

Proposed
Summary of Safety and Effectiveness
CryoLife , Inc. BioGlue® Surgical Adhesive

1 General Information

Device Generic Name:.....Surgical Adhesive

Device Trade Name:.....BioGlue® Surgical Adhesive
(BioGlue®)

Applicant's Name and Address.....CryoLife, Inc.
1655 Roberts Boulevard, NW
Kennesaw, Georgia 30144

Premarket Approval (PMA) Number:.....P010003

Date of PMA:.....January 31, 2001

Date of PMA Preapproval Inspection.....April 16-26, 2001

Date of Panel Recommendation:.....September 11, 2001

Date of Notice of Approval to Applicant:.....

2 Indications For Use

BioGlue® Surgical Adhesive is indicated for use as an adjunct to standard methods of cardiac and vascular repair such as sutures (or staples) to provide hemostasis.

3 Device Description

BioGlue Surgical Adhesive (BioGlue), manufactured by CryoLife, Inc., Kennesaw, GA, may be used prophylactically or after a leak is detected to seal and reinforce anastomoses in cardiac and vascular surgical repairs.

BioGlue is a two-component surgical adhesive composed of purified bovine serum albumin (BSA) and glutaraldehyde. The BSA is derived from serum obtained from cattle exclusively from bovine spongiform encephalopathy (BSE) free countries and undergoes processing that removes/inactivates viruses. The solutions are dispensed by a controlled delivery system, composed of a reusable delivery device, applicator tips, and applicator tip extenders. Once dispensed, the adhesive solutions (in a predefined ratio) are thoroughly mixed *in vitro* through the tortuous path of the applicator tip where cross-linking starts to occur. The glutaraldehyde molecules covalently bond (cross-link) the BSA molecules to each other and, upon application, to the tissue proteins at the anastomotic repair site thereby creating a flexible mechanical seal, independent of the

body's clotting mechanism. The device-mediated application is designed to provide reproducible mixing of the components *in vitro* and higher bonding strength than manual on-site (*in situ*) mixing and application. BioGlue begins to set up within 20 to 30 seconds and reaches its bonding strength within 2 minutes. BioGlue also adheres to synthetic graft materials via mechanical interlocks within the interstices of the graft matrix.

4 Contraindications, Warnings and Precautions

4.1 Contraindications

- Do not use in patients with known allergies to materials of bovine origin.
- Not for intravascular use.
- Not for cerebrovascular repair.

4.2 Warnings

- BioGlue Surgical Adhesive is not intended as a substitute for sutures or staples.
- Do not expose tissue to the device if it may be adversely affected by contact with the device, e.g., aortic valve cusps and intra-cardiac structures.
- Do not allow device in either the uncured or polymerized form to contact circulating blood flow.
- Avoid exposing any nerves to surgical adhesive.
- Avoid contact with skin or other tissue not intended for application.
- Glutaraldehyde treated tissue has an enhanced propensity for mineralization. Laboratory experiments indicate that unreacted glutaraldehyde may have mutagenic effects.
- Unreacted glutaraldehyde may cause irritation to eye, nose, throat, or skin; induce respiratory distress; and local tissue necrosis. Prolonged exposure to unreacted glutaraldehyde may cause a central nervous system or cardiac pathology. Operators using the device should ensure that staff are adequately risk protected.
- BioGlue should not be used in the presence of infection and should be used with caution in contaminated areas of the body.
- Exposure to bovine serum albumin may cause a reaction such as swelling or edema at the application site.
- BioGlue Surgical Adhesive contains a material of animal origin, which therefore may be capable of transmitting infectious agents.

4.3 Precautions

- It is recommended that surgical gloves, sterile gauze pads/towels, and surgical instruments be maintained moist to minimize the potential for BioGlue inadvertently adhering to these surfaces.
- Wear gloves, mask, protective clothing, and safety glasses. If contact with solutions occurs, flush affected areas immediately with water and seek medical attention.
- BioGlue Surgical Adhesive solutions cartridges, applicator tips, and applicator tip extenders are for single patient use only. Do not re-sterilize.

- Do not use if packages have been opened or damaged.
- Do not prime delivery device until ready for immediate use. Premature priming may cause the applicator tip to become obstructed with polymerized adhesive.
- Take care not to spill solutions out of the cartridge.
- Do not compress the handle of the adhesive delivery device while attaching the cartridge to the delivery device.
- Attempting to apply the adhesive in a surgical field that is too wet may result in poor adherence.
- Ensure priming material does not come into contact with the surgical site.
- BioGlue Surgical Adhesive sets up immediately. Priming must occur quickly, followed immediately by the application of adhesive. Pausing between priming and application can cause set-up of adhesive within the applicator tip.
- If the BioGlue Surgical Adhesive adheres to an undesired location, allow the adhesive to polymerize and then attempt to gently dissect the adhesive away from the affected area with forceps and scissors. Do not attempt to peel away the BioGlue Surgical Adhesive as this could result in tissue damage at the application site.

