SUMMARY OF SAFETY AND EFFECTIVENESS

I. GENERAL INFORMATION

Device Generic Name:	Polymerizing Sealant
Device Trade Name:	ArterX™ Surgical Sealant (ArterX)
Device procode:	NBE
Applicant's Name and Address:	Tenaxis Medical, Inc. 835 Maude Ave Mountain View, CA 94043 Phone: (650) 691-9016 x115 Fax: (650) 691-9056
PMA Number:	P100030
Date of Panel Recommendation:	Not applicable
Date of Notice of Approval:	March 1, 2013

II. INDICATIONS FOR USE

ArterX Surgical Sealant is indicated for use in vascular reconstructions to achieve adjunctive hemostasis by mechanically sealing areas of leakage.

III. CONTRAINDICATIONS

Contraindications

- Not for use in patients with known allergies to materials of bovine or shellfish origin.
- Not for intravascular use.
- Not for cerebrovascular repair or cerebrospinal leak repair.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the ArterX Surgical Sealant labeling.

V. DEVICE DESCRIPTION

The ArterX Surgical Sealant (ArterX) is a sealant developed to seal suture holes or gaps formed during surgical repair of the circulatory system and to reinforce anastomoses. When applied, ArterX creates an elastic biocompatible gel that seals suture holes or gaps formed between synthetic grafts or patches and native vessel anastomoses. ArterX adheres to the native tissues as well as synthetic materials, including PTFE and Dacron grafts, and facilitates sealing along anastomotic closure lines.

ArterX is provided in a double-barreled syringe assembly containing equal volumes of purified bovine serum albumin ("BSA" protein solution) and a proprietary crosslinking solution of polyaldehyde. The BSA is obtained from a Bovine Spongiform Encephalopathies (BSE)-free source and is covered by a Certificate of Suitability concerning Transmissible Spongiform Encephalopathies issued by the European Directorate for the Quality of Medicines, according to the Eu Ph.

The product is ready to use after the pouch is opened, the syringe cap removed, the delivery tip is attached to the end of the syringe and the tip is primed. When the plunger is depressed, the two components are evenly mixed as they are coextruded through the delivery tip. ArterX is then ready to use and can be applied in a dry field or in a field where blood and blood components are present. ArterX is terminally sterilized by e-beam irradiation and is provided in a double pouch with two delivery tips. Additional sterile delivery tips are provided separately.

The sterile device is provided for single-use only.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several alternative practices and procedures to control bleeding, include the use of direct pressure, sutures, staples, 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, and cyanoacrylate/cyanoacylate. Each alternative has its own advantages and disadvantages.

VII. MARKETING HISTORY

The ArterX Surgical Sealant received the CE Mark and began commercial distribution in the European Union in 2008. ArterX has also been shipped to South Africa, Saudi Arabia, Israel and Turkey. It has not been withdrawn from any market at any time in any country.

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 this class of surgical sealants:

- Application of the sealant to tissue not targeted for the procedure
- Failure of the sealant to adhere to the tissue
- Hypersensitivity reaction such as swelling or edema at the application site
- Possible transmission of infectious agents from materials of animal origin
- Thrombosis and thromboembolism

Below is a list of the potential adverse effects (e.g., complications) associated with cardiac and vascular procedures:

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

For the specific adverse events that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF NON-CLINICAL STUDIES

A. Laboratory Studies

Biocompatibility

Biocompatibility testing was conducted in accordance with ISO 10993 (Biological evaluation of medical devices, Part 1, Guidance on selection of tests, 1997) for the entire ArterX implant, delivery system and component materials.

Formal biocompatibility testing on the implantable component of the ArterX formulation demonstrated satisfactory results in all sensitization, systemic toxicity and pyrogenicity tests.

In genotoxicity tests, no genotoxicity was observed at any extract dilution level in the presence of metabolic activation. In the absence of metabolic activation, dilutions were non-genotoxic, but showed cytotoxicity at more concentrated dilutions. The observed effects of polyaldehyde are expected to be limited to short-term cytotoxicity at the site of contact with no long term complications.

The sensitization study conducted in rabbits examined intact polymerized devices and the immunological response at 2 weeks and 3 months (12 weeks). The results supported the absence of humoral immunity or delayed hypersensitivity. These *in vivo* data provide no indication of active immunological reaction systemically or locally at the implantation site. In the large animal studies described below, the animals were observed for 3 to 24 months and did not show any signs of immunological reaction or hypersensitivity.

Since ArterX is intended to be used with the application site clamped with no active bleeding the ArterX will not come into intraluminal contact with actively flowing blood, hemocompatibility testing was not considered necessary and was not performed.

The biocompatibility of the ArterX Delivery Device (syringe, plunger, piston, cap and delivery tip) was evaluated as an acute tissue-contacting device. Device extracts were shown to have full compatibility in all cytotoxic, sensitization, irritation, systemic toxicity and pyrogenicity tests.

None of the raw materials used in the ArterX formulation have been reported as carcinogenic or suspected of carcinogenicity. Toxicity and genotoxicity testing has demonstrated safety and does not indicate additional need for carcinogenicity testing.

The biocompatibility testing results are summarized below in Tables 1a and 1b.

