SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Polymerizing Sealant
Device Trade Name:	TRIDYNE™ Vascular Sealant (TRIDYNE™ VS)
Device Procode:	NBE
Applicant's Name and Address:	Neomend, Inc. Subsidiary of BARD/Davol, Inc. 60 Technology Drive Irvine, CA 92618
Date(s) of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P150016
Date of FDA Notice of Approval:	April 11, 2016

II. INDICATIONS FOR USE

The TRIDYNE™ Vascular Sealant is indicated for use in aortic surgery when adjunctive measures to achieve hemostasis are required by mechanically sealing areas of leakage.

III. CONTRAINDICATIONS

- TRIDYNE™ VS is not for intravascular use.
- Do not use TRIDYNE™ VS in patients who have a history of allergic reaction to Human Serum Albumin, Polyethylene Glycol or other device components.
- Do not apply TRIDYNE™ VS on oxidized regenerated cellulose, absorbable gelatin sponges or any other surface or material other than the target tissue or graft as adherence and intended outcome may be compromised.
- Do not use TRIDYNE™ VS in patients who have insufficient renal capacity for clearance of the polyethylene glycol load.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the TRIDYNE™ VS labeling.

V. DEVICE DESCRIPTION

TRIDYNE™ VS is a single-use medical device that is formed as a result of mixing two components:

(1) a solution of Human Serum Albumin (HSA); and
(2) a synthetic crosslinking component of polyethylene glycol (PEG).

HSA is a large protein molecule derived from plasma collected from screened donors; it is provided as an amber colored liquid. PEG is provided as a dry white powder. In the process of setting up the TRIDYNE™ VS Kit, this powder is reconstituted with sterile water and forms a clear to somewhat cloudy liquid. A delivery system is used to deliver the hydrogel at the intended treatment site. Upon mixing of the HSA and reconstituted PEG, a clear, flexible hydrogel is formed at the treatment site.

TRIDYNE™ VS is supplied as a sterile, single-use, 2-component kit. A 4 mL total sealant volume can be made from each kit. Each kit includes:

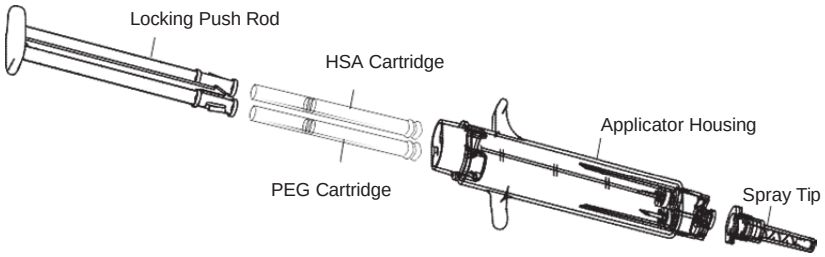
- One (1) – Chemistry Kit
  – One (1) preloaded cartridge containing 2 mL of Human Serum Albumin (HSA)
  – One (1) preloaded cartridge containing polyethylene glycol (PEG) as a dry white powder
- One (1) – Applicator Kit
  – One (1) 3 mL plastic syringe with needle
  – One (1) 5 mL vial of USP sterile water
  – One (1) Applicator assembly with locking push rod
  – Two (2) Spray tips
- One (1) – Instructions for Use (Labeling)

Optional replacement and extended spray tips are also available:

– TRIDYNE™ VS Standard Spray Tips (pack of 2), 10 units/box
– TRIDYNE™ VS Extended Spray Tip 6 in, 4 units/box

Figure 1 is a schematic of TRIDYNE™ VS. The sterile water and syringe for drawing up the water, which are included in the Applicator Kit, are not shown in the schematic.

Figure 1. TRIDYNE™ Vascular Sealant



Please see the Instructions for Use for additional details.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several alternative practices for adjunctive measures to achieve hemostasis. Each alternative has its own advantages and disadvantages. Conventional methods to control bleeding include the use of direct pressure, sutures, electrocautery, and pledgets. Other commercially available devices such as sealants, absorbable hemostatic agents and adhesives are also used to control bleeding, including products composed of gelatin, cellulose, bovine collagen, thrombin, fibrinogen, polyethylene glycol polymers, bovine albumin/glutaraldehyde. Each alternative has its own advantages and disadvantages.

VII. MARKETING HISTORY

TRIDYNE™ VS has not been marketed in the United States or any foreign country.

PROGEL™ PLEURAL AIR LEAK SEALANT (PROGEL™ PALS; P010047), which has the same device design and manufacturing as TRIDYNE™ VS, has been marketed in the United States since January 14, 2010 for use on visceral pleura during open thoracotomy after visceral closure with, for example, sutures or staples, of visible air leaks (≥2 mm) incurred during open resection of lung parenchyma. PROGEL™ PALS is not currently approved in any foreign countries.

A recombinant version (recombinant Human Albumin) of the PROGEL™ PALS is CE Marked and available in some countries in Europe. It is marketed under the name Progel™ Platinum Surgical Sealant for use on visceral pleura to seal air leaks.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device (**Table 1**).

Table 1. Potential Adverse Events Associated with Surgical Sealants

A hypersensitivity reaction such as swelling or edema at the application site
Thrombosis and thromboembolism
An exacerbation of renal dysfunction in patients with pre-existing or unknown renal disease
Failure of the sealant to adhere to target tissue
Failure of the sealant to stop diffuse persistent bleeding
Possible transmission of infectious agents from materials of human origin.
Application of the sealant to tissue not targeted for the procedure.

Below is a list of the potential adverse effects associated with aortic procedures (**Table 2**).