5 Alternative Practices and Procedures

Conventional procedures used to control bleeding include the use of direct pressure, sutures, pledgets, and/or electrocautery. Absorbable hemostatic agents such as bovine gelatin powder and sponges, hemostatic agents made from bovine collagen and oxidized cellulose are used for stopping bleeding. Additionally products containing thrombin and/or fibrinogen are used to assist the body's natural clotting mechanism to achieve hemostasis.

6 Marketing History

BioGlue was approved in the United States for use in the repair of acute thoracic aortic dissection under the HDE regulations (H990007) in December 1999 and has been marketed in the U.S. since that time.

Commercial distribution of the device outside of the U.S. started in April 1998. Currently the device is marketed in the following countries: Argentina, Australia, Austria, Belgium, Bolivia, Brazil, Bulgaria, Canada, China, Czech Republic, Denmark, Egypt, Finland, France, Germany, Greece, Hungary, India, Iceland, Ireland, Israel, Italy, Lebanon, Liechtenstein, The Netherlands, New Zealand, Norway, Portugal, South Africa, Spain, Sweden, Switzerland, Syria, Turkey, United Arab Emirates, United Kingdom, and Venezuela.

BioGlue Surgical Adhesive has not been withdrawn from marketing for any reason relating to safety or effectiveness of the device.

7 Potential Adverse Effects of the Device on Health

The following adverse events could potentially occur due to the composition of the device, the mode of application, or the disease process:

- Failure of product to adhere to tissue
- Application of adhesive to tissue not targeted for procedure
- Inflammatory, immune, or local and systemic allergic reaction
- Mineralization of tissue
- Local tissue necrosis
- Thrombosis and thromboembolism
- Possible transmission of infectious agents from material of animal origin

Reference Table 12 for procedure related complications observed within the U.S. IDE cardiac and vascular repair clinical trial.

8 Summary of Preclinical Studies

8.1 Laboratory Studies

8.1.1 Biocompatibility

CryoLife conducted biocompatibility testing of the cured BioGlue implant material and all delivery system materials contacting the patient or adhesive solutions in accordance with GLPs (Good Laboratory Practices). All of the irradiated materials that come in contact with the BioGlue adhesive solutions during storage were also assessed for extractables. The following table summarizes testing done on the cured BioGlue implant:

Table 1. Biocompatibility Testing Results – Cured BioGlue Implant

Test Performed	Extract(s)	Test and Control(s)	Results/Comments
Cytotoxicity (ISO)	MEM	Natural rubber (+) Silicone tubing (-)	L-929 cells gave a grade 2 (mild) reactivity score with test extract at 48 hours
Sensitization (Maximization)	Saline and CSO	Saline and CSO (-) DNCB (+) with and without activation	No sensitization was observed
Intracutaneous Toxicity (ISO/USP)	Saline and CSO	Saline and CSO	No toxicity observed in either extract
Systemic Toxicity (ISO/USP)	Saline (IV) and CSO (IP)	Saline and CSO	No signs of toxicity
Hemolysis (DHEW)	Saline	Saline (-) Water (+)	4.45% hemolysis, considered to be non-hemolytic
Rabbit pyrogen (ISO)	Saline	Saline (-)	<0.5 °C rise in all rabbits- non-pyrogenic

Biocompatibility tests conducted on the applicator tip and solutions cartridge components include cytotoxicity, systemic and intracutaneous

toxicity, sensitization, and pyrogenicity. All test results are “pass” or are “non-toxic”. There was also data in the file regarding the applicator tip connector extenders and extender tubing. These passed the cytotoxicity, sensitization, irritation/intracutaneous toxicity, and systemic toxicity tests.

CryoLife also evaluated BioGlue implant tissue response as part of a three month implant study to determine the effects of BioGlue in the surgical repair of aortic dissection in sheep (see section 8.2 Animal Studies). The observations of inflammation, necrosis, calcification and fibrosis in the BioGlue treated group were found to be consistent with a normal foreign body reaction.

Conclusions from the biocompatibility testing:

Based on these test results, the device is biocompatible for its intended use.

8.1.2 Analytical and Functional Testing

Analytical and functional testing is conducted on each lot of BioGlue® Surgical Adhesive to ensure that it meets established product specifications designed to ensure the device is safe for its intended use. Analytical Tests include: UV-Vis Spectrophotometric Profile of Bovine Serum Albumin, pH Determination of Bovine Serum Albumin Solutions, Monomeric Content of Bovine Serum Albumin by SDS-PAGE, Protein Concentration of Bovine Serum Albumin Solutions by Colorimetric Assay, Glutaraldehyde Concentration Determination by Hydroxylamine-HCl Titration, and Extent of Autopolymerization of Glutaraldehyde by Absorbance Ratio. Functional tests include Adhesive Cure Rate and Adhesive Shear.

