ANESTHESIOLOGY AND RESPIRATORY THERAPY DEVICES PANEL

Gaithersburg, Maryland

June 12, 2008

NeoMend Inc. ProGEL™ Surgical Sealant

PMA P010047

SPONSOR'S SUMMARY OF CLINICAL DATA

1 SYNOPSIS

Name of Sponsor: NeoMend, Inc. (Original Sponsor for the study was 3M Medical-Surgical Division)
Name of Product: NeoMend ProGEL™ Surgical Sealant (Formerly 3M™ Surgical Sealant)
Study Title: A Randomized Study to Evaluate a Polymeric Patch for Sealing Intraoperative Air Leaks Occurring During Pulmonary Resection (LIN4S 7806)
Investigator(s): Multi-Center
Objective: The primary objective of this study was to evaluate the safety and efficacy of NeoMend ProGEL™ Surgical Sealant ("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, for closing air leaks (ALs), when used adjunctively with standard techniques, was compared with performance of standard techniques alone (Control) such as sutures, staples, and cautery.
Methodology: This was an open-label, randomized (2:1 ratio), controlled, multi-center study. Thoracotomy patients who met the initial screening criteria, had signed an informed consent form, and who had at least one clinically significant IOAL (≥2 mm in size) following surgery, as determined by a saline submersion test (*i.e.*, "air leak test"), were enrolled in the study. After recording the size, location, and source of the air leak(s), investigators used standard techniques to close air leaks. Subjects were then randomized into either the Sealant or Control group. For subjects assigned to the Control group, a second "air leak test" was conducted following randomization to determine the success of the standard technique in sealing or reducing those leaks. For subjects assigned to the Sealant group, the Sealant was applied to the air leak sites that were first closed with standard technique. Up to three applications of Sealant per air leak were permitted. Additionally, in both groups, there may have been some IOALs that the investigators did not attempt to close with standard methods, (*e.g.*, the leak was too small or tissue was too fragile to use sutures, staples, or cautery) because they felt that standard closure methods were not necessary or might worsen the clinical situation. For subjects assigned to the Sealant group, investigators were instructed to apply Sealant to these sites as well to assess the use of Sealant where normally no specific intervention would or could be undertaken. Following the application of Sealant, a second "air leak test" was conducted on the Sealant subjects to assess IOALs. Following the second "air leak test," if air leaks were observed in either group, the investigators could use other surgical techniques (*e.g.*, pleural flap/tent, pneumoperitoneum) to close the air leak and record the action taken. At this point the intraoperative evaluation of the assigned treatment was completed and the investigators closed the thoracotomy per standard

procedures.

In the immediate postoperative period, while subjects were in the recovery room, follow-up assessments included: 1) a chest x-ray (CXR) within six hours of surgery and post-endotracheal extubation to determine lung expansion; 2) measurement of chest tube (CT) drainage; and 3) air leak categorization as determined from the CT.

During the postoperative hospital stay, until the subjects' CT was removed or upon discharge, whichever came first, the following assessments were performed daily: 1) measurement of vital signs measurement; 2) measurement of CT drainage; 3) determination of air leak status; and 4) occurrence of adverse events (AEs). In addition, CXRs were obtained prior to and following CT removal and as clinically indicated. Prior to discharge from the hospital, a final physical examination, blood work, and any ongoing AEs were noted.

As an adjunct to safety monitoring, the protocol was amended in June, 2000, to provide for follow-up telephone calls two weeks post surgery to assess the subjects' experience with certain targeted symptoms/complaints since discharge from the hospital. For those subjects scheduled to return for a two-week follow-up clinic visit the same questions were asked. Subjects returned to the study site for a one month follow-up (1MFU) visit (4-6 weeks post-surgery) that included a physical exam, CXR, laboratory tests, and assessment of AEs.

Number of Subjects: Enrolled: 275; Randomized: 161

Study Centers: Five U.S. Centers enrolled patients in this study

Eligibility Criteria: Patients undergoing thoracotomy who met the following key eligibility criteria:

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)

Test Product: NeoMend ProGEL™ supplied as a sterile, single-use, 2 component kit, 2 ml application
Quantity: Up to three applications per air leak
Mode of Administration: Applied topically to external lung surface

Standard Treatment: Standard sutures, staples or cautery devices supplied by the hospital for thoracic surgery and utilized per individual investigator judgment or preference

Study Endpoints:
Primary Efficacy Endpoint: Proportion of subjects who remained air leak free, through the 1MFU period or the duration of hospitalization, whichever was longer
Secondary Efficacy Endpoints:

- Proportion of IOALs that were sealed or reduced, as demonstrated by the air leak test, prior to completion of the surgery
- Proportion of subjects who were free of air leaks immediately following surgery as measured by the presence of air leaks from the CT at the first postoperative timepoint once the subject was in the recovery room
- Duration of POALs measured from the time of surgery until the air leak sealed
- Duration of CT placement
- Duration of hospitalization

Safety Measures: Included a clinical assessment and laboratory assessments. The clinical assessment was based on the investigators' assessment of AEs related to the device that were reported during the postoperative hospitalization through the 1MFU 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 and which was used as a specific marker for humoral immunity. Both assays were performed preoperatively and at one month postoperatively.

Results: A total of 275 subjects at 5 clinical sites were enrolled. Of the 275, 114 were not randomized, principally because they were not found to have IOALs. One hundred and sixty-one (161) subjects were randomized: 103 to the Sealant group and 58 to the Control group.

The results of this study demonstrated that the Sealant achieved statistically significant superiority over the Control for the Primary Efficacy Endpoint and 3 of the 5 Secondary Efficacy Endpoints. For the other 2 Secondary Efficacy Endpoints, there was no statistically significant difference. There was no statistically significant difference in the incidence of AEs between the Sealant and Control groups.

For the primary efficacy endpoint, a significantly greater proportion of Sealant subjects (35%) remained air leak free following surgery through the 1MFU visit or the duration of

hospitalization, whichever was longer, compared to the Control subjects (14%) ($p=0.005$). In other words, proportionally, Sealant patients were more than twice as likely to avoid an air leak following surgery compared to the Control subjects.

For the secondary efficacy endpoints, a significantly greater proportion of Sealant subjects had their IOALs sealed (71%) compared to the Control subjects (10%) and, of the 318 individual IOALs tracked, a significantly greater proportion were sealed in the Sealant group (161/210, or 77%) compared to the Control group (17/108, or 16%) ($p<0.001$). Furthermore, significantly more Sealant subjects (54%) were air leak free at the recovery room observation period compared to Control subjects (33%) ($p=0.002$) and the length of hospital stay was also significantly shorter ($p<0.05$) for subjects in the Sealant Group compared with subjects in the Control group (median = 6 and 7 days, respectively).

The duration of ALs, defined as the last POD on which the AL was noted, was comparable for both treatment groups, with a majority of ALs lasting less than 3 days (median=2 days in both groups). The duration of CT placement was also comparable, with a median duration of 5 days for both groups.

There was no statistically significant difference in the incidence of AEs between the Sealant and Control groups. However, the rate of pneumonia was lower among Sealant subjects (4.9%) than among Control subjects (12.1%). Pneumonia is a serious complication of lung resection surgery often causing significantly greater morbidity and mortality, and a longer hospital stay and the study results indicated that the Sealant may help reduce the incidence of pneumonia.
A total of 14 serious AEs (SAEs) was recorded: 9 deaths (5 Sealant, 4 Control), and 5 other SAEs (2 Sealant, 3 Control), all considered not device related. There was one other SAE in the Sealant group (pneumothorax 3 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. There were no significant changes observed in humoral and cellular immune responses between the Sealant and Control groups, indicating the lack of immune response to the Sealant.

Conclusions: 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.

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3 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviations	Definitions
1MFU	One Month Follow-up
AE	Adverse Event
AL	Air Leak
ALT	Alanine Aminotransferase (SGPT)
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartate Aminotransferase (SGOT)
ATS	American Thoracic Society
BP	Blood Pressure
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
COPD	Chronic Obstructive Pulmonary Disease
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organization
CT	Chest Tube
CXR	Chest X-ray
ECCS	European Community Coal and Steel
ECG	Electrocardiogram
ELISA	Enzyme-Linked Immunosorbent Assay
FDA	Food and Drug Administration
FEV_1	Forced Expiratory Volume in 1 Second
FVC	Forced Vital Capacity
GI	Gastrointestinal
HCG	Human Chorionic Gonadotropin
Hg	Mercury
HR	Heart Rate
IEC	Independent Ethics Committee
IDE	Investigational Device Exemption
IOALs	Intraoperative Air Leaks
IRB	Institutional Review Board
ISO	International Standards Organization
l	Liter
L	Lateral
LDH	Lactate Dehydrogenase
LOS	Length of Stay (Hospital)
LPA	Lymphocyte Proliferation Assay
mg	Milligram
ml	Milliliter

mm	Millimeter
NETT	National Emphysema Treatment Trial
ODE	Office of Device Evaluation
OR	Operating Room
PA	Posterior-Anterior
PEG	Polyethylene Glycol
POALs	Postoperative Air Leaks
POD	Postoperative Day
RR	Respiratory Rate
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
UADE	Unanticipated Adverse Device Effect
USP	United States Pharmacopeia
VATS	Video Assisted Thoracic Surgery
WHOART	World Health Organization Adverse Reaction Terminology

4 INTRODUCTION

Air leaks (ALs) are one of the most common complications of pulmonary surgery. They can develop from suture/staple lines and other types of surgical manipulation or simply be due to the fragile state of the diseased lung tissue. Without prompt and effective treatment, ALs can lead to increased morbidity and extended hospitalization. Traditionally, suture techniques and stapling devices have been used to seal parenchymal defects. Both can exacerbate rather than remedy the AL. Consequently, there has been a recognized clinical need for a product that effectively seals intraoperative air leaks during pulmonary surgery.

Fibrin sealants have been in use for years by surgeons and are an important adjunct to surgical procedures. Patch type materials for sealing ALs in lungs have met with limited success due to difficulty of use, ineffective closure of ALs, poor adhesion, or poor cost/benefit. While synthetic tissue sealants are emerging as another important adjunct to surgical procedures, there are no products currently marketed in the U.S. for sealing ALs in lungs.

3M Corporation developed a polymeric sealant previously called the 3M Polymeric Patch. In 2007 NeoMend acquired the 3M Polymeric Patch and renamed it the NeoMend ProGEL™ Surgical Sealant ("Sealant"). The Sealant consists of a synthetic cross-linking component and a component derived from human albumin USP. The polyethylene-glycol (PEG) based cross-linker component is functionalized with succinate groups, and reacts with the albumin component to form a clear, pliant hydrogel. The cross-linker component is provided as a powder, which is reconstituted with sterile water. Following reconstitution of the cross-linker, the two liquid components are housed in an applicator that mixes them within a spray tip, initiating a polymerization reaction. Polymerization is essentially completed within 30 seconds, without the need for additional equipment or energy sources, and polymerization does not generate any heat. The gel strength is sufficient to withstand 30 mmHg air pressure in two minutes and 90 mmHg in less than ten minutes. After application, the material forms a flexible seal over the surface of the tissue around the AL. The clear hydrogel remains soft and compliant and does not harden or turn brittle. The Sealant degrades and is completely resorbed within two to three weeks.

The Sealant has been demonstrated to be biocompatible based on studies performed in accordance with recommendations for prolonged tissue implants set forth in US FDA ODE Guidance # G95-1, "Use of International Standard ISO-10993, Biological Evaluation of Medical Devices Part 1: Evaluation and Testing", dated May 1, 1995, and animal testing performed to evaluate tissue wound healing and biodegradation (mass balance). The efficacy of the device as a sealant for pulmonary ALs has been demonstrated in animal models. The results of preclinical studies indicate that the Sealant is suitable for its intended use.

5 INVESTIGATIONAL PLAN

5.1 Study Objective and Purpose

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 for closing air leaks.

The primary efficacy endpoint was the proportion of subjects without POALs as measured by daily observation of air leaks (ALs) via the chest tube (CT) through the one month follow-up period (1MFU) or duration of hospitalization, whichever was longer.

The primary safety measures were: 1) the incidence of AEs related to the device that were reported during the study period; and, at the specific request of the Agency, 2) any significant changes observed in LPA and ELISA tests conducted on pre- and post-surgical blood/serum samples between the Sealant and Control groups to determine any humoral and/or cellular response elicited against the Sealant or its decomposition products.

5.2 Overall Study Design and Plan Description

This was an open-label, randomized (2:1 ratio), controlled, multicenter study with a projected sample size of 156 subjects who met the final eligibility criteria for enrollment and who completed the trial. It was anticipated that approximately 220 subjects would need to be enrolled in order to randomize up to 174 subjects who met the final intraoperative criteria for ALs. All subjects provided written consent prior to being enrolled for possible randomization into the trial.

5.3 Study Design

Thoracotomy patients who met the initial screening criteria and had signed an informed consent form were enrolled into the study. Those subjects who had at least one significant IOAL (≥2 mm in size) following surgery, as determined by an air leak test, were eligible to be randomized into the study. After recording the size, location, and source of the ALs, investigators used standard techniques to close the ALs. Subjects were then randomized into either the Sealant or Control group.

For subjects assigned to the Control group, only standard methods of closure (staples, cautery, and suturing) were used to close ALs. At the time of protocol development, there were no FDA approved adjuncts to standard methods of closure. After standard closure methods were used, a second air leak test was conducted on the Control subjects to determine the success of the standard technique in sealing or reducing ALs.