Table 2. Potential Adverse Events Associated with Aortic Procedures

Adhesions	Lymphocele / lymph fistula
Aneurysm and anastomotic pseudoaneurysm	Myocardial infarction
Aortic insufficiency	Neurological deficits
Cardiac tamponade	Organ system dysfunction / failure
Cerebral emboli	Pain
Coagulopathy	Paraplegia
Death or irreversible morbidity	Pleural effusion
Dissection	Pulmonary Emboli
Edema	Pyrexia
Emboli	Renal dysfunction / failure
Erythema	Stroke or cerebral infarction
Graft occlusion	Thrombosis
Hematoma	Vasospasm
Hemorrhage	Vessel dissection
Infection	Vessel occlusion
Injury to normal vessels or tissue	Vessel rupture and hemorrhage
Ischemia	

For the specific adverse events that occurred in the clinical study, please see Section X.D.1. Safety Results below.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

Given the identical device design and manufacturing of TRIDYNE™ VS and PROGEL™ PALS, biocompatibility and *in vitro* (i.e., bench) data were leveraged from the PROGEL™ PALS PMA.

Biocompatibility

Biocompatibility testing was based on FDA's blue book memorandum #G95-l, "Use of International Standard IS0-10993, Biological Evaluation of Medical Devices Part 1: Evaluation and Testing" dated May 1, 1995. The device was categorized as a prolonged (> 24 hours, < 30 days) tissue contact implant. All biocompatibility, toxicity, and animal effectiveness studies were performed in compliance with current Good Laboratory Practices, 21 CFR Part 58, and the human safety study (Human Repeat Insult Patch Test - HRIPT) was conducted in compliance with Good Clinical Practices, and 21 CFR Part 50.

In Vitro Laboratory Studies

In vitro (bench) testing (i.e., burst pressure, gel time, crosslinker dissolution time, presence of spray and stream purge) was conducted on the device to ensure that the product reproducibly met product specifications. In addition, analytical and functional

tests are conducted as release tests on each lot of TRIDYNE™ VS to verify that the product meets established specifications.

See the PROGEL™ PALS Summary of Safety and Effectiveness for additional details (available online at http://www.accessdata.fda.gov/cdrh_docs/pdf/P010047b.pdf).

B. Animal Studies

Acute Animal Data

Four (4) acute animal studies were conducted to evaluate the safety and effectiveness of TRIDYNE™ VS in vascular surgery applications. The studies involved surgical sites including the carotid artery, coronary artery, right atrial appendage, and abdominal aorta of swine with or without involvement of vascular grafts. Twenty two (22) swine were treated with TRIDYNE™ VS. The following acute endpoints were evaluated in the studies: time to hemostasis following an acute surgically-created vascular leak; and gross ex vivo assessment and qualitative angiography to determine if topically applied product entered the lumen of the target site.

The results of the studies support effectiveness of the device in achieving hemostasis. TRIDYNE™ VS successfully sealed all bleeding vessels in a single application (4 mL), requiring no additional time for hemostasis beyond the instructed 2 minute curing dwell time. Post-treatment angiography generally demonstrated patency of treated arteries/grafts. One TRIDYNE™ VS treated carotid artery graft anastomosis site was observed to have an angiographic filling defect. At necropsy, there was what appeared to be device ingress at that site; however, no histopathology was performed to provide conclusive evidence of device ingress.

Chronic Animal Data

Two (2) swine studies were conducted to evaluate the chronic safety and effectiveness of TRIDYNE™ VS. The chronic studies involved coronary artery anastomosis (n=6 animals) and carotid artery vascular graft (n=4 animals) surgical sites. All animals surviving the initial post-operative period were followed in life for 30-36 days after treatment with TRIDYNE™ VS. Then, a complete necropsy and histopathological assessment was performed. Histologic sections, which included the arteriotomy and sealant, were critically evaluated and histologic features such as inflammation, necrosis, fibrosis, thrombosis and potential ingress of sealant into the target vessel were assessed.

In the study involving the coronary artery anastomosis surgical site, four (4) out of six (6) animals developed occlusive thrombosis at the device test site and subsequent left ventricular myocardial infarction (MI); three in the acute postoperative period (2 hours to 4 days) and one which was discovered following the chronic survival period (36 days). One of the objectives of the study was to assess for potential ingress of the test article sealant into the vessel, which may have contributed to the occlusive thrombosis and subsequent MI observed. However, on standard hematoxylin and eosin (H&E) histologic evaluation and also a variety of special stains (Congo Red, Trichrome, Giemsa, PAS and PTA1), the test article exhibited similar staining characteristics as the serum proteins in the luminal

thrombus at the test sites. As such, the test article could not be consistently distinguished from serum proteins due to the proteinaceous nature and degradation characteristics of both. Reliable conclusions related to safety of the test device were therefore not able to be drawn from these data.

In the study involving the carotid artery graft surgical site, four (4) animals were survived to the prescribed in life period of 30-35 days. There were no unusual changes in overall animal condition throughout the study or unusual findings or trends found in the preoperative and explant blood analysis attributed to the devices. Angiograms performed prior to sacrifice showed three (3) animals treated with TRIDYNE™ VS had 50% carotid artery narrowing and one (1) with total carotid artery occlusion. Occlusive intraluminal thrombus was identified via gross and histopathological assessment in the animal with total occlusion adjacent the TRIDYNE™ VS treated vascular anastomosis suture line. Observed foreign body inflammation and fibrosis were seen histologically in all animals and considered normal, given the graft implant surgery. The surgical model (e.g., diameter mismatch between the surgical graft and native vessel) may have contributed to the carotid artery stenoses and occlusion.

The results of the chronic animal studies were inconclusive from a safety standpoint. Although there were complications that resulted in unfavorable findings, these could have been attributed to the study design and technical complications (e.g., diameter differences between vascular graft and native vessel in the carotid artery graft study). As a result, it was not possible to discern whether the complications were device-related, animal model-related, or surgical model-related. Due to the limitations of the chronic animal studies, FDA relied on the clinical data regarding longer-term (30 day) safety of the device when used during aortic surgery. A broader, vascular surgery indication (beyond use in aortic surgery) was not supported by the animal or clinical data.

C. Additional Studies

Identical packaging and sterilization are used for the TRIDYNE™ VS and PROGEL™ PALS. Therefore, packaging and sterilization data was appropriately leveraged from the PROGEL™ PALS PMA. Similar to PROGEL™ PALS, TRIDYNE™ VS expiration dating has been established and approved at 2 years.