Conclusions from functional testing:

The device possesses adequate bonding strength and is reproducible in its chemical characteristics.

8.2 **Animal studies**

8.2.1 Surgical Repair of Aortic Dissections in Sheep

A three-month study to determine the effects of BioGlue in the surgical repair of aortic dissection in sheep was conducted to evaluate device performance. This study involved use of a prototype device, the BG2000, which utilized aseptically transferred solutions that had been sterilized by filtration and aseptically filled into the cartridges at the time of surgery. The current BG3000 device uses pre-filled cartridges that have been gamma irradiated. Additional animal studies employing the BG3000 were not conducted because the results of *in vitro* testing of the BG3000 demonstrated that the adhesive (shear strength) and monomeric impurity properties were not altered by the gamma irradiation.

A previously reported model of descending aortic dissection¹ was created in 30 sheep. After the aortic dissection was created, the surgeon determined if the dissection met the acceptance criteria established in the study protocol (i.e., a false lumen volume <50% of the total aortic volume, length of <7.1 cm and width < 2.6 cm). Dissections that did not meet these criteria were considered unstable for repair. Animals with acceptable dissections were then randomized in a blinded fashion to surgical repair of the proximal flap alone, or repair by gluing the layers of the dissection together with BioGlue and surgical repair of the proximal flap. There were 26 aortic dissections that met the acceptance criteria, with 13 animals randomized to surgical repair alone and 13 to BioGlue repair. The dissections varied in size from 5.0 to 7.0 cm long (average 5.2), 1.2 to 2.5 cm wide (average 1.4), encompassing 20-50% (average 35%) of the aortic volume. There were no statistical variations between the dimensions of the dissection in the surgical and BioGlue groups.

In the BioGlue group, four animals died of causes unrelated to the BioGlue (3 pneumonia/weather stress, 1 tension pneumothorax immediately following surgery). In all four of these animals, the aortic dissection was completely obliterated or healed. In the 9 remaining BioGlue animals, one animal died of chronic aortic aneurysm rupture at 51 days (due to mycotic super-infection of a technical glue failure) and in 8 animals surviving > 90 days the aortic dissection was completely healed (i.e. all of the layers of the aorta were fused and no false lumen or blind pouch observed) without signs of proximal or distal progression.

In the surgical control group, 1 animal died of pneumonia/weather stress. Four animals died within 24 hours of proximal or distal aneurysm progression and rupture. Eight animals survived 90 days. In 2 of the 8, the dissection healed after 3-3.5 cm of progression. In 2 of the 8, a

¹ Eddy CA, Choo S, McNally B, Elkins R, Creation and Repair of Acute Descending Aortic Dissection in Sheep. Abstract submitted to Aortic Surgery Symposium VI. 1998.

chronic dissection formed at the surgical repair distal suture line and in 4 of the 8, a chronic dissection formed at re-entry points unrelated to the surgical repair site. In the chronic dissections, the false lumen made up 25-75% of the total aortic lumen. In all of the chronic dissections, the wall of the aorta was thinning and the diameter of the aorta was expanding, suggesting early aortic aneurysm formation.

Tissue response evaluations were also conducted.

Conclusions from the animal studies:

Based on the results of this study, repair of aortic dissection using BioGlue® as an adjuvant to surgery in the sheep model was superior to surgery alone because:

- BioGlue decreased the incidence of acute post-repair rupture of the aorta from 30% to 0%.
- BioGlue decreased the incidence of re-dissection at the site of distal surgical repair from 17% to 0% in animals surviving 90 days.
- BioGlue decreased the incidence of dissection progression prior to healing from 17% to 0% in animals surviving 90 days.
- BioGlue decreased chronic dissection formation from 75% to 0% in animals surviving 90 days.

8.2.2 Thoracic Aorta Repair with BioGlue in Coagulopathic Sheep

Summary

The objective of this study was to investigate the efficacy of BioGlue for thoracic aortic surgical repair. The coagulopathic sheep model, which was developed for this study, simulates needle hole and surgical bleeding from the anastomoses of synthetic graft to the thoracic aorta in coagulopathic surgical patients. The study hypothesized that induction of coagulopathy in sheep would model clinical needle hole and surgical bleeding from synthetic graft anastomoses and that the tissue bioadhesive would control post-operative blood loss.

A secondary objective of the study was to evaluate the histopathology of the treated area over twenty-four months.

