NEOMEND INC. ProGEL™ SURGICAL SEALANT

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

1.0 GENERAL INFORMATION

Device Generic Name: Surgical Sealant

Device Trade Name: NeoMend Inc. ProGEL™ Surgical Sealant

Applicant's Name and Address: NeoMend, Inc.
13900 Alton Parkway, #123
Irvine, CA 92618

PMA Application Number: P010047

Date of Panel Recommendation: TBD

Date of Notice of Approval to the Applicant: TBD

2.0 INDICATIONS AND USAGE

NeoMend Inc. ProGEL™ Surgical Sealant ("Sealant") is intended as an adjunct to standard tissue closure techniques for sealing or reducing air leaks (ALs) incurred during pulmonary surgery.

3.0 DEVICE DESCRIPTION

The Sealant (**Figure 1**) is comprised of a single use, sterile chemistry component kit (polyethylene-glycol based cross-linker, functionalized with succinate groups (PEG(SS) 2), and Human Serum Albumin - USP) and a single use, sterile applicator kit (push rod, tip assembly, applicator housing, a vial of sterile water for injection - USP, and a syringe). Both the cross-linker and albumin components are individually contained within hermetically sealed cartridges.

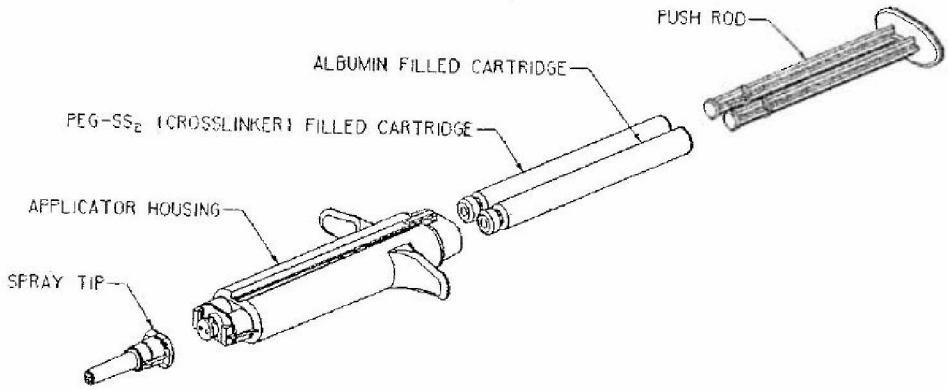

Figure 1 NeoMend Inc. ProGEL™ Surgical Sealant
(Sterile water and syringe not shown)

The applicator is designed to mix the two solutions and deliver the Sealant as a spray to the target site. Once mixed, the Sealant polymerizes to form a cross-linked, clear, flexible hydrogel matrix that adheres to the lung tissue. The polymerization process does not require peripheral equipment, such as light sources or heating elements to allow for proper device function.

When the Sealant contacts lung tissue, it conforms to the tissue by adhering to the microstructure of the lungs. The Sealant stays in place and allows for the expansion and relaxation of the lung tissue until it biodegrades (less than 30 days). Based on information from animal experiments, the hydrogel first swells, loses mechanical strength and then undergoes breakdown primarily by hydrolysis. As the Sealant biodegrades it is cleared primarily through the kidneys or locally metabolized.

4.0 CONTRAINDICATIONS

- Do not use the Sealant in patients who have a history of an allergic reaction to Human Serum Albumin.

5.0 WARNINGS

- The safety and effectiveness of the Sealant has not been evaluated in humans less than 18 years of age, nor in pregnant or nursing women.

6.0 PRECAUTIONS

- Ventilation of the target area should be stopped temporarily if possible to reduce air leakage from the targeted sites and to minimize tissue movement during sealant application. If the patient needs ventilation, a reduced tidal volume is recommended.
- Sealant use has not been studied with other sealants or hemostatic materials.
- Use of additives (*e.g.*, antibiotics) with the Sealant has not been studied.
- The safety of the Sealant has not been evaluated in patients receiving more than 30 mL. of the Sealant.
- Keep the applicator tip approximately 5 cm (2 in) away from target area to avoid creating bubbles in the sealant material during application. Bubbles may compromise the adherence and/or mechanical properties of the Sealant.
- Do not use rehydrated cross-linker after 20 minutes, as the performance of the Sealant may be compromised.
- The Sealant is intended for single use only. Do not resterilize or reuse.
- Inspect sterile package and seal prior to use. Do not use if sterile package or seal are damaged or open. Discard unused material.

7.0 ALTERNATIVE PRACTICES OR PROCEDURES

A few highly specialized surgical techniques have been utilized for pulmonary AL cessation, (*e.g.*, muscle wraps, pleural tenting). Products made of bovine pericardium or collagen have also been used, and are applied as patches or strips.