Table 1a: Results of Biocompatibility Testing - Sealant

Test	Method Reference	Results
Cytotoxicity (Elution and End-Point Titration Method)	International Organization for Standardization: Biological Evaluation of Medical Devices, Part 5. 10993-5: *Tests for Cytotoxicity*	No cytotoxic effect at extract dilutions at or above 1:8 at 24, 48 and 72 hours with extractions performed in saline and MEM in the presence of serum with a 72 hour extraction time. Polar and non-polar extracts of the product may be cytotoxic at concentrations above what would be expected clinically.
ISO Maximization Sensitization Study (Guinea Pigs)	International Organization for Standardization: Biological Evaluation of Medical Devices, Part 10. 10993-10: *Tests for Irritation and Sensitization*	No evidence of delayed dermal contact sensitization
ISO Intracutaneous Study (Rabbits)	International Organization for Standardization: Biological Evaluation of Medical Devices, Part 10. 10993-10: *Tests for Irritation and Sensitization*	No evidence of significant irritation
ISO Systemic Toxicity	International Organization for Standardization: Biological Evaluation of Medical Devices, Part 11. 10993-11: *Tests for Systemic Toxicity*	No mortality or systemic toxicity
USP Pyrogenicity	International Organization for Standardization: Biological Evaluation of Medical Devices, Part 11. 10993-11: *Tests for Systemic Toxicity*	Non-pyrogenic
Bacterial Reverse Mutation Study	International Organization for Standardization: Biological Evaluation of Medical Devices, Part 3. 10993-3: *Tests for Genotoxicity, Carcinogenicity, and Reproductive Toxicity*	Non-mutagenic
In Vitro Chromosomal Aberration Study In Mammalian Cells (CHO cells)	*In vitro* Chromosome Abberation Test evaluates the potential clastogenic properties of a test material solution.	1) Non-genotoxic in the presence of metabolic activation (10% and 1% dilutions). 2) Non-genotoxic in the absence of metabolic activation (1% and 2.5% dilution). Cytostatic at 10% dilution. 3) Non-genotoxic in the absence of metabolic activation (5% and 7.5% dilution). Cytostatic at 5%, 7.5% and 10% dilutions. 4) Repeat assay: Non-genotoxic in the absence of metabolic activation (2.5% and 5% dilutions). Cytostatic at 7.5% dilution.
In Vivo Mouse Peripheral Blood Micronucleus Study	International Organization for Standardization: Biological Evaluation of Medical Devices, Part 3. 10993-3: *Tests for Genotoxicity, Carcinogenicity, and Reproductive Toxicity*	Non-genotoxic
ISO Subcutaneous Implantation Study (2 Weeks)	International Organization for Standardization: Biological Evaluation of Medical Devices, Part 6. 10993-6: *Tests for Local Effects after*	No significant macroscopic reaction. Microscopically, material classified as a slight irritant.

	Implantation	
ISO Subcutaneous Implantation Study (12 Weeks)	International Organization for Standardization: Biological Evaluation of Medical Devices, Part 6. 10993-6: *Tests for Local Effects after Implantation*	No significant macroscopic reaction. Microscopically, material classified as a moderate irritant.

Table 1b: Results of Biocompatibility Testing – Delivery System

Test	Method Reference	Results
Cytotoxicity (Elution and End-Point Titration Method)	International Organization for Standardization: Biological Evaluation of Medical Devices, Part 5. 10993-5: *Tests for Cytotoxicity*	No cytotoxic effects observed.
ISO Maximization Sensitization Study (Guinea Pigs)	International Organization for Standardization: Biological Evaluation of Medical Devices, Part 10. 10993-10: *Tests for Irritation and Sensitization*	No evidence of delayed dermal contact sensitization
ISO Intracutaneous Study (Rabbits)	International Organization for Standardization: Biological Evaluation of Medical Devices, Part 10. 10993-10: *Tests for Irritation and Sensitization*	No evidence of significant irritation
ISO Systemic Toxicity	International Organization for Standardization: Biological Evaluation of Medical Devices, Part 11. 10993-11: *Tests for Systemic Toxicity*	No mortality or systemic toxicity
USP Pyrogenicity	International Organization for Standardization: Biological Evaluation of Medical Devices, Part 11. 10993-11: *Tests for Systemic Toxicity*	Non-pyrogenic

The data from these evaluations support an overall conclusion that ArterX is biocompatible.

In Vitro Laboratory Studies

In vitro (bench) testing was conducted on finished ArterX product to ensure that the product reproducibly meets product specifications. The tests conducted are listed in **Table 2**.

Table 2: Results of In Vitro Testing

Test	Purpose	Acceptance Criteria	Results
Burst Pressure	The sealant must be able to withstand expected physiological pressures without bursting.	Mean burst pressure ≥200 mmHg	The mean burst pressure after gelling was 501 mmHg, meeting the product specification.
Elasticity at 1 minute	The sealant must be able to accommodate expected	Mean elongation ≥20%.	The mean elongation was

	elongations without failure		132%, meeting the product specification.
Flexibility at 1 minute	The sealant must be able to withstand expected bending without cracking	Mean bend angle of ≥90°.	The mean angle was 180°, meeting the product specification.
Assembly time	A clinician must be able to prepare the product within a reasonable time.	The time to assemble the device must be ≤ 2 minutes.	The mean time to assemble the device was 6 seconds with a maximum time of 11seconds, meeting the product specification.
Extrusion force	The force required to extrude the sealant from the syringe must not be excessive.	Peak force of ≤ 32 N.	The mean peak force was 18 N, meeting the product specification.
Swelling	The sealant must not swell excessively in the presence of liquid.	Swelling ≤ 10%.	The mean swell was -2.57%, meeting the product specification.
Mixing uniformity	During delivery, the sealant must be mixed to an acceptable degree.	Mixing must be uniform, as observed using dyed components	Mixed samples showed a uniform mixed color, meeting the product specification.

In addition, analytical and functional tests are conducted as release tests on each lot of ArterX to verify that product meets established specifications.