Packaging Testing

Packaging System Performance Test was performed per ASTM D4169, *Standard Practice for Performance Testing of Shipping Containers and Systems*, and passed all acceptance criteria. Accordingly, the requirements of ISO 11607-1, *Packaging for Terminally Sterilized Medical Device, Part 1: Requirements for Materials, Sterile Barrier Systems and Packaging Systems* were met.

Sterilization Validation

Sterilization for the Applicator Kit and Chemistry Kit components were performed in accordance with ISO 11137-1, *Sterilization of health care products – Radiation, Part 1 – Requirements for development, validation and routing control of sterilization process for*

medical devices and ISO 11137-2, *Sterilization of health care products – Radiation, Part 2 – Establishing the sterilization dose*.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of TRIDYNE™ VS for use in aortic surgery as an adjunctive measure to achieve hemostasis in the US under IDE # G130119. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were treated between November 2013 and November 2014. The database for this PMA reflected data collected through December 2014 and included 156 treated patients. There were 19 investigational sites.

The study was a prospective, multicenter, randomized, single-blind (subject), superiority clinical study to evaluate the safety and effectiveness of the TRIDYNE™ VS compared with a Control for the control of intraoperative bleeding after conventional repair during thoracic surgery on the aorta. Patients were randomized 2:1 to TRIDYNE™ VS or Control, respectively. Patients were followed for 30 days post-operatively. The Control was GELFOAM® PLUS, supplied as a ready to use medical device kit containing GELFOAM® Sterile Sponge, Thrombin (Human) lyophilized powder, two 10 mL Prefilled Saline Syringes (0.9% Sodium Chloride Injection USP), and a Vial Access Device. The GELFOAM® Sterile Sponge component is an absorbable gelatin sponge (USP) measuring 100 cm^2 (8 x 12.5 cm). GELFOAM PLUS® is a legally marketed alternative with a similar clinical use during aortic surgery.

Subjects scheduled for non-emergent, thoracic surgery involving the aortic valve, ascending aorta, or aortic arch on cardiopulmonary bypass with or without concomitant coronary artery bypass graft (CABG) procedure(s) were assessed for eligibility.

Sample size was calculated based on the following assumptions:

- The true difference between the two treatment arms in mean time to achieve hemostasis at the aortic leaking site per patient is 1.5 minutes (based on preliminary porcine animal model data).
- The standard deviation of time to hemostasis is 3 minutes (based on published data).[1]
- The Type 1 error, $\alpha = 0.05$ (two-sided).
- The Type 2 error, $\beta = 0.20$ (Power = 1 - β = 80%).

The calculated sample size in a 2:1 randomization was 96 patients in the TRIDYNE™ VS arm and 48 patients in the Control arm. Assuming a 10% attrition rate, the total sample size of randomized patients was 160, where 107 patients are treated with TRIDYNE™ VS and 53 patients are treated with Control.

The primary endpoint of this study was the time to hemostasis (TTH). TTH measurement began after either TRIDYNE™ VS or Control (GELFOAM® PLUS) was applied to the anastomotic suture line(s) and the bypass cross clamp was released. Hemostasis was assessed visually (i.e., the lack of any observable extravascular bleeding) and was monitored continuously until hemostasis was achieved at each applied anastomotic site or until 10 minutes had passed. If hemostasis was not achieved within 10 minutes, 10 minutes was used as the TTH. Immediate hemostasis was defined as zero (0) seconds or no observable bleeding from the time the clamps were released to achieving hemostasis.

Safety data were reviewed by an independent Clinical Events Committee (CEC), comprised of 3 members with relevant therapeutic experience and who were not directly involved in the conduct of the study and were blinded to treatment assignment. The CEC was responsible for reviewing and adjudicating the seriousness and relationship to the device and/or procedure for each serious adverse event.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the TRIDYNE™ VS study was limited to patients who met the following inclusion criteria:

   Preoperative Inclusion Criteria:

   1. Subject must be ≥ 18 years of age.
   2. Subject is scheduled for elective, primary thoracic surgery involving the aortic valve, ascending aorta, or aortic arch on cardiopulmonary bypass.
   3. Subject has an expected life expectancy ≥ 6 months.
   4. Subject is willing and able to comply with all aspects of the study including follow-up schedule.
   5. Subject or authorized representative, has the ability to provide voluntary written informed consent.

   Intraoperative Inclusion Criteria:

   6. Subject is able to undergo an antegrade cardioplegia injection for evaluation of a leak at the aortic anastomotic site(s) during the procedure.
   7. Following this injection, subject has a leaking site where a topical sealant/hemostatic agent may be used to control bleeding.

   Patients were not permitted to enroll in the TRIDYNE™ VS study if they met any of the following exclusion criteria:

   Exclusion Criteria:

   1. Subject has Type A or other acute thoracic aortic dissection.
   2. Subject has undergone prior thoracic surgery (open thoracotomy not including interventional cardiology procedures).
   3. Subject is undergoing a planned concomitant procedure other than coronary artery bypass graft (CABG).
   4. Subject has a previous organ transplant.
   5. Subject has known or suspected preoperative coagulation disorder.

6. Subject is allergic to human thrombin or has a history of allergic reactions after application of human thrombin.
7. Subject is allergic to protamine.
8. Subject has a Left Ventricular Assist Device (LVAD) or planned to receive an LVAD.
9. Subject is undergoing emergency surgery.
10. Subject is in chronic renal failure.
11. Subject has a hematocrit < 21% pre-operatively.
12. Subject has a serum creatinine ≥ 2.5 mg/dl at baseline or is currently on dialysis.
13. Subject has a cardiac ejection fraction < 25%.
14. Subject is scheduled for another cardiac surgery within 30 days of enrollment.
15. Subject has an active or latent infection which is systemic or at the intended surgery site.
16. Subject is immuno-compromised such as that resulting from chronic oral steroid use, chemotherapeutic agents, or immune deficiency disorders.
17. Subject is pregnant by a positive pregnancy test or has plans to become pregnant during the study period or is currently breast-feeding.
18. Subject is unwilling to receive blood products.
19. Subject has participated in another investigational research study within 30 days of enrollment.
20. In the opinion of the Investigator, the subject has a clinical condition that would preclude the use of the study device, preclude the subject from completing the follow-up requirements, or would complicate the evaluation of this study.