Methods

Sheep were given 600 mg aspirin suppositories for two days prior to surgery, and two IV boluses of heparin (400 units/kg) during surgery. A bypass conduit was created by two end-to-side anastomoses of synthetic graft to the partially occluded thoracic aorta. The bypassed native aorta was then occluded. Experimentals (n=9) were treated with BioGlue and controls (n=5) were treated with Surgicel® to effect hemostasis intra-operatively. Post-operative bleeding was measured by chest tube output.

Statistics were analyzed by the student T-test on normal or log transformed data or the rank-sum test.

Results

Post-surgical bleeding was significantly and dramatically controlled in the experimental group compared to controls as determined by total chest tube output (CON median = 955 ml vs. EXP median = 470 ml, $p < 0.003$). Intra-operative blood loss was also reduced in the experimental group compared to the control group (CON = 422 ml vs. EXP = 241 ml) but, this was not significant ($p = 0.3$). The average hourly rate of blood loss in the BioGlue group showed a significant reduction over both the first two hours (EXP = 92.5 cc/hr, CON = 210 cc/hr, $p = 0.005$) and the duration of recovery (EXP = 85.5 cc/h vs. CON = 158.3 cc/h, $p = 0.046$). Additionally, total blood loss (post-operative and intra-operative) was significantly reduced in the experimental group ($p < 0.008$).

No inflammatory response to BioGlue was noted within 3 months post-operative. There was no fibrotic response and no foreign body granulomatous response. No giant cells were present in any of the samples. Following long-term (>two years) survival, histopathology revealed bland appearing areas of BioGlue, which were interpreted to be areas of degradation and resorption. These areas were relatively acellular, and the mechanisms of the degradation remain unknown. Potentially, some of the adjacent collagen strands may represent remodeled BioGlue in these specimens.

During the follow-up period one of the BioGlue treated animals gave birth to a healthy lamb.

Conclusions

The end-to-side anastomosis of synthetic graft to the thoracic aorta in sheep treated with heparin and aspirin provides a clinically relevant coagulopathic model. BioGlue® demonstrated significant intra- and post-operative hemostasis in a coagulopathic sheep model when compared to the control treatment (Surgicel®). The host's reaction to the BioGlue was minimal. Following long-term (>two years) survival, histopathology revealed bland appearing areas of BioGlue, which were interpreted to be areas of degradation and resorption of BioGlue. This tissue bioadhesive should prove extremely beneficial, clinically, for coagulopathic patients needing thoracic aortic or vascular surgery.

8.2.3 Biodegradation

Once BioGlue is fully polymerized, it is an insoluble material. Polymerized BioGlue remained intact *in vitro* when kept in water over 30 days. Additionally, the histopathology of early (30 days) time points does not indicate dissolution of the implant.

When studied in various species (including human) and in varied implant sites, no implant degradation was observed for up to 12 months (Gundry *et al.*, 2000). The sole observation of biodegradation was in a long-term (24-month) vascular BioGlue implant in the sheep (See section 8.2.2). In previously reported animal explants a chronic inflammatory response was observed, with giant cells and granulomatous inflammation, typical of a foreign body response. In humans, the paucity of a chronic inflammatory response up to 9 months was noted (Hewitt *et al.*, 2000 and the animal study discussed in section 8.2.2). In the animal study discussed in 8.2.2, the hosts' (sheep) reaction to BioGlue at 3 months was strikingly lacking an inflammatory response. A foreign body response was observed at 83 days, though minimal and inconsistent.

The 24-month sheep explant showed a range of phases of the remodeling of the BioGlue implant. Some regions exhibited no degradation (regions of encapsulation), while others showed signs of incipient degradation (representing a phase in the putative process whereby BioGlue was remodeled via a normal healing response). Basically, cells infiltrate BioGlue as the degradation and resorption process evolves. Prior to resorption, BioGlue has frequently been reported to become encapsulated with tissue in a normal foreign body healing response or to elicit a minimal inflammatory response. The lack of histopathologic response in humans suggests that the implant may remain for a longer period than that observed in animals.

BioGlue is a protein cross-linked at its lysine side chains with glutaraldehyde. The remainder of the BSA molecule is open to attack by proteinases. The sensitivity of glutaraldehyde cross-linked proteins and tissues to proteinases has been well studied in bioprosthetic grafts. These cross-linked tissues remain sensitive to natural proteolysis, albeit at a substantially slower rate.