8.0 MARKETING HISTORY

The Sealant has not been marketed anywhere in the world, and therefore has not been withdrawn from any market for reasons relating to the safety and effectiveness of the device.

9.0 ADVERSE EVENTS

An Investigational Device Exemption ("IDE") study of the Sealant was conducted (G90283). A total of 161 patients (103 Sealant patients and 58 control patients) were randomized in the pivotal multicenter clinical study. **Table 1** presents the incidence of AEs observed in more than 2% of the patients in either treatment group. The most common AEs, with an incidence greater than 10% in both the Sealant and Control groups were fever, atrial fibrillation, dyspnea, and constipation. Additional AEs reported only in the Control group at an incidence greater than 10% were nausea, anemia, tachycardia, hypotension, vomiting, and pneumonia.

There were no statistically significant differences in the incidence of AEs between the Sealant and Control groups. There was one AE (a pneumothorax three weeks post surgery) considered

by the investigator to be an unanticipated adverse device effect due to the temporal relationship of the event with the use of the Sealant.

Table 1 Incidence of AEs Reported by > 2% of Subjects by Treatment Group

Preferred Term	Sealant (N=103)	Control (N=58)
Fever	22 (21.4%)	12 (20.7%)
Fibrillation, Atrial	12 (11.7%)	7 (12.1%)
Dyspnea	12 (11.7%)	10 (17.2%)
Constipation	11 (10.7%)	6 (10.3%)
Nausea	10 (9.7%)	7 (12.1%)
Confusion	8 (7.8%)	5 (8.6%)
Pneumothorax	8 (7.8%)	5 (8.6%)
Hypotension	8 (7.8%)	6 (10.3%)
Anemia	8 (7.8%)	6 (10.3%)
Pain	7 (6.8%)	4 (6.9%)
Subcutaneous Emphysema	7 (6.8%)	5 (8.6%)
Tachycardia	7 (6.8%)	6 (10.3%)
Death	5 (4.9%)	4 (6.9%)
Oliguria	5 (4.9%)	1 (1.7%)
Vomiting	5 (4.9%)	7 (12.1%)
Pneumonia	5 (4.9%)	7 (12.1%)
Pulmonary Infiltration	4 (3.9%)	0 (0.0%)
Chest Pain	4 (3.9%)	1 (1.7%)
Pleural Effusion	4 (3.9%)	3 (5.2%)
Urinary Retention	3 (2.9%)	0 (0.0%)
Ileus	3 (2.9%)	0 (0.0%)
Tachycardia, Supraventricular	3 (2.9%)	0 (0.0%)
Abdominal Pain	3 (2.9%)	0 (0.0%)
Arrhythmia	3 (2.9%)	0 (0.0%)
Extrasystoles	3 (2.9%)	0 (0.0%)
Coughing	3 (2.9%)	1 (1.7%)
Hypoxia	3 (2.9%)	1 (1.7%)
Renal Failure, Acute	3 (2.9%)	1 (1.7%)
Atelectasis	2 (1.9%)	2 (3.4%)
Postoperative Wound Infection	2 (1.9%)	2 (3.4%)
Pruritus	1 (1.0%)	2 (3.4%)
Delirium	1 (1.0%)	2 (3.4%)
Hypertension	1 (1.0%)	2 (3.4%)
Angina Pectoris	1 (1.0%)	2 (3.4%)
Hemoptysis	1 (1.0%)	3 (5.2%)

10.0 SUMMARY OF PRECLINICAL STUDIES

Biocompatibility tests selected for the Sealant were based on FDA's blue book memorandum #G95-1, "Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part 1: Evaluation and Testing" dated May 1, 1995. The Sealant is 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, 21 CFR Part 50.

10.1 Biocompatibility Studies

Cytotoxicity studies conducted on extracts, *in situ* polymerization, and individual components of the sealant demonstrated materials to be non-cytotoxic.

Topical application of Sealant was non-irritating to the skin of rabbits. Intracutaneous injection of Sealant, allowed to polymerize *in situ*, was moderately to severely irritating to rabbits. When saline and polyethylene glycol (PEG) 400 extracts of polymerized Sealant were injected intracutaneously in rabbits, the extracts were non-irritating.

Saline extracts of the Sealant were non-hemolytic in human whole blood and were not pyrogenic in rabbits.

The initial Guinea Pig Maximization Test with saline extracts of Sealant caused a hypersensitization response. Additional animal studies attributed this immune response to cross-species interaction between the animal model and the human albumin component of the device. To address the concern of human dermal sensitization, an HRIPT study was conducted which clearly showed the Sealant not to be a sensitizer.