2. Follow-up Schedule

All patients were scheduled to have an in-hospital follow-up examination at 24 ± 2 hours from the index procedure, at the time of hospital discharge, and 30 ± 5 days from index procedure.

Preoperatively, a physical exam, laboratory tests (Clinical Chemistry, Hematology and Coagulation) including pregnancy test (for women of child bearing potential), and ejection fraction were obtained. Intraoperatively, the objective information collected included an antegrade cardioplegia injection for evaluation of a leak at the aortic anastomotic suture line, the amount of the sealant/hemostatic agent applied at the leaking site, and the time from cross clamp removal to the request of wires for sternal closure. Postoperatively, blood transfusion volumes and chest tube output was collected. At discharge, a physical exam and laboratory test were performed and blood transfusion volumes and chest tube output was collected. At the 30-day follow-up visit, a physical exam and laboratory test were performed. Adverse events and complications were recorded at all visits.

Table 3 summarizes the study visit schedule and the information collected at each of the visits.

Table 3. Study Visit Schedule

	Screening and Baseline	Intra-op	Post-op 24 ± 2 hours	Discharge	1 Month Follow-up	Unscheduled Visit
Visit scheduling windows	30 days Prior to Procedure	Day 0 (During Surgery)	Day 1 (After Surgery)		30 ± 5 Days Post-op	
Describe study to potential subject	X					
Informed consent/Enrollment	X[1]					
Inclusion/Exclusion criteria	X[2]	X[3]				
Demographics and medical history	X					
Physical exam	X			X[4]	X[4]	X[4]
Laboratory tests	X[5]			X	X	X
Pregnancy test	X[6]					
Index procedure and operative summary		X[7]				
Suture leak test (antegrade cardioplegia injection)		X				
Randomization		X				
Time from clamp removal to request for wires sternal closure		X				
Blood Transfusion Volumes			X	X		
Chest tube status (drainage and duration)			X	X		
Adverse Events	X[8]	X	X	X	X	X

1 Obtain prior to entering into study and before any study related testing is conducted. Tests not specific to study and normally conducted prior to surgery may be completed prior to informed consent.
2 Ejection fraction (%) can be confirmed via echocardiogram, MUGA, CT, or nuclear cardiac imaging.
3 Assess intraoperative eligibility criteria.
4 To be performed at discharge, 1 month, and unscheduled visits, if clinically indicated.
5 Review of screening/baseline lab results required prior to surgery.
6 Women of childbearing potential will undergo pregnancy testing within 7 days prior to surgery.
7 Patients must have anti-fibrinolytic agents (e.g., Amicar) administered at the beginning of the procedure.
8 Adverse events are to be collected from the time of enrollment (AE onset after signing ICF). Events with an onset prior to enrollment should be reported in the medical history

3. Clinical Endpoints

Safety Endpoints

With regards to safety, there was no formal primary endpoint, but adverse events and device-related adverse events were observed and reported during the procedure, hospitalization, and from hospital discharge through the follow-up period (30 ± 5 days from index procedure).

Primary Effectiveness Endpoint

With regards to effectiveness, the primary endpoint of this study was the time to hemostasis (TTH). TTH measurement began after either TRIDYNE™ VS or Control was applied to the anastomotic suture line(s) and bypass cross clamp was released. Hemostasis was assessed continuously until hemostasis was achieved at each applied anastomotic site or until 10 minutes had passed. If hemostasis was not achieved

within 10 minutes, 10 minutes was used as the TTH. For patients with more than one treated aortic anastomotic suture line, the site with longest time to hemostasis was used for analysis.

The primary effectiveness endpoint was evaluated by the following hypothesis:

H_0: The mean time to hemostasis for patients receiving TRIDYNE™ VS at leaking sites involving the aortic valve, ascending aorta, or aortic arch is the same as for patients receiving Control.

H_1: The mean time to hemostasis for patients receiving TRIDYNE™ VS at leaking sites involving the aortic valve, ascending aorta, or aortic arch is different for patients receiving Control.

A non-parametric method, a Wilcoxon Rank-Sum test was employed to test the hypothesis.

Superiority of TRIDYNE™ VS was considered as demonstrated if the p-value was less than 0.05, and there was an observed decrease in the median time to hemostasis (TRIDYNE™ VS versus Control).

Secondary Endpoints

Secondary endpoints included the following:

- Proportion of subjects who achieve successful hemostasis at all treated aortic anastomotic suture lines following assigned treatment. Success is defined as hemostasis obtained within 5 minutes.
- Proportion of subjects who achieve immediate hemostasis, defined as 0 seconds, at all treated aortic anastomotic suture lines following assigned treatment.
- Chest tube drainage volume within 24 hours following surgery.
- Total transfusion volume within 24 hours following surgery.
- Time between cross clamp removal and request of surgical wires for sternal closure.
- Incidence of reoperations for aortic bleeding complications following assigned treatment through 30 days.
- Number of device-related serious adverse events per patient following assigned treatment through 30 days.

B. Accountability of PMA Cohort

At the time of database lock, of 204 patients enrolled in the PMA study, 76.5% (156) patients were treated and available for analysis at the completion of the study (the 30 day follow-up visit). **Table 4** provides a summary of the subject accountability.