9 Summary of Clinical Studies

In June 1998, CryoLife, Inc. began a clinical trial investigating the use of BioGlue as an adjunct in the surgical repair of acute, Stanford Type A aortic dissections. CryoLife filed a Humanitarian Device Exemption (HDE) for the use of BioGlue in the surgical repair of acute thoracic aortic dissections, which was approved by FDA in December 1999 (H990007). The data is suggestive of a benefit in terms of 1) decreased rate of reoperation for bleeding and other bleeding complications without the need for other hemostatic devices and/or pharmacological agents, 2) fewer intraoperative blood transfusions, and 3) reinforcement of friable tissue of the dissected aorta without the need for pledgets. CryoLife gained approval in May 2000 to investigate the use of BioGlue for sealing anastomotic sites in cardiac and vascular repairs. Following is information from the cardiac and vascular repair investigation:

9.1 Study Design

The “BioGlue Surgical Adhesive Effectiveness and Safety Trial as a Surgical Adjunct in Cardiac and Vascular Surgical Repairs (“BEST” Trial) was a prospective, multi-center, randomized controlled trial. Randomized cardiac and vascular repairs include an adjunctive BioGlue prophylactic treatment and a control group (standard surgical repair). The overall objective was to collect clinical data concerning the safety and effectiveness of BioGlue used as an anastomotic sealant to provide hemostasis.

Cardiac and vascular repair procedures included but were not limited to the surgical repair/reconstruction of the following clinical conditions: ventricular aneurysm/rupture; aortic aneurysm/dilatation (root, ascending arch, descending thoracic, thoracoabdominal, abdominal, and aortoiliac); traumatic aortic transection; annulo-aortic ectasia; and vascular bypass or repair.

Patients were randomized to receive standard surgical repair with BioGlue applied to the anastomotic site (BioGlue group) or standard surgical anastomotic repair alone (control group).

9.2 Patient Assessment

Effectiveness Evaluations

The BioGlue group and the standard surgical repair group were compared to determine BioGlue’s effectiveness for the following endpoints:

Primary Evaluation

Anastomotic hemostasis (yes or no) of each of the repaired anastomotic sites. Anastomotic hemostasis was defined as an anastomosis that does not require additional agents (pledgets, sutures, hemostatic devices, antifibrinolytic agents, thrombin glues, fibrin glues) at the treated site(s) to control bleeding at any point during the course of the original operation. Results were also evaluated on a “per patient” basis. Patients with anastomotic hemostasis at all anastomotic sites were considered successful.

Secondary Evaluations

- Quantity, type, and number of donor exposures of blood replacement products administered.
- Type of additional agents used (pledgets, sutures, hemostatic devices, antifibrinolytic agents, thrombin glues, fibrin glues)
- Re-operation due to anastomotic site bleeding.
- Major complications/adverse events through final follow-up.
- Minor complications/adverse events through final follow-up.
- Early hospital discharge mortality and mortality through last follow-up.

Cost Benefit Evaluations

- Total cardiopulmonary bypass time (when applicable).
- Time required for aortic cross-clamp (when applicable).
- Total operative time (skin incision to skin closure).
- Total time in Intensive Care Unit.
- Total hospitalization time.

Safety Evaluations

The criteria for evaluating safety in this patient population were:

- Unanticipated Adverse Device Effects (UADE).
- Device complications.
- Surgical procedure complications.

9.3 Demographic Data

A total of 151 patients were treated at 6 investigational sites in the cardiac and vascular repair arm of the U.S. IDE clinical trial. Pertinent information about the patient population is presented in Tables 2 and 3. Surgical procedures performed are shown in Table 4.

Table 2 – Summary of Subjects

Population	Treatment Group		Total
	Surgical Repair with BioGlue	Conventional Surgical Repair	
All Randomized	76	75	151
Cross Over	N/A	1	1
Intent-to-Treat	76	74	150
Evaluable	76	74	149
Safety	77	74	151

Table 3 – Demographic Characteristics (All randomized patients)

Characteristic	Treatment Group		Crossover	Total
	Surgical Repair with BioGlue	Conventional Surgical Repair		
Age (years)				
N	76	74	1	151
Mean (SD)	63.4 (17.2)	66.3 (12.7)	73.8 (N/A)	64.8 (15.1)
Min, Max	21, 87	25, 86	N/A	20, 87
Gender				
Male	49	48	0	97
Female	27	26	1	54
Total	76	74	1	151
Race				
African-American	6	6	0	12
Asian	1	1	0	2
Caucasian	67	66	1	133
Hispanic	2	1	0	3
Total	76	74	1	151

Table 4 – Cardiac and Vascular Procedures Included

System	Treatment Group		Crossover	Total
	Surgical Repair with BioGlue	Conventional Surgical Repair		
Cardiac Procedures ^{**}	24	25	0	49
Aortic Procedures [†]	57	47	1	105
Peripheral Vascular Procedures ^{***}	25	23	0	48
Total	106	95	1	202

^{**}Cardiac repairs include: aortic root replacements (4), aortoplasty (1), aortic valve annuloplasty (5), aortic valve resuspension (1), aortic valve replacement (23), Bentall procedure (2), composite valved conduit procedures (8), mitral valve replacements (2), Ross procedure (2), coronary artery bypass grafting (1).