Saline extracts of polymerized Sealant were administered as a single intravenous injection to mice. Sesame oil extracts of the cured Sealant were administered via intraperitoneal injection to mice. Neither extract of Sealant exhibited acute systemic toxicity in mice.

No systemic effects were noted. Acute segmental hemorrhagic enteropathy was noted at the implantation contact sites at day 8 but no anatomical pathological findings were present at day 29. A 7 day follow-up study demonstrated that the enteropathy was mitigated by the instillation of saline into the peritoneal cavity post implantation. It was concluded that the enteropathy was caused by the hygroscopic nature of the Sealant.

The Sealant was not mutagenic nor clastogenic.

Mass balance studies in rats indicated the Sealant degrades readily (within 14 days) and is rapidly excreted primarily in the urine within 72 hours.

10.2 Animal Efficacy And Tissue Healing Studies

In 7-Day efficacy and 28-Day tissue healing pig studies, *in situ* polymerized Sealant, when applied to air leaks in the lungs of pigs, was successful in sealing severe air leaks >1,000 cc/min. No immune response or adverse tissue effects were observed. Tissue healing progressed normally in the presence of the Sealant.

Summaries of the preclinical studies are presented in **Table 2**.

Table 2 Preclinical Testing for the Sealant

Study	Test Article(s) Preparation	Findings
Histopathology - Pig 7 Day Efficacy	*In situ* polymerization[1]	No evidence of an immune response.
Tissue Healing - Pig 28 Day Study	*In situ* polymerization[2]	No evidence of an immune response. Wound healing progressed normally.
Efficacy Study- Pig	*In situ* polymerization[1]	Thoracotomy procedure in 6 pigs. Sealant applied to ALs >1000 cc/min. No leaks at day 7, original test sites remained closed.

[1]NS-lH: Sealant containing human albumin component, gamma sterilized.
[2]NS-1H(e): Sealant containing human albumin component, e-beamed.

11.0 SUMMARY OF CLINICAL STUDY

11.1 Study Objectives

The primary objective of this study was to evaluate the safety and efficacy of the Sealant to seal or reduce intraoperative air leaks (IOALs) in patients undergoing a thoracotomy for pulmonary resection, decortication, or biopsy and thereby reduce the incidence of postoperative air leaks (POALs). Performance of the Sealant, when used adjunctively with standard techniques, was compared with performance of standard techniques alone (sutures, staples, cautery) for closing air leaks (ALs).

11.2 Study Design

This was an open-label, randomized (2:1 ratio), controlled, multi-center study with a total of 161 subjects randomized into the trial (103 Sealant and 58 Control) at five U.S. centers. Key patient eligibility criteria included the following:

Inclusion Criteria

- Scheduled for an open thoracotomy for lung resection (*i.e.*, lobectomy, bilobectomy, segmentectomy, wedge resection/lung volume reduction), decortication, or biopsy within 30 days of the screening evaluation
- At least one or more IOALS (≥2 mm) following surgery
- 18 years or older

Exclusion Criteria

- Pregnant or breastfeeding
- Significant clinical disease or condition that might complicate the surgery and/or postoperative recovery, and in the opinion of the investigators, would be difficult to evaluate the safety and/or efficacy of the Sealant
- Known hypersensitivity to human albumin
- Enrolled in the National Emphysema Treatment Trial (NETT)
- Enrolled in any other study involving tissue sealant materials, synthetic, or natural, (*e.g.*, fibrin sealant, cyanoacrylates)

11.2.1 Study Treatment

After completing the lung resection, decortication or biopsy, subjects in both the Control and Sealant groups received standard treatment for closure of ALs including sutures, staples, or cautery as determined by the investigators' judgment and/or preference. The Control group received standard treatment only. The Sealant group received this standard treatment plus Sealant. Additional surgical techniques (*e.g.* pleural flap/tent, pneumoperitoneum) could be used for persistent ALs as appropriate.

11.2.2 Study Endpoints

The primary efficacy endpoint was the proportion of subjects who remained air leak-free following surgery, through the one month follow-up period or duration of hospitalization, whichever was longer. The presence of ALs was assessed by daily observation of air leakage from the chest tube drainage system. Subjects were also monitored for any recurrence of ALs after chest tube removal.

The secondary efficacy endpoints included: (1) proportion of IOALs in each group that were sealed or reduced, as demonstrated by the air leak test, prior to completion of the surgery; (2) proportion of subjects in each group who were air leak-free immediately following surgery as measured by the presence of ALs from the chest tube at the first postoperative time point once the subject was in the recovery room; (3) duration of POALs measured from the time of surgery until the AL sealed; (4) duration of chest tube placement; and (5) duration of hospitalization.