Table 4. Subject Accountability

	TRIDYNE™ VS n (%)	Control n (%)	Total n (%)
Enrolled			204
Not randomized			46
Eligibility Criteria Not Met[1]			38
Sponsor's Decision[2]			5
Withdrawal of Consent			3
Randomized (Intent to Treat)	107 (100.0)	51 (100.0)	158 (100.0)
Treated (Modified Intent to Treat)[3]	106 (99.1)	50 (98.0)	156 (98.7)
Randomized Not Treated[4]	1 (0.9)	1 (2.0)	2 (1.3)
Discharged after Index Procedure	107 (100.0)	50 (98.0)	157 (99.4)
Completed one month follow-up	104 (97.2)	49 (96.1)	153 (96.8)
Primary reason for discontinuation			
Death	2[5] (1.9)	1[6,7] (2.0)	3 (1.9)

1. Preoperative Inclusion not met: One Subject was not scheduled for elective, primary thoracic surgery involving the aortic valve, ascending aorta, or aortic arch on cardiopulmonary bypass. Intraoperative Inclusion Criteria not met: Two subjects were unable to undergo an antegrade cardioplegia injection for evaluation of a leak at the aortic anastomotic site(s) during the procedure. Twenty subjects did not have a leaking site where a topical sealant/hemostatic agent may be used to control bleeding following cardioplegia injection. Exclusion Criteria: One subject had thoracic surgery (open thoracotomy not including interventional cardiology procedures). Eight subjects had a planned concomitant procedure other than coronary artery bypass graft (CABG). One subject had a previous organ transplant. Two subjects had a known or suspected preoperative coagulation disorder. One subject had a serum creatinine greater than or equal to 2.5 mg/dl at baseline. Three subjects had an active or latent infection which is systemic or at the intended surgery site. One subject was immuno-compromised such as that resulting from chronic oral steroid use, chemotherapeutic agents, or immune deficiency disorders. One subject had participated in another investigational research study within 30 days of enrollment. Three subjects in opinion of investigator had a clinical condition that would preclude use of study device, preclude subject from completing follow-up requirements, or complicate evaluation of study.
2. Subjects met eligibility criteria but were not randomized as enrollment numbers were already met.
3. The subjects that were treated represent the modified intent to treat population.
4. Two Control subjects and one TRIDYNE™ VS subject were randomized, however, the cross clamp was removed prior to application of the sealant.
5. Subject deaths due to cardiac arrest and ischemic cardiomyopathy.
6. Subject died during hospitalization and therefore was not discharged.
7. Subject death due to gastrointestinal bleed.

All subsequent data presented utilize the Modified Intent-to-Treat population unless otherwise indicated.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for an aortic surgery study performed in the US. **Table 5** provides a summary of subject demographic characteristics.

Table 5. Subject Demographics

	TRIDYNE™ VS	Control	Total
Number of subjects treated	**106**	**50**	**156**
Age (years) Mean (SD)	61.5 (14.42)	62.4 (14.30)	61.8 (14.34)
Median	63.5	64.0	64.0
Min-Max	23.0 - 87.0	20.0 - 89.0	20.0 - 89.0

		TRIDYNE™ VS	Control	Total
Number of subjects treated		**106**	**50**	**156**
Age Categories (years)				
	< 65	54 (50.9%)	28 (56.0%)	82 (52.6%)
	≥ 65	52 (49.1%)	22 (44.0%)	74 (47.4%)
Gender	Male	74 (69.8%)	35 (70.0%)	109 (69.9%)
	Female	32 (30.2%)	15 (30.0%)	47 (30.1%)
BMI (kg/ m^2)	Mean (SD)	31.2 (7.52)	28.3 (5.50)	30.2 (7.05)
Median		30.1	27.5	29.2
Min-Max		19.9 - 60.1	17.4 - 41.9	17.4 - 60.1
Ethnicity	Hispanic or Latino	2 (1.9%)	3 (6.0%)	5 (3.2%)
	Not Hispanic or Latino	100 (94.3%)	44 (88.0%)	144 (92.3%)
	Unknown	4 (3.8%)	3 (6.0%)	7 (4.5%)
Race				
	American Indian	2(1.9%)	0 (0.0%)	2 (1.3%)
	Asian	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Black or African American	3 (2.8%)	3 (6.0%)	6 (3.8%)
	Native Hawaiian or Other Pacific Islander	0 (0.0%)	1 (2.0%)	1 (0.6%)
	White Caucasian	94 (88.7%)	43 (86.0%)	137 (87.8%)
	Other	1 (0.9%)	0 (0.0%)	1(0.6%)
	Unknown	6 (5.7%)	3 (6.0%)	9 (5.8%)

There were 156 subjects treated with 172 treated suture lines treated overall; 119 suture lines in the TRIDYNE™ VS group and 53 treated suture lines in the Control group. The most frequent type of surgery was aortic valve replacement (42% TRIDYNE™ VS, 56.6% Control). In both the TRIDYNE™ VS and Control groups, the full sternotomy was the most frequently used surgical approach. Intraoperative characteristics were similar between the TRIDYNE™ VS and Control groups for the surgical procedures characteristics evaluated (**Table 6**).

Table 6. Surgery Type and Characteristics

	TRIDYNE™ VS n = 119	Control n = 53
Surgery Type		
Aortic Aneurysm Repair	18 (15.1%)	7 (13.2%)
Aortic Root Replacement	16 (13.4%)	8 (15.1%)
Aortic Valve Procedure	50 (42.0%)	30 (56.6%)
Ascending Aorta Replacement	28 (23.5%)	5 (9.4%)
Other	7[1] (5.9%)	3[2] (5.7%)
Location of Leaking		
Distal	26 (21.8%)	13 (24.5%)
Graft To Graft	24 (20.2%)	8 (15.1%)
Proximal	59 (49.6%)	26 (49.1%)
Other*	10 (8.4%)	6 (11.3%)
Type of Graft		
Polyester	56 (47.1%)	21 (39.6%)

	TRIDYNE™ VS n = 119	Control n = 53
None	42 (35.3%)	26 (49.1%)
Other	21 (17.6%)	6 (11.3%)
Pre-treatment bleeding		
Slow Steady Flow	13 (10.9%)	5 (9.4%)
Oozing	98 (82.4%)	46 (86.8%)
Pumping	8 (6.7%)	2 (3.8%)

1. One subject had hemiarch. One subject had aortic root replacement and aortic aneurysm repair. Two subjects had aortic valve procedure and aortic aneurysm repair. Two subjects had aortic valve replacement, ascending aorta replacement and aortic root replacement. One subject had aortic root replacement and ascending aorta replacement.
2. One subject had aortic valve replacement and hemiarch procedure. One subject had aortic valve replacement. One subject had David procedure, aorta root replacement and ascending aorta replacement.