[†]Aortic aneurysm repairs include: abdominal aortic aneurysm (21), ascending aortic aneurysm (21), ascending/ transverse aortic arch aneurysm (9), ascending/ transverse arch/ descending aortic aneurysm (1), descending aortic aneurysm (8), thoracoabdominal aortic aneurysm (32), transverse aortic arch aneurysm (12), Type B aortic dissection (1)

^{***}Peripheral vascular repairs include: aorto-femoral bypass (5), aorto-iliac bypass (2), aorto-innominate bypass (1), carotid bypass (1), carotid endarterectomy (19), femoral-distal bypass (3), femoral-femoral bypass (2), femoral-popliteal bypass (5), hepatic-renal bypass (1), popliteal-dorsalis pedis bypass (1), profunda endarterectomy (1), renal bypass (6), renal endarterectomy (1)

9.4 Data Analysis and Results

The tables and figures in this section present information from the cardiac and vascular repair arm of the U.S. IDE clinical trial.

Efficacy Data

Table 5 presents the intra-operative hemostasis data for the intent-to-treat patients on both a “per patient” and a “per anastomotic repair site” basis. The proportion of both patients and anastomotic repair sites achieving hemostasis based upon the protocol definition was statistically greater in the BioGlue group (Fisher’s Exact Test, $p < 0.05$).

**Table 5 – Intra-operative Hemostasis – Intent-to-Treat Patients
(Success/Total)**

	Treatment Group		P value
	Surgical Repair With BioGlue	Conventional Surgical Repair	
Per patient*	61% (46/76)	39% (29/74)	0.014
Per Repair Site**	81% (164/202)	57% (105/184)	<0.001

* Hemostasis on a “per patient” basis was defined as hemostasis of 100% of the anastomotic repair sites.

** The average number of repair sites (anastomoses) per patient were 2.6 (range: 1 to 8).

Use of intra-operative blood products is outlined in Table 6. No statistically significant differences were noted between the BioGlue group and the control group based upon a one-sided 95% confidence interval of the difference between the treatment means.

**Table 6 –Intra-operative Blood Products and Donor Exposures
(Intent-to-Treat Patients)**

	Treatment Group	
	Surgical Repair With BioGlue	Conventional Surgical Repair
Red Blood Cells		
N	76	74
Mean (SD)	2.3 (3.6)	1.9 (2.4)
Min, Max	0, 22	0, 12
Platelets		
N	76	74
Mean (SD)	5.1 (10.1)	5.2 (10.0)
Min, Max	0, 60	0, 50
Fresh Frozen Plasma		
N	75	73
Mean (SD)	3.8 (6.6)	3.3 (5.0)
Min, Max	0, 30	0, 19
Cryoprecipitate		
N	74	72
Mean (SD)	4.3 (11.9)	2.0 (8.3)
Min, Max	0, 60	0, 40
Total Number of Donor Exposures		
N	48	51
Mean (SD)	20.6 (26.3)	14.2 (18.2)
Min, Max	0, 106	0, 89

Investigators in this trial documented their usage of pledgeted sutures to reinforce their primary repair. Anastomotic sites treated with BioGlue had a statistically lower incidence of pledget usage on the primary repair when compared to the control group (Table 7).

**Table 7 – Pledgets on Primary Repair - Intent-to-Treat Anastomotic Sites
(Success/Total Number of Anastomotic Sites)**

	Treatment Group		P Value
	Surgical Repair with BioGlue	Conventional Surgical Repair	
Pledgets Used on Primary Repair	26% (53/202)	36% (66/184)	0.047

Any anastomotic repair site that was not immediately hemostatic was evaluated to determine the additional methods used to obtain hemostasis. There was no statistical difference noted in the additional measures taken to obtain hemostasis, which indicates that BioGlue did not inhibit the surgeons ability to obtain hemostasis through use of conventional measures or additional BioGlue. These results are summarized in Table 8 below:

Table 8 – Measures Required to Obtain Hemostasis - Intent-to-Treat Bleeding Anastomotic Sites (Bleeding Anastomotic Sites Requiring Measure/Total Bleeding Sites)

	Treatment Group		P value
	Surgical Repair With BioGlue	Conventional Surgical Repair	
Make-up Stitches	82% (31/38)	81% (64/79)	1.00
Hemostatic Device [*]	8% (3/38)	10% (8/79)	1.00
Additional BioGlue	55% (21/38)	N/A	N/A
Other [†]	8% (3/38)	19% (15/79)	0.17

^{*} Hemostatic Devices included Surgicel®, Avitene®, Gelfoam®, Fibrin Glue, Thrombin Glue.