These laboratory tests demonstrate acceptable and reproducible safety and effectiveness for the ArterX product.

B. Animal Studies

The safety and effectiveness of ArterX was evaluated in the placement and sealing of synthetic grafts into the aorta of sheep. A PTFE bypass graft was attached at both ends using end-to-side anastomoses to the descending thoracic aorta of a heparinized sheep. All gaps or suture holes along the anastomotic joints were sealed prophylactically using

the ArterX sealant. In the case of control animals, no sealant was used. The primary endpoint for the evaluation of effectiveness was the extent of bleeding at the anastomotic sites (both distal and proximal) with success defined as absence of bleeding or presence of only minor oozing at the zero-minute time point. Secondary endpoints included the extent of bleeding at 1, 3, 5 and 10 minute time points (absence of bleeding, no oozing) and the volume of blood lost. Animals were sacrificed at 3, 6, 12 and 24 months post-surgery. Following sacrifice, the implant sites, adjacent tissues and major organs were evaluated grossly and microscopically.

A total of twenty-one sheep in two separate studies had a prosthetic PTFE graft successfully anastomosed to the descending thoracic aorta. One animal was lost during surgery due to a complication (pneumothorax) unrelated to the surgical procedure or device. The ArterX test article was able to be deployed over the anastomotic incisions and significantly reduced the degree of hemorrhage that occurred from the test graft anastomotic sites when compared to the control sites.

All organs and tissues examined grossly at necropsy and microscopically at 3, 6, 12 and 24 months were normal or, if abnormal, were unrelated to the test article (pleural adhesions from the surgical procedure) and were referred to as spontaneous incidental findings.

Test and control animals from these studies had similar fibrous deposition and foreign body response to the graft/suture/aorta/anastomosis at 3, 6, 12 and 24 months. In addition, normal fibrillation, hyalinization and mineralization of elastic fibers within the aortic wall were presumed a result of the surgical procedure. A mild foreign body response with fibrous deposition was observed encapsulating the sealant that was similar to the tissue response to the prosthetic graft and suture. There was no significant difference in microscopic findings among the 3, 6, 12 and 24 month test animals when each was compared to the other. Progressive ongoing biodegradation was evident at each time point.

The animal studies support the pre-clinical safety and effectiveness of the ArterX product for its intended use.

C. Additional Studies

Sterilization

ArterX is validated for e-beam irradiation sterilization in accordance with ISO 11137-1, 2, & 3: 2006 - Sterilization Validation Requirements using Method VD Max $_{20}$ to achieve a sterility assurance level of 10^{-6} SAL.

Shelf Life

A 12-month shelf life was established based on results from two real-time stability studies and one accelerated study which met the acceptance criteria for all parameters

through 12 months. Based on these results, the product demonstrates that an expiration date of 12 months shelf life may be applied when stored at the labeled storage conditions of 2-8°C.

X. SUMMARY OF CLINICAL STUDIES

The applicant performed a pivotal clinical study to establish a reasonable assurance of safety and effectiveness of the ArterX Surgical Sealant when used during vascular surgical procedures to provide adjunctive hemostasis. This study was a prospective, randomized, controlled trial conducted in the United States under IDE #G070211. Data from this clinical study were the primary basis for the PMA approval decision. In addition, data collected from a multi-center, non-randomized clinical study in Europe were also provided and considered in support of this PMA. A summary of the pivotal clinical study is presented below.

A. Study Design

Patients were treated between October 2008 and December 2009. The database for this PMA reflected data collected through March 2010 and included 217 patients. There were 11 investigational sites.

The study was a prospective, multi-center, two-arm, randomized clinical study conducted to evaluate the safety and effectiveness of the ArterX Surgical Sealant versus a control in sealing suture lines at the anastomosis between native vessels and synthetic (e.g. PTFE/Dacron) vascular grafts or patches used during open vascular reconstruction, vascular repair or hemodialysis access. Subjects were randomly assigned 1:1 to either receive ArterX or the control device (Gelfoam Plus [Gelfoam/thrombin], a legally marketed alternative with a similar intended use), just prior to the time it was administered, for all treatment sites during the surgical procedure. All subjects were followed for 3 months following treatment.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the study was limited to patients who met the following key inclusion criteria:

1. The subject must be ≥ 18 years old.
2. The subject must be scheduled for the surgical placement of a PTFE or Dacron vascular graft or patch for large vessel repair/arterial reconstruction or hemodialysis access or arteriotomy.
3. The subject has no child bearing potential or has a negative serum or urine pregnancy test within 7 days of the index procedure.
4. The subject is willing and able to be contacted for the follow up visits at 6 weeks (± 7 days) and 3 months (± 7 days).
5. The subject or guardian must provide written informed consent using a form that is reviewed and approved by the Institutional Review Board.

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

1. The subject has a known hypersensitivity or contraindication to heparin, bovine or seafood products.
2. The subject has a history of bleeding diathesis or coagulopathy, or will refuse blood transfusions.
3. The subject is currently enrolled in this, or another investigational device or drug trial that has not completed the required follow-up period.

2. Follow-Up Schedule

All patients were examined during their hospital stay, and were scheduled to return for follow-up examinations at 6 weeks (±7 days) and at 3 months (±7 days) post-operatively. Adverse events and complications were recorded at all visits.

3. Clinical Endpoints

With regards to safety, the primary endpoint was the cumulative incidence of significant bleeding, infection, neurological deficit or immune/inflammatory allergic response observed within 6 weeks post treatment. Additional safety endpoints included adverse event assessment at the following time points: in-hospital, 6 weeks and 3 months post-surgery.