11.2.3 Safety Measures

The safety measures included both clinical and laboratory assessments. Clinical assessment was based on the investigators' evaluation of adverse events reported during the study period. The laboratory assessment of safety was based primarily on two immunologic assays: (1) the lymphocyte proliferation assay (LPA), which is an in vitro measure of generalized lymphocyte reactivity, independent of antibody type or level; and (2) an enzyme-linked immunosorbent assay (ELISA) that detects the presence of circulating IgG antibodies directed against the Sealant. The ELISA was used as a specific marker for humoral immunity. Both assays were performed preoperatively and at one month postoperatively. The results of the Sealant group were compared with the Control group to determine whether there was any significant between group difference in the change in pre- and post-operative responses.

11.3 Patient Accountability

Of the 161 subjects randomized into the study, 148 completed the trial. Of the 13 subjects who discontinued, or were lost to follow-up from the study, nine died, one had a post-Sealant lung transplant, one had a post-Sealant lobectomy of the treated lung, and two subjects were lost to follow-up. The per treatment distribution of these subjects was similar, with 8 (7.8%) in the Sealant group and 5 (8.6%) in the Control group.

11.4 Study Results

11.4.1 Demographic Characteristics

Table 3 presents the demographic characteristics of the study population. Almost two-thirds of the patients were males and the mean age was about 64 years. There were no significant differences between treatment groups.

Table 3 Demographic Characteristics

Demographic Characteristic		Sealant (N=103)	Control (N=58)
Gender N (%)	Male	66 (64.1%)	36 (62.1%)
	Female	37 (35.9%)	22 (37.9%)
Age (years)	Mean	63.6	65.9
	SD	13.6	11.1
	Range	18-86	42-85

11.4.2 Medical History and Clinical Risk Factors

Subjects in both the Sealant and Control groups were similar with respect to medical history and clinical risk factors, as seen in **Table 4**.

Table 4 Medical History and Clinical Risk Factors

Risk Factor	Sealant (N=103)	Control (N=58)	P-value[a]
Hypertension	40 (38.8%)	26 (44.8%)	0.506
Immunosuppression	5 (4.9%)	3 (5.2%)	1.000
Hx of MI	11 (10.7%)	10 (17.2%)	0.329
Coronary Artery Disease	21 (20.4%)	19 (32.8%)	0.090
Renal Disease	13 (12.6%)	5 (8.6%)	0.604
Hx of Neurological Event	7 (6.8%)	5 (8.6%)	0.758
Diabetes	13 (12.6%)	7 (12.1%)	1.000
CHF	4 (3.9%)	3 (5.2%)	0.703
COPD	35 (34.0%)	16 (27.6%)	0.481
Previous Thoracic Surgery	15 (14.6%)	10 (17.2%)	0.657
Radiation Exposure-Chest	9 (8.7%)	5 (8.6%)	1.000
Chemotherapy	9 (8.7%)	2 (3.4%)	0.330
Steroid Use	4 (3.9%)	3 (5.2%)	0.703
Smoking			
Never	20 (19.4%)	11 (19.0%)	1.000
Current	18 (17.5%)	11 (19.0%)	
Former	65 (63.1%)	36 (62.1%)	
Pack Years			
N	78	46	0.055
Mean ± SD	59.8 ± 36.0	47.6 ± 27.3	

Risk Factor	Sealant (N=103)	Control (N=58)	P-value[a]
Median	50.0	40.5	
Minimum	1	1	
Maximum	175	120	
Recent Weight Loss	13 (12.6%)	9 (15.5%)	0.637
Alcohol Dependency			
No	82 (79.6%)	44 (75.9%)	0.691
Current	6 (5.8%)	7 (12.1%)	
Past	15 (14.6%)	7 (12.1%)	
Prior Cancer	36 (35.0%)	25 (43.1%)	0.316
ECOG Score			0.465
Fully active	72 (69.9%)	38 (65.5%)	
Ambulatory	23 (22.3%)	18 (31.0%)	
In bed <50%	2 (1.9%)	0 (0.0%)	
Bedridden	1 (1.0%)	0 (0.0%)	
Missing	5 (4.9%)	2 (3.4%)	

[a] Wilcoxon rank sum test or Fisher's exact test.

11.4.3 Primary Diagnosis And Operative Summary

Table 5 presents a summary of primary diagnoses. The primary surgical diagnoses for subjects in both the Sealant and Control groups were primary tumor, followed by metastatic tumor.