* Other includes: aortotomy site, Right Coronary Artery button to aorta, Sinotublar Junction graft, right coronary suture line, graft to aorta.

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the treated cohort of 156 patients available for the 30 day post-op evaluation. The key safety outcomes for this study are presented below in **Tables 7 and 8**.

Adverse effects that occurred in the PMA clinical study:

Almost all treated patients reported at least one Adverse Event (AE) during the study (92.5% of patients treated with TRIDYNE™ VS 100.0% of patients treated with Control). None of the AEs reported in either treatment group or Control group were considered to be definitely related to the device. Overall, there were no major differences in the incidence of adverse events between treatment groups.

Serious Adverse Events (SAE)

Approximately half of the subjects in each treatment group experienced an SAE while in the study (51 subjects [48.1%] treated with TRIDYNE™ VS, 29 subjects [58.0%] treated with Control). Seven SAEs, described below, were considered by the Clinical Events Committee (CEC) to be possibly device-related (3 patients [2.8%] treated with TRIDYNE™ VS 4 patients [8.0%] treated with Control).

Nearly all CEC adjudicated SAEs were considered to be related to the procedure (87 of 88 SAEs in patients treated with TRIDYNE™ VS, 48 of 48 SAEs in patients treated with the Control). Most SAEs occurred in only one or two patients in either treatment group, with the exception of atrial fibrillation that occurred in 27 patients (25.5%) treated with TRIDYNE™ VS and 17 patients (34.0%) treated with the Control. Some of these were considered not to be serious by the Investigator and were upgraded by the CEC as a result of treatment by cardioversion or prophylactic use of antiarrythmics.

The CEC adjudicated seven patients' SAEs to be possibly device-related following completed surgery through the follow-up evaluation; 3 (2.9%) in the TRIDYNE™ VS

treatment group and 4 (8.2%) in the Control treatment group. None of the SAEs were unexpected given the procedures performed. The events are described below and **Table 7** provides a summary:

TRIDYNE™ VS SAEs

- Patient had a cerebrovascular accident on Study Day 1, which was severe in intensity.
- Patient had a cerebrovascular accident on Study Day 15, which was severe in intensity.
- Patient had pericardial effusion on Study Day 4, which was considered moderate in intensity. The subject underwent mediastinal re-exploration which found serosanguineous pericardial effusion with no active bleeding. Surgery was completed without complication and the event was considered resolved on Study Day 9.

Control SAEs

- Patient had a cerebrovascular accident on Study Day 1, which was moderate in intensity.
- Patient had a cerebrovascular accident on Study Day 0, which was moderate in intensity.
- Patient had a hematoma on Study Day 0, which was moderate in intensity. The patient was taken back to the operating room on the same day for mediastinal re-exploration where a large amount of hematoma in the mediastinum was noted and evacuated.
- Patient reported hypotension on Study Day 0, which was moderate in intensity.

Table 7. Incidence of Serious Adverse Events in TRIDYNE™ VS Group Considered Probably Device Related by CEC Adjudication

Preferred Term	TRIDYNE™ VS (n = 106)	Control (n = 50)
Cerebrovascular Accident	2 (1.9%)	2 (4.0%)
Pericardial Effusion	1 (0.9%)	0 (0.0%)
Hematoma	0 (0.0%)	1 (2.0%)
Persistent Hypotension	0 (0.0%)	1 (2.0%)

Non-Serious Adverse Events

At least one non-serious AE was reported in almost all of the patients in this study (92.5% of patients treated with TRIDYNE™ VS and 100.0% of patients treated with Control).

Table 8 lists AEs occurring in 5% or more of either treated or Control patients. None of these were CEC adjudicated to be device-related.

Table 8. Number of Patients with Frequently Reported Adverse Events

Adverse Event	TRIDYNE™ VS n = 106	Control n = 50
Pleural effusion	43 (40.6%)	18 (36.0%)
Anemia	39 (36.8%)	13 (26.0%)
Atelectasis	37 (34.9%)	15 (30.0%)
Atrial fibrillation	27 (25.5%)	17 (34.0%)
Leukocytosis	25 (23.6%)	13 (26.0%)
Thrombocytopenia	19 (17.9%)	8 (16.0%)
Peripheral Edema	18 (17.0%)	4 (8.0%)
Nausea	16 (15.1%)	7 (14.0%)
Fluid overload	14 (13.2%)	9 (18.0%)
Hypotension	13 (12.3%)	5 (10.0%)
Pulmonary Edema	11 (10.4%)	2 (4.0%)
Pneumothorax	10 (9.4%)	5 (10.0%)
Hyperglycemia	9 (8.5%)	6 (12.0%)
Hypoxia	8 (7.5%)	3 (6.0%)
Hypokalemia	7 (6.6%)	2 (4.0%)
Back pain	7 (6.6%)	2 (4.0%)
Tachycardia	6 (5.7%)	2 (4.0%)
Dizziness	6 (5.7%)	3 (6.0%)
Renal injury	5 (4.7%)	3 (6.0%)
Dyspnea	4 (3.8%)	3 (6.0%)
Fatigue	3 (2.8%)	5 (10.0%)
Hyponatremia	3 (2.8%)	3 (6.0%)
Respiratory failure	3 (2.8%)	3 (6.0%)
Atrial flutter	2 (1.9%)	3 (6.0%)
Pyrexia	2 (1.9%)	3 (6.0%)
Musculoskeletal pain	2 (1.9%)	4 (8.0%)
Vomiting	1 (0.9%)	4 (8.0%)
Musculoskeletal chest pain	0 (0.0%)	3 (6.0%)

There were 2 patients, one in each treatment group, with reported AEs considered device-related by the Investigator. The subject treated with TRIDYNE™ VS reported azotemia on Study Day 10, which the Investigator considered to both related to the device and procedure. The event was mild in severity and was adjudicated by the CEC not related to the device. The subject treated with the Control reported nausea on Study Day 5, which the Investigator considered possibly related to the device and definitely related to the procedure. The event was mild in severity and was adjudicated by the CEC not related to the device.