For subjects assigned to the Sealant group, standard methods were used to close IOALs followed by application of the Sealant. Up to three applications of Sealant per IOAL were permitted. Additionally, in both groups, there may have been some IOALs that the investigators did not attempt to close with standard methods because they felt that standard closure methods were not necessary or might worsen the clinical situation (*e.g.*, the leak was too small or tissue was too fragile to use sutures, staples, or cautery). For subjects assigned to the Sealant group, investigators were instructed to apply Sealant to these sites as well to assess the use of Sealant where normally no specific intervention would or could be undertaken. Following the

application of Sealant, a second air leak test was conducted on the Sealant subjects to assess IOALs.

Following the second air leak test, if IOALs were observed in either group, the investigators could use other surgical techniques (*e.g.*, pleural flap/tent, pneumoperitoneum) to close the IOAL and were to record the action taken. At this point, the intraoperative evaluation of the study subjects was completed and the investigators closed the thoracotomy per standard procedures.

5.4 Study Population

The study population consisted of subjects undergoing a thoracotomy for pulmonary resection, decortication, or biopsy. Subjects were evaluated according to the following inclusion and exclusion criteria prior to participation. Subjects who met such and were judged by the investigators to be suitable for study participation were preliminarily eligible for enrollment in the study. However, only those subjects with one or more clinically significant IOALs (defined as ≥2 mm in size) following surgery were randomized into the study.

5.4.1 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 intraoperative air leaks (≥2 mm) following the lung resection surgery.
- Male or female and is 18 years or older.
- Able to understand the study procedures and either the patient, patient's guardian, or legally appointed representative has signed the Informed Consent Form.
- Willing and able to complete the entire study as specified in the protocol, including the follow-up visit.
- Female of chilbearging age and not sterilized, willing to be on an acceptable method of birth control for the duration of the study, 4-6 weeks post surgery.

5.4.2 Exclusion Criteria

- Pregnant or breastfeeding
- Significant clinical disease or condition that may complicate the surgery and/or postoperative recovery such that in the opinion of the investigator it would preclude enrollment in the study because it would be difficult to evaluate the safety and/or effectiveness of the Sealant as set forth in the study protocol.
- Known hypersensitivity to human albumin.

- Enrolled in the National Emphysema Treatment Trial (NETT) study.

- Enrolled in any other study involving tissue sealant materials, synthetic or natural, *e.g.*, fibrin sealant, cyanoacrylates.

- Participating in any other study without prior sponsor approval.

5.4.3 Removal of Subjects From Therapy or Assessment

Subjects could withdraw or be withdrawn from the study by the investigators at any time without prejudice. Every attempt was made to see all subjects at the 1MFU visit. The subject was considered lost to follow-up if they failed to return for the 1MFU visit and could not be reached after two documented telephone calls and one certified letter.

5.5 Treatment group

5.5.1 Standard Treatment

After completing the lung resection, decortication or biopsy, subjects in both the Control and Sealant groups received standard treatment for closure of IOALs including sutures, staples, or cautery as determined by the investigators' judgment and/or preference. Sutures, staples or cautery devices, supplied by the hospital for thoracic surgery, were utilized. The sponsor did not supply these materials. There was no attempt to standardize these materials across participating centers in this trial. The Control group received standard treatment only. The Sealant group received this standard treatment plus Sealant.

5.5.2 Investigational Treatment

The Sealant was provided in a 2.0 ml dose applicator kit. Each kit included a liquid component, derived from human albumin USP at 290 mg/ml, and a powder component, polyethylene glycol disuccinimidyl-succinate ($PEG[SS]_2$), at 130 mg/ml. The powder component was rehydrated with sterile water just prior to delivery. Both components were housed in a dual-chamber, syringe-like mechanical system that mixed them at the point of delivery, initiating a polymerization reaction that resulted in the formation of an occlusive, compliant hydrogel material on the tissue surface.

Each 2 ml applicator supplies enough Sealant to cover an area 20 cm^2 (3 $inch^2$), 1 mm thick. Investigator input suggested that 2 ml of Sealant should be sufficient to treat an average IOAL. Investigators were instructed to apply the Sealant to all detected IOALs and that they could reapply the Sealant up to two additional times, if necessary, to close or reduce individual IOALs. There were no restrictions on the total amount of sealant applied per subject.

The Sealant was applied after applying standard closure methods (sutures, staples, cautery) to seal IOALs. Investigators were instructed to: 1) irrigate the area to be sealed with the Sealant to remove any pooled blood or blood clots; 2) remove any excess moisture from the area; and 3)

stop or reduce ventilation to the affected area to minimize air leakage and lung movement prior to application of the Sealant.

5.5.3 Prior and Concomitant Therapy

No prior treatment with Sealant was allowed nor were any other tissue sealants allowed to be used concurrently with the Sealant. Standard surgical technique (sutures, staples, cautery or no specific intervention) was permitted per protocol. All concomitant medications and postoperative procedures necessary for the subjects' management were allowed.

5.6 Investigator Training

Investigators underwent training in preparation and use of the Sealant at an Investigator Meeting, prior to study start. Each investigator was guided through the preparation of the crosslinker, the specific steps for assembling the product, and spraying the Sealant. The investigators practiced until they felt comfortable with the assembly and delivery of the product.

To simulate the clinical setting, investigators practiced on anesthetized pigs in the animal laboratory. Midsternal incisions were made in each animal so both right and left lungs could be utilized in the training session. For demonstration purposes, lung resections were performed and various techniques were used to create small to large sized ALs, similar to those encountered in practice.

Proper application techniques were demonstrated on one of the animals. As ALs were created, the investigators practiced sealing them with Sealant. The training session ended after the investigators demonstrated consistent application of the Sealant.

5.7 Randomization

An initial stratification of subjects was performed according to the subject's preoperative pulmonary function as measured by percent of predicted forced expiratory volume in one second (FEV_1). Subjects were randomized within the strata of ≤40% of predicted FEV_1 and >40% of predicted FEV_1. This stratification was employed to maintain comparability of treatment groups with regard to this significant risk factor.

Following lung surgery and after standard IOAL closure methods had been applied, eligible subjects were randomly assigned to either the Sealant or Control group in a 2:1 ratio (Sealant:Control).

5.8 Blinding

This was an open-label study. To minimize bias, subjects were randomized to a study group after they had completed standard closure methods.

5.9 Study Procedures

Figure 1 presents a flow chart of study procedures. A summary of study activities is presented in **Table 1**.

Figure 1 Flowchart of Study Procedures

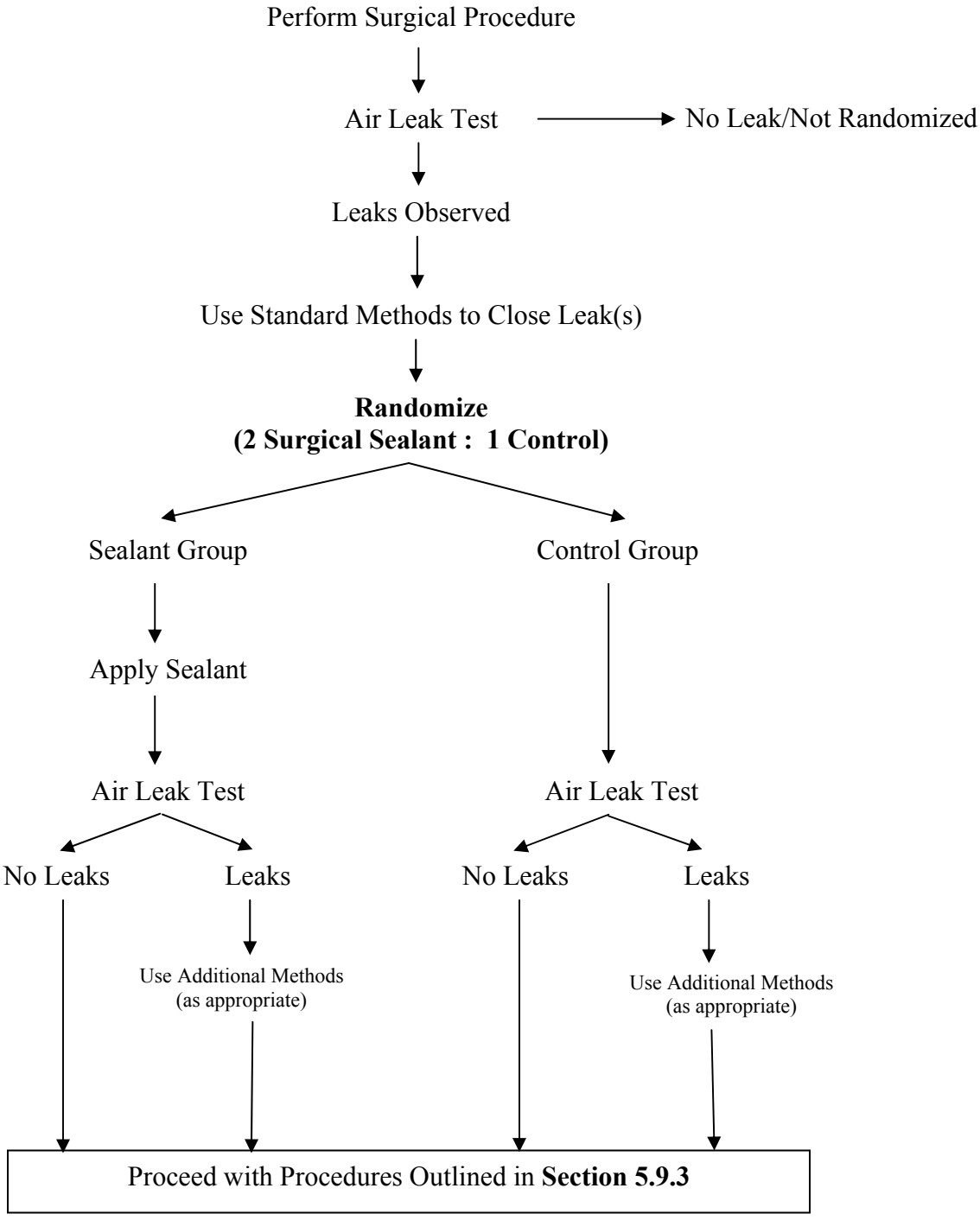


Table 1 Summary of Study Activities

Procedure	Screening Within 30 Days of Surgery[1]	Interop	POD0	POD1-7 or Discharge	Discharge	2-Week Follow-up Phone Call	1MFU Visit
Informed Consent[2]	X						
History	X						
Physical Exam	X				X		X
Vital Signs (BP, RR, HR, Temp)	X			X	X		X
Laboratory Tests (CBC, Blood Chem)	X				X		X
Spirometry (FEV_1, FVC)	X (w/in 90 days)						
Chest X-ray	X (w/in 45 days) (PA&L)		X (PA)	X[3] (PA)			X (PA&L)
12-lead ECG	X						
Pregnancy Test[4]	X						
Immunologic Testing (LPA, ELISA)	X						X
Demographics	X						
Eligibility Assessment	X	X (final)					
Operative Summary		X					
Initial AL Test		X					
Randomization		X					
Final AL Test		X					
Post-op CT AL			X	X[5]			
Chest Tube Drainage/Duration			X	X[5]			
Phone Questionnaire						X	
Adverse Events		X	X	X	X	X	X

[1] Unless otherwise noted

[2] Obtained prior to enrolling in study and before any study-related testing was conducted. Tests not specific to study and normally conducted prior to surgery could be completed prior to informed consent

[3] Taken prior to removing CT (within 24 hrs) and after removing CT (within 24 hrs) and as clinically indicated

[4] Females of childbearing potential only, within 7 days of surgery

[5] For those subjects who remained hospitalized beyond Day 7, the CT was monitored daily until removed. Those subjects discharged with a Heimlich valve were monitored at each follow-up visit, until the valve was removed

5.9.1 Screening and Baseline Information

Subject screening and other baseline information was completed within 30 days prior to surgery with the exception of 45 days for CXR, 90 days for spirometry, and 7 days for the pregnancy test.

5.9.2 Intraoperative Procedures (Day 0)

After the investigators had completed the designated resection employing standard surgical techniques and prior to closing the thoracotomy, the following intraoperative study procedures were performed.

5.9.2.1 AL Test and Randomization

The investigators conducted an AL test by filling the chest cavity with warm saline solution or water to submerge the entire lung, simultaneously inflating the lung to 20-30 mmHg (30-40 cm H_2O) and looking for air bubbles, indicating the presence of ALs. The investigators then estimated the size of each AL. Any AL ≥2 mm in size was considered clinically significant.

If no leaks or only clinically insignificant leaks (<2 mm in size) were observed, the subject was not randomized. Subjects with one or more ALs ≥2 mm in size met the eligibility criteria and were randomized into the study.

5.9.2.2 IOAL Sealing and Assessment Procedures

For subjects assigned to the Control group, the success in sealing or reducing IOALs was assessed by repeating the AL test and observing for air bubbles at the same air pressure parameters as the initial test. Using the criteria listed below, the investigators assessed each treated IOAL:

- Completely closed (no bubbles)
- <2 mm bubbles
- 2-5 mm bubbles
- >5 mm bubbles

For subjects assigned to the Sealant group, the investigators applied Sealant to each of the sites closed by standard technique. In addition, the investigators could apply Sealant to leaks considered too small or to tissue too fragile to use sutures or staples. If an IOAL treated with Sealant was still leaking after the first application of the Sealant, the investigators were permitted to reapply the Sealant up to two more times, if necessary, to close or reduce the IOAL. After all IOALs had been treated, the success in sealing or reducing the IOALs was assessed by repeating the air leak test and observing for air bubbles at the same air pressure parameters as the initial test. The investigators assessed each treated IOAL using the same criteria as listed above for the Control group.