Table 5 Primary Diagnoses

Parameter	Response	Sealant N=103	Control N=58
Primary Diagnosis	**Primary Tumor**	70 (68.0%)	42 (72.4%)
	Metastatic Tumor	19 (18.4%)	8 (13.8%)
	Benign Tumor	6 (5.8%)	3 (5.2%)
	COPD/Bronchitis/Emphysema	3 (2.9%)	0 (0.0%)
	Other	5 (4.9%)	5 (8.6%)

Table 6 presents a summary of operative characteristics. The most frequent type of surgery was lobectomy for both groups. In both the Sealant and Control groups, the posterolateral thoracotomy was the most frequently used surgical approach. The operative characteristics were similar between the Sealant and Control groups for the individual parameters evaluated.

Table 6 Operative Summary

Parameter	Response	Sealant N=103	Control N=58
Types of Surgery	**Bilobectomy**	4 (3.9%)	1 (1.7%)
	Lobectomy	55 (53.4%)	34 (58.6%)
	Segmentectomy	5 (4.9%)	4 (6.9%)
	Single Wedge	12 (11.7%)	7 (12.1%)
	Multiple Wedge	8 (7.8%)	2 (3.4%)
	Lobectomy with Wedge(s)	10 (9.7%)	5 (8.6%)
	Lobectomy/Segmentectomy/Other	5 (4.9%)	2 (3.4%)
	Lung Volume Reduction	1 (1.0%)	1 (1.7%)
	Other	3 (2.9%)	2 (3.4%)
Surgical Approach	**Median Sternotomy**	1 (1.0%)	1 (1.7%)
	Posterolateral Thoracotomy	85 (82.5%)	45 (77.6%)
	Anterolateral Thoracotomy	3 (2.9%)	6 (10.3%)
	Mini-thoracotomy	13 (12.6%)	6 (10.3%)
	Other	1 (1.0%)	0 (0.0%)
Lymphadenectomy	**Partial**	30 (29.1%)	14 (24.6%)
	Complete	43 (41.7%)	32 (56.1%)
	Not Done	30 (29.1%)	11 (19.3%)
Pleural Adhesions	**Yes**	53 (51.5%)	30 (51.7%)
	No	49 (47.6%)	27 (46.6%)
	Missing	1 (1.0%)	1 (1.7%)
Extent of Adhesions[1]	**Minimal**	28 (52.8%)	14 (46.7%)
	Extensive	22 (41.5%)	15 (50.0%)
	Unspecified	3 (5.7%)	1(3.3%)
No. of Chest Tubes	**1**	19 (18.4%)	7 (12.1%)
	2	83 (80.6%)	48 (82.8%)
	≥3	1 (1.0%)	3 (5.2%)
Time in OR (min)	**N**	102	58
	Mean ± SD	226.7 ± 61.2	236.8 ± 61.5
	Median	225.5	225.5
	Minimum	115	145
	Maximum	455	430
Time to Skin Closure	**N**	91	50
(min)	**Mean ± SD**	156.8 ± 54.9	165.0 ± 62.6
	Median	151.0	143.5
	Minimum	52	81
	Maximum	355	387

[1] Percents based on the number of subjects who had pleural adhesions rated at the time of surgery.

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11.4.4 IOAL Characterization Summary

Table 7 presents the number of IOALs per subject. A total of 318 individual air leaks (ALs) were tracked, with 210 in the Sealant group and 108 in the Control group. The number of IOALs per subject, before intervention, was significantly greater in the Sealant group than in the Control group: 68% of the Sealant subjects had two or more IOALs compared with 48% of the Control subjects.

Table 7 Number of IOALs Prior to Closure

Parameter	Response	Sealant N (%)	Control N (%)	P-value[a]
Total Subjects		103	58	
Total IOAL		210	108	
Number of IOAL/Subject	1	33 (32.0%)	30 (51.7%)	0.0051[a]
	2	46 (44.7%)	14 (24.1%)	
	3	16 (15.5%)	6 (10.3%)	
	4	2(1.9%)	5(8.6%)	
	5	4 (3.9%)	0 (0.0%)	
	>5	2(1.9%)	3(5.2%)	

[a]Fisher s exact test.

11.4.5 Primary Efficacy Endpoint

Table 8 presents a summary of the primary efficacy endpoint. The percentage of subjects who remained air leak-free through 1MFU visit was significantly greater (p=0.005) in the Sealant group 36/103 (35%) compared with the Control group 8/58 (14%).

Table 8 Primary Endpoint Results

Air Leak Status Through 1MFU Visit	Sealant N=103	Control N=58	P-value
No POAL	36 (35.0%)	8 (13.8%)	0.005
With POAL	67 (65.0%)	50 (86.2%)	

Logistic regression analysis was used for the primary endpoint analysis.