Unanticipated Adverse Device related Events (UADE)
No adverse events were considered to be UADEs.

Patient Deaths

There were three patient deaths during the study; two deaths (cardiac arrest, ischemic cardiomyopathy) in the TRIDYNE™ VS group and one death (gastrointestinal bleed) in the Control group. None of the deaths were considered by the Investigators or adjudicated by the CEC to be device related**.**

2. Effectiveness Results

The analysis of effectiveness was based on the 156 evaluable patients at the one-month post index procedure time point. Key effectiveness outcomes are presented in **Tables 9 and 10**.

Primary Effectiveness Endpoint

The distribution of time to hemostasis was significantly different between the TRIDYNE™ VS treatment group and Control treatment group (Wilcoxon rank-sum test p-value < 0.0001). The adjusted mean time to hemostasis was lower in subjects in the TRIDYNE™ VS treatment group compared to subjects in the GELFOAM® PLUS treatment group (124.3 seconds compared to 377.8 seconds). The term 'adjusted' is used because an imputation to a value of 600 seconds was used in subjects that did not achieve hemostasis in 10 minutes. This imputation technique underestimated the time to hemostasis for the subjects who did not achieve hemostasis by 600 seconds. Since more subjects in Control group did not achieve hemostasis by 600 seconds, this likely provided a conservative assessment of the TTH comparison.

Table 9 provides the adjusted mean and min-max hemostasis time. The time to hemostasis was missing for one subject treated with TRIDYNE™ VS; therefore, the denominator is 105 subjects.

Table 9. Time to Hemostasis (Seconds) for Individual Subjects

Treatment	n	Adjusted Mean*	Adjusted Min-Max*
TRIDYNE™ VS	105	124.3	0.0 - 600.0
Control	50	377.8	0.0 - 600.0

* If immediate hemostasis was achieved, 0 minutes was used as time to hemostasis (TTH). If hemostasis was not achieved within 10 minutes (600 seconds), 600 seconds was used as the TTH.
For subjects with more than one aortic anastomotic suture line treated, the site with longest TTH was used for analysis.

Secondary Effectiveness Endpoints

Immediate hemostasis, defined as hemostasis at 0 seconds, was achieved in 60.0% of subjects treated with TRIDYNE™ VS compared to 16.0% of subjects treated with Control. The percentage of subjects that achieved hemostasis within 10 minutes for TRIDYNE™ VS was 87.6% compared to 52.0% for the Control. By the 10-minute cut-off, only 12.4% of subjects in the TRIDYNE™ VS treatment group failed to achieve hemostasis, compared to 48.0% of the subjects in the Control treatment group.

Table 10 provides the information regarding whether hemostasis was achieved at the pre-determined time points. The time to hemostasis was missing for one subject treated with TRIDYNE™ VS; therefore, the denominator is 105 subjects.

Table 10. Summary of Time to Hemostasis for Individual Subjects

	TRIDYNE™ VS n = 105	**Control n = 50**
Immediate (0 second)	63 (60.0%)	8 (16.0%)
0 ≤ TTH < 5 minutes	90 (85.7%)	20 (40.0%)
0 ≤ TTH < 10 minutes	92 (87.6%)	26 (52.0%)

If the immediate hemostasis was achieved, 0 minutes was used as time to hemostasis (TTH). For subjects with more than one aortic anastomotic suture line treated, the site with longest TTH was used for analysis.

Use of Additional Adjunctive Agents to Achieve Hemostasis

As described above, additional standard of care surgical hemostatic measures could be performed if hemostasis was not achieved at the anastomotic suture line after 10 minutes or it was deemed by the surgeon to be medically necessary.

Table 11 describes the adjunctive treatments of the anastomotic suture lines. The denominator is the total number of suture lines treated per treatment group.

Table 11. Summary of Adjunctive Treatment of Aortic Anastomotic Suture Lines[1]

	TRIDYNE™ VS n = 119	**Control n = 53**	**Total n = 172**
None	86 (72.3%)	17 (32.1%)	103 (59.9%)
Additional application(s) of assigned treatment	16 (13.4%)	13 (24.5%)	29 (16.9%)
Sutures	18 (15.1%)	14 (26.4%)	32 (18.6%)
Pledgets	2 (1.7%)	2 (3.8%)	4 (2.3%)
Protamine	3 (2.5%)	8 (15.1%)	11 (6.4%)
Manual Pressure	0 (0.0%)	3 (5.7%)	3 (1.7%)
Other[2]	4 (3.4%)	6 (11.3%)	10 (5.8%)

1. Data was analyzed by suture line, not per subject.
2. Other includes: BioGlue, Gelfoam, and Thrombin.

3. Other Secondary Endpoints Results

- The amount of chest tube drainage within 24 hours of surgery was not significantly different between groups.
- There was no significant difference in the total transfusion volume between the treatment groups.
- There was no appreciable difference in surgical time between subjects treated with TRIDYNE™ compared to subjects treated with Control.
- There was no appreciable difference in the time between cross clamp removal and request of surgical wires for sternal closure.

- One subject (Control treatment group) required a reoperation for aortic bleeding complications following completed surgery through 30 days.

4. Subgroup Analyses

The following preoperative characteristics were evaluated for potential association with the secondary effectiveness outcome of successful hemostasis: age, gender, whether a CABG procedure was performed, the type of aortic procedure performed, and the recent use of an antithrombotic drug.

The subgroup analyses were completed in order to evaluate the effect of certain risk factors on successful hemostasis, which was defined as hemostasis within 5 minutes (**Table 12**). These analyses were for exploratory purposes only and no specific conclusions were drawn.