For both groups, if IOALs persisted, the investigators could use other surgical techniques considered appropriate, (*e.g.*, pleural flap/tent, pneumoperitoneum) to close the IOAL, record the action(s) taken, and the results. At this point, the intraoperative evaluation of the two study groups was completed and the investigators closed the thoracotomy per standard procedures.

5.9.3 In-Hospital Postoperative Follow-up (POD0, and POD1-7 or Discharge)

To ensure consistency among investigators and across study sites, and to allow for comparison of AL and CT duration, the postoperative management of subjects' CTs was handled similarly across all study centers. Chest tubes were assessed daily by the investigator or other qualified personnel until removal.

Postoperative care proceeded according to currently accepted standards of medical practice. All subjects in both groups were observed for any AEs occurring throughout the course of the study.

A CXR was obtained within six hours of surgery and post-endotracheal extubation to determine lung expansion. Within 24 hours, prior to and after CT removal, a CXR was obtained to confirm adequate lung expansion and then as clinically indicated.

CTs were placed on suction (20-25 cm H_2O) for the first 24 hours following surgery. After 24 hours, the CT would be transferred to water seal at the discretion of the investigator. CT status (*i.e.*, on suction or water seal) was recorded. The CT was removed when the following occurred: 1) there was no more air leakage; 2) the lung had expanded sufficiently and/or, in the investigator's opinion, there was no significant increase in the size of a pneumothorax that would prevent discontinuation; and 3) drainage had reduced to <5 cc/kg/24 hours or <2.5 cc/kg/12 hours.

The amount of CT drainage (cc/24 hours) was recorded immediately postoperatively in the recovery room and daily until the CT was removed.

The amount of air leakage was measured by the presence of air bubbles in the water seal chamber in the recovery room, and daily thereafter until the CT was removed.

Daily vital signs (supine blood pressure, heart rate, respiratory rate, and body temperature) were measured and recorded through POD7.

The following procedures were performed and/or data collected upon hospital discharge:

- Date/time discharged from hospital;
- General physical examination;
- Vital signs;
- CBC, blood chemistry;
- Date air leakage ceased;
- Date CT removed; and

- AE assessment.

Occasionally the investigator would decide to discharge a subject, who still had an AL, with a Heimlich valve. When this occurred, the subject was asked to return on a weekly basis until the valve was removed.

5.9.4 Two-Week Postoperative Follow-up Telephone Call

As an adjunct to safety monitoring, for those subjects enrolled after a June, 2000 amendment, at two weeks post surgery the investigators or their designees telephoned the subjects and asked a standard set of questions with targeted symptoms/complaints related to the subject's health since discharge. These included difficulty breathing, persistent cough, elevated temperature (101°F), upper respiratory infection (or common cold), and pain, redness, swelling, or drainage from the surgical incision. Spontaneously reported AEs were also documented. For subjects scheduled to return for a two-week postoperative clinic visit, the same questions were asked.

5.9.5 One Month Follow-up Visit

Subjects returned to the study site for a one month follow-up visit (1MFU), 4-6 weeks post surgery. The following evaluations were performed:

- General physical examination;
- Vital signs;
- AE evaluation, including any continuous AEs from the last day subject was hospitalized and any new AEs since hospital discharge;
- CXR (PA&L);
- CBC, Blood Chemistry;
- Whole Blood for LPA; and
- Serum for ELISA testing.

5.10 Efficacy and Safety Variables

5.10.1 Efficacy Variables

The primary efficacy endpoint was the proportion of subjects who remained air leak free following surgery, through the 1MFU period or the duration of hospitalization, whichever was longer. The presence of ALs was assessed by daily observation of air leakage from the CT. The subject was monitored after removal of the CT for clinical evidence of pneumothorax.

The secondary efficacy endpoints included:

- Proportion of IOALs in each group that were sealed or reduced, as demonstrated by the air leak test, prior to completion of the lung surgery;
- Proportion of subjects in each group who were free of ALs immediately following surgery as measured by the presence of ALs from the CT at the first postoperative time

point once the subject was in the recovery room;

- Duration of POALs measured from the time of surgery until the air leak sealed;
- The duration of CT placement; and
- The duration of hospitalization.

5.10.2 Safety Variables

The primary measures of safety were: 1) the incidence of AEs related to the device that were reported during postoperative hospitalization and the follow-up period; and 2) any significant changes observed in LPA and ELISA tests conducted on pre- and post-surgical blood/serum samples between the Sealant and Control groups.

5.10.3 Laboratory Methods

Clinical laboratory values were generated by standard protocols within each investigational institution. Information concerning methodology, normal ranges, and units of measurement were submitted to Sponsor before commencement of the study.

Pulmonary function tests were performed in compliance with the American Thoracic Society (ATS): Standardization of Spirometry. Predicted values for FEV_1 and FVC were determined using the prediction equations from European Community Coal & Stee1 (ECCS).

Immunologic testing to assess a subject's humoral and cell-mediated immune response to the Sealant and/or its degradents was conducted by Dr. Judith B. Ulreich, Ph.D., Director of Research Laboratories, University of Arizona, in compliance with 21 CFR 58, Good Laboratory Practice regulations and the laboratory's standard operating procedures (SOPs). The specific tests used to evaluate possible changes in the two arms of the immune system included the LPA, which is an *in vitro* measure of generalized lymphocyte reactivity, independent of antibody type or level, and an 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 were any significant differences in responses.

5.11 Statistical Methods

5.11.1 Sample Size Determination

Review of studies published in the literature revealed considerable variability in the expected average duration of ALs, CT drainage, CT duration, and length of hospital stay for subjects undergoing a variety of lung resection surgeries. Results varied depending on the type and extent of surgery as well as any risk factors present in the subject population.

Thus, for purposes of this study, reduction of POALs was chosen as the primary efficacy measure of interest. Previously published studies suggested that POALs occur in 60-70% of

subjects who have IOALs following pulmonary resection surgery even after various surgical techniques were used to attempt to seal them. To determine sample size, a clinically significant decrease in the percent of subjects with POALs was determined to be a least 25%. Based on a two-sided alpha level of 0.05, statistical power of 80%, and a 2:1 randomization of subjects to Sealant and standard techniques for sealing ALs, a total sample size of 156 subjects was required. To allow for 10% dropouts, 116 subjects were to be randomized to the Sealant group and 58 subjects were to be randomized to the Control group.

5.11.2 Analysis of Primary Efficacy Endpoint

The proportion of subjects without POALs at any time following surgery up to the 1MFU period or the duration of hospitalization, whichever was longer, was compared between the Sealant and Control groups using a logistic regression model. The impact of important risk factors on the primary endpoint was assessed by covariance analysis or logistic regression methods as deemed appropriate. Covariates of interest included but were not limited to age, gender, pre-surgical pulmonary function and medical/surgical risk factors.

Any subject who was lost to follow-up or for whom the status of any AL was unknown was considered a "treatment failure" in the analysis of the primary efficacy endpoint. All randomized subjects were included in the denominator in calculating the proportion of subjects who remained air leak free during the study period.

5.11.3 Analysis of Secondary Efficacy Endpoints

The secondary efficacy endpoints of interest in this study included sealing of IOALs, duration of POALs, incidence of persistent ALs (>7 days), duration of CT placement, and duration of hospitalization.

For the analysis of the number and extent of IOALs, due to the logistical difficulties associated with recording and classifying IOALs, only up to 5 of the largest leaks for any individual subject were included in this analysis.

For the analysis of duration of POALs, a subject who did not have a POAL was included in the analysis of AL duration with a value of 0.5 days assigned. This arbitrary non-zero value was based on the need to include all subjects in the time-to-event analysis. Essentially all subjects were considered "at risk" since by definition they must have had an AL during surgery to qualify for randomization in the trial. In the event a subject developed an AL following a postoperative period with the absence of ALs, the duration of the AL would be regarded as the total elapsed time since surgery until the AL terminated. Therefore, in this situation, the leak free period from the end of surgery to the onset of the AL was included in the calculation of the duration of the AL for that subject. In this study, some subjects were able to be discharged early with a Heimlich valve. This impacted the assessment of the duration of POALs since these subjects were not in the hospital for daily observation but returned on a weekly basis for assessment of ALs. In these instances, the duration of ALs was the number of days elapsed from surgery until the subject returned to the clinic with no evidence of an AL.

For comparison of means (continuous variables), the two-sample t-test or the Wilcoxon rank sum test was used as appropriate. For comparison of proportions (categorical variables), the Chi-square test or Fisher's exact test was used as appropriate. Time to event analysis using log-rank test was performed to analyze the duration of POALs and length of hospital stay data.

5.12 Protocol Amendments

Conditional approval of the IDE G980283 and study protocol (Version 6) was received on June 29, 1999. Subsequent to FDA approval, the following changes were made to the protocol:

- Amendment 1 (November 1, 1999): made minor changes to Appendix F "Guidelines for Blood and Serum Sample Preparation, Labeling, Storage, Packaging and Shipment" that reflected changes in laboratory material supplies and names of laboratory contacts.

- Amendment 2 (February 15, 2000): added the exclusion of subjects enrolled in the NETT study, studies involving other tissue sealant materials and subjects participating in any other study without prior sponsor approval. In addition, the amendment expanded the window for screening CXR from 30 days to 45 days and screening spirometry tests from 30 days to 90 days.

- Notice of IDE Change 1 (submitted to the FDA on April 19, 2000): changed the data capture of vital signs, CT drainage and air leakage from "daily morning" to "daily," instructed study sites to use a PM assessment when an AM assessment had been missed and changed the leak assessment from recording the size of ALs (scale of 0-3) to an indication of whether an AL was present or absent.

- Amendment 3 (June 15, 2000); added a two-week follow-up telephone call for subjects who were not scheduled to be seen at a two-week postoperative clinic visit . Amendment 3 received FDA approval on July 19, 2000.

- Addendum to Amendment 3 (June 20, 2000): provided a specific checklist of complaints and symptoms to be used during the follow-up telephone call. Further, the addendum clarified the checklist, described the manner in which any AEs reported from these solicited responses were treated and provided a template for revision of the Consent Form.

Study protocol Version 7 (July 13, 2000) incorporated all of the above changes and was submitted to FDA on July 18, 2000.

6 STUDY RESULTS

6.1 Patient Accountability

Ten investigators at five clinical sites screened and enrolled subjects for participation in this trial. A total of 275 subjects were enrolled and signed informed consent forms. Of the 275, 114 were not randomized, principally because they were not found to have IOALs. One hundred and sixty-one (161) subjects were randomized; 103 subjects were assigned to the Sealant group and

58 subjects were assigned to the Control group. The participating clinical sites and investigators are shown in **Table 2**.

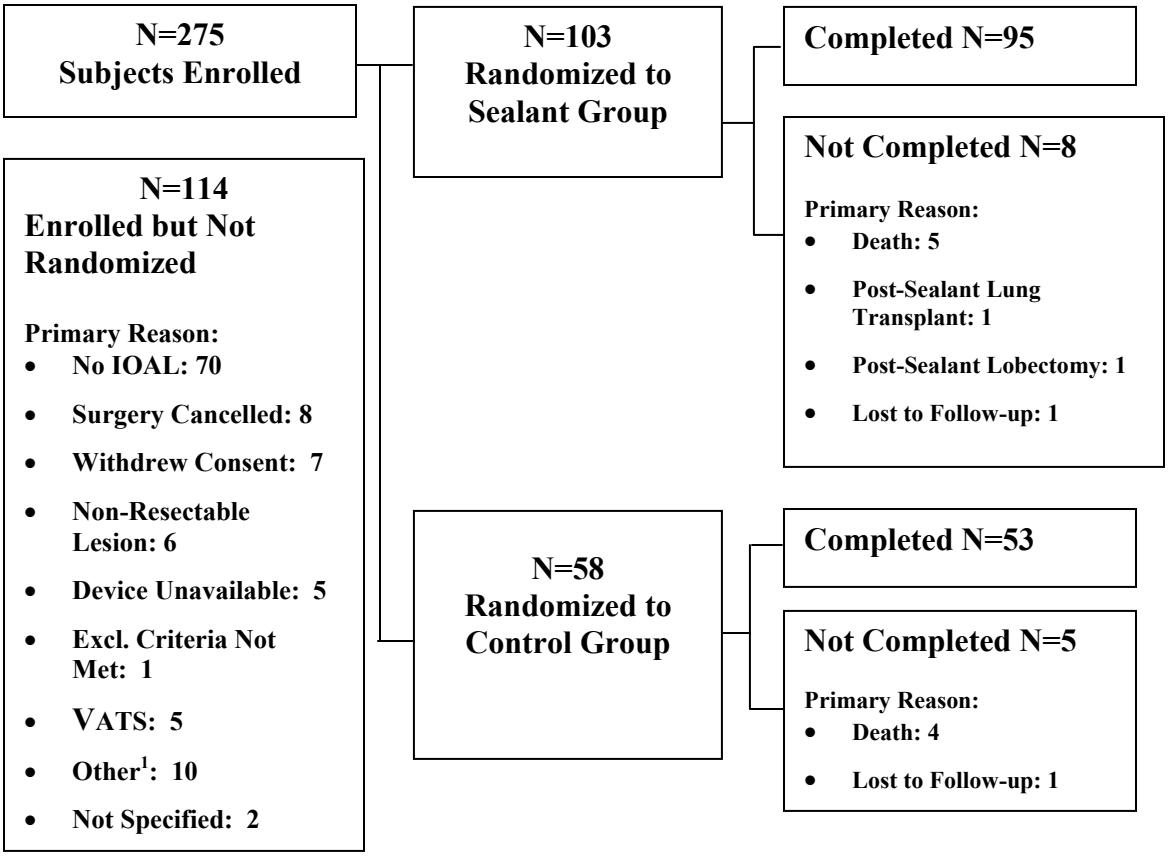
Table 2 Participating Clinical Sites and Investigators

	Clinical Site	Investigator(s)
CSMC	**Cedars-Sinai Medical Center Los Angeles, CA**	Robert J. McKenna, MD
DUMC	**Duke University Medical Center Durham, NC**	R. Duane Davis, Jr. MD
		David H. Harpole, MD
MAYO	**Mayo Clinic Rochester, MN**	Mark S. Allen, MD
		Daniel L. Miller, MD
		Francis C. Nichols III, MD
MDACC	**MD Anderson Cancer Center Houston, TX**	Garrett L. Walsh, MD
		William R. Smythe, MD
UWMC/VA	**University of Washington Medical Center/ VA Medical Center Seattle, WA**	Douglas E. Wood, MD
		Eric Vallieres, MD*

*Dr. Vallieres performed surgeries at University of Washington Medical Center and at the VA Medical Center. His subjects were identified according to where the surgery was performed.