11.4.6 Secondary Efficacy Endpoints

11.4.6.1 IOAL Assessment

Table 9 presents a summary of IOALs sealed. Of the 210 IOALs tracked in the Sealant group, 77% were sealed after the application of Sealant compared with 16% of the 108 IOALs in the Control group. IOALs were sealed in 71% of Sealant subjects compared with 10% of Control subjects following the final AL test. The differences between Sealant and Control groups were statistically significant (p<0.001).

Table 9 IOAL Closure Summary

Parameter	IOALs	Sealant	Control	P-value[a]
Sealed IOAL/Individual AL	N	210	108	<0.001
	No IOAL	161 (76.7%)	17 (15.7%)	
	With IOALs	49 (23.3%)	90 (83.3%)	
	Missing	0 (0.0%)	1 (0.9%)	
Sealed IOAL/Subject	N	103	58	<0.001
	No IOALs	73 (70.9%)	6 (10.3%)	
	With IOALs	30 (29.1%)	51 (87.9%)	
	Missing	0 (0.0%)	1 (1.7%)	

[a]Fisher's exact test.

11.4.6.2 Recovery Room POAL Assessment

Table 10 presents a summary of ALs observed in the recovery room. Following surgery, subjects were transferred to the recovery room where chest tubes (CTs) were placed on suction and the subjects' air leakage was determined by observing air bubbles from the CT drainage system. A significant number of Sealant subjects were air leak-free at the recovery room observation period compared to Control subjects. No ALs were observed in 54% of subjects in the Sealant group compared with 33% of subjects in the Control group.

Table 10 Summary of POALs in the Recovery Room

Observation Period	Response	Sealant N=103	Control N=58	P-value[a]
Recovery Room	No AL	56 (54.4%)	19 (32.8%)	0.002
	Occasional Infrequent Bubbles	30 (29.1%)	20 (34.5%)	
	Frequent Bubbles	7 (6.8%)	16 (27.6%)	
	Continuous Bubbles	8 (7.8%)	2 (5.2%)	
	Missing	2 (1.9%)	0 (0.0%)	

[a]Fisher's exact test.

11.4.6.3 Duration of POALs

Table 11 presents a summary of POAL duration. Duration of POAL was defined as the last postoperative day (POD) when no AL was noted during the study period. The duration of POALs was comparable for both treatment groups with a majority of POALs lasting less than three days (median was two days in both groups). While there were more patients in the Sealant group with slightly longer POAL duration than the Control group, this difference was directly related to the fact that more Sealant subjects were able to be discharged early with a Heimlich valve (HV); determination of duration of POAL could not be assessed in those patients until they returned for a hospital visit. The proportion of patients with POAL >11 days excluding patients discharged from the hospital with an HV was similar in the Sealant and Control groups, 4.3% (4/93) and 3.5% (2/57), respectively.

Table 11 Summary of POAL Duration

Duration of POAL (Days)	Sealant N=103	Control N=58
0-2	54 (52.4%)	29 (50.0%)
3-4	18 (17.5%)	14 (24.1%)
5-6	7 (6.8%)	6 (10.3%)
7-9	6 (5.8%)	1 (1.7%)
10-11	3 (2.9%)	3 (5.2%)
>11	13 (12.6%)	3 (5.2%)
Missing	2 (1.9%)	2 (3.4%)
N[1]	101	56
Mean ± SD	4.7 ± 6.8	3.6 ± 3.9
Median	2.0	2.0
Minimum	0.5	0.5
Maximum	42	22

[1] Only included those subjects for whom an end of the AL could be determined.

11.4.6.4 Duration of CT Placement

As shown in **Table 12**, the duration of chest tube placement was comparable for both treatment groups. The median duration of CT placement for both groups was five days. Similar to the results for POAL duration, the slightly longer duration of CT placement in the Sealant group than the Control group was directly related to the use of HV. The proportion of patients with CT placement >11 days excluding patients discharged from the hospital with a Heimlich valve was similar in the Sealant and Control groups, 4.3% (4/93) and 3.5% (2/57), respectively.

Table 12 Summary of Duration of CT Placement

Duration of CT Placement (Days)	Sealant N=103	Contol N=58
0-2	2 (1.9%)	0 (0.0%)
3-4	34 (33.0%)	19 (32.8%)
5-6	37 (35.9%)	21 (36.2%)
7-9	11 (9.7%)	9 (12.1%)
10-11	3 (1.9%)	3 (6.9%)
> 11	13 (15.6%)	3 (6.9%)
Missing	3 (2.9%)	3 (5.2%)
N	100	55
Mean ± SD	6.8 ± 5.5	6.2 ± 3.5
Median	5.0	5.0
Minimum	2	3
Maximum	42	22

11.4.6.5 Length of Hospital Stay

Table 13 presents the length of hospital stay by treatment group. The median length of hospital stay (LOS) was significantly shorter for subjects in the Sealant group compared with subjects in the Control group (p=0.028). Although more Sealant patients were discharged with a Heimlich valve than Control patients, it should be noted the LOS was shorter in the Sealant group than in the Control group irrespective of whether or not patients were discharged with a Heimlich valve. The higher frequency of pneumonia in the Control group than Sealant group may partially explain the difference in LOS.