Table 12. Successful Hemostasis Subgroup Analysis

Subgroup	TRIDYNE™ VS	Control
Age		
< 65 years	45/54 (83.3%)	13/28 (46.4%)
≥ 65 years	45/51 (88.2%)	7/22 (31.8%)
Gender		
Female	25/32 (78.1%)	4/15 (26.7%)
Male	65/73 (89.0%)	16/35 (45.7%)
CABG Procedure		
Yes	21/22 (95.5%)	2/9 (22.2%)
No	69/83 (83.1%)	18/41 (43.9%)
Aortic Procedure Type		
Aortic Valve Procedure	48/50 (96.0%)	11/30 (36.7%)
Aortic Aneurysm Repair	12/16 (75.0%)	2/6 (33.3%)
Aortic Root Replacement	10/13 (76.9%)	5/7 (71.4%)
Ascending Aorta Replacement	19/23 (82.6%)	1/5 (20.0%)
Other	3/6 (50.0%)	1/3 (33.3%)
Use of any antithrombotic drug within 7 days prior to surgery		
Yes	51/56 (91.1%)	9/28 (32.1%)
No	39/49 (79.6%)	11/22 (50.0%)

Successful hemostasis was defined as hemostasis obtained within 5 minutes for all anastomotic suture lines.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 59 investigators of which none were full-time or part-time employees of the sponsor and 1 had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: none

- Significant payment of other sorts: 1 investigator
- Proprietary interest in the product tested held by the investigator: none
- Significant equity interest held by investigator in sponsor of covered study: none

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Please see the PROGEL™ Pleural Air Leak Sealant (Progel™ PALS) P010047 Summary of Safety and Effectiveness for additional clinical information regarding the use of the device for application to visceral pleura after standard visceral pleural closure with visible air leaks incurred during resection of lung parenchyma.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Cardiovascular Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

In the clinical study, the distribution of time to hemostasis was significantly different between the TRIDYNE™ VS treatment group and Control treatment group (Wilcoxon rank-sum test p-value < 0.0001). The following additional effectiveness results were reported:

- A higher proportion of patients in the TRIDYNE™ VS treatment group achieved immediate hemostasis compared to patients in the Control treatment group (60.0% versus 16.0%).
- A higher proportion of patients in the TRIDYNE™ VS treatment group achieved successful hemostasis within 5 minutes compared to patients in the Control treatment group (85.7% versus 40.0%).
- A higher proportion of patients in the TRIDYNE™ VS treatment group achieved hemostasis within 10 minutes compared to patients in the Control treatment group (87.6% versus 52.0%).

As a result, the clinical data derived from this pivotal study provide a reasonable assurance of effectiveness for the TRIDYNE™ VS when indicated for use in aortic surgery when

adjunctive measures to achieve hemostasis are required by mechanically sealing areas of leakage.

B. Safety Conclusions

The risks of the device are based on data collected in a clinical study conducted to support PMA approval as described above. During the clinical study, three patient deaths occurred; two deaths in the TRIDYNE™ VS group and one death in the Control group. None of the deaths were considered by the Investigators or adjudicated by the CEC to be device related.

There were no major differences in the incidence of adverse events between the treatment groups. Approximately half of the subjects in each treatment group experienced a Serious Adverse Event (SAE) while in the study (48.1% treated with TRIDYNE™ VS; 58.0% treated with Control). Nearly all Clinical Events Committee (CEC) adjudicated SAEs were considered to be related to the procedure (87 of 88 SAEs in patients treated with TRIDYNE™ VS; 48 of 48 SAEs in patients treated with Control group). The CEC adjudicated a total of 7 adverse events (all SAEs) to be possibly related to the device, 3 events in patients treated with TRIDYNE™ VS and 4 events in patients treated with Control.

Additionally, there was only one surgical reintervention due to aortic bleeding, which occurred in the Control group.

A review of the adverse events in the TRIDYNE™ VS and Control groups indicates that they are similar in rate and severity and do not raise any significant concerns. Therefore, the clinical data derived from this pivotal study provide a reasonable assurance of safety for the TRIDYNE™ VS when indicated for use in aortic surgery when adjunctive measures to achieve hemostasis are required by mechanically sealing areas of leakage.

C. Benefit-Risk Conclusions

The probable benefits of the device are based on data collected in a clinical study conducted to support PMA approval as described above. When used in aortic surgery to achieve hemostasis, the probable benefit is reduced time to achieve hemostasis when compared to a marketed alternative. Also, immediate hemostasis was achieved in more than half of the subjects treated with the device. Coupled with the fact that there was no increase in adverse events when compared with a marketed alternative, there is a reasonable benefit-risk profile to support the use of TRIDYNE™ VS in aortic surgery.

In conclusion, given the available information above, the data support that for TRIDYNE™ VS, the probable benefits outweigh the probable risk for use in aortic surgery when adjunctive measures to achieve hemostasis are required by mechanically sealing areas of leakage.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

The combination of nonclinical and clinical experience with the TRIDYNE™ VS supports the safety of the device. In vitro, biocompatibility, and animal studies confirmed that the TRIDYNE™ VS met performance and design specifications.

In addition, the results of the clinical study demonstrate the safety and effectiveness of the TRIDYNE™ VS when used to achieve hemostasis during aortic surgery. With regard to safety, there were no clinically relevant differences in the safety endpoints between the TRIDYNE™ VS and Control groups. With regard to effectiveness, the primary effectiveness endpoint of the study was met, as the distribution of time to hemostasis was significantly different between the TRIDYNE™ VS treatment group and Control treatment group (Wilcoxon rank-sum test p-value < 0.0001).

Overall, the results from this study demonstrate that TRIDYNE™ VS is safe and effective when used as an adjunct to achieve hemostasis in patients who are undergoing aortic surgery.

XIV. CDRH DECISION

CDRH issued an approval order on April 11, 2016.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

1 Nasso G, Piancone F, Bonifazi R, Romano V, Visicchio G, De Filippo CM, Impiombato B, Fiore F, Bartolomucci F, Alessandrini F, Speziale G. Prospective, Randomized Clinical Trial of the FloSeal Matrix Sealant in Cardiac Surgery. Ann ThoracSurg2009; 88:1520-1526.

2 Tanawuttiwat T, O'Neill BO, Cohen MG, Chinthakanan O, and Heldman AW et al. New-onset Atrial Fibrillation After Aortic Valve Replacement: Comparison of Tranfemoral, Transapical, Transaortic, and Surgical Approaches. J Am Coll Cardiol. 2014;63(15):1510-1519.