Figure 2 presents overall subject disposition, as well as the reasons for non-randomization. Ninety-five (95) of 103 (92%) subjects in the Sealant group and 53/58 (91%) subjects in the Control group completed the study. The primary reason for not completing the study was subject death in both groups.

Figure 2 Disposition of Subjects and Primary Reasons Subjects Enrolled but Not Randomized



[1]Subject required pneumonectomy (5), surgeon forgot to randomize in surgery (1), subject had pneumothorax (1), study enrollment closed (1), investigator moved to another institution (2).

Table 3 presents the number of subjects randomized by site.

Table 3 Number of Randomized Subjects by Site

Sites	Sealant	Control	Total
CSMC	13	8	21
DUMC	19	8	27
MAYO	36	20	56
MDACC	17	9	26
UWMC/VA	18	13	31
Totals	103	58	161

Table 4 summarizes the days from surgery to the 1MFU visit. Eighty percent (80%) of the Sealant subjects and 78% of the Control subjects had follow-up visits that were at least four weeks post surgery. Of those subjects whose follow-up visit did not occur 4-6 weeks post surgery, logistics (*e.g.*, scheduling issues, traveling arrangements back to the site, etc.) tended to be the cause.

Table 4 Summary of Days From Surgery to 1MFU Visit

Parameter	Range of Response	Sealant Group N = 103	Control Gruup N = 58
Days from Surgery to One Month Follow-up (PODs)	<15	1 (1.0%)	0 (0.0%)
	15-28	13 (12.6%)	7 (12.1%)
	29-42	43 (41.7%)	34 (58.6%)
	43-56	29 (28.2%)	10 (17.2%)
	57-70	6 (5.8%)	0 (0.0%)
	>70	4 (3.9%)	2 (3.4%)
	Missing[1]	7 (6.8%)	5 (8.6%)
	Mean ± SD	41.5 ± 14.4	39.1 ± 14.6
	Median	41.0	36.0
	Minimum	13	20
	Maximum	113	109

[1] Subjects with missing 1MFU information include 9 subjects who died (5 Sealant, 4 Control), 2 loss to follow-up (1 Sealant, 1 Control) and 1 subject (Sealant), with a lung transplant, who was discontinued from the study. One subject in the Sealant group, who had a post-Sealant lobectomy, was followed for one month to collect safety data

Of the 12 subjects missing 1MFU information (7 Sealant; 5 Control), 9 subjects died (5 Sealant; 4 Control) and 1 (Sealant) had a lung transplant and was discontinued from the study. Only two subjects (1 Sealant; 1 Control) could not be accounted for after trying to contact by phone or mail and were considered lost to follow-up.

6.2 Analysis Issues

6.2.1 Protocol Deviations

Protocol departures fell into five broad categories: 1) randomization; 2) stratification; 3) protocol; 4) institutional; and 5) procedural. The details are provided below.

1. Randomization: Five subjects were randomized out of sequence (**Table 5**). It was felt that these discrepancies in the assignment of subjects to treatment were not critical departures to the conduct and interpretation of the study findings. The data from all of these subjects were included in analyses according to the treatment assigned.

Table 5 Randomization Assignments Out of Sequence

Investigator	Subject	Date of Surgery (mm/dd/yr)	Treatment	Explanation
03-01	----------	N/A	None	Subject number was not assigned; logistical error at site.
03-01	-----	--------	Sealant	Subjec----- randomized after subjec----- who had surgery----- -------- randomization envelope included in subject folder in advance of actual surgery.
03-02	-----	---------	Sealant	Subject----- ized after subject----- who had surgery on----- Subject-----was ------led and randomized over the telephone due to the absence of the study coordinator at the time of surgery. The subject number was inadvertently used again at a later date ----------
03-02	-----	--------	Sealant	---- ject was initially randomized by mistake as -------- ---- which had---------- been assigned; subje-- ----- ----- mbered to---------- --inguish this subject from the original----------
04-01	-----	--------	Control	Subject----randomized after subjects-----and ----- who ha----- gery on---- ---

2. Stratification: There were 9 subjects who were randomized using incorrect stratum: 6 subjects had no pulmonary function test performed and 3 had incorrect stratum assigned (**Table 6**). All of the subjects who had missing pulmonary function tests at the preoperative visit were from Mayo Clinic and were randomized using the randomization schedule for the >40% of predicted FEV_1 stratum. All of these subjects were regarded as having healthy lung function and were felt to be appropriately randomized in the correct stratum by the investigators. Three subjects who had % predicted FEV_1<40% were randomized in the >40% stratum in error. There was no randomization error in subjects with % predicted FEV_1>40%.

The primary purpose of stratification based on % predicted FEV_1 was to maintain a balance between the Sealant and Control groups with respect to this potential risk factor. It was not intended that there would be a sufficient number of subjects in the two stratum to perform a subset analysis based on this risk factor. Due to the small number of subjects randomized who had % predicted FEV_1 at or below 40%, the errors in the use of the proper randomization

schedule for the above subjects was not considered critical for interpretation of the study results. Any analysis performed which included % predicted FEV_1 used the calculated value based on the standardized ECCS equations as the estimate for the subject rather than the value recorded on the CRF.

Table 6 Subjects With Incorrect Stratification Assignment

Investigator	Subject	% Predicated FEV_1[1]	Treatment	Deviation/Departure
02-02	-----	36%	Sealant	Subject assigned using the randomization for the >40% stratum
03-01	-----	Missing	Sealant	No baseline FEV_1 tests performed; subject randomized for the >40% stratum group
03-01	-----	Missing	Sealant	No baseline FEV_1 tests performed; subject randomized for the >40% stratum group
03-01	-----	Missing	Sealant	No baseline FEV_1 tests performed; subject randomized for the >40% stratum group
03-01	-----	Missing	Sealant	No baseline FEV_1 tests performed; subject randomized for the >40% stratum group
03-02	-----	Missing	Control	No baseline FEV_1 tests performed; subject randomized for the >40% stratum group
03-02	-----	39%	Sealant	Subject assigned using the randomization for the >40% stratum
03-03	-----	Missing	Sealant	No baseline FEV_1 tests performed; subject randomized for the >40% stratum group
05-12	-----	35%	Control	Subject assigned using the randomization for the >40% stratum

[1]Based on percent predicted FEV_1 reported on the CRF.

3. Protocol: One subject was enrolled but did not have any IOAL ≥2 mm; 1 subject was randomized to the Sealant group but only 1 of 3 IOALs was treated with the Sealant.

4. Institutional: Subjects at two institutions signed consent forms that had been approved by the IRB but were the wrong version date or the wrong IRB format.

5. Procedural: Procedures not performed per protocol (*e.g.*, out-of window, partial blood chemistry/hematology collected) or not done.

None of the departures significantly impact the interpretation and conclusions of the study results.

6.2.2 Analysis Populations

All 161 randomized subjects, 103 Sealant subjects and 58 Control subjects, were included in the analysis of the primary endpoint according to the intent-to-treat principle. **Table 7** lists the 13 subjects who died, discontinued, or were lost to follow-up during the course of the trial.

Table 7 Discontinued Subjects

Investigator	Subject	Date Discontinued	Treatment	Reason
02-01	----------	1/14/00	Sealant	Death
02-01	-----	5/10/00	Sealant	Lung transplant performed, discontinued study
02-02	----------	3/01/01	Sealant	Death
03-02	-----	10/08/00	Sealant	Death (see comment below)
04-02	----------	5/25/00	Sealant	Death
04-02	-----	9/01/00	Sealant	Lobe removed after Sealant application; followed for safety-discontinued (see comment below)
05-02	-----	7/10/00	Sealant	Lost to follow-up
05-12	----------	7/24/00	Sealant	Death
01-01	----------	2/08/00	Control	Death
02-02	----------	3/23/00	Control	Death
03-01	----------	1/16/01	Control	Death
05-01	-----	9/07/00	Control	Death, after hospital discharge, did not return to 1MFU (see comment below)
05-12	----------	11/19/00	Control	Lost to follow-up

Ten of these 13 subjects had documented ALs during their postoperative---------- tion---------- e considered "treatment failures" for the primary endpoint. Subjects---------- and---------- in the Sealant group did not have any POAL documentation prior to their discontin---------- the study while in the hospital; both subjects ---------- ered "treatment failures" for the purposes of the primary endpoint analysis. Subject---------- in the Control group remained air leak free du---------- ays of hospitalization following surgery. He was discharged from the hospital on---------- and died on---------- without completing his 1MFU visit. Since there was no AL during hospitalization and no indication that the subject had an AL following discharge from the hospital, he was considered a "treatment success" in the analysis of the primary endpoint.

The number of subjects who discontinued from the study was comparable between the Sealant (8/103; 7.8%) and Control group (5/58; 8.6%). Since all subjects were included in the intent-to-treat analysis, and all but three subjects actually reached the study endpoint prior to discontinuing from the trial, no additional subset analyses of the discontinued subjects were performed.

6.3 Demographic and Other Baseline Characteristics

6.3.1 Demographic Characteristics

Table 8 provides a summary of demographic characteristics. Almost two-thirds of the patients were males and the mean age was about 64 years. There were no statistically significant differences between treatment groups.

Table 8 Demographic Characteristics

Demographic Characteristic		Sealant N=103	Control N=58	P-value[1]
Gender	Male	66 (64.1%)	36 (62.1%)	0.865
	Female	37 (35.9%)	22 (37.9%)	
Age (years)	Mean ± SD	63.6 ± 13.6	65.9 ± 11.1	0.567
	Median	67	67	
	Minimum	18	42	
	Maximum	86	85	

[1] P-value associated with Witcoxon Rank Sum Test comparing Sealant and Control groups or Fisher's Exact Test for categorical data

6.3.2 Medical History and Clinical Risk Factors

Table 9 presents a summary of subjects' medical history and clinically important risk factors. Subjects in both the Sealant and Control groups were similar with respect to medical history and clinical risk factors.

Table 9 Medical History and Clinical Risk Factors

Risk Factor	Sealant N=103	Control N=58	P-value[1]
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	
Median	50.0	40.5	
Minimum	1	1	

Risk Factor	Sealant N=103	Control N=58	P-value[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%)	

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

6.3.3 Pulmonary Function Test

Table 10 presents the results of preoperative pulmonary function testing. Subjects in the Sealant and Control groups were similar with respect to their pulmonary function tests results. Most subjects (>90%) in both groups had % predicted FEV_1 values >40%. The % predicted FEV_1 values were determined at each site for each subject. To standardize across sites, the % predicted FEV_1 values were also calculated using the ECCS prediction equations and these values were used for statistical analyses.

Table 10 Preoperative Pulmonary Function Test Results

Parameter	Response	Sealant	Control	P-Value[1]
FEV_1 (liter/1 second)	N	98	57	0.669
	Mean ± SD	2.27 ± 0.70	2.33 ± 0.87	
	Minimum	0.56	0.81	
	Maximum	4.32	4.60	
FEV_1 (% predicted[2])	N	97	56	0.217
	Mean ± SD	80.5 ± 23.0	84.6 ± 21.8	
	Minimum	16.9	36.2	
	Maximum	155.7	121.1	
FEV_1 (% predicted[2])	≤40%	3 (2.9%)	3 (5.2%)	0.669
	>40%	94 (91.3%)	53 (91.4%)	
	Missing	6 (5.8%)	2 (3.4%)	
FEV_1 (% predicted[3])	≤40%	5 (4.9%)	4 (6.9%)	0.726
	>40%	93 (90.3%)	53 (91.4%)	
	Missing	5 (4.9%)	1 (1.7%)	

Parameter	Response	Sealant	Control	P-Value[1]
FVC (liter)	N	98	57	0.703
	Mean ± SD	3.29 ± 0.83	3.34 ± 1.01	
	Minimum	1.29	1.59	
	Maximum	5.30	6.05	
FVC (% predicted[2])	N	97	56	0.120
	Mean ± SD	92.2 ± 19.8	96.8 ± 17.0	
	Minimum	39.1	52.2	
	Maximum	152.2	133.9	
FEV_1/FVC	N	98	57	0.938
	Mean ± SD	0.69 ± 0.13	0.69 ± 0.12	
	Minimum	0.22	0.32	
	Maximum	0.99	0.88	

[1] Wilcoxon rank sum test or Fisher's exact test.
[2] Predicted value based on the ECCS prediction equations for %predicted FEV_1 and FVC.
[3] Predicted value based on information recorded on CRF.