Table 13 Summary of Length of Hospital Stay

Duration of Hospital Stay (Days)	Sealant Group (N=98)	Control Group (N=55)	P-value[a]
Mean	7.1	8.6	0.028
SD	3.4	5.6	
Median	6.0	7.0	

[a]Wilcoxon rank sum test.

11.4.7 Safety Results

11.4.7.1 Adverse Events

Table 14 presents all AEs with an incidence of >2% by treatment group. Most of the AEs were mild to moderate in severity. The most frequently reported AE was fever, with an incidence of 21% in both groups. The only other AEs occurring with an incidence greater than 10% were: atrial fibrillation, dyspnea, and constipation. Additional AEs reported only in the Control group at an incidence greater than 10% were: nausea, anemia, tachycardia, hypotension, vomiting, and pneumonia.

The most frequently reported "severe" AEs in the Sealant group were pain (4.9%), atrial fibrillation (3.9%), followed by chest pain, dyspnea, hypoxia, and acute renal failure (2.9% each). The most frequently reported "severe" AEs in the Control group were dyspnea (6.9%), anemia, haemoptysis, and pneumonia (3.4% each).

There was no significant difference in the incidence of any AE between treatment groups.

Table 14 Incidence of AEs Reported by > 2% of Subjects by Treatment Group

Preferred Term	Sealant (N=103)	Control (N=58)
Fever	22 (21.4%)	12 (20.7%)
Fibrillation, Atrial	12 (11.7%)	7 (12.1%)
Dyspnea	12 (11.7%)	10 (17.2%)
Constipation	11 (10.7%)	6 (10.3%)
Nausea	10 (9.7%)	7 (12.1%)
Confusion	8 (7.8%)	5 (8.6%)
Pneumothorax	8 (7.8%)	5 (8.6%)
Hypotension	8 (7.8%)	6 (10.3%)
Anemia	8 (7.8%)	6 (10.3%)
Pain	7 (6.8%)	4 (6.9%)

Preferred Term	Sealant (N=103)	Control (N=58)
Subcutaneous Emphysema	7 (6.8%)	5 (8.6%)
Tachycardia	7 (6.8%)	6 (10.3%)
Death	5 (4.9%)	4 (6.9%)
Oliguria	5 (4.9%)	1 (1.7%)
Vomiting	5 (4.9%)	7 (12.1%)
Pneumonia	5 (4.9%)	7 (12.1%)
Pulmonary Infiltration	4 (3.9%)	0 (0.0%)
Chest Pain	4 (3.9%)	1 (1.7%)
Pleural Effusion	4 (3.9%)	3 (5.2%)
Urinary Retention	3 (2.9%)	0 (0.0%)
Ileus	3 (2.9%)	0 (0.0%)
Tachycardia, Supraventricular	3 (2.9%)	0 (0.0%)
Abdominal Pain	3 (2.9%)	0 (0.0%)
Arrhythmia	3 (2.9%)	0 (0.0%)
Extrasystoles	3 (2.9%)	0 (0.0%)
Coughing	3 (2.9%)	1 (1.7%)
Hypoxia	3 (2.9%)	1 (1.7%)
Renal Failure, Acute	3 (2.9%)	1 (1.7%)
Atelectasis	2 (1.9%)	2 (3.4%)
Postoperative Wound Infection	2 (1.9%)	2 (3.4%)
Pruritus	1 (1.0%)	2 (3.4%)
Delirium	1 (1.0%)	2 (3.4%)
Hypertension	1 (1.0%)	2 (3.4%)
Angina Pectoris	1 (1.0%)	2 (3.4%)
Hemoptysis	1 (1.0%)	3 (5.2%)

11.4.7.2 Humoral And Cell-Mediated Immune Response

An ELISA was developed to detect antibodies to pulverized Sealant. Subject serum, collected pre- and postoperatively, was analyzed to determine serum antibody levels in response to the Sealant. Sera were tested at six dilutions (neat, 1:10, 1:100, 1:1000, etc.). The antibody response of a subject's postoperative serum was compared to their preoperative serum.

Of the 161 subjects (103 Sealant, 58 Control) randomized into the study, both pre- and postoperative serum samples were obtained from 71 (69%) of the Sealant subjects and 37 (64%) of the Control subjects. Seventy (70) of the Sealant subjects and 36 of the Control subjects, showed no reaction to the Sealant. One (1) subject in each group had a postoperative serum level consistent with the formation of Sealant antibodies. In each case, the subject's preoperative serum also showed high values indicating that their serum contained antibodies that cross-reacted with the Sealant. These results demonstrated that the use of the Sealant during surgery did not result in the formation of Sealant antibodies.