With regards to effectiveness, the primary endpoint was immediate sealing, as evidenced by no bleeding after clamp release during the surgical procedure. Additional effectiveness endpoints included sealing at intervals of 1, 3, 5 and 10 minutes after clamp release, measured as both bleeding status and time to sealing; device malfunctions and ability to deliver the sealant; and type and quantity of additional hemostatic agents used during the procedure.

B. Accountability of PMA Cohort

At the time of database lock, of the 217 patients enrolled in PMA study, 91% (197/217) were available for analysis at the completion of the study, the 3-month post-operative visit. The subject accountability is provide in **Table 3**.

Table 3: Subject Accountability

	ArterX Surgical Sealant (n = 110)	**Control (n = 107)**
Randomized	110 (100%)	107 (100%)
Treated	110 (100%)	107 (100%)
Discharged	110 (100%)	107 (100%)
Completed 6-Week Follow-Up	102 (92.7%)	100 (93.5%)
Completed 3-Month Follow-Up	100 (90.9%)	97 (90.7%)

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a peripheral vascular sealant study performed in the US. **Table 4** depicts the key patient demographics.

Table 4: Patient Demographics

	ArterX Surgical Sealant (n = 110)	Control (n = 107)	P value
Age (Years)			0.7415
Mean ± SD (N)	66.2 ± 12.3	65.7 ± 12.3	
Range	20.8 – 86.6	26.2 – 95.1	
Gender			
Male	37.3%	34.6%	0.6793
Female	62.7%	65.4%	
Race/Ethnicity			
White	68.9%	69.2%	0.3053
Black	30.2%	27.9%	
Hawaiian/Pacific Islander	0.9%	0.0%	
Asian	0.0%	2.9%	
Hispanic/Latino	11.0%	10.3%	0.8622
Body Mass Index (kg/m^2)			
Mean ± SD (N)	28.8 ± 6.5	28.1 ± 7.2	0.4874
Range	14.5 – 49.3	17.9 – 59.3	

The surgical procedures during which the ArterX product was used are described in **Table 5**.

Table 5: Surgical Procedure Characteristics

	ArterX Group (N=110 subjects, 167 sites)	Control Group (N=107 subjects, 164 sites)	Difference (95% C.I.)	p-value
Type of Surgical Procedure				
Aortic Procedures	10.9% (12/110)	14.0% (15/107)	-3.1% (-11.9, 5.7)	0.7156
Extremity Bypass Procedures	18.2% (20/110)	17.8% (19/107)	0.4% (-9.8, 10.6)	
Carotid Procedures	27.3% (30/110)	19.6% (21/107)	7.7% (-3.6, 18.9)	
Hemodialysis Access	22.7% (25/110)	24.3% (26/107)	-1.6% (-12.9, 9.7)	
Grafting	20.9% (23/110)	24.3% (26/107)	-3.4% (-14.5, 7.7)	
Other				
Type of Graft				
PTFE	67.7% (113/167)	62.8% (103/164)	4.9% (-5.4, 15.1)	0.3532
Dacron	32.3% (54/167)	37.2% (61/164)	-4.9% (-15.1, 5.4)	
Diameter of Graft (mm)				
Mean ± SD (N)	8.2±4.0 (128)	8.6±4.9 (131)		
Range (min, max)	(4.0, 28.0)	(3.0, 34.0)		

% of Grafts = Patch	23.4% (39/167)	19.5% (32/164)		
Number of anatomical sites treated				
One	53.6% (59/110)	54.2% (58/107)		
Two	40.9% (45/110)	38.3% (41/107)		
Three	5.5% (6/110)	7.5% (8/107)		

There were no statistically significant differences between the two randomized treatment groups with respect to basic demographics, surgical procedure performed or the type of graft utilized.

D. Safety and Effectiveness Results

1. Safety Results

The primary analysis of safety was based on the total cohort of 217 subjects who were evaluated at six weeks post-procedure. As indicated in **Table 6**, there were no statistically significant differences between the treatment and control groups with regards any of the primary safety endpoints treated individually, as listed in **Table 6**. The difference between the two groups with respect to the cumulative incidence of safety measures, i.e., the incidence of subjects having one or more safety endpoints occurring within 6 weeks, was statistically significant (46.4% ArterX compared to 59.8% control, $p < 0.05$).

Table 6: Primary Safety Endpoint Events through 6 Weeks

Safety Measure within 6 Weeks Post Treatment	ArterX Group (N=110)	Control Group (N=107)	Difference (95% C.I.)	p-value
Significant Bleeding	35.5% (39/110)	45.8% (49/107)	-10.3% (-23.3, 2.7)	0.1209
Infection	14.8% (16/108)	23.6% (25/106)	-8.8% (-19.3, 1.7)	0.1031
Neurological Deficit	5.6% (6/108)	3.8% (4/105)	1.8% (-3.9, 7.4)	0.7482
Immune/Inflammatory Allergic Response	0% (0/108)	0.9% (1/106)	-0.9% (-2.8, 0.9)	0.4953
Cumulative Incidence of Safety Measures	46.4% (51/110)	59.8% (64/107)	-13.5% (-26.6, -0.3)	0.0472

Adverse effects that occurred in the pivotal study:

The serious adverse events that occurred in this study are presented in **Table 7** and **8**. There were no significant differences between the two randomized groups with respect to the prevalence of other serious adverse events potentially associated with vascular procedures occurring within 6 weeks or between 6 weeks and 3 months post-treatment.

Table 7: Serious Adverse Events through 6 Weeks

Serious Adverse Event	ArterX Group (N=110)	Control Group	Difference (95% C.I.)	p-value

		(N=107)		
Death	3.6% (4)	0.9% (1)	2.7% (-1.2, 6.7)	0.3694
Hypotension	2.7% (3)	0.0% (0)	2.7% (-0.3, 5.8)	0.2467
Thrombosis/ Thromboembolism	1.8% (2)	0.0% (0)	1.8% (-0.7, 4.3)	0.4978
Ischemia	1.8% (2)	0.9% (1)	0.9% (-2.2, 4.0)	1.0000
Respiratory Failure/ Dysfunction	1.8% (2)	0.9% (1)	0.9% (-2.2, 4.0)	1.0000
Steal Syndrome	1.8% (2)	0.0% (0)	1.8% (-0.7, 4.3)	0.4978
Myocardial Infarction	0.9% (1)	0.0% (0)	0.9% (-0.9, 2.7)	1.0000
Pleural Effusion	0.0% (0)	0.9% (1)	-0.9% (-2.8, 0.9)	0.4931

A total of seven deaths were reported with six deemed related to the subjects' underlying condition and one due to natural causes.

Table 8: Serious Adverse Events - 6 Weeks through 3 Months

Serious Adverse Event	ArterX Group (N=110)	Control Group (N=107)	Difference (95% C.I.)	p-value
Infection	2.7% (3)	1.9% (2)	0.9% (-3.1, 4.8)	1.0000
Thrombosis/ Thromboembolism	0.9% (1)	0.9% (1)	-0.0% (-2.6, 2.5)	1.0000
Death	0.9% (1)	0.9% (1)	-0.0% (-2.6, 2.5)	1.0000

2. Effectiveness Results

The primary analysis of effectiveness, a comparison of immediate suture line sealing, was conducted on the 331 anatomic sites treated as part of the study. As indicated in **Table 9**, the difference in suture line sealing between the two groups was statistically significant, indicating superior sealing in the ArterX group. This effectiveness analysis was also conducted on a per-patient basis, with no change in the results or conclusions.

Table 9: Primary Effectiveness Analysis: Immediate Suture Line Sealing

Parameter	ArterX Group	Control Group	Difference (95% C.I.)	Conclusion
Immediate Suture Line Sealing	60.5% (101/167)	39.6% (65/164)	20.8% (10.3, 31.4)	ArterX is Superior to Control

A significantly higher percentage of ArterX sites achieved immediate sealing compared to the control group when PTFE grafts were used for the bypass procedure, while no such difference was observed for Dacron grafts **(Table 9**). In addition, no statistically significant difference in immediate sealing between the ArterX and control groups was observed during aortic or carotid procedures, while immediate sealing was significantly

higher for the ArterX sites in extremity bypass, hemodialysis access grafting procedures, and all other types of vascular procedures, as seen in **Table 11**. It is important to note that the study was not designed to be powered for these types of comparisons.

Table 10: Primary Effectiveness by Type of Graft

	% of Sites with No Bleeding on Clamp Release			
Type of Graft	**ArterX Group (N=167)**	**Control Group (N=164)**	**Difference (95% C.I.)**	**p-value**
PTFE	62.8% (71/113)	34.0% (35/103)	28.9% (16.1, 41.6)	<0.0001
Dacron	55.6% (30/54)	49.2% (30/61)	6.4% (-11.9, 24.6)	0.4946

Table 11: Primary Effectiveness by Surgical Procedure

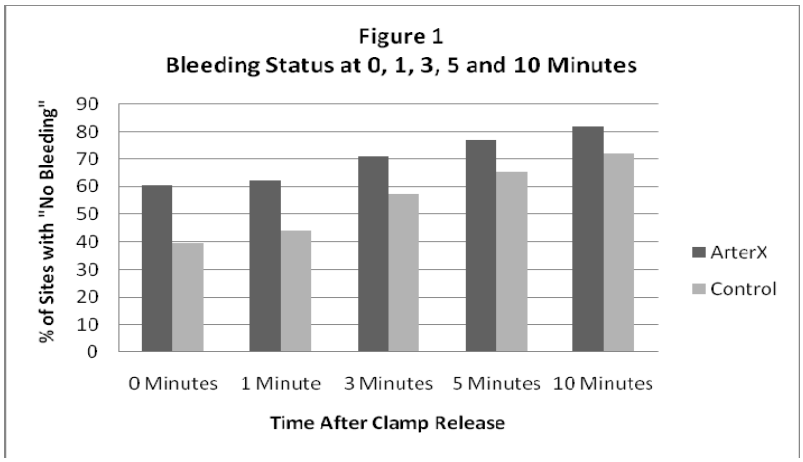
	% of Sites with No Bleeding on Clamp Release			
Surgical Procedure	**ArterX Group (N=167)**	**Control Group (N=164)**	**Difference (95% C.I.)**	**p-value**
Aortic Procedures	77.3% (17/22)	70.0% (21/30)	7.3% (-16.7, 31.3)	0.5591
Extremity Bypass Procedures	62.5% (20/32)	26.7% (8/30)	35.8% (12.8, 58.9)	0.0046
Carotid Procedures	30.0% (9/30)	38.1% (8/21)	-8.1% (-34.6, 18.4)	0.5461
Hemodialysis Access Grafting	69.6% (32/46)	32.6% (14/43)	37.0% (17.7, 56.3)	0.0005
Other Vascular Procedures	62.2% (23/37)	35.0% (14/40)	27.2% (5.7, 48.7)	0.0172

b. Bleeding Status through 10 Minutes

As a secondary endpoint, bleeding status was recorded for each treatment site immediately following clamp release, and at 1, 3, 5 and 10 minute intervals following clamp release. At each time point, the clinical investigator recorded either "Bleeding" or "No Bleeding." The percent of treated sites achieving hemostasis at each time point is presented in **Table 12** and **Figure 1**.

Table 12: Bleeding Status at 0, 1, 3, 5 and 10 Minutes

	% of Sites with "No Bleeding"		
Time After Clamp Release	**ArterX Group (N=167)**	**Control Group (N=164)**	**Difference (95% C.I.)**
Immediate (0 Minutes)	60.5% (101/167)	39.6% (65/164)	20.8% (10.3, 31.4)
1 Minute	62.3% (104/167)	43.9% (72/164)	18.4% (7.8, 28.9)
3 Minutes	70.7% (118/167)	57.3% (94/164)	13.3% (3.1, 23.6)
5 Minutes	77.2% (129/167)	65.2% (107/164)	12.0% (2.3, 21.7)
10 Minutes	82.0% (137/167)	72.0% (118/164)	10.1% (1.1, 19.1)



At ten minutes, there was no statistically significant difference in bleeding between the ArterX control groups with respect to the type of graft used or the type of procedure performed, as seen in **Tables 13** and **14.**

Table 13: Bleeding Status at 10 Minutes by Type of Graft

Type of Graft	**% of Sites with "No Bleeding" at 10 Minutes**			
	ArterX Group (N=167)	**Control Group (N=164)**	**Difference (95% C.I.)**	**p-value**
PTFE	83.2% (94/113)	72.8% (75/103)	10.4% (-0.7, 21.4)	0.0650
Dacron	79.6% (43/54)	70.5% (43/61)	9.1% (-6.6, 24.8)	0.2601

Table 14: Bleeding Status at 10 Minutes by Surgical Procedure

Surgical Procedure	**% of Sites with "No Bleeding" at 10 Minutes**			
	ArterX Group (N=167)	**Control Group (N=164)**	**Difference (95% C.I.)**	**p-value**
Aortic Procedures	95.5% (21/22)	80.0% (24/30)	15.5% (-1.3, 32.2)	0.2165
Bypass-Extremities	71.9% (23/32)	63.3% (19/30)	8.5% (-14.7, 31.8)	0.4721
Carotid Procedures	70.0% (21/30)	57.1% (12/21)	12.9% (-13.9, 39.6)	0.3444
Hemodialysis Access Grafting	93.5% (43/46)	83.7% (36/43)	9.8% (-3.4, 22.9)	0.1876
Other	78.4% (29/37)	67.5% (27/40)	10.9% (-8.8, 30.5)	0.2842

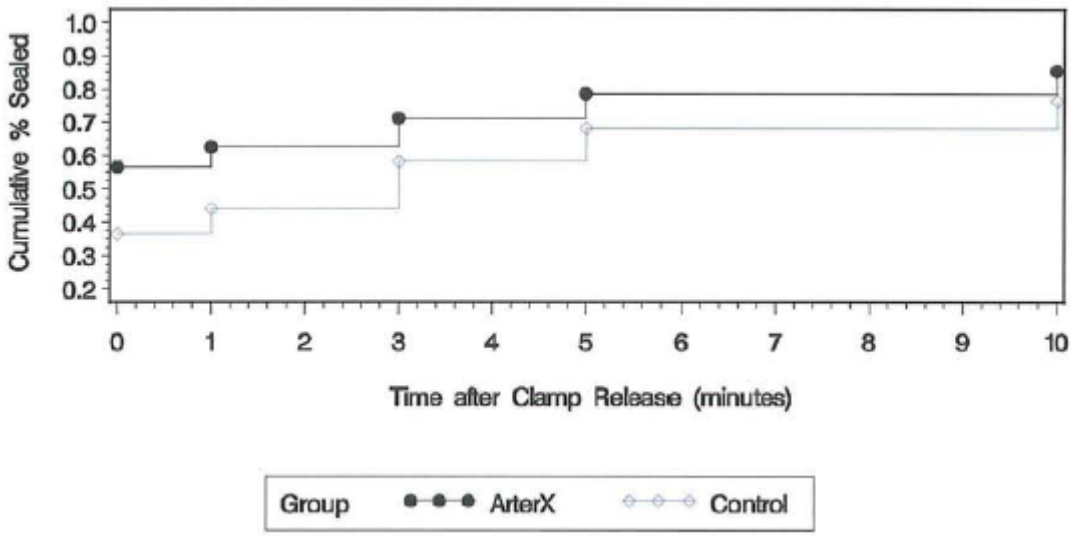
c. Time to Sealing through 10 Minutes

Time to sealing refers to the time the incision site was completely sealed, i.e., the last time point in which bleeding status equaled "No Bleeding" for each treatment site.

Kaplan-Meier methods were employed to summarize the cumulative time to sealing for all treated sites and compare the results between treatment groups. Censored observations include treatment sites where the clinical investigator intervened and used additional methods to achieve hemostasis prior to 10 minutes after clamp release. Among the 167 sites treated in the ArterX group, 56.6% were sealed at 0 minutes, 62.7% at 1 minute, 71.3% at 3 minutes, 78.7% at 5 minutes, and 85.5% at 10 minutes after clamp

release. Among the 164 sites treated in the Control group, 36.6% were sealed at 0 minutes, 44.1% at 1 minute, 58.2% at 3 minutes, 68.1% at 5 minutes, and 76.5% at 10 minutes after clamp release. Time to sealing was significantly better for ArterX compared to the Control group ($p < 0.0005$) (**Table 15**).

Table 15: Cumulative Time to Sealing – Kaplan Meier Results



	Time Period after Clamp Release				
	0 minutes	**1 minute**	**3 minutes**	**5 minutes**	**10 minutes**
ArterX Group					
# Sites at beginning of Interval	167	72	62	43	32
# Censored Prior to Interval	1	0	6	0	4
# at Risk	166	72	56	43	28
# sealed	94	10	13	11	9
% Sealed	56.6	62.7	71.3	78.7	85.5
Standard error (%)	3.9	3.8	3.6	3.3	2.9
Control Group					
# Sites at beginning of Interval	164	104	90	62	45
# Censored Prior to Interval	0	2	7	3	3
# at Risk	164	102	83	59	42
# sealed	60	12	21	14	11
% Sealed	36.6	44.1	58.2	68.1	76.5
Standard error (%)	3.8	3.9	3.9	3.8	3.5

Wilcoxon Test Between Groups, p-value = 0.0004

d. Surgery and Hospitalization Data

The total surgery time was defined as the time the initial incision was made to the time the dressings were placed. The average surgery time was 3.2 ± 1.4 hours for the ArterX group, which was statistically significantly less than the 3.8 ± 2.2 hours for the Control group ($p < =0.01$). The total hospitalization time was defined as the number of days between the initial study procedure and the date of hospital discharge. The average hospitalization time was 4.1 ± 5.5 days for the ArterX group and 5.4 ± 7.0 days for the Control group, which does not represent a statistically significant difference (**Table 15**).

Table 15: Procedural Data for all Treated Sites

Procedural Data	ArterX (N=110 pts / 167 sites)	Control (N=107 pts / 164 sites)	Difference (95% C.I.)	p-value
Time between Clamp release and Bleeding Stopped (min) Mean ± SD (N) Median Range (min, max)	 5.1±15.1 (166) 0.0 (0, 132)	 5.3±7.6 (164) 3.0 (0, 40)	---	0.0008[1]
Total Surgery Time (hrs) Mean ± SD (N) Range (min, max)	 3.2±1.4 (110) (1.0, 7.7)	 3.8±2.2 (106) (1.0, 11.1)	-0.7 (-1.2, -0.2)	0.0085
Total Hospitalization Time (days) Mean ± SD (N) Range (min, max)	 4.1±5.5 (110) (0, 42)	 5.4±7.0 (107) (0, 43)	-1.3 (-3.0, 0.4)	0.1273

[1]Wilcoxon, 2 sample test.

3. Subgroup Analyses

Gender analysis

Enrollment in the pivotal study was balanced between males and females. While the study was not powered to detect differences in safety and effectiveness outcomes as a function of gender, post-hoc analyses were conducted to assess this. Gender was included in a mixed-effects logistic regression model utilized to assess the potential effects of covariates on primary effectiveness, and was determined to not be associated with the effectiveness outcome ($p > 0.10$). In addition, there were no statistically significant differences between males and females forany of the protocol-specified safety events (bleeding events, infections, neurological deficits, inflammatory/allergic response, and the cumulative rate of safety events). These analyses indicate similar safety and effectiveness outcomes for males and females in this patient population.

XI. SUMMARY OF SUPPLEMENTARY CLINICAL INFORMATION

European Clinical Study

Prior to initiation of the US pivotal study, a prospective, multi-center, single-arm study was conducted to evaluate the safety and effectiveness of ArterX in patients scheduled to receive a patch or graft during a surgical procedure. During surgery, ArterX was used in

all patients to seal suture lines at anastomoses between native vessels and synthetic grafts. The primary and secondary study endpoints mirrored those used in the US pivotal study, although there were no pre-specified statistical hypotheses.

The study enrolled 32 subjects who were treated at 56 application sites. The distributions of patients by age, gender, surgical procedure, and graft material are shown in **Tables 16 - 18**.

Table 16: Distribution of Patients by Age and Gender

	Age
Mean / Median	66 (STD = 10.07) / 64.5
Min / Max	46 / 86
Males / Females	26 / 6

Table 17: Distribution of Patients and Sites by Surgical Procedure

	Bypass Graft n (%)	**AV Access Graft n (%)**	**Arteriotomy n (%)**	**Total n (%)**
Patients	22 (69%)	2 (6%)	8 (25%)	32 (100%)
Suture Sites	46 (82%)	2 (4%)	8 (14%)	56 (100%)

Table 18: Distribution of Patients and Sites by Graft Material in Intent-to-Treat Category

	PTFE (n)	**Dacron (n)**	**Total (n)**
Patients	10	23	33
Suture Sites	19	38	57*

*One procedure used 2 graft materials

1. Safety Results

There were no device-related adverse events reported immediately post-procedure, at 6 weeks, or at 3 months in the European study.

2. Effectiveness Results

Immediate sealing occurred in 100% of subjects and sites treated with ArterX, as did sealing at 10 minutes after clamp release. When any amount of oozing/bleeding was classified as a failure, the study demonstrated 93% success at the immediate time point and 98% success at 10 minutes. Results were comparable across procedure and graft types, as indicated in **Tables 19 – 22**.

Table 19: Sites Achieving Sealing by Procedure Immediately Following Clamp Release

Surgical Procedure	Intent-To-Treat Sites	Number of Failures if oozing is acceptable	Success Rate % if oozing is acceptable	Number of Failures if oozing is unacceptable	Success Rate % if oozing is unacceptable
Bypass Graft	46	0	100%	3	94%
AV Access Graft	2	0	100%	0	100%
Arteriotomies	8	0	100%	1	88%
Totals	56	0	100%	4	93%

Table 20: Sites Achieving Sealing by Procedure: 10 Minutes After Clamp Release

Surgical Procedure	Total Sites	Number of Failures if oozing is acceptable	Success Rate % if oozing is acceptable	Number of Failures if oozing is unacceptable	Success Rate % if oozing is unacceptable
Bypass Graft	46	0	100%	1	98%
AV Access Graft	2	0	100%	0	100%
Arteriotomies	8	0	100%	0	100%
Totals	56	0	100%	1	98%

Table 21: Sites Achieving Sealing by Graft Material Immediately Following Clamp Release

Surgical Procedure	Intent-to-Treat Sites	Number of Failures if oozing is acceptable	Success Rate % if oozing is acceptable	Total Sites Achieving Sealing at T=0	Success Rate % if oozing is unacceptable
PTFE	19	0	100%	19	100%
Dacron	38	0	100%	34	89%
Totals	57*	0	100%	53	93%

*One procedure used 2 graft materials

Table 22: Sites Achieving Sealing by Graft Material: 10 Minutes After Clamp Release

Surgical Procedure	Total Sites	Number of Failures if oozing is acceptable	Success Rate % if oozing is acceptable	Total Sites Achieving Sealing at T=10	Success Rate % if oozing is unacceptable
PTFE	19	0	100%	19	100%
Dacron	38	0	100%	37	97%
Totals	57*	0	100%	56	98%

*One procedure used 2 graft materials.

XII. PANEL MEETING RECOMMENDATION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to an FDA Advisory Committee Panel 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

The primary effectiveness endpoint, immediate sealing at the anastomosis site, was evaluated in all enrolled patients and was significantly higher at anatomic sites treated with ArterX Surgical Sealant as compared to the control treatment (60.5% vs. 39.6%). Therefore, the primary effectiveness endpoint was met and the results demonstrate a reasonable assurance of device effectiveness.

B. Safety Conclusions

The risks of the device are based on non-clinical laboratory and animal studies, as well as on data collected in a clinical study to support PMA approval as described above. The primary safety endpoint of the clinical study, the cumulative incidence of significant bleeding, infection, neurological deficit, and immune inflammatory response occurring within 6 weeks of the procedure, was evaluated in all enrolled subjects with evaluable 6-week data and was significantly lower in the ArterX group as compared to the control (46.4% vs 59.8%). Therefore, the primary safety endpoint was met and the results demonstrate a reasonable assurance of device safety.

C. Benefit-Risk Conclusions

The probable benefits of the device are based on data collected in a clinical study conducted to support PMA approval along with supplemental data, as described above. The probable benefit of the ArterX Surgical Sealant is improved hemostasis at anastomosis sites during vascular reconstruction procedures, as compared to a marketed alternative.

The pivotal study that provided the primary clinical safety and effectiveness evidence was a multi-center, randomized, controlled study conducted in the United States. Important clinical outcomes, such as excessive bleeding and infection, occurred at rates typical of vascular surgical procedures using other sealants, and complete follow-up data were available for the majority of subjects. Subject enrollment was appropriately diverse, and there are no reasons to expect that the results of the study will differ from "real world" performance.

Alternative treatments, including the use of other surgical sealants or hemostasis methods, were carefully considered. The use of surgical sealants is valued by physicians because it can improve outcomes and decrease the procedure time. The results of the pivotal study indicate that the study subject outcomes compare favorably to a currently marketed alternative. Patient risk is minimized via appropriate patient selection and device usage, as communicated in the physician labeling.

In conclusion, given the available information above, the data support that the probable benefits outweigh the probable risks for adjunctive sealing of areas of leakage during vascular reconstructions,

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 preclinical and clinical experience with the ArterX Surgical Sealant supports the safety of the device. *In vitro*, biocompatibility, and animal studies confirmed that the ArterX Surgical Sealant met performance and design specifications. In addition, the results of the clinical study demonstrate that the primary safety and effectiveness endpoints were met. The primary effectiveness endpoint, immediate sealing at the anastomosis site, was significantly higher at anatomic sites treated with ArterX Surgical Sealant as compared to the control treatment (60.5% vs. 39.6%). The primary safety endpoint of the clinical study, the cumulative incidence of significant bleeding, infection, neurological deficit, and immune inflammatory response occurring within 6 weeks of the procedure, was significantly lower in the ArterX group as compared to the control (46.4% vs 59.8%). The incidence of longer-term adverse events out to 3 months post-procedure was low.

These data confirm that the overall clinical benefit outweighs the overall clinical risk.

XIV. CDRH DECISION

CDRH issued an approval order on March 1, 2013. The final conditions of approval cited in the approval order are described below:

The applicant has agreed to provide the following data as part of a future report, as indicated below:

1. Within 12 months of PMA approval, they should submit a non-clinical post-approval report discussing the comparability of ArterX product manufactured and stored under the conditions used in the pivotal clinical study with product manufactured and stored for commercial release. Such studies will include evaluation of bovine serum albumin (BSA) monomer and polymer content via chemical and mechanical studies. In addition, within 36 months of PMA approval, they should submit a report discussing the comparability of the in vitro residence times of product manufactured and stored under these two sets of conditions. If any of this information indicates that

tightening the percent BSA monomer specification is appropriate, they should submit a PMA supplement requesting such a change.

2. Within 12 months of PMA approval, they should submit a non-clinical post-approval report providing data confirming that sealant manufactured at the extremes of the pH range for the crosslinker stays within product specifications over the duration of the product shelf-life.

The applicant's manufacturing facilities were inspected and found to be in compliance with the Quality System Regulations (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