6.3.4 Primary Diagnosis

Table 11 presents a summary of primary diagnoses. The primary diagnoses for surgery in both the Sealant and Control groups were primary tumor, followed by metastatic tumor. The distribution of primary diagnoses was similar between groups.

Table 11 Primary Diagnoses

Parameter	Response	Sealant N=103	Control N=58	P-Value[1]
Primary Diagnosis	**Primary Tumor**	70 (68.0%)	42 (72.4%)	0.620
	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%)	

[1] Fisher's Exact Test.

6.3.5 Concomitant Medications

All medications taken by subjects during the study were recorded. The number and percent of subjects using each medication was grouped by generic name and drug class using the drug dictionary established by 3M Pharmaceuticals. No statistical analyses were performed to compare the groups with regard to the use of concomitant medications.

6.4 Operative Characteristics

6.4.1 Operative Summary

Table 12 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 12 Operative Summary

Parameter	Response	Sealant N=103	Control N=58	P-Value[1]
Types of Surgery	**Bilobectomy**	4 (3.9%)	1 (1.7%)	0.883
	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%)	0.269
	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%)	0.201
	Complete	43 (41.7%)	32 (56.1%)	
	Not Done	30 (29.1%)	11 (19.3%)	
Pleural Adhesions	**Yes**	53 (51.5%)	30 (51.7%)	0.597
	No	49 (47.6%)	27 (46.6%)	
	Missing	1 (1.0%)	1 (1.7%)	
Extent of Adhesions[2]	**Minimal**	28 (52.8%)	14 (46.7%)	0.815
	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%)	0.141
	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	0.428
	Median	225.5	225.5	
	Minimum	115	145	
	Maximum	455	430	

Parameter	Response	Sealant N=103	Control N=58	P-Value[1]
Time to Skin Closure	**N**	91	50	
(min)	**Mean ± SD**	156.8 ± 54.9	165.0 ± 62.6	0.702
	Median	151.0	143.5	
	Minimum	52	81	
	Maximum	355	387	

[1] Wilcoxon rank sum test or Fisher's exact test.
[2] Percents based on the number of subjects who had pleural adhesions rated at the time of surgery.

6.4.2 IOAL Characterization Summary

Table 13 presents the number of IOALs per subject. A total of 318 individual ALs were tracked: 210 in the Sealant group and 108 in the Control group. The proportion of subjects with 2 or more IOALs before intervention was significantly higher in the Sealant group (68%) than in the Control group (48%).

Table 13 Number of IOALs per Subject Prior to Treatment/Closure

Parameter		Sealant N (%)	Control N (%)	P-value[1]
Total No. of Subjects		103	58	
Total No. of IOALs		210	108	
No. of IOALs/Subject	**1**	33 (32.0%)	30 (51.7%)	0.0051
	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%)	
	Mean ± SD	3.0 ± 9.7	2.0 ± 1.4	0.1345
	Median	2.0	1.0	
	Minimum	1	1	
	Maximum	100	7	

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

The numbers, locations and sources of IOALs were evaluated to determine if certain locations or sources had more IOALs than others. The most frequent sources of IOALs were fissures, followed by staple line, torn lung, adhesions, suture line, and blebs (**Table 14**). There was no significant difference between the Sealant and Control groups with respect to source of IOALs.

Table 14 Source of IOALs

Source of IOALs	Sealant N=210	Control N=108
Suture Line	11 (5.2%)	8 (7.4%)
Bleb	6 (2.9%)	1 (0.9%)
Torn Lung	30 (14.3%)	14 (13.0%)
Staple Line	50 (23.8%)	23 (21.3%)
Adhesion	11 (5.2%)	10 (9.3%)
Fissure	97 (46.2%)	44 (40.7%)
Other	5 (2.4%)	3 (2.8%)
Missing	0 (0.0%)	5 (4.6%)

Prior to randomization, investigators reported using sutures and/or staples to close 51% of IOALs in the Sealant group and 56% of IOALs in the Control group. There was no significant difference between the two groups (p=0.478).

6.4.3 Sealant Treatment

Investigators were required to apply Sealant to all IOALs. In addition, they were to use no more than 3 applications of Sealant per IOAL.

Table 15 presents the number of Sealant applications used per IOAL. Investigators used one application of Sealant to treat the majority of IOALs.

Table 15 Sealant Applications

Number of Sealant Applications	Sealant N=210
1	125 (59.5%)
2	70 (33.3%)
3	9 (4.3%)
N/A[1]	2 (1.0%)
Missing	4 (1.9%)

[1] One subject in the Sealant group had 3 IOALs; however, the Sealant was only applied to one of the three IOALs; 2 IOALs had no Sealant applied.

6.4.3.1 Extent of Exposure

Table 16 presents a description of the amount of Sealant used per subject and the total application time per subject. The mean number of units used was 2.5 (2 ml/unit) per subject. The mean total volume of Sealant used was 4.8 ml/subject. The minimum number of units used per subject was 1 (2 ml); the maximum was 15 (30 ml). The average time to assemble and use

one unit of Sealant (mean application time) was relatively short, 3.3 minutes, and the mean total application time/subject was 7.9 minutes.

Table 16 Description of Tissue Sealant Use

Parameter	Response	Sealant
Number of Units Used/Subject (N=103)	**Mean ± SD**	2.5 ± 1.8
	Median	2.0
	Minimum	1
	Maximum	15[1]
Time (minutes) of Application/Unit (N=220)	**Mean ± SD**	3.3 ± 4.7
	Median	2.0
	Minimum	1
	Maximum	53[2]
Total Application Time (minutes)/Subject (N=93)	**Mean ± SD**	7.9 ± 8.4
	Median	6.0
	Minimum	1
	Maximum	63[3]
Total Volume (ml) Used/Subject (N=101)	**Mean ± SD**	4.8 ± 3.6
	Median	4.0
	Minimum	2
	Maximum	30

[1] Only 1 of 103 Subjects had more than 10 units
[2] Only 4 of 220 Applications took longer than 10 minutes/Unit
[3] Only 10 of 93 Applications took longer than 15 minutes/Subject

6.4.3.2 Out of Specification Sealant

During the study, the initial lot of Sealant failed to pass one of the product specifications during ongoing shelf life testing. At that point, it was decided to retrieve that lot from the clinical sites and replace it with a new clinical lot of Sealant material. Since the exact date at which the Sealant material fell out of specification could not be determined, any subjects enrolled during the study between the last test point when the lot was within specification limits (March 29, 2000) and the first test point when it was out of specification (May 11, 2000) were identified. There were a total of 23 (18 Sealant and 5 Control) subjects who were enrolled in the study during this period. No product-related adverse events were suspected to have occurred due to use of this out-of-specification product. The efficacy endpoints were not significantly different during the time when the lot of Sealant material was possibly out of specification.

6.5 Efficacy Evaluations

6.5.1 Primary Efficacy Endpoint

Table 17 presents a summary of the primary efficacy endpoint result. The percentage of subjects who remained air leak-free following surgery through the 1MFU visit was significantly greater (p=0.005) in the Sealant group 36/103 (35%) compared with the Control group 8/58 (14%).

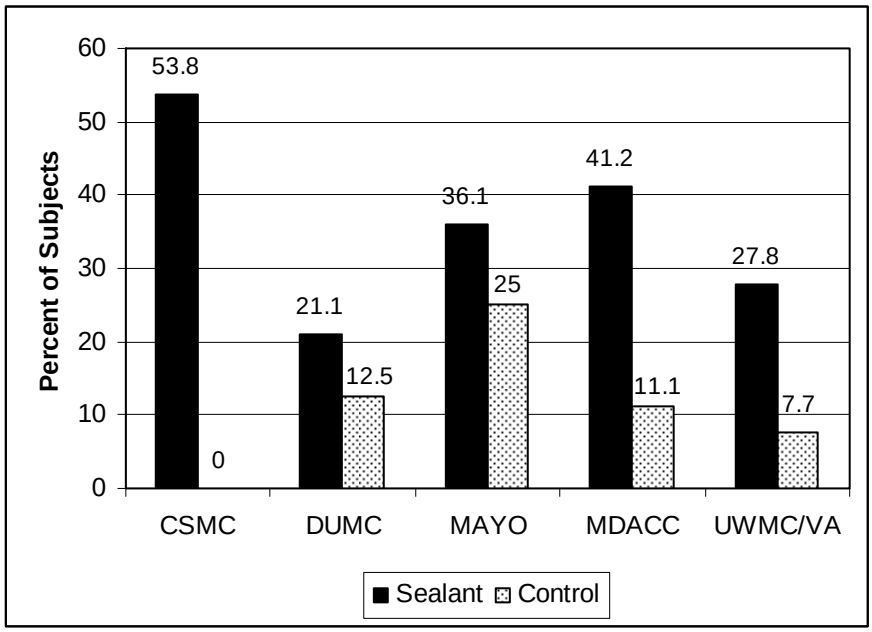
Table 17 Summary of POALs

	Response	Sealant N=103	Control N=58	P-value[1]
AL Endpoint	**No POAL**	36 (35.0%)	8 (13.8%)	0.005
	With POAL	67 (65.0%)	50 (86.2%)	

[1]Logistic regression analysis was used for the primary endpoint analysis.

Figure 3 presents success (AL free at 1MFU) by site and treatment group. All sites showed higher success with the Sealant compared to the Control. The results for CSMC, while appearing to be quite different, are in part due to CSMC being the only site with only one investigator. Also, the investigator at this site is probably the most experienced in the use of sealants for pulmonary resection surgery. When comparing his results to other individual investigators (see **Section 6.5.4.1**), they do not appear unusual.

Figure 3 Success by Site and Treatment Group



6.5.2 Prognostic Variables for POALs

As part of the statistical analysis plan, a stepwise logistic regression analysis was performed primarily to evaluate the effect of treatment (Sealant vs. Control) on the primary endpoint after adjusting for other potential prognostic variables. The covariates included in the analysis were treatment, age, gender, % predicted FEV_1, any medical risk factor present in at least 10% of both the Sealant and Control groups, number of IOALs identified, maximum AL size of any IOAL, presence of pleural adhesions, and lymphadenectomy status.

The stepwise logistic regression model was used to evaluate the effect of the covariates. The term for treatment was included in the model at the initial step and remained in the analysis for all subsequent steps. The significance level for a covariate to enter into the model was set at p=0.15, while the significance level for removing a covariate from the model was set at p=0.25. The interaction term with treatment was considered for inclusion in the logistic model if the main effect term for a covariate was entered.

The stepwise procedure selected treatment group (p=0.001), number of IOAL leaks (p=0.064), presence of pleural adhesions (p=0.103), hypertension (p=0.083), and history of smoking (p=0.056) as the most important prognostic variables for remaining air leak free from surgery through 1MFU. The results of the final model are shown in **Table 18**.

Table 18 Results of Stepwise Logistic Regression Analysis on the Likelihood of Remaining Air Leak Free Following Lung Surgery

Variable	Odds Ratio (95% CI) (Sealant vs. Control)	P-value
Intercept	-	0.003
Treatment group (Sealant vs. Control)	5.03 (1.88, 13.4)	0.001
Pleural adhesions (Yes vs. No)	0.51 (0.23, 1.15)	0.103
No. of IOALs (2 vs. 1)	0.76 (0.31, 1.88)	0.303
No. of IOALs (≥3 vs. 1)	0.23 (0.07, 0.79)	0.023
Hypertension (Yes vs. No)	2.07 (0.91, 4.69)	0.083
Hx of Smoking (Current/Past vs. None)	0.37 (0.14, 1.02)	0.056

Importantly, Sealant treatment was associated with a significantly higher odds of remaining air leak free postoperatively through 1MFU compared to the Control group even after adjusting for the effects of these other prognostic variables (odds ratio (OR)=5.03; 95% confidence interval (CI)=1.88 to 13.43). More IOALs was associated with a lower odds of remaining air leak free post-surgery. This was especially true when comparing subjects with 3 or more IOALs identified during surgery to those with only one IOAL identified (OR=0.23; 95% CI=0.07 to 0.79). There were also trends detected in the analysis that did not reach statistical significance which included higher odds of success with no history of smoking, absence of pleural adhesions, and presence of hypertension. **Table 19** summarizes the percent of subjects without POALs in each group according to the prognostic variables identified in the stepwise logistic regression analysis.

Table 19 Percent of Subjects without POALs According to Prognostic Variables Identified in Stepwise Logistic Regression Model

Variable	Response	Sealant		Control	
		n / N	%	n / N	%
No. of IOALs	1	16/33	48%	6/30	20%
	2	16/46	35%	2/14	14%
	≥3	4/24	17%	0/14	0%
Pleural adhesions	Yes	15/53	38%	2/30	7%
	No	21/49	43%	5/27	19%
Hypertension	Present	17/40	43%	5/26	19%
	Absent	19/63	30%	3/32	9%
Hx of Smoking	Current / Past	25/83	30%	6/47	13%
	None	11/20	55%	2/11	18%

6.5.3 Secondary Efficacy Endpoints

6.5.3.1 IOAL Assessment

Table 20 presents a summary of IOALs sealed. Of 210 individual IOALs tracked in the Sealant group, 77% were sealed in the Sealant group 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 the Sealant and Control groups were statistically significant ($p<0.001$).

Table 20 IOAL Closure Summary

Parameter	Response	Sealant	Control	P-value[1]
Sealed IOAL/Individual AL	N	210	108	<0.001
	No IOAL	161 (76.7%)	17 (15.7%)	
	<2 mm	23 (11.0%)	13 (12.0%)	
	2-5 mm	21 (10.0%)	60 (55.6%)	
	>5 mm	5 (2.4%)	17 (15.7%)	
	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%)	

[1] Fisher's exact test.

Table 21 presents the number of IOALs sealed or reduced, by initial size and treatment group; in the table "Reduced" includes those IOALs that were also sealed. As shown, the use of Sealant and the size of the initial IOAL were significantly associated with the proportion of sealed

IOALs. Of the small to medium sized ALs (≤5 mm), 84% (128/152) sealed in the Sealant group as compared to 17% (12/71) in the Control group. Of the IOALs >5 mm, 58% (33/57) were sealed in the Sealant group as compared to 14% (5/37) in the Control group.

Table 21 IOALs Sealed or Reduced by AL Size and Treatment

	Sealant			Control		
IOAL Size	**Number of IOALs**	**Reduced N (%)**	**Sealed N (%)**	**Number of IOALs**	**Reduced N (%)**	**Sealed N (%)**
<2 mm	20	16 (80%)	16 (80%)	5	1 (20%)	1 (20%)
2–5 mm	132	124 (94%)	112 (85%)	66	18 (27%)	11 (17%)
>5 mm	57	52 (91%)	33 (58%)	37	21 (57%)	5 (14%)

Additionally, as shown in **Table 22**, the Sealant, when used alone (*i.e.*, without suture/staples), sealed or reduced the size of IOALs 93% of the time (96/103). When used as an adjunct to standard closure methods, the Sealant reduced the size of IOALs 91% (96/106) of the time as compared to 58% (35/60) in the Control group. The interaction between Sealant and other closure methods was significant. This interaction was primarily due to the increase in the proportion of reduced IOALs observed in the control group where sutures/staples were used. The benefits of using the Sealant were more evident in those situations where no other closure method was used.

Table 22 IOALs Sealed or Reduced by Whether Suture/Staples Were Used

	Sealant			Control		
IOAL Size	**Number of IOALs**	**Reduced N (%)**	**Sealed N (%)**	**Number of IOALs**	**Reduced N (%)**	**Sealed N (%)**
IOALs: Without Suture/Staples						
<2 mm	17	13 (76%)	13 (76%)	3	0 (0%)	0 (0%)
2–5 mm	78	75 (96%)	67 (83%)	38	4 (11%)	2 (5%)
>5 mm	8	8 (100%)	8 (100%)	7	1 (14%)	0 (0%)
Total	**103**	**96 (93%)**	**88 (85%)**	**48**	**5 (10%)**	**2 (4%)**
IOALs: With Suture/Staples						
<2 mm	3	3 (100%)	3 (100%)	2	1 (50%)	1 (50%)
2–5 mm	54	49 (91%)	45 (83%)	28	14 (50%)	9 (32%)
>5 mm	49	44 (90%)	25 (51%)	30	20 (67%)	5 (17%)
Total	**106**	**96 (91%)**	**73 (69%)**	**60**	**35 (58%)**	**15 (25%)**

Table 23 presents a summary of the IOALs sealed by the source of the AL. A Cochran-Mantel-Haenszel Test stratifying the individual IOALs based on their source was performed. The results indicated that the Sealant was still significantly associated with a higher proportion of sealed IOALs (p=0.0001) after stratification based on source of AL.

Table 23 Summary of IOALs Sealed by Source of AL

Source of AL	IOAL Success			
	Sealant		Control	
	n/N	%	n/N	%
Torn Lung	12/30	40%	3/14	21%
Staple Line	44/50	88%	7/23	30%
Adhesions	6/11	55%	1/10	10%
Fissure	79/97	81%	3/43	7%
Other[1]	20/22	91%	3/12	25%

[1] Includes suture line, bleb, and other.

The results also indicated that IOALs associated with torn lung were more difficult to seal with the Sealant than other sources of IOALs, but that Sealant was still more effective than control for subjects with torn lung. However, leaks associated with torn lung tended to be larger; they are typically deeper within the lung parencyhma, with larger airways. Thus, the lower success in torn lung may be a reflection of IOAL size and not IOAL source. As shown in **Table 24**, 67% and 93% of the IOALs originated from torn lung were >5 mm in size in the Sealant and Control group, respectively.

Table 24 Percent of IOALs >5 mm in Size

Source of IOAL = N	Sealant n/N (%)	Control n/N (%)
Torn Lung	20/30 (67%)	13/14 (93%)
Staple Line	12/49 (24%)	6/23 (26%)
Adhesion	0/11 (0%)	4/10 (40%)
Fissure	20/97 (21%)	5/44 (11%)
Other	5/22 (23%)	5/12 (42%)

6.5.3.2 Recovery Room POAL Assessment

Table 25 presents a summary of ALs observed in the recovery room. Following surgery, subjects were transferred to the recovery room where CTs were placed on suction and the subjects' air leakage was determined by observing air bubbles from the CT drainage system.

A significantly greater number of Sealant subjects were air leak free at the recovery room observation period compared to Control subjects (p=0.002). No ALs were observed in 54% of subjects in the Sealant group compared with 33% of subjects in the Control group.

Table 25 Summary of POALs in the Recovery Room

Observation Period	Response	Sealant N=103	Control N=58	P-value[1]
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%)	3 (5.2%)	
	Missing	2 (1.9%)	0 (0.0%)	

[1] Fisher's Exact Test.

6.5.3.3 Duration of POALs

Each subject was required to have an IOAL in order to be randomized into the study. Those subjects who had an AL identified intraoperatively which was subsequently sealed and remained sealed throughout the 1MFU period were assigned an arbitrary value of 0.5 days for the duration of their air leaks. The duration of the AL for all other subjects who had ALs that occurred during the postoperative period was determined by the last POD on which the AL was noted. In those subjects who had their CT removed before a recording of the absence of AL, it was assumed that the CT was removed because there was no AL pre----------e day of the CT removal was taken as the end of the AL. There was one subject---------- in the Sealant group with a pneumothorax which developed 3 weeks after surg----------ired hospitalization. For this subject, the duration of AL included in the analysis was 29 days, corresponding to the resolution of this event and discharge from the hospital. This subject was also counted as having a late AL.

There were a few subjects for whom the duration of the AL could not be determined because no end to the AL was documented. A survival analysis using a log rank test for time to the end of AL was performed to included these subjects in the analysis. In the survival analysis, the duration of AL for these subjects was considered censored observations at the time that they were discontinued from the study. The censored duration of AL assigned for these subjects are listed in **Table 26**. One subject----------in the Sealant group whose status with regard to POALs was not reported. This ---------- lobectomy following the initial surgery and was excluded from the analyses of duration of POALs.

Table 26 Subjects With Censored Results for Air Leak Duration

Investigator	Subject	Treatment	Explanation
01-01	-----	Control	Subject died prior to end of AL, censored data at 20 days
02-01	-----	Sealant	Subject died prior to end of AL, censored data at 3 days
03-01	-----	Control	Subject died on day of surgery, censored data at 1 day

As shown in **Table 27**, the duration of POALs was comparable for both treatment and control groups with the majority of POALs lasting less than three days (the median duration was two days in both groups). Comparison of the duration of ALs between the Sealant and Control

groups was performed using both the Wilcoxon rank sum test and a log rank test. Neither analysis showed a statistically significant difference between groups with respect to duration of ALs (p=0.410 and 0.816, respectively). Nevertheless, it should be noted that 43 (42%) of Sealant subjects had no ALs after discharge from the recovery room compared to only 15 (26%) Control subjects (**Figure 4**).

There were more patients in the Sealant group than the Control group with POAL >11 days (13 Sealant vs. 3 Control). This difference is directly impacted by the use of Heimlich valves (HV) and the method by which the cessation of an AL for these patients was calculated. The leak duration for subjects who were discharged from the hospital with a HV was determined from initial onset of the AL to the time when the valve was removed; it was a conservative estimate of the duration of POALs for such patients, since they were assessed on a weekly, rather than daily basis, after they were discharged with a HV.

In this study, the study investigators were permitted to consider the use of a HV if the study subject had a persistent AL with minimal drainage, and no other significant clinical events to preclude discharging them from the hospital. The use of HV could have affected the mean duration of POALs in either study group. As noted above, subjects discharged with an HV had their AL status assessed on a weekly basis, as compared with a daily basis for hospitalized subjects without an HV, and AL duration was calculated to the first time point at which a POAL was not detected. There were ten (10%) subjects in the Sealant group and one (2%) subject in the Control group who were discharged from the hospital with a HV (p=0.099). As a consequence, AL duration could have been biased toward a longer time period in the Sealant group which had the larger percentage of HV use. However, even if it were assumed that the AL terminated one day after discharge from the hospital with a HV, the difference in duration of POALs would not be significantly different between the Sealant and Control groups. Furthermore, 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. A more complete discussion of patients received HV at discharge can be found in **Section 6.5.4.2.**

Table 27 Summary of POAL Duration

Duration of POAL (Days)	Sealant N=103	Control N=58	P-value[2]
0-2	54 (52.4%)	29 (50.0%)	0.410
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.
[1] Wilcoxon rank sum test using all available data.

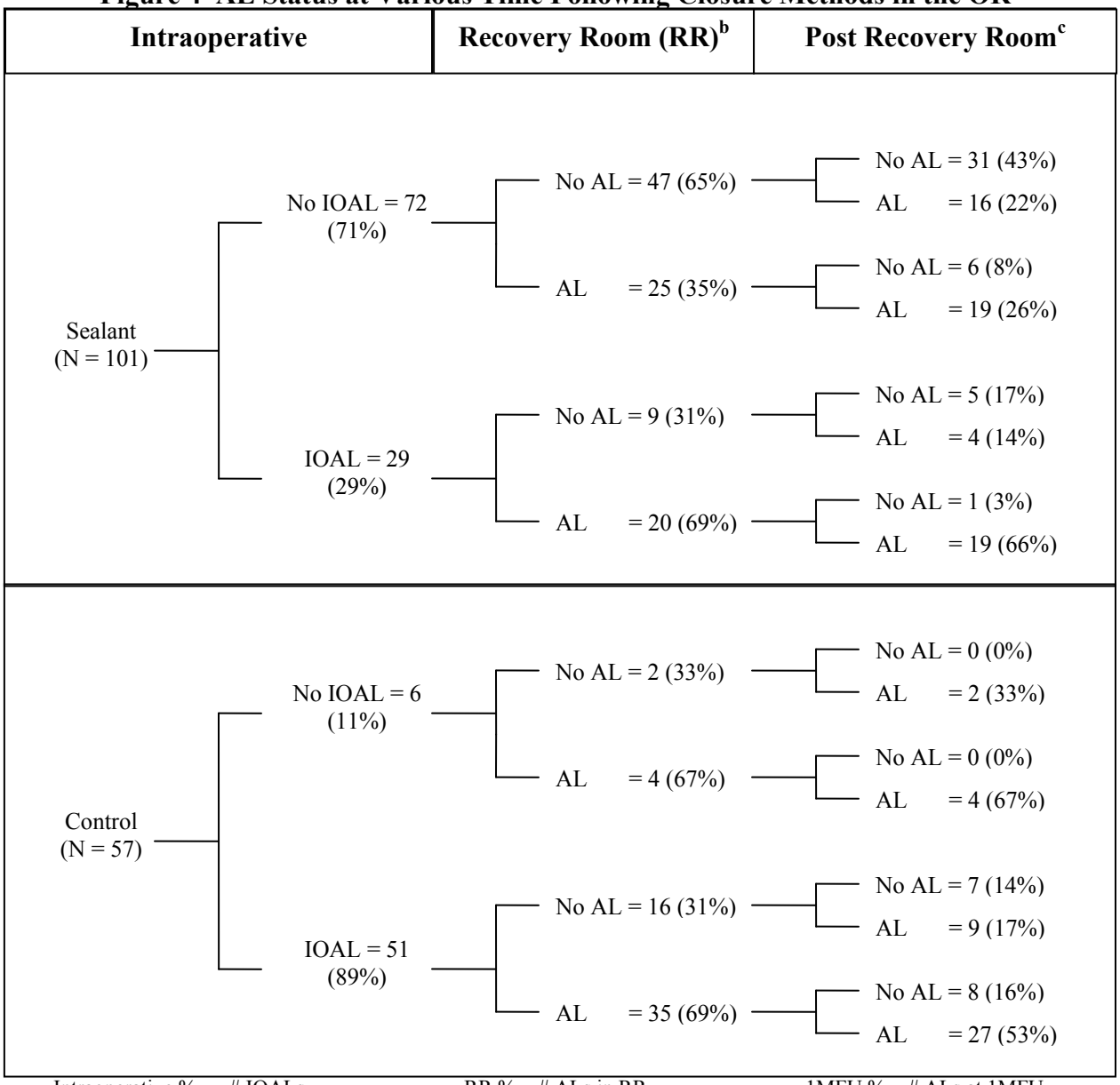
Additional analyses were performed to examine the occurrence of late ALs and prolonged AL. A late AL was defined as an AL that first occurred on or after POD2. A prolonged AL was defined as any AL that was present in the recovery room or on POD1 that was still present after POD7. There was no statistically significant between group difference in the occurrence of late ALs: 8% (8/102) of the Sealant subjects and 2% (1/58) of the Control subjects had late ALs (p=0.157). The incidence of prolonged ALs was also shown to be similar between groups: 14% (14/102) of the subjects in the Sealant group and 12% (7/58) of the subjects in the Control group had prolonged ALs (p=0.813).

6.5.3.4 Relationship of Postoperative Success to IOAL Closure

Figure 4 presents AL status at various times following application of closure methods in the operating room (OR). Of the 72 subjects in the Sealant group who did not have any IOALs on their final air leak test, 31 (43%) were treatment successes and remained air leak-free through 1MFU. Of the 6 subjects in the Control group who did not have any IOALs on their final air leak test, none (0%) remained air leak-free following surgery through 1MFU.

Of the 29 subjects in the Sealant group who had an IOAL remaining in the OR, 5 (17%) did not have any subsequent AL in the recovery room or during the postoperative period. The results in the Control group were similar with 7/51 subjects (14%).

Figure 4 AL Status at Various Time Following Closure Methods in the OR[a]



Intraoperative % = # IOALs / # ALs/group RR % = # ALs in RR / # ALs in OR 1MFU % = # ALs at 1MFU / ALs in OR

a AL status in recovery room was missing for two subjects in the Sealant group and and missing for final intraoperative assessmend for one subject in the Control group (03-01-2120). These are noted in the table.

b Subjects with ALs in recovery room were considered "FAILURES."

c No ALs at 1MFU.

6.5.3.5 Duration of CT Placement

Table 28 presents a summary of the duration of CT placement. With the exception of the placement duration of >11 days (which was impacted by the greater number of Heimlich valves used in the Sealant group in the same manner as the determination of the duration of POALs), it can be observed that the duration of CT placement was similar for both treatment groups. The median duration of CT placement for both groups was five days. Further, 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. A more complete discussion of patients received HV at discharge can be found in **Section 6.5.4.2.**

Table 28 Summary of Duration of CT Placement

Duration of CT Placement (Days)	Sealant N=103	Control N=58	P-value[1]
0-2	2 (1.9%)	0 (0.0%)	0.679
3-4	34 (33.0%)	19 (32.8%)	
5-6	37 (35.9%)	21 (36.2%)	
7-9	11 (10.7%)	9 (15.5%)	
10-11	3 (2.9%)	3 (5.2%)	
> 11[2]	13 (12.6%)	3 (5.2%)	
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	

[1] Wilcoxon rank sum test using all available data.
[2] Includes 9 subjects in the Sealant group and 1 subject in the Control group discharged from the hospital with a Heimlich valve.

There were 6 subjects (3 Sealant, 3 Control) for whom the duration of the CT placement could not be determined because no removal of CT was documented. A survival analysis using a log rank test for time to CT removal was performed to included these subjects in the analysis as censored observations. The results of the survival analysis were consistent with the analysis using all available data. The Kaplan-Meier estimate of median time to CT removal was 5 days in both groups; the difference in time to CT removal was not statistically significant between groups (log rank p=0.896).

6.5.3.6 CT Drainage

Table 29 presents CT drainage (cc/24 hours) from POD1 through CT removal. The median cumulative drainage was less for the Sealant group (960 cc) than the Control group (1360 cc); however, the difference was not statistically significant (p=0.117).

Table 29 Cumulative CT Drainage From POD1 Through CT Removal

Cumulative Drainage (cc)	Sealant	Control	P-value[1]
N	99	53	
Mean ± SD	1322 ± 974	1533 ± 889	0.117
Median	960	1360	

[1]Wilcoxon rank sum test.

6.5.3.7 Length of Hospital Stay

Table 30 presents the length of hospital stay (LOS). The LOS was significantly shorter for subjects in the Sealant group compared with subjects in the Control group (p=0.028). The median LOS was 6 days and 7 days for the Sealant and Control group, respectively.

Table 30 Summary of Length of Hospital Stay

Duration of Hospital Stay (Days)	Sealant N=103	Control N=58	P-value[1]
3-4	11 (10.7%)	4 (6.9%)	0.028
5-6	49 (47.6%)	23 (39.7%)	
7-9	22 (21.4%)	16 (27.6%)	
10-11	7 (6.8%)	5 (8.6%)	
> 11	9 (8.7%)	7 (12.1%)	
Missing	5 (4.9%)	3 (5.2%)	
N	98	55	
Mean ± SD	7.1 ± 3.4	8.6 ± 5.6	
Median	6.0	7.0	
Minimum	3	4	
Maximum	23	38	

[1]Wilcoxon rank sum test using all available data.

There were 8 subjects (5 Sealant, 3 Control) for whom length of stay could not be determined because no discharge was documented. A survival analysis using a log rank test for time to discharge was performed to included these subjects in the analysis as censored observations. The estimated median LOS for the two groups did not change using the Kaplan-Meier method and the difference remained statistically significant (log rank p=0.0413).

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 regardless whether or not patients were discharged with a Heimlich Valve (**Table 31**). A more complete discussion of patients received HV at discharge can be found in **Section 6.5.4.2.**

Table 31 Length of Hospital Stay by Use of Heimlich Valve at Discharge

Duration of Hospital Stay (Days)	Sealant	Control	P-value[1]
No HV at Discharge			
N	88	54	0.011
Mean ± SD	6.8 ± 3.3	8.5 ± 5.6	
Median	6.0	6.5	
HV at Discharge			
N	10	1	0.45
Mean ± SD	9.6 ± 4.1	12	
Median	9	12	

[1]Wilcoxon rank sum test using all available data.

A higher percent of Control subjects had extended hospital stay compared with Sealant patients. There were a total of 27 (17%) subjects with LOS >10 days: 14 (14%) in the Sealant group and 13 (22%) in the Control group. Prolonged ALs that resulted in LOS >10 days occurred in 5% (5/103) of the Sealant subjects and 3% (2/58) of the Control subjects. Other complications that led to LOS >10 days occurred in 9% (9/103) of the Sealant subjects and 19% (11/58) of the Control subjects. The most frequent such complication was pneumonia, with 2 in the Sealant group and 6 in the Control group. The frequency of other complications appears to be comparable. The higher frequency of pneumonia in the Control group than Sealant group may partially explain the increase in LOS in the Control group. A listing of subjects with extended hospital stay is presented in **Table 32**.

Table 32 Details on Subjects With Hospital Stays Greater Than 10 Days

Treatment	Subject ID	LOS (days)	Duration of CT (days)	Duration of AL (days)	Reason(s) for Extended Hospital Stay
Sealant	----------	13	11	8	Pneumothorax, subcutaneous. Emphysema, hypotension, anemia
Sealant	----------	28	10	5	Respiration distress, hepatic failure, pulmonary edema, acidosis, hematuria, death
Sealant	----------	14	13	13	Prolonged air leak
Sealant	----------	17	6	3	Atrial fibrillation
Sealant	----------	11	11	9	Chest wall pain, SOC, air leak
Sealant	----------	14	14	13	Fever, pain nausea, air leak
Sealant	----------	16	19*	19*	Transient hypotension, dizziness, air leak
Sealant	----------	29	16	15	Bilateral pneumonia, small bowel obstruction, death
Sealant	----------	17	42*	42*	Pneumonia, RLE claudication, hyponutremia
Sealant	----------	18	15	9	Subcutaneous emphysema, wound infection
Sealant	----------	11	7	5	Hypoxic event, cardiac arrest, anoxic encephalopathy, respiratory arrest, bilateral pleural effusions & atelectasis, death

Treatment	Subject ID	LOS (days)	Duration of CT (days)	Duration of AL (days)	Reason(s) for Extended Hospital Stay
Sealant	----------	12	6	5	Atrial fibrilation[1]
Sealant	----------	11	22*	22*	Air leak
Sealant	----------	11	10	7	Atrial flutter
Control	----------	20	20	20	Pneumonia, severe respiratory metabolic acidosis, MRSA in blood, death
Control	----------	38	10	10	Pneumonia, ARDS
Control	----------	23	13	11	Respiratory distress secondary pneumonia, renal failure, organ failure, death
Control	----------	23	11	6	Thrombocytopenia; elevated creatinine
Control	----------	12	22*	22*	Fluid on lung, reaction to Zithromax
Control	----------	19	18	16	Prolonged air leak, fever, constipation
Control	----------	11	8	None	Pain
Control	----------	11	7	5	Confusion, atrial fib, fever
Control	----------	11	4	2	Pneumonia, confusion, atrial fib, anemia, fever
Control	----------	16	10	9	Pneumonia, tachycardia, subq. Emphysema
Control	----------	14	13	9	Prolonged air leak
Control	----------	11	5	3	Delirium, hypotension, atrial fib, tachycardia
Control	----------	17	7	4	Pneumonia, hypoxia, thoracotomy wound infection

*discharged with a Heimlich valve
[1] Subject had a history of chronic atrial fibrillation prior to surgery

6.5.4 Additional Efficacy Results

6.5.4.1 Primary Efficacy Endpoint by Clinical Site

Table 33 presents a summary of the primary efficacy endpoint by site and investigator. The success rate was variable among investigators for both the Sealant and Control groups with individual investigators showing success rates from 0% to 54% for the Sealant group and 0% to 33% for the Control group. Higher success rates were observed with use of the Sealant for each of the investigators with the exception of Miller (Mayo), who had a slightly higher success rate in the Control group.

Table 33 Primary Efficacy Endpoint Summary by Site and Investigator

Site	Investigator	Sealant			Control		
		# Success	Total N	% Success	# Success	Total N	% Success
CSMC	01-McKenna	7	13	53.8%	0	8	0.0%
	Site Overall	**7**	**13**	**53.8%**	**0**	**8**	**0.0%**
DUMC	01-Davis	0	3	0.0%	0	0	0.0%
	02-Harpole	4	16	25.0%	1	8	12.5%
	Site Overall	**4**	**19**	**21.1%**	**1**	**8**	**12.5%**
MAYO	01-Allen	11	21	52.4%	4	12	33.3%
	02-Miller	1	10	10.0%	1	6	16.7%
	03-Nichols	1	5	20.0%	0	2	0.0%
	Site Overall	**13**	**36**	**36.1%**	**5**	**20**	**25.0%**
MDACC	01-Walsh	5	13	38.5%	1	7	14.3%
	02-Smythe	2	4	50.0%	0	2	0.0%
	Site Overall	**7**	**17**	**41.2%**	**1**	**9**	**11.1%**
UWMC/VA	01-Wood	3	7	42.9%	1	5	20.0%
	02-Vallieres	2	11	18.2%	0	8	0.0%
	Site Overall	**5**	**18**	**27.8%**	**1**	**13**	**7.7%**

6.5.4.2 Duration of Air Leak and Chest Tube >11 Days

For the secondary efficacy endpoints, FDA noted that there were more patients in the Sealant group than the Control group with air leak or chest tube duration >11 days (13 Sealant vs. 3 Control, respectively). The differences in air leak and chest tube duration between the Sealant and Control groups are directly affected by the imbalance in the use of the Heimlich valves between the two groups (10 Sealant vs. 1 Control). The extended durations (*i.e.*, >11 days) in many cases were related to the fact that daily determinations of air leaks were not performed on subjects discharged with a Heimlich valve (HV), as discussed below.

Heimlich Valve and Persistent Air Leaks >11 Days

During the course of the study, some patients were discharged from the hospital with a HV. The investigators considered the use of a HV if the subject had a persistent air leak but had minimal drainage and no other significant clinical events to preclude discharging them from the hospital. Following discharge from the hospital, subjects with HV would return to the clinic only on a weekly basis to be checked for the presence of air leak(s). This made it impossible to accurately determine the actual end date of air leaks because only upon the patients' return to the clinic and removal of the chest tube (HV), was it possible to give an estimate of when the air leak terminated. To be conservative, the study Sponsor chose to estimate the end date of air leaks in these instances as the day of the chest tube (HV) removal (the CT duration also included the time that the HV was in place).

In the clinical study, an imbalance with regard to the use of HV was observed between the Sealant and Control groups with more Sealant subjects discharged with a HV than Control subjects (10 Sealant subjects and 1 Control subject). This imbalance likely occurred either because: 1) more Sealant subjects met the criteria for use of HV than Control subjects; or 2) Sealant subjects were more likely to be discharged with a HV than Control subjects while the proportion of subjects met the criteria for use of HV were similar in each group (*i.e.,* bias). To evaluate whether there was any bias towards the use of HV in Sealant subjects, a subset of subjects with air leaks that existed beyond the 5th postoperative day were identified. These subsets were thought to be the "candidates" for the use of a HV, especially if their hospital stay could be shortened by sending them home with a HV. The reasons for the use or nonuse of the Heimlich valves in these subjects were reviewed and compared between groups.

The proportion of subjects with a persistent air leak >5 days was similar between the Sealant (21/103; 20.4%) and Control (11/58; 19.0%) groups. Each subject with a persistent air leak >5 days was classified into one of six categories according to possible reasons for their extended hospital stay beyond 5 days: 1) air leak only; 2) air leak and fluid (>125 cc/day); 3) fluid (>125 cc/day); 4) adverse events; 5) air leak and AE; and 6) fluid (>125 cc/day) and AE. The results of this review are summarized below in **Table 34**.

Table 34 Summary of Heimlich Valve Use in Subjects with POAL >5 Days

Reason	Sealant N=21	Control N=11
Air Leak Only: 5 Sealant 1 Control	----------*(H)** – water seal POD2-3 ----------*(H)* – water seal POD2-3 ----------*(H)* – water seal POD4-6 ----------*(H)* – water seal POD2-5 ---------- – water seal POD6, suction POD10, persistent leak >11days	---------- – water seal POD5; air leak resolved --------
Air Leak and Fluid: 8 Sealant 4 Control	---------- – not discharged on HV – CT reinserted ---------- to pneumothorax ----------*(H)* – water seal; drainage of 80 cc/day ---------- ----------*(H)* – water seal; drainage of 45cc/day ---------- ----------*(H)* – water seal; drainage of 10cc/day ----- ---------7-9 ---------- air leak stopped POD9; drainage ---------- POD1-8 ---------- – air leak stopped POD12; drainage ---------- POD10-12 ----------*(H)* – on suction POD7-13; water seal ---------- th drainage <125cc/day ---------- *(H)* – on water seal POD 9-10 with ---------- 125 cc/day until POD10	----------*(H)* – on water seal POD6-9 with drainage ---------- ---------- – air leak stopped POD7 ---------- – on suction POD9-17; drainage ---------- y POD9-17 ---------- – air leak stopped POD6
Fluid Drainage	---------- – on water seal with drainage >125cc/day POD3-6; air leak resolved POD7	

Reason	Sealant N=21	Control N=11
Adverse Events: 4 Sealant 4 Control	---------- – SVT, confusion; air leak resolved -------- ---------- – pneumonia; HV on POD13; on suction POD1-13; drainage <125cc/day POD12-13; ---------- ir leak >11 days ---------- – lung effusion; air leak resolved POD8; ---------- ion POD1-12, water seal POD 13-14; ---------- ainage ---------- – atrial flutter; air leak resolved POD6	---------- – pneumonia; air leak resolved POD10, ---------- POD38 ---------- – died; air leak absent POD1-7; air leak ---------- D8-10 ---------- – pneumonia; air leak resolved POD9 ---------- – pleural effusion, air leak resolved POD9
Air Leaks and AEs: 3 Sealant 1 Control	---------- – air leak resolved POD7 ---------- – air leak resolved POD8 ---------- – persistent air leak >11 days; small bowel obstruction (surgery); bilateral pneumonia; died	---------- – air leak continued to POD18; expired POD19; anemia, pneumonia, respiratory metabolic acidosis, SOB, hypertension, MRSA
Fluids and AEs		---------- – air leak resolved POD6; CT removed POD9; low hematocrit; thrombocytopenia, low creatine

*(H) discharged from the hospital with a Heimlich valve

As shown in **Table 34**, HV was used primarily in subjects in the categories of either "air leak only" or "air leak with fluid" (n=10). The only subject with a HV that was not in either of these two categories was a Sealant subject who had an adverse event.

The disparity in the proportion of subjects in the category "air leak alone" between the Sealant (5/22) and control group (1/11) is a contributing factor to the greater use of HV in the Sealant group. In the category "air leak only", 4 of 5 subjects in the Sealant group who met this criterion were sent home with a HV. There was only one subject in the Control group who met this criterion. This subject was not discharged with a HV, whose air leak resolved on POD6 and chest tubes were removed.

The proportion of subjects in the category "air leak and fluid" is the same in the Sealant (8/22) and Control (4/11) groups. However, 5 of the 8 subjects in the Sealant group went home with a HV compared to only 1 of 4 subjects in the Control group. Further examination of the individual data for these subjects indicated that the other three subjects in the Control group either had their air leak resolve prior to discharge (on POD6 and POD7, respectively) or had significant fluid drainage which extended beyond the resolution of their postoperative air leak.

These data suggest that the greater use of HV in the Sealant group than Control group is primarily associated with the fact that a larger proportion of the subjects in the Sealant group than Control group met the criteria that allowed for HV use (*i.e.*, air leak only or air leak with minimal fluid drainage). There does not appear to be any bias in the use of HV on the part of the investigators based on treatment assignment.

The fact that a larger number of Sealant subjects were able to be discharged with HV resulted in air leak durations that were biased upwards in the Sealant group because for these subjects an accurate ascertainment of the end date of air leaks was not possible. This was the contributing factor to why the proportion of subjects with air leaks >11 days was higher in the Sealant group

than Control group. The estimated air leak durations used in the analysis for subjects discharged with HV are shown in **Table 35**.

Table 35 Calculated Air Leak Duration for Subjects Discharged with Heimlich Valves

Subject		Heimlich Valve Use	Air Leak Duration Used in Analysis
Air Leak Only			
----------	Sealant	HV placed POD4, DC = POD4, HV removed POD14[1]	15
----------	Sealant	HV placed POD4, DC = POD5, HV removed POD7	8
----------	Sealant	HV placed POD6, DC = POD6, HV removed POD12	13
----------	Sealant	HV placed POD4, DC = POD5, HV removed POD18	19
Air Leak and Fluid			
----------	Sealant	HV placed POD7, DC = POD7, HV removed POD13	14
----------	Sealant	HV placed POD9, DC = POD9, HV removed POD21	22
----------	Sealant	HV placed POD8, DC=POD8, HV removed POD17	18
----------	Sealant	HV placed POD14, DC = POD15, HV removed POD18	19
----------	Sealant	HV placed POD9, DC = POD10, HV removed POD21	22
----------	Control	HV placed POD10, DC = POD11, HV removed POD21	22
Adverse Event			
----------	Sealant	HV placed POD12, DC = POD16, HV removed POD41	42

[1] HV: Heimlich valve; DC: Discharge

6.5.5 Efficacy Discussion and Conclusion

The proportion of subjects who remained air leak free following surgery through 1MFU (or the duration of hospitalization whichever was longer) was significantly greater in the Sealant group compared with the Control group (35% vs. 14%; p=0.005). The difference remained statistically significant even after adjusting for the effects of other prognostic variables (odds ratio=5.03; 95% confidence limits 1.88 to 13.43; p=0.001).

IOALs were sealed in 71% of Sealant subjects compared with 10% of Control subjects following the final AL test in the OR (p<0.001). Of the small to medium sized ALs (≤5 mm), 84% (128/152) were sealed in the Sealant group as compared to 17% (12/71) in the Control group. Of the ALs >5 mm, 58% (33/57) were sealed in the Sealant group as compared to 14% (5/37) in the Control group.

Of the 72 subjects in the Sealant group who did not have IOALs on the final AL test, 31 (43%) were treatment successes and remained air leak-free through their 1MFU visit. Of the 6 subjects in the Control group who were air leak-free in the OR, none remained leak-free following surgery.

A significantly higher number of Sealant subjects were air leak free during observation period in the recovery room 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 (p=0.002).

The duration of ALs was comparable for both treatment groups with the majority of ALs lasting less than 3 days (the median duration was 2 days in both groups). The incidence of prolonged ALs was similar between groups: 14% and 12% in the Sealant and Control groups, respectively. The duration of CT placement was also comparable between treatment groups. The median duration of CT placement was 5 days in both groups.

The LOS was significantly shorter for subjects in the Sealant Group compared with subjects in the Control group. The median LOS was 6 days in the Sealant group and 7 days in the Control group ($p<0.05$). This difference may be attributed to the higher rate of complications in the Control group.

Overall, the study results demonstrated the efficacy of the Sealant when used as an adjunct to standard closure methods to successfully seal IOALs and reduce the incidence of POALs compared to the Control group.

6.6 Safety Evaluations

6.6.1 Summary Adverse Events

Subjects in both the Sealant and Control groups had similar adverse event (AE) profiles. The AEs reported in both groups were consistent with the diagnoses of the patients and the operative procedures performed. Most of the AEs were mild to moderate in severity. The most frequently reported "severe" AEs in the Sealant group were pain, atrial fibrillation, followed by chest pain, dyspnea, hypoxia, and acute renal failure. The most frequently reported "severe" AEs in the Control group were dyspnea, anemia and pneumonia. There was no significant difference in the incidence of each AE between treatment groups.

There were 15 serious AEs (SAEs) reported during this study: 9 deaths, 5 other SAEs, and 1 unanticipated adverse device effect (UADE). None of deaths reported during the study were considered device related by the investigators. Of the 5 subjects with other SAEs (2 Sealant, 3 Control), all resulted in extended hospital stays or re-hospitalization. Four subjects recovered from these events and 1 subject continues on dialysis.

6.6.2 Analysis of Adverse Events

Table 36 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: 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 was no significant difference in the incidence of any AE between treatment groups.

Table 36 Incidence of AEs Reported by > 2% of Subjects by Treatment Group

Preferred Term	Sealant (N=103)	Control (N=58)	P-Value[1]
Fever	22 (21.4%)	12 (20.7%)	1.000
Fibrillation, Atrial	12 (11.7%)	7 (12.1%)	1.000
Dyspnea	12 (11.7%)	10 (17.2%)	0.346
Constipation	11 (10.7%)	6 (10.3%)	1.000
Nausea	10 (9.7%)	7 (12.1%)	0.790
Confusion	8 (7.8%)	5 (8.6%)	1.000
Pneumothorax	8 (7.8%)	5 (8.6%)	1.000
Hypotension	8 (7.8%)	6 (10.3%)	0.573
Anemia	8 (7.8%)	6 (10.3%)	0.573
Pain	7 (6.8%)	4 (6.9%)	1.000
Subcutaneous Emphysema	7 (6.8%)	5 (8.6%)	0.758
Tachycardia	7 (6.8%)	6 (10.3%)	0.548
Death	5 (4.9%)	4 (6.9%)	0.723
Oliguria	5 (4.9%)	1 (1.7%)	0.420
Vomiting	5 (4.9%)	7 (12.1%)	0.120
Pneumonia	5 (4.9%)	7 (12.1%)	0.120
Pulmonary Infiltration	4 (3.9%)	0 (0.0%)	0.298
Chest Pain	4 (3.9%)	1 (1.7%)	0.655
Pleural Effusion	4 (3.9%)	3 (5.2%)	0.703
Urinary Retention	3 (2.9%)	0 (0.0%)	0.554
Ileus	3 (2.9%)	0 (0.0%)	0.554
Tachycardia, Supraventricular	3 (2.9%)	0 (0.0%)	0.554
Abdominal Pain	3 (2.9%)	0 (0.0%)	0.554
Arrhythmia	3 (2.9%)	0 (0.0%)	0.554
Extrasystoles	3 (2.9%)	0 (0.0%)	0.554
Coughing	3 (2.9%)	1 (1.7%)	1.000
Hypoxia	3 (2.9%)	1 (1.7%)	1.000
Renal Failure, Acute	3 (2.9%)	1 (1.7%)	1.000
Atelectasis	2 (1.9%)	2 (3.4%)	0.620
Postoperative Wound Infection	2 (1.9%)	2 (3.4%)	0.620
Pruritus	1 (1.0%)	2 (3.4%)	0.295
Delirium	1 (1.0%)	2 (3.4%)	0.295
Hypertension	1 (1.0%)	2 (3.4%)	0.295
Angina Pectoris	1 (1.0%)	2 (3.4%)	0.295
Hemoptysis	1 (1.0%)	3 (5.2%)	0.134

[1]P-value associated with Fisher's Exact Test for categorical data.

Table 37 shows all "severe" AEs by treatment group. Detailed information on deaths can be found in **Section 6.6.3**. 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 difference in the incidence of each AE between treatment groups.

Table 37 Severe AEs by Treatment Group

Adverse Events	Sealant N=103	Control N=58
Death	5 (4.9%)	4 (6.9%)
Pain	5 (4.9%)	0
Atrial fibrillation	4 (3.9%)	1 (1.7%)
Acute renal failure	3 (2.9%)	1 (1.7%)
Chest Pain	3 (2.9%)	0
Dyspnea	3 (2.9%)	4 (6.9%)
Hypoxia	3 (2.9%)	0
Cardiac arrest	2 (1.9%)	0
Pleural infusion	2 (1.9%)	0
Abdominal pain	1 (1.0%)	0
Abnormal renal function	1 (1.0%)	0
Acidosis	1 (1.0%)	0
Adult respiratory stress syndrome	1 (1.0%)	1 (1.7%)
Anemia	1 (1.0%)	2 (3.4%)
Arrhythmia	1 (1.0%)	0
Ascites	1 (1.0%)	0
Atelectasis	1 (1.0%)	0
Blood pressure fluctuation	1 (1.0%)	0
Bundle Branch Block	1 (1.0%)	0
Cardiac failure	0	1 (1.7%)
Delirium	1 (1.0%)	0
Dysuria	1 (1.0%)	0
Encephalopathy	1 (1.0%)	0
Extrasystoles	1 (1.0%)	0
GI Haemorrhage	1 (1.0%)	1 (1.7%)
Haematuria	1 (1.0%)	0
Hepatic failure	1 (1.0%)	0
Hypotension	1 (1.0%)	1 (1.7%)
Infection Staphylococcal	1 (1.0%)	1 (1.7%)
Influenza-like symptoms	1 (1.0%)	0
Intestinal obstruction	1 (1.0%)	0
Myocardial infarction	1 (1.0%)	0
Oedema	1 (1.0%)	0
Peripheral ischaemia	1 (1.0%)	0
Pneumonia	1 (1.0%)	2 (3.4%)
Post-operative haemorrhage	1 (1.0%)	0
Pulmonary haemorrhage	1 (1.0%)	0
Pulmonary Oedema	1 (1.0%)	0
Respiratory insufficiency	1 (1.0%)	1 (1.7%)

Adverse Events	Sealant N=103	Control N=58
Sepsis	1 (1.0%)	1 (1.7%)
Syncope	1 (1.0%)	0
Skin ulceration	1 (1.0%)	0
Tachycardia	1 (1.0%)	1 (1.7%)
Tachycardia supraventricular	1 (1.0%)	0
Urinary retention	1 (1.0%)	0
Acidosis respiratory	0	1 (1.7%)
Arthropathy	0	1 (1.7%)
Bronchial obstruction	0	1 (1.0%)
Confusion	0	1 (1.7%)
Dehydration	0	1