[†] Other includes: Additional pledgets (16), FloSeal (1), Teflon felt ring (1)

The study protocol allowed investigators to “cross-over” and use BioGlue for control patients who suffered uncontrollable bleeding. Only one patient was noted to have uncontrollable bleeding. The investigator was able to obtain hemostasis at all anastomotic sites after using BioGlue for this patient.

Incidence of re-operation for anastomotic site bleeding is presented in Table 9. Only one patient had a re-operation due to anastomotic site bleeding.

Table 9 – Re-operation Due to Anastomotic Site Bleeding

	Treatment Group		One-Sided 95% Confidence Interval
	Surgical Repair With BioGlue N (%)	Conventional Surgical Repair N (%)	
Re-operation	0 (0.0%)	1 (1.4%)	[-, 0.9]

Table 10 shows a summary of intra-operative times, days spent in the ICU, and total hospitalization time. The differences between the BioGlue group and the control group were not statistically significant.

Table 10 – Procedure, ICU, and Hospitalization Times (*Intent-to-Treat*)

	Treatment Group	
	Surgical Repair With BioGlue	Conventional Surgical Repair
Procedure Times		
Cardiopulmonary Bypass Time* (minutes)		
N	34	35
Mean (SD)	168.1 (67.4)	144.2 (60.6)
Min, Max	54, 358	54, 387
Cross-Clamp Time* (minutes)		
N	54	55
Mean (SD)	74.0 (46.1)	69.1 (41.3)
Min, Max	10, 196	19, 196
Total Operative Time (minutes)		
N	75	73
Mean (SD)	237.7 (125.1)	228.7 (100.8)
Min, Max	85, 650	60, 515
ICU Time		
Days in ICU*		
N	70	72
Mean (SD)	3.9 (5.6)	4.8 (7.1)
Min, Max	0, 32	0, 36
Hospitalization Time		
Days in Hospital		
N	72	73
Mean (SD)	9.5 (10.6)	10.9 (9.7)
Min, Max	1, 81	1, 55

* Where applicable.

Safety Data

Mortality rates for intent-to-treat in this trial are presented in Table 11. No differences were observed in either early (through hospital discharge) mortality or late (through final follow-up) mortality.

Table 11 – Mortality Rates – Intent-to-Treat Patients (Event/Total)

	Treatment Group		One-Sided 95% Confidence Interval
	Surgical Repair With BioGlue	Conventional Surgical Repair	
Early/Hospital Discharge (<30 days)	3.9% (3/76)	2.7% (2/74)	[--, 6.1]
Post-operative Follow-up (3 months)	1.3% (1/76)	4.1% (3/74)	[--, 3.9]

Table 12 shows a complete listing of all procedure related complications reported for the patients in this trial. There were no statistically significant differences in complication rates between the BioGlue group and the control group. There were two complications that were device-related. One adverse event occurred from application of BioGlue to non-target tissue and the other adverse event occurred when BioGlue was applied to a wet field. Both complications are included in the Instructions for Use as a warning and a precaution, respectively.

Table 12 - Observed Adverse Events

Adverse Event Description	BioGlue Group N = 77			Control Group N = 74			P-Value
	n	%	#events	n	%	#events	
Application of Adhesive to Non-Targeted Tissue ¹	1	1.3%	1	0	0%	0	1.000
Death	5	6.5%	5	5	6.8%	5	0.999
Failure of Products to Adhere to Tissue ¹	1	1.3%	1	0	0%	0	1.000
Hemorrhage	3	3.9%	3	3	4.1%	3	1.000
Infection	13	16.9%	15	10	13.5%	13	0.653
Inflammatory, Immune Systemic Allergic Reaction ²	2	2.6%	2	0	0%	0	0.497
Irreversible Morbidity	0	0%	0	1	1.4%	1	0.490
Ischemia	3	3.9%	3	2	2.7%	2	1.000
Myocardial Infarction	3	3.9%	3	1	1.4%	1	0.620
Neurological Deficits	5	6.5%	6	16	21.6%	18	0.009
Organ System Dysfunction/Failure	3	3.9%	4	2	2.7%	2	1.000
Paraplegia	1	1.3%	3	2	2.7%	3	0.615
Pleural Effusion	20	26.0%	25	21	28.4%	22	0.855
Renal Dysfunction/Failure	13	16.9%	13	9	12.2%	10	0.492
Respiratory Dysfunction/Failure	13	16.9%	18	12	16.2%	15	1.000
Stroke or Cerebral Infarction	1	1.3%	1	3	4.1%	5	0.360
Thromboembolism	1	1.3%	1	1	1.4%	4	1.000
Thrombosis	0	0%	0	1	1.4%	1	0.490
Other ^{3,4}	46	59.7%	108	40	54.1%	100	0.514

¹ These adverse events were device related. Both complications were clearly warned against in the IFU.