The LPA was used to measure the proliferative response of peripheral blood mononuclear cells to various concentrations of mitogens and antigens in pre- and postoperative whole blood samples. Cells were tested against a standard screen of mitogens (Con A, PHA, and PWM), recall antigens *(Candida* and Tetanus), and the Sealant using 2-5 concentrations of each mitogen and antigen. The mitogenic response indicated the cell population involved and whether it was impaired or stimulated by the presence of the Sealant. The cellular response to recall antigens

indicated whether the Sealant had altered the cell's response to the antigenic stimulus. Testing against the Sealant as an antigen indicated cell sensitization.

Only subjects with pre- and postoperative samples were included in comparative analyses. There were 59 Sealant/34 Control samples for mitogen analysis and 69 Sealant/32 Control samples for recall antigen and Sealant analyses. The only significant difference was the Control group's lower preoperative value for tetanus. Higher preoperative values in the Sealant group were not clinically meaningful since they were generated on blood prior to Sealant exposure. The cell-mediated immune response of the subjects in the Sealant group was not different from that of the Control group. These results indicate that the Sealant did not significantly alter cellular response to antigenic stimuli.

11.4.7.3 Deaths and Other SAEs

Table 15 presents a summary of subject deaths. There were *5* deaths among subjects in the Sealant group and 4 deaths in the Control group. None of the deaths were considered by the investigators to be device related.

Table 15 Summary of Subject Deaths

Age/Gender	Day of Death	Relationship to Device	Cause of Death
Sealant (n=5)			
69/Male	POD7	Not Related	ARDS
82/Male	POD28	Not Related	Pneumonia
61/Male	POD10	Not Related	Acute Airway Obstruction or Pulmonary Embolism
66/Male	POD6	Not Related	ARDS & Multisystem Failure
65/Male	POD23	Not Related	ARDS & Multisystem Failure
Control (n=4)			
80/Female	POD15	Not Related	Pneumonia
71/Male	POD22	Not Related	Atrial Fibrillation
82/Male	POD0	Not Related	Ventricular Fibrillation
67/Male	POD38	Not Related	Anoxic Brain Injury

In addition to the deaths described above, there were 5 other SAEs: 2 in the Sealant group and 3 in the Control group (**Table 16**). Both of the SAEs in the Sealant group were considered probably not related to the device by the investigators. All of these SAEs resulted in extended hospital stays or re-hospitalization. Four subjects recovered from these events and 1 subject continues on dialysis.

Table 16 Other SAEs

Subject ID	Age/Gentler	Relationship To Device	Event	Outcome
Sealant (n=2)				
	70/Female	Probably Not Related	Acute Renal Failure	Continues on Dialysis
	70/Male	Probably Not Related	Myocardial Infarction	Recovered
Control (n=3)				
	83/Male	Not Related	Fluid/Air in Lung & GI Bleed	Recovered
	67/Female	Probably Not Related	ARDS	Recovered
	70/Male	Not Related	Dehydration	Recovered

11.4.7.4 Device Related Adverse Events

Eight AEs occurred in 3 subjects in the Sealant group considered to be possibly or probably related to the device by the investigators, which included chest pain, constipation, gastroesophageal reflux, nausea, cough, dyspnea, pneumothorax, and subcutaneous emphysema. All were reported as a single occurrence in the Sealant group.

Two of the AEs, dyspnea and chest pain, were reported as "severe" and "serious," respectively, and occurred in the same subject. The patient did well until POD20 when she developed left chest pain and dyspnea. She was found to have a large pneumothorax in the left hemithorax requiring CT placement on POD21. Her shortness of breath and chest pain resolved with CT insertion. The AE resolved on POD29.

All other AEs were reported as mild or moderate.

12.0 CONCLUSIONS DRAWN FROM THE STUDY

The primary study endpoint was met, with significantly more Sealant patients remaining air leak free at 1 month than Control subjects. The Sealant group demonstrated statistically significant improvement over the Control group in 3 of 5 secondary endpoints (IOALs sealed, air leak free immediately following surgery, and duration of hospitalization). Results for the remaining 2 secondary endpoints were comparable between groups. The pivotal study results support the safety and efficacy of the Sealant when used as an adjunct to standard methods for closure of ALs incurred during pulmonary surgery.

13.0 PANEL RECOMMENDATION

TBD

14.0 FDA DECISION

TBD

15.0 APPROVAL SPECIFICATIONS

TBD