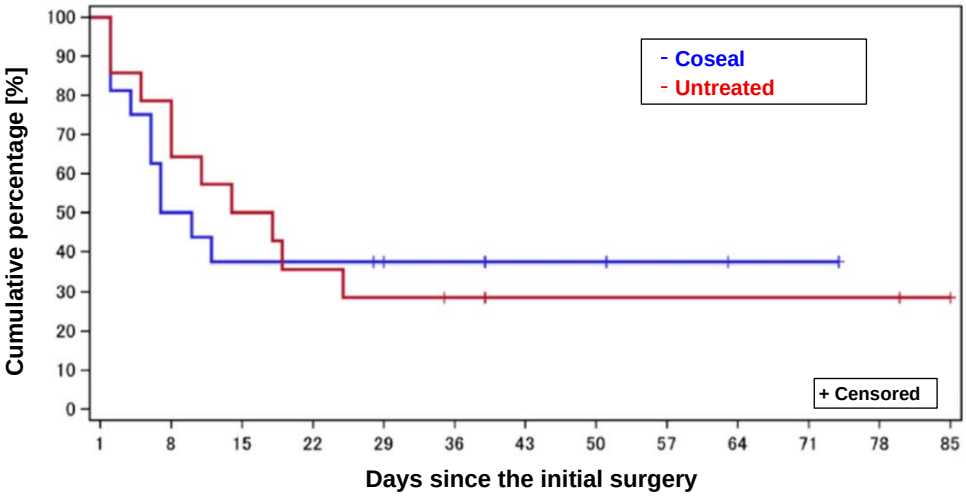
	Days	Day of initial surgery	14	28	84
Coseal	At risk	16	16	14	-
	Cumulative number of deaths		0	0	-
	Cumulative survival proportion (%)		100.0	100.0	-
Untreated	At risk	14	14	11	1
	Cumulative number of deaths		0	0	1
	Cumulative survival proportion (%)		100.0	100.0	80.0

Log-rank test (exact method), $P = 0.9372$

Figure 6. Kaplan–Meier estimate of overall survival

6.A.(5).4) Performance of resternotomy for hemostasis

Figure 7 shows the Kaplan–Meier curve showing avoidance of resternotomy for hemostasis up to 12 weeks after the initial surgery in the efficacy analysis population. In this clinical study, up to 3 resternotomies for hemostasis were confirmed prior to the resternotomy for adhesion assessment (Table 12). No significant difference in the incidence of resternotomy for hemostasis was observed between the 2 groups (log-rank test [exact method], $P = 0.9394$).



	Days	Date of initial surgery	14	28	84
Coseal	At risk	16	6	5	-
	Cumulative number of resternotomies for hemostasis		10	10	-
	Cumulative avoidance proportion (%)		37.5	37.5	-
Untreated	At risk	14	7	4	1
	Cumulative number of resternotomies for hemostasis		7	10	10
	Cumulative avoidance proportion (%)		50.0	28.6	28.6

Log-rank test (exact method), $P = 0.9394$

Figure 7. Kaplan–Meier estimate of avoidance of resternotomy for hemostasis

6.A.(5).5) Blood transfusion volume during resternotomy surgery

Table 21 shows summary statistics for the blood transfusion volume during resternotomy for adhesion assessment in the 28 subjects who underwent resternotomy and adhesion assessment. The blood transfusion volume during resternotomy was 2909.3 ± 1106.8 mL in the Coseal group and 1890.0 ± 955.6 mL in the untreated group. The blood transfusion volume was significantly lower in the untreated group than in the Coseal group (Wilcoxon rank-sum test [exact method], $P = 0.0469$).

Table 21. Blood transfusion volume during resternotomy for adhesion assessment

Blood transfusion volume [mL]	Coseal (N = 14)	Untreated (N = 14)
Mean ± SD	2909.3 ± 1106.8	1890.0 ± 955.6
Median (Min, Max)	2520.0 (1960, 5600)	2190.0 (0,† 3360)
[95% CI for median]	[2240.0, 3360.0]	[1360.0, 2520.0]
Difference in median*	765.0	
[95% CI for difference in mean]*	[0.0, 1680]	

* Hodges–Lehmann estimation method; the difference in medians corresponds to the Hodges–Lehmann point estimate.
† Includes 1 subject who underwent organ harvesting and VAD removal following a legally determined brain death diagnosis.

Table 22 shows additional analyses of blood transfusion volume during resternotomy for adhesion assessment, stratified by primary reason for transfusion. The primary reason for transfusion was recorded by the investigator for each subject. Use of cardiopulmonary bypass (CPB) during the resternotomy was reported in 14 subjects (100.0%) in the Coseal group and in 9 subjects (69.2%) in the untreated group. Transfusions due to bleeding associated with adhesiolysis were less frequent in the Coseal group (1 subject) than the untreated group (6 subjects).

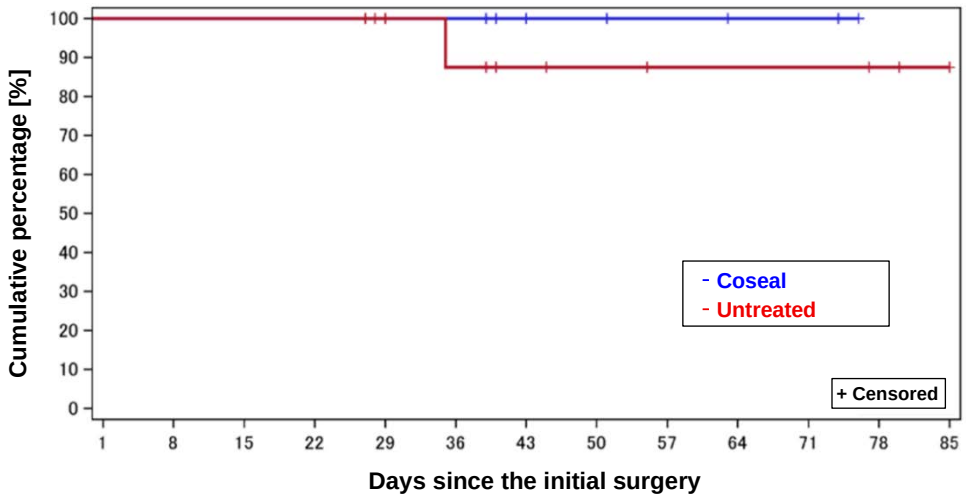
Table 22. Blood transfusion volume during resternotomy for adhesion assessment by primary reason for transfusion

	Overall		Bleeding due to adhesiolysis		Use of CPB*		Anaemia	
	Coseal	Untreated	Coseal	Untreated	Coseal	Untreated	Coseal	Untreated
Number of subjects	14	13†	1 (7.1%)	6 (46.2%)	12 (85.7%)	6 (46.2%)	1 (7.1%)	1 (7.7%)
Use of CPB	14 (100.0%)	9 (69.2%)	1 (100.0%)	3 (50.0%)	12 (100.0%)	6 (100.0%)	1 (100.0%)	0 (0.0%)
Blood transfusion volume [mL]								
Mean	2909.3	2035.4	2520.0	1750.0	2984.2	2566.7	2400.0	560.0
SD	1106.8	817.7	-	661.6	1185.0	543.3	-	-
Median	2520.0	2420.0	2520.0	1680.0	2660.0	2520.0	2400.0	560.0
Min	1960	560	-	840	1960	1680	-	-
Max	5600	3360	-	2520	5600	3360	-	-

* Includes procedures performed as part of transition to subsequent therapies such as VAD removal or replacement, RVAD implantation, or implantation of an implantable LVAD.
† Excludes one subject who underwent organ harvesting and VAD removal following legally determined brain death.

6.A.(5).6) Avoidance of mediastinitis requiring surgical intervention

Figure 8 shows the Kaplan–Meier curve for avoidance of mediastinitis requiring surgical intervention up to 12 weeks after the initial surgery in the efficacy analysis population. No significant difference was observed between the 2 groups (log-rank test [exact method], $P = 0.3496$).



	Days	Date of initial surgery	14	28	84
Coseal	At risk	16	16	14	-
	Cumulative number of surgical interventions		0	0	-
	Cumulative avoidance proportion (%)		100.0	100.0	-
Untreated	At risk	14	14	11	1
	Cumulative number of surgical interventions		0	0	1
	Cumulative avoidance proportion (%)		100.0	100.0	87.5

Log-rank test (exact method): $P = 0.3496$

Figure 8. Kaplan–Meier estimate of avoidance of mediastinitis requiring surgical intervention

6.A.(5).7) Time required for adhesiolysis during resternotomy

To confirm the clinical relevance and magnitude of the anti-adhesion effect, the duration of adhesiolysis during resternotomy was calculated from operative video recordings and analyzed additionally. The

duration of adhesiolysis was defined as the time “from the moment of sternal division to completion of adhesiolysis, including the time required for CPB establishment.” The CPB establishment time was defined as “from the initiation of suturing to completion of venous cannula fixation.” Among the 28 subjects who underwent resternotomy and adhesion assessment, 27 subjects (14 in the Coseal group and 13 in the untreated group) were included in this analysis, and the remaining 1 subject was excluded because assessment of the left ventricular lateral wall was not performed for safety reasons during a BiVAD to an RVAD weaning. Figure 9 presents a histogram of adhesiolysis time, and Table 23 presents the analysis results. The mean duration of adhesiolysis was approximately 23 minutes overall, although considerable variability was observed among subjects, with some requiring prolonged procedures. The mean adhesiolysis time was relatively shorter in the Coseal group than in the untreated group (approximately 12 minutes and 33 minutes, respectively) and this difference was statistically significant (Welch’s t-test, $P < 0.005$).

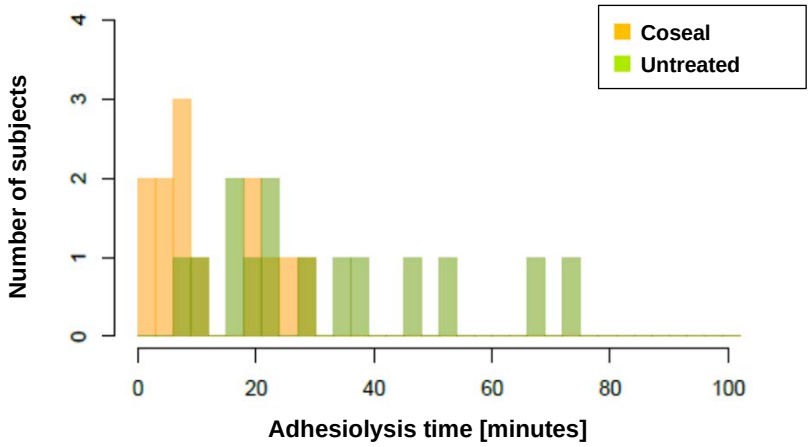


Figure 9. Histogram of adhesiolysis time (by group)

Table 23. Results of the analysis of adhesiolysis time

Adhesiolysis time [minutes]	Overall	Coseal (N = 14)	Untreated (N = 13)
Mean	22.96	12.17	32.98
Median	20.17	7.17	25.17
Minimum	0.75	0.75	7.83
First quartile	7.50	5.83	18.29
Third quartile	27.50	21.00	43.42
Maximum	75.00	27.67	75.00
Welch’s t-test	-	$P < 0.005$	
Difference in means	-	-20.80	
[95% CI for difference in means]	-	[-33.75, -7.86]	

6.A.(6) Safety

6.A.(6).1) Adverse events

Table 24 shows the incidence of adverse events reported in this clinical study. Adverse events were observed in all subjects in both the Coseal group and the untreated group. As shown in Table 25, serious adverse events occurred in 4 subjects (6 events) in the Coseal group (cerebral infarction [2 events], cerebral haemorrhage [1 event], cardiac tamponade [1 event], pancreatitis acute [1 event], and device-related thrombosis [1 event]) and in 2 subjects (2 events) in the untreated group (haematoma muscle [1

event] and multiple organ dysfunction syndrome [1 event]). A causal relationship to Coseal was ruled out for all adverse events observed in the Coseal group.

Deaths occurred in 1 subject (cerebral infarction) in the Coseal group during the adverse event observation period, and 1 subject (cerebral haemorrhage) in the untreated group during the efficacy evaluation period outside the adverse event observation period. In addition to the above, 2 subjects (pancreatitis acute in 1 subject and multiple organ dysfunction syndrome in 1 subject) were reported in which the outcome of the adverse event was death.

Table 24. Incidence of adverse events

Event	Coseal (N = 16)		Untreated (N = 14)	
	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)
All events	64	16 (100.0)	59	14 (100.0)
Infections and infestations	10	9 (56.3)	6	5 (35.7)
Pneumonia	4	4 (25.0)	3	3 (21.4)
Bacteraemia	2	2 (12.5)	0	0 (0.0)
Urinary tract infection	2	2 (12.5)	0	0 (0.0)
Cytomegalovirus infection	1	1 (6.3)	0	0 (0.0)
Systemic candida	1	1 (6.3)	0	0 (0.0)
Sepsis	0	0 (0.0)	1	1 (7.1)
Fungal sepsis	0	0 (0.0)	1	1 (7.1)
Vascular device infection	0	0 (0.0)	1	1 (7.1)
Blood and lymphatic system disorders	1	1 (6.3)	2	2 (14.3)
Leukopenia	1	1 (6.3)	0	0 (0.0)
Anaemia	0	0 (0.0)	2	2 (14.3)
Metabolism and nutrition disorders	1	1 (6.3)	0	0 (0.0)
Hyperkalaemia	1	1 (6.3)	0	0 (0.0)
Psychiatric disorders	2	2 (12.5)	3	3 (21.4)
Delirium	2	2 (12.5)	3	3 (21.4)
Nervous system disorders	10	8 (50.0)	2	2 (14.3)
Cerebral haemorrhage	3	3 (18.8)	0	0 (0.0)
Cerebral infarction	3	3 (18.8)	2	2 (14.3)
Subarachnoid haemorrhage	1	1 (6.3)	0	0 (0.0)
Transient ischaemic attack	1	1 (6.3)	0	0 (0.0)
Brain oedema	1	1 (6.3)	0	0 (0.0)
Intensive care unit acquired weakness	1	1 (6.3)	0	0 (0.0)
Cardiac disorders	15	11 (68.8)	20	12 (85.7)
Cardiac tamponade	11	8 (50.0)	11	10 (71.4)
Atrial fibrillation	1	1 (6.3)	2	2 (14.3)
Mitral valve incompetence	1	1 (6.3)	0	0 (0.0)
Pericardial effusion	1	1 (6.3)	3	2 (14.3)
Ventricular arrhythmia	1	1 (6.3)	0	0 (0.0)
Arrhythmia	0	0 (0.0)	1	1 (7.1)
Arrhythmia supraventricular	0	0 (0.0)	1	1 (7.1)
Atrial tachycardia	0	0 (0.0)	1	1 (7.1)
Pericardial haemorrhage	0	0 (0.0)	1	1 (7.1)
Vascular disorders	2	2 (12.5)	0	0 (0.0)
Haemorrhagic infarction	1	1 (6.3)	0	0 (0.0)
Deep vein thrombosis	1	1 (6.3)	0	0 (0.0)
Respiratory, thoracic and mediastinal disorders	3	3 (18.8)	3	3 (21.4)
Pleural effusion	2	2 (12.5)	1	1 (7.1)
Atelectasis	1	1 (6.3)	1	1 (7.1)
Respiratory failure	0	0 (0.0)	1	1 (7.1)

Event	Coseal (N = 16)		Untreated (N = 14)	
	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)
Gastrointestinal disorders	6	5 (31.3)	1	1 (7.1)
Pancreatitis acute	2	2 (12.5)	0	0 (0.0)
Colitis ischaemic	1	1 (6.3)	0	0 (0.0)
Diarrhoea	1	1 (6.3)	0	0 (0.0)
Pancreatic pseudocyst	1	1 (6.3)	0	0 (0.0)
Pancreatitis	1	1 (6.3)	0	0 (0.0)
Ileus paralytic	0	0 (0.0)	1	1 (7.1)
Hepatobiliary disorders	0	0 (0.0)	3	3 (21.4)
Cholecystitis	0	0 (0.0)	1	1 (7.1)
Hepatorenal failure	0	0 (0.0)	1	1 (7.1)
Hyperbilirubinaemia	0	0 (0.0)	1	1 (7.1)
Skin or subcutaneous tissue disorders	1	1 (6.3)	0	0 (0.0)
Drug eruption	1	1 (6.3)	0	0 (0.0)
Musculoskeletal and connective tissue disorders	0	0 (0.0)	1	1 (7.1)
Haematoma muscle	0	0 (0.0)	1	1 (7.1)
Renal and urinary disorders	0	0 (0.0)	3	3 (21.4)
Nephropathy toxic	0	0 (0.0)	1	1 (7.1)
Renal disorder	0	0 (0.0)	1	1 (7.1)
Renal dysfunction	0	0 (0.0)	1	1 (7.1)
General disorders and administration site conditions	12	9 (56.3)	12	8 (57.1)
Device related thrombosis	8	7 (43.8)	9	7 (50.0)
Pyrexia	2	2 (12.5)	2	2 (14.3)
Pain	1	1 (6.3)	0	0 (0.0)
Injection site injury	1	1 (6.3)	0	0 (0.0)
Multiple organ dysfunction syndrome	0	0 (0.0)	1	1 (7.1)
Investigations	0	0 (0.0)	1	1 (7.1)
Thrombocytopenia	0	0 (0.0)	1	1 (7.1)
Injury, poisoning and procedural complications	1	1 (6.3)	2	2 (14.3)
Post procedural haemorrhage	1	1 (6.3)	0	0 (0.0)
Wound dehiscence	0	0 (0.0)	2	2 (14.3)

Table 25. Incidence of serious adverse events

Event	Coseal (N = 16)		Untreated (N = 14)	
	No. of events	No. of subjects (%)	No. of events	No. of subjects (%)
All events	6	4 (25.0)	2	2 (14.3)
Nervous system disorders	3	3 (18.8)	0	0 (0.0)
Cerebral haemorrhage	2	2 (12.5)	0	0 (0.0)
Cerebral infarction	1	1 (6.3)	0	0 (0.0)
Cardiac disorders	1	1 (6.3)	0	0 (0.0)
Cardiac tamponade	1	1 (6.3)	0	0 (0.0)
Gastrointestinal disorders	1	1 (6.3)	0	0 (0.0)
Pancreatitis acute	1	1 (6.3)	0	0 (0.0)
Musculoskeletal and connective tissue disorders	0	0 (0.0)	1	1 (7.1)
Haematoma muscle	0	0 (0.0)	1	1 (7.1)
General disorders and administration site conditions	1	1 (6.3)	1	1 (7.1)
Device related thrombosis	1	1 (6.3)	0	0 (0.0)
Multiple organ dysfunction syndrome	0	0 (0.0)	1	1 (7.1)

6.A.(6).2) Device malfunction

One malfunction (failure of compressed air spraying) was observed in the Coseal group. This malfunction occurred when Coseal was used during the initial surgery, where compressed air failed to discharge from the EasySpray device, resulting in Coseal being applied by dripping rather than spraying (a protocol deviation). At the time the malfunction was recognized, the investigator had already begun dripping PEG; therefore, the procedure was not interrupted, and manual application was continued. No health damage was judged to have resulted from this malfunction.

6.B Outline of the review conducted by PMDA

PMDA conducted its review focusing on the following points:

(1) The efficacy and safety of Coseal

(2) The target patient population for Coseal

(3) Post-marketing safety measures

6.B.(1) Efficacy and safety of Coseal

6.B.(1).1) Study design based on the clinical need of Coseal

PMDA's view on the study design of this clinical study:

In the clinical study evaluating the efficacy and safety of Coseal, it is necessary to ensure a sufficient period for adhesion formation, taking into account actual clinical conditions. The primary clinical need for adhesion barriers in cardiac surgery is anticipated in pediatric patients with congenital heart disease. Taking these into consideration, in principle, evaluation should be conducted in pediatric patients with congenital heart disease who are scheduled to undergo planned multi-stage surgeries, allowing an adequate interval for adhesion formation before resternotomy. However, in order to facilitate the early introduction of Coseal, the applicant conducted this clinical study in patients undergoing implantation of an extracorporeal VAD, in whom resternotomy for VAD removal can be performed relatively early compared with the above-mentioned population, thereby allowing evaluation of adhesion status.

PMDA understands the applicant's intent. However, clinical evidence directly demonstrating that inhibition of adhesion formation during the acute postoperative phase leads to suppression of adhesion formation in the long-term period is currently limited. A study design targeting patients undergoing implantation of an extracorporeal VAD may not adequately demonstrate the long-term adhesion prevention effect of Coseal.

Based on the above, PMDA determined that the efficacy and safety of Coseal should first be confirmed in patients undergoing implantation of an extracorporeal VAD, who constituted the subjects of this clinical study, and that the long-term postoperative adhesion prevention effect of Coseal should subsequently be investigated. The long-term postoperative adhesion prevention effect of Coseal is discussed in Section "6.B.(1).4) Effect on prevention of adhesion in the long term" described below.

6.B.(1).2) Efficacy

PMDA's view on the efficacy of Coseal:

In this clinical study, the superiority of Coseal over the untreated control was demonstrated for all primary endpoints. However, a considerable number of cases were confirmed in which components of the "extracorporeal VAD" used in this study were unapproved for use as extracorporeal VADs. Frequent performance of thoracotomy before adhesion assessment was also observed. Therefore, it is necessary to carefully evaluate how these factors, such as the types of components used and the details of the procedures performed, may have affected the efficacy of Coseal. Since the amount of blood transfusion during resternotomy for assessment was significantly higher in the Coseal group than in the untreated group, the clinical usefulness of Coseal's anti-adhesion effect should also be examined based on detailed review of individual cases.

PMDA examined the potential impact of the extracorporeal VAD components used in this study, the thoracotomy procedures before adhesion assessment on the efficacy of Coseal, and the clinical usefulness of its anti-adhesion effect of Coseal, as described below.

6.B.(1).2).(a) Types of components used in the extracorporeal VAD

As shown in Tables 10 and 11, many cases involved the use of unapproved components, such as blood pumps, inflow and outflow cannulae, when used as extracorporeal VADs. Multiple inflow and outflow sites were confirmed, and a certain number of treatments incorporated an extracorporeal membrane oxygenator (ECMO) into the blood circuit. Based on the above findings, PMDA asked the applicant to explain the following points:

i) The reasons why unapproved medical devices (e.g., blood pumps, inflow/outflow cannulae) and ECMO as extracorporeal VAD components were used in some cases.
ii) The potential impact of differences in the extracorporeal VAD components used on adhesion assessment results.

The applicant's explanation:

i) Reasons why the unapproved medical devices (e.g., blood pumps, inflow/outflow cannulae) and ECMO as extracorporeal VAD components were used in some cases

In the relevant clinical practice guidelines, extracorporeal VADs are defined as follows: "Devices that assist cardiac function with the pump unit placed outside the body. In the case of a left ventricular assist device, an inflow cannula is connected to the thoracic aorta, an outflow cannula is inserted into the left ventricle or left atrium, and both cannulae pass through the skin to connect to the pump unit. In the case of a right ventricular assist device, an inflow cannula is connected to the pulmonary artery, an outflow cannula is inserted into the right ventricle or right atrium, and both cannulae pass through the skin to connect to the pump unit."[20] This definition was adopted for the present clinical study. The usage status of extracorporeal VAD components in this clinical study was consistent with the above definition, and the procedures were conducted within the range of medical practice, taking into account individual patient conditions.

In particular, the single-use centrifugal pump "Biofloat Centrifugal Pump" (Approval number 22800BZX00321000) was used in 24 cases in this clinical study. During the conduct of this clinical study, the "Biofloat Ventricular Assist Device Set HC" (Approval number 30300BZX00093000), which includes the same product, was approved as a single-use extracorporeal assist artificial cardiac pump. The cases using the Biofloat Centrifugal Pump can be regarded as equivalent to cases using an already approved extracorporeal VAD. Regarding other blood pumps used in this clinical study that were unapproved as extracorporeal VAD components, their pump functions (e.g., stroke volume) were considered to be largely comparable to those of approved extracorporeal VADs. As for the inflow and outflow cannulae used in this study that were unapproved as extracorporeal VAD components, these were artificial vessels or venous/arterial cannulae already widely used in clinical settings. Therefore, the applicant considers that the use of such unapproved medical devices as extracorporeal VAD components itself does not pose any problem.

ii) Potential impact of differences in the extracorporeal VAD components used on adhesion assessment results

As shown in Table 15, which presents adhesion scores by evaluation site, similar scores were observed between the Coseal group and the untreated group at all sites. The adhesion scores in the Coseal group were significantly lower than those in the untreated group. Considering that there were no notable differences between the 2 groups in the status of extracorporeal VAD implantation and surgical procedures (Table 10) or the usage status of device components (Table 11), factors such as the type of extracorporeal VAD components or the use of an RVAD were not matters of concern regarding adhesion formation. The influence of these factors on adhesion assessment in this study was considered minimal.

PMDA's view:

Regarding the frequent use of unapproved blood pumps, inflow cannulae, and outflow cannulae as extracorporeal VADs in this clinical study, in principle, when the use of an unapproved medical device is unavoidable in performing study-related procedures, such a device should be defined as a study device, and safety data should be collected and appropriate evaluation should be conducted. However, at the time this clinical study was initiated, the extracorporeal VADs approved for adult use were limited to pulsatile-flow systems such as the "Nipro Ventricular Assist Device Set" (Approval number between the surface of the heart/great vessels and the surrounding tissues). Considering clinical practice, the selection of the most appropriate device based on the patient's condition for treatment implementation is understandable. Since no notable safety concerns were identified in these patients within this study, the inclusion of such cases in the efficacy and safety evaluation is considered acceptable.

With regard to the potential impact of differences in extracorporeal VAD components on the adhesion assessment, PMDA judged that inclusion of these cases in the evaluation is acceptable, taking account of comments raised in the Expert Discussion, for the following reasons: Both "single-use centrifugal pumps" and "ECMO," which are components of CPB circuits used in thoracotomy procedures, are extracorporeally placed, and there are no major differences in how the inflow and outflow cannulae are connected.

6.B.(1).2).(b) Thoracotomy performed before adhesion assessment

Since several thoracotomy procedures had been performed before the resternotomy for adhesion assessment, mainly for hemostasis, PMDA asked the applicant to explain the potential impact of such thoracotomies on adhesion formation and on the evaluation of Coseal.

The applicant's explanation:

In this clinical study, the patients' conditions were monitored under intensive care unit (ICU) management, and when the need for resternotomy arose, surgery was promptly performed. When resternotomy required adhesiolysis, or when some form of intervention was necessary at the adhesion assessment sites, adhesion evaluation was performed only in those cases where intervention occurred at the assessment site (Table 13). The appropriateness of the timing of resternotomy for adhesion assessment was confirmed by the heart team during case review meetings.

Thoracotomies before adhesion assessment were conducted a total of 26 times in 18 of 28 patients in which resternotomy and adhesion assessment were performed (Table 12). In most cases, the purpose of these surgeries was hemostasis (mainly drainage or hematoma removal). No intervention was made at the assessment sites. To reduce patient burden and prevent the occurrence of adverse events associated with surgical intervention, adhesion assessment was not performed in such cases. As a result, no notable differences were observed between the Coseal group and the untreated group in the number of thoracotomies before adhesion assessment. In the analysis population for the primary endpoint, no specific association was found between the number of thoracotomies before adhesion assessment and adhesion scores (Figure 10). The applicant considers that the impact of thoracotomies performed before assessment on adhesion formation and on the evaluation of Coseal was minimal.

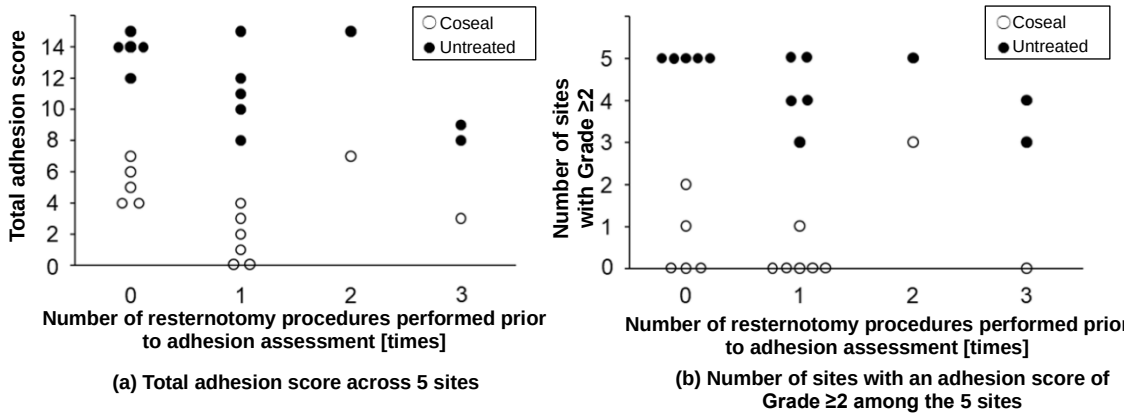


Figure 10. Relationship between the number of thoracotomies performed before adhesion assessment and adhesion status (≥ 2 weeks after initial surgery)

PMDA's view:

To appropriately evaluate the efficacy and safety of Coseal, in principle, a clinical study should be designed taking account of the influence of thoracotomy procedures performed before adhesion assessment, for the following reasons:

- Even if no direct intervention is performed at the evaluation site during thoracotomy before adhesion assessment, changes in contact between the evaluation site and surrounding tissue or body fluids may occur depending on the type of surgical procedure and the condition of the chest closure after surgery. Therefore, the possibility of an impact on adhesion formation cannot be completely ruled out. In addition, the cardiac inflammatory response and mechanism of inflammation that trigger adhesion formation may differ from those of cardiac surgery other than extracorporeal VAD procedures, due to such interventions.
- In adhesion assessment, evaluation should be performed after a sufficient period has elapsed to allow adhesion formation. However, in this clinical study, the potential influence of resternotomy procedures during that period on adhesion formation was not considered, raising the possibility that the anti-adhesion effect of Coseal may not have been adequately evaluated.

Nevertheless, taking also account of comments raised in the Expert Discussion, PMDA concluded that inclusion of the cases in the evaluation was acceptable for the following reasons: Due to the therapeutic characteristics of extracorporeal VAD, resternotomy for hemostasis or hematoma removal is an integral

part of the overall treatment; there were no notable differences between 2 groups in the status of thoracotomy for hemostasis, the number of resternotomies, or the degree of adhesion before adhesion assessment.

6.B.(1).2).(c) Blood transfusion volume and adhesiolysis time

In this clinical study, the mean blood transfusion volume during resternotomy in which adhesion assessment was conducted was 2909.3 ± 1106.8 mL in the Coseal group and 1890.0 ± 955.6 mL in the untreated group, showing a significantly higher value in the Coseal group (Table 21). The mean adhesiolysis time was approximately 12 minutes in the Coseal group and approximately 33 minutes in the untreated group, showing a statistically significant reduction in the Coseal group; however, there was considerable variability among individual cases (Table 23).

In examining the clinical usefulness of Coseal, PMDA asked the applicant to explain the following points:

i) The reason for the higher blood transfusion volume in the Coseal group than in the untreated group
ii) The reason for the variability in adhesiolysis time and potential influence of operator technique and skill
iii) The clinical usefulness of the anti-adhesion effect of Coseal based on the results for blood transfusion volume and adhesiolysis time

The applicant's explanation:

i) Reason for the higher blood transfusion volume in the Coseal group

During resternotomy for adhesion assessment, the use of cardiopulmonary bypass (CPB) was observed in all 14 patients (100.0%) in the Coseal group and in 9 of 13 patients (69.2%) in the untreated group (Table 22). In all patients who required CPB, surgical procedures such as removal of the extracorporeal VAD or transition to an implantable LVAD were performed, which inherently required CPB. Of the 4 patients in the untreated group who did not require CPB, 1 patient underwent mediastinitis treatment and 1 patient underwent hemostasis surgery, both of which were clearly cases where CPB was not needed. Considering that the "use of CPB" was cited as the reason for transfusion in 12 patients (85.7%) in the Coseal group and 6 patients (46.2%) in the untreated group, the blood transfusion volume is considered to depend primarily on the nature of the surgical procedure at resternotomy.

ii) Reason for variability in adhesiolysis time and potential influence of surgical technique and skill

At sites where adhesion was severe, careful detachment of adhesions and neovascularization was required, which prolonged the adhesiolysis time and increased procedural complexity (e.g., blunt or sharp dissection, hemostasis). Because the degree and extent of adhesion varied across cases, adhesiolysis time tended to show large variability. Indeed, as shown in Figure 11, more cases with higher total adhesion scores (total adhesion score across 5 sites) were observed in the untreated group, and both adhesiolysis time and its variability tended to be greater in this group.

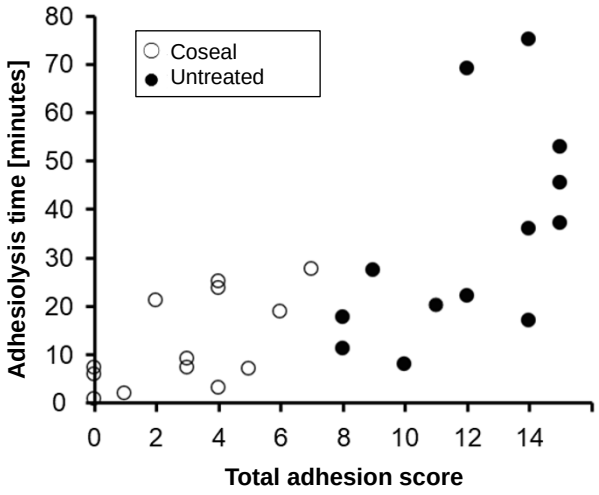


Figure 11. Adhesion score and adhesiolysis time (≥2 weeks after initial surgery)

The anti-adhesion effect of Coseal is expected to act on adhesions of the undersurface of the sternum, pericardium, visceral pleura, and major cardiac vessels. Because the time from skin incision to sternal splitting is unrelated to adhesiolysis, the starting point for measuring adhesiolysis time was defined as the "moment of sternal division." Except for cases in which CPB was established during adhesion detachment, in principle, surgical procedures during resternotomy in which adhesion was assessed were performed after adhesiolysis was completed. Resternotomies were conducted by 2 to 3 highly experienced surgeons. Therefore, the potential influence of individual surgical technique and skill on detachment time is considered to have been minimized. Because adhesion was assessed at the same study site in 26 of 27 patients (except for 1 patient in the untreated group) , institutional differences were considered negligible. Although assessors bias was expected due to the open-label design of the study, surgeons who performed assessments were blinded to treatment allocation, and adhesion was assessed by both surgeons and independent blinded assessors, minimizing potential bias in evaluation of adhesiolysis time.

iii) The clinical usefulness of the anti-adhesion effect based on blood transfusion volume and adhesiolysis time

Transfusions due to "bleeding caused by adhesion detachment" were observed in 1 patient (7.1%) in the Coseal group and 6 patients (46.2%) in the untreated group, suggesting that Coseal may reduce the risk of haemorrhagic complications through its anti-adhesion effect.

In cardiac reoperations requiring CPB, rapid establishment of CPB is essential. When CPB is established during adhesiolysis, adhesions around major vessels and the right atrium must first be detached, followed by operations for CPB establishment from suturing into the great vessels through placement and fixation of cannulae before resuming and completing adhesion detachment. Among the 27 subjects in whom adhesion assessment was performed, for the 9 subjects who underwent establishment of CPB during adhesiolysis, both the adhesiolysis time before initiation of the CPB establishment procedure and the total adhesiolysis time showed a tendency toward reduction in the Coseal group compared with the untreated group (Table 26), according to a comparison of the point estimates. In clinical practice at the study site, the total time required for adhesiolysis and CPB establishment is generally around 60 minutes.

In this study, the total time to complete detachment in the untreated group (6 subjects) was 52.3 ± 26.2 minutes. The adhesiolysis time observed in the untreated group of this clinical study is thus considered to reflect the clinical practice in Japan.

The anti-adhesion effect of Coseal can reduce the technical difficulty and risk of complications during adhesiolysis, demonstrating a high level of clinical usefulness.

Table 26. Analysis of adhesiolysis time in cases with CPB established during adhesiolysis

Parameter	Coseal (N = 3)	Untreated (N = 6)
Total time to complete adhesiolysis [min]	34.6 ± 6.9	52.3 ± 26.2
Total adhesiolysis time	22.5 ± 3.2	44.0 ± 24.2
- Pre-CPB adhesiolysis time (completion of great vessel/right atrium detachment)	16.9 ± 3.4	33.3 ± 18.6
- Post-CPB adhesiolysis time	5.6 ± 0.6	10.6 ± 8.3
CPB establishment time	12.1 ± 4.3	8.3 ± 3.4
Total adhesion score across 5 sites	4.7 ± 1.2	13.5 ± 1.6
Number of sites with adhesion Grade ≥2 among 5 sites	0.7 ± 0.6	4.8 ± 0.4

PMDA's view on the clinical usefulness of Coseal's anti-adhesion effect:
The applicant's explanation that the higher transfusion volume in the Coseal group was due in part to the greater number of surgical procedures requiring CPB is reasonable at a certain level. Although this was a post hoc analysis, the number of transfusions attributed to "bleeding caused by adhesiolysis" was smaller in the Coseal group (1 patient) than in the untreated group (6 patients). Considering the above findings, along with the favorable results for the primary endpoint demonstrating anti-adhesion efficacy, PMDA concluded, taking account of comments raised in the Expert Discussion, that the results suggest a reduced risk of haemorrhagic complications attributable to the anti-adhesion effect of Coseal.

Although the number of patients in which CPB was established during adhesiolysis was limited, both total adhesiolysis time and pre-CPB detachment time tended to be shorter in the Coseal group, consistent with overall trends in both groups and the results of primary endpoint. As the applicant noted, rapid establishment of CPB is crucial for ensuring patient's safety during cardiac surgery which required the use of CPB. Based on the above results, taking also account of comments raised in the Expert Discussion, PMDA determined that a shortening of adhesiolysis time due to Coseal's anti-adhesion effect can be reasonably expected.

In conclusion, PMDA concluded that the efficacy of Coseal is supported by the results of this clinical study.

6.B.(1).3) Safety

In this clinical study, PMDA asked the applicant to explain the cause of a malfunction of the EasySpray device (failure of compressed air spraying) observed in 1 case in the Coseal group, as well as the risk reduction measures implemented in response. Considering that adverse events presumed to be caused by excessive spraying of Coseal have been reported in foreign use, PMDA also asked the applicant to explain the amount of Coseal used in this clinical study and the incidence of adverse events for which a causal relationship to Coseal could not be ruled out.

The applicant's explanation:
An investigation by the manufacturer regarding this malfunction did not identify the cause. However, during the subsequent investigation of a similar malfunction observed in a pediatric clinical study, it was found that the malfunction was due to a defect in the junction between the 9V stacked battery of the domestically distributed EasySpray unit and the internal battery case, which resulted in abnormal spraying. After completion of this clinical study, the design of the battery case was improved, and the modified product will be distributed at the time of introduction into Japan. In this clinical study, the prescribed amount (8 mL) was sprayed in all subjects in the Coseal group. No adverse events for which a causal relationship to Coseal could not be ruled out were observed.

PMDA concluded that the response to the malfunction that occurred in this clinical study was appropriate. In order to reduce the risk of adverse events associated with excessive use of Coseal, PMDA instructed the applicant to provide information on the amount of Coseal used in this clinical study, in addition to the precautions on the amount and method of use described in Section "1.A.(3) Malfunctions and adverse events reported in foreign countries" above. The applicant agreed to this instruction.

6.B.(1).4) Effect on prevention of adhesion in the long term

The mean number of days from the initial surgery to the resternotomy for adhesion assessment was approximately 1 month (31.5 days in the Coseal group and 48.0 days in the untreated group). The maximum duration was 74 days in the Coseal group and 195 days in the untreated group (Table 14).

The applicant' explanation about the long-term adhesion-preventive effect of Coseal after surgery, based on the results of this clinical study:
The mechanism of adhesion formation after cardiac surgery, as reported in previous studies,[21,22] is summarized below.

- In the acute postoperative phase (up to approximately 7 days), bleeding, inflammation (accumulation of inflammatory cells, release of various bioactive substances, etc.), and exfoliation of pericardial mesothelial cells occur, leading to fibrin accumulation at sites of mesothelial cell loss.
- In the subacute postoperative phase (up to approximately 30 days), further fibrin accumulation occurs on the pericardial surface, and a newly formed connective tissue layer covered with inflammatory cells and fibroblasts develops. Collagen deposits between the degenerated pericardial surface and areas of inflammatory cell infiltration, and neovascularization leads to the formation of new vascular networks.
- In the late postoperative phase (beyond approximately 30 days), although connective tissue remains at pericardial adhesion sites, the tissue reaction and neovascularization at these sites regress, while non-adherent pericardial areas become covered by normal pericardial mesothelial cells.

Since the major bioactive substances that promote postoperative adhesion are mobilized during the acute postoperative phase, preventing physical contact between damaged tissues or cell surfaces during this phase is considered to suppress subsequent adhesion formation.

Moreover, in the analysis related to the primary endpoint of this clinical study, the degree of adhesion in the untreated group remained consistently high throughout the observation period, whereas that in the

Coseal group was markedly lower than that in the untreated group (Figure 5 and Table 20). In several foreign case reports[23,24] in which Coseal was used in adult patients with implanted LVADs, suppression of adhesion formation was observed at approximately 1 year and 695 days postoperatively. These findings suggest that the adhesion-preventive effect of Coseal is stable over time.

PMDA's view:
Based on the results of analyses related to the primary endpoint in this clinical study, PMDA understands that Coseal may be expected to exert adhesion-preventive effects for a certain period after surgery beyond the observation period of the study. However, considering the diversity of adult patients with cardiac surgery who are likely to undergo resternotomy, the observation period of this clinical study is definitely short. Discussions based solely on the results of analyses of the observation period and adhesion scores have limitations. For the mechanism of pericardial adhesion formation after cardiovascular surgery, basic research has provided insights into the pathophysiology and mechanisms of adhesion. However, clinical evidence regarding the duration required for resolution of the adhesion reaction and its relationship with adhesion status remains insufficient. Furthermore, clinical evidence demonstrating that suppression of adhesion formation in the acute postoperative phase leads to suppression in the long term is currently limited. Even in foreign countries, adhesion barriers applicable to cardiac surgery are limited. Clinical data, including those for similar foreign products, are restricted to case reports and small-scale clinical studies. No clinical studies evaluating long-term postoperative adhesion status in adult patients with cardiac surgery have been identified to date. As described in Section "6.B.(1).1) Study design based on the clinical need of Coseal," it would be preferable to evaluate the efficacy of Coseal in pediatric patients with congenital heart disease who are expected to undergo planned multistage surgeries. Therefore, discussions on the long-term postoperative efficacy should be conducted in consideration of the results of the forthcoming pediatric clinical study.

In conclusion, although the applicant explained the long-term adhesion-preventive effect of Coseal based on the results of this clinical study from the perspective of early introduction, the clinical study results and the applicant's explanations alone are insufficient to demonstrate the long-term adhesion-preventive effect of Coseal. Taking account of the comments raised in the Expert Discussion, PMDA concluded that the use of Coseal should be limited to patients for whom early resternotomy after surgery is anticipated. The target patient population of Coseal is described in Section "6.B.(2) Target patients for Coseal" below.

6.B.(2) Target patients for Coseal

6.B.(2).1) Appropriateness of the target patients for Coseal based on the results of this clinical study

The applicant's explanation about the target patients for Coseal:
The applicant assumed use of Coseal in adult cardiovascular surgeries involving thoracotomy, as listed below:

- Surgeries for severe heart failure: Implantation of extracorporeal VADs or implantable VADs, and heart transplantation

- Surgeries for coronary artery disease, angina pectoris, myocardial infarction, or ischaemic cardiomyopathy: Coronary artery bypass grafting, ventricular septal rupture closure, cardiac rupture repair, and ventricular aneurysmectomy
- Surgeries for valvular diseases: Repair or replacement of the mitral, aortic, or tricuspid valve
- Surgeries for the aorta: Prosthetic graft replacement and aortic root reconstruction
- Surgeries for arrhythmia (atrial fibrillation): Maze procedure
- Surgeries for adult congenital heart diseases: Ventricular septal defect closure, arterial switch operation, radical repair of tetralogy of Fallot, atrioventricular septal defect repair, extracardiac conduit conversion, and total cavopulmonary connection (TCPC) conversion, among others
- Others: Cardiac tumor resection, etc.

The possibility and timing of resternotomy after these primary surgeries vary, and the reasons for such reoperations are diverse, including postoperative infections or complications following the primary surgery, reintervention at the site of primary surgery, and treatment of new lesions. In all such cases, it is well known that the risk of death and severe complications during resternotomy is higher than that during the primary surgery. One of the contributing factors is the increased technical difficulty and complication risk associated with adhesions. It is considered appropriate to include these cardiovascular surgeries as target procedures for Coseal.

PMDA's view:
Most of the adult cardiovascular surgeries presented by the applicant are radical procedures. When resternotomy becomes necessary, it is generally performed several to 30 years after the initial surgery, except for patients undergoing extracorporeal VAD implantation, who were the subjects in this clinical study. Although resternotomy not planned at the time of the initial surgery may occasionally be performed relatively early due to postoperative complications or new lesions, even in such cases, the target patient population should be discussed after clarifying the long-term postoperative anti-adhesion effect of Coseal.

Based on the results of this clinical study and taking also account of comments raised in the Expert Discussion, the target patients for Coseal should appropriately be limited to those undergoing extracorporeal VAD implantation.

The applicant also explained that the indication of Coseal considering its long-term postoperative anti-adhesion effect would be further investigated based on the results of the ongoing pediatric clinical study, and PMDA accepted this explanation.

6.B.(2).2) Specification of the target patients by age

The applicant explained that the target patients were specified by age (≥12 years of age) based on the inclusion criteria of this clinical study.

PMDA's view on the age specification for the target patients of Coseal:
In this clinical study, "patients aged <12 years" were excluded, and the applicant intended to exclude "patients aged <12 years" from the indication of Coseal. However, factors related to age that should be

considered in evaluating Coseal include not only the type of surgery and treatment strategy for the disease but also the anatomical and histological characteristics of the patient, particularly the influence of growth on the mechanism of adhesion formation. As these conditions vary among individual cases, case-by-case judgments should be made.

The indication of Coseal should not be determined solely on the basis of age, taking also account of comments from the Expert Discussion. PMDA instructed the applicant to include a statement that the efficacy and safety of Coseal have not been evaluated in "patients aged <12 years" in the Information on Precautions, etc., as well as to provide information on the ages of the subjects enrolled in this clinical study. The applicant agreed with this instruction.

6.B.(2).3) Intended use or indication

In the results of clinical study of Coseal, no efficacy was demonstrated in preventing postoperative adhesions in the late postoperative period. Considering that, among patients undergoing cardiovascular surgery, those for whom early resternotomy after surgery is anticipated are limited to patients with extracorporeal VAD, PMDA concluded that the intended use or indication of Coseal should be specified as shown below, taking account of comments raised in the Expert Discussions.

Intended Use or Indication (revised text underlined)

Coseal is applied to the surface of the heart, pericardial tissues, and great vessels in patients undergoing <u>extracorporeal ventricular assist device implantation</u> surgery, in order to reduce the frequency, extent, and severity of postoperative adhesions.

6.B.(3) Post-marketing safety measures

The applicant's explanation about the post-marketing safety measures for Coseal:

Extracorporeal VAD therapy is performed by certified cardiovascular surgeons and at qualified training institutions accredited by the "The Japanese Board of Cardiovascular Surgery" established jointly by 3 academic societies of The Japanese Association for Thoracic Surgery, The Japanese Society for Cardiovascular Surgery, and The Japanese Society for Vascular Surgery. The users and institutions where Coseal will be used are expected to comply with the same requirements as those for extracorporeal VAD therapy. The assessment of indications for Coseal will, in principle, follow the same criteria as for extracorporeal VAD therapy. Regarding its method of use, hands-on training and lectures provided to the aforementioned certified cardiovascular surgeons would be sufficient and that no particular concerns would arise.

PMDA's view:

The clinical study results revealed no specific safety concerns regarding Coseal. Ensuring the efficacy and safety of Coseal requires adherence to the recommended usage conditions, such as uniform spraying at the recommended dose (1 mL/10 cm^2), spray pressure, and distance. However, since the operation itself is not complicated and no safety concerns were identified, appropriate precautions and information regarding the method of use in the Information on Precautions, etc. would be sufficient to reduce risk. There are no Coseal-specific considerations regarding postoperative patient management, and no

changes are required to the management practices currently applied to extracorporeal VAD therapy by physicians or institutions.

Based on the above considerations and taking also account of the comments raised in Expert Discussion, PMDA concluded that the applicant's proposed post-marketing safety measures, including training programs, are appropriate.

7. Plan for Post-marketing Surveillance, etc. Stipulated in Paragraph 1 of Article 2 of Ministerial Ordinance on Good Post-marketing Study Practice for Medical Devices

7.A Summary of the data submitted

The applicant's explanation:

Post-marketing use-results surveys are unnecessary, as there are no safety concerns requiring confirmation through such surveys, for the following reasons:

- Coseal, including its previous-generation product, has been used in Europe and the US for over 20 years, with more than [redacted] units sold over the past 15 years. During that period, no adverse events of concern were reported, and the overall incidence of reported adverse events was as low as 117 cases ([redacted]%).
- In the present clinical study, a causal relationship to Coseal was ruled out for all adverse events observed in the Coseal group, and no Japan-specific events were identified.

7.B Outline of the review conducted by PMDA

PMDA's view:

Although the foreign post-marketing experience of Coseal includes its use as a local hemostatic material and in fields other than cardiovascular surgery, a certain amount of experience has been accumulated. Taking into account that no specific safety concerns were identified in the present clinical study, the likelihood of new safety concerns arising after marketing is low. As stated in Section "6.B Outline of the Review Conducted by PMDA," adequate risk control can be achieved through safety measures, including regular post-marketing defect and malfunction reporting. Taking also account of comments raised in the Expert Discussion, as the efficacy and safety of Coseal in the Japanese post-marketing setting can be appropriately ensured, a use-results survey for Coseal is unnecessary.

8. Documents Relating to Information on Precautions, etc., Specified in Paragraph 1 of Article 63-2 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices, in Relation to Notification Pursuant to the Same Paragraph of the Act

8.A Summary of the data submitted

The applicant submitted Information on Precautions, etc. (draft) as an attachment in accordance with the Notification titled "Application for Marketing Approval of Medical Devices" (PFSB Notification No. 1120-5, dated November 20, 2014).

8.B Outline of the review conducted by PMDA

On the basis of the conclusion of the Expert Discussion, as described earlier in Sections "1.B. Outline of the review conducted by PMDA," and "6.B. Outline of the review conducted by PMDA," PMDA

concluded that there were no particular problems with the proposed Information on Precautions, etc., provided that necessary precautions are included.

III. Results of Compliance Assessment Concerning the New Medical Device Application Data and Conclusion Reached by PMDA

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

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

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

The medical device application data (6-1-1 Clinical Study Report) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

IV. Overall Evaluation

In the review of Coseal, PMDA's review primarily focused on (1) the efficacy and safety of Coseal and (2) the post-marketing safety measures. PMDA reached the following conclusions, taking account of deliberations at the Expert Discussion.

(1) Efficacy and safety of Coseal

In this clinical study targeting primarily adult patients undergoing implantation of an extracorporeal VAD, the superiority of Coseal over the untreated control was demonstrated for both primary endpoints, i.e., (1) the degree of adhesion between the surface of the heart/great vessels and surrounding tissues (≥2 weeks after the initial surgery); and (2) the number of sites where the adhesion between the surface of the heart/great vessels and the surrounding tissues was classified as Grade ≥2 (≥2 weeks after the initial surgery). No specific safety concerns regarding Coseal were identified in the clinical study results.

On the other hand, the clinical study results did not demonstrate the efficacy of Coseal in preventing postoperative adhesions in the late postoperative period. In addition, they did not establish the clinical significance or usefulness of using Coseal in all types of cardiovascular surgery, regardless of whether resternotomy is planned. Therefore, PMDA concluded that the eligible patient population should be limited to those undergoing extracorporeal VAD implantation surgery.

(2) Post-marketing safety measures

Given that no specific safety concerns regarding Coseal were identified in the clinical study, and that it will be used by physicians and institutions already experienced in extracorporeal VAD therapy, PMDA determined that sufficient risk reduction can be achieved through the inclusion of precautions and

information on the method of use in the Information on Precautions, etc. No safety issues of particular concern have been reported in the foreign post-marketing experience, and the new safety concern is unlikely to arise in the post-marketing setting . PMDA concluded that a use-results survey is unnecessary.

As a result of the above review, PMDA concluded that Coseal may be approved after modifying the intended use as shown below.

Intended Use or Indication
Coseal is applied to the surface of the heart, pericardial tissues, and great vessels in patients undergoing extracorporeal ventricular assist device implantation surgery, in order to reduce the frequency, extent, and severity of postoperative adhesions.

The product is not classified as a biological product or a specified biological product.

PMDA has concluded that the application should be deliberated at the Committee on Medical Devices and *In-vitro* Diagnostics.

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