² These adverse events were not device related. One patient had an allergic reaction to a preoperative antibiotic and the other patient had an allergic reaction to Protamine.

³ Other adverse events observed in the BioGlue treated clinical trial patients were as follows: Acidosis (1%), Acute shortness of breath (1%), Altered mental status (3%), Anemia (5%), Atelectasis (8%), Cardiac arrhythmia (22%), Cerebral hemorrhage (1%), Colectystitis (1%), Coagulopathy (1%), Congestive Heart Failure (4%), Decreased femoral pulse (1%), Deep Vein Thrombosis (1%), Depression (4%), Diarrhea (3%), Dysphagia (5%), Edema (3%), Fever (3%), Heart enlargement (4%), Hematuria (1%), Hemoptysis (1%), Hernia (4%), Hoarseness (1%), Hypotension (1%), Ileus (4%), Incisional pain (3%), Lymphatic fistula (1%), Malnutrition (5%), Nausea (3%), Perforated viscus (1%), Pericardial effusion (1%), Pneumothorax (3%), Rectal bleeding (1%), Seizure (1%), Thigh and back pain (3%), Thrombocytopenia (1%), Urinary retention (4%), Vocal cord paralysis (3%).

- 4 Other adverse events observed in the Control Group clinical trial patients were as follows: Abdominal pain (1%), Abnormal lab value (5%), Acidosis (1%), Altered mental status (3%), Anemia (3%), Angina (1%), Aphasia (1%), Atelectasis (4%), Back pain (1%), Cardiac arrhythmia (19%), Cerebral hemorrhage (3%), Congestive heart failure (1%), Diarrhea (3%), Dizziness (1%), Duodenal ulcer (1%), Dysphagia (1%), Edema (1%), Emphysema (1%), Encephalopathy (1%), Failed extubation (1%), Fever (3%), Heart block (2%), Hematuria (1%), Hemothorax (1%), Hernia (1%), Hoarseness (4%), Hypotension (4%), Ileus (3%), Incisional pain (5%), Lower extremity weakness (1%), Nausea (4%), Near syncope (1%), Neck deformity (1%), Pericardial effusion (3%), Pneumothorax (3%), Post-kidney collection (3%), Reintubation (1%), Seizure (1%), Sexual dysfunction (1%), Shortness of breath (1%), Thrombocytopenia (4%), Thrombophlebitis (1%), Transfusion reaction (3%), Urinary retention (1%), Valve surgery (1%), Vocal cord paralysis (3%).

Adverse events were equal in severity in both the BioGlue group and the standard surgical repair group. There were no unanticipated device effects (UADE) in this investigation.

9.5 Device Failures and Replacements

No device failures or replacements occurred in the cardiac and vascular arm of the IDE clinical trial.

10 Conclusions Drawn from the Studies

10.1 Risk/Benefit Analysis

The absence of any significant adverse event related to the use of BioGlue, and the effectiveness of BioGlue in achieving immediate anastomotic hemostasis independent of the body's clotting mechanism and tissue reinforcement in cardiac and vascular repair, attest to the acceptable risk/benefit ratio of BioGlue in sealing cardiac and vascular repair anastomoses.

10.2 Safety

The BioGlue Surgical Adhesive implant and accessories demonstrated acceptable biocompatibility in *in vitro* and *in vivo* studies. In the U.S. IDE clinical trial, the absence of any significant adverse events related to BioGlue and similar rates of adverse events for the BioGlue group and standard surgical repair group support the safety of BioGlue in cardiac and vascular repair procedures for sealing anastomoses, providing hemostasis, and reinforcing tissue.

10.3 Effectiveness

The results of the preclinical and clinical testing have demonstrated a reasonable assurance of safety and effectiveness for BioGlue for its stated indication for use. A multi-center, randomized controlled trial compared cardiac and vascular repair patients treated with a prophylactic adjunctive BioGlue treatment to a standard surgical repair control group. BioGlue was noted to have a statistically higher rate of intra-operative hemostasis when compared to the control group on both a "per patient" and a "per anastomotic site" basis. BioGlue-treated patients demonstrated a lower incidence of adjunctive pledgets use on their primary repairs to achieve hemostasis. There were no statistical differences in other endpoints, such as blood products or operative times, between study and control patients.

11 Panel Recommendations

To be completed by FDA.

12 CDRH Decision

To be completed by FDA.

CDRH issued an approval order on _____.

13 Approval Specifications

Direction for Use: See the labeling.

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

Postapproval Requirements and Restrictions: See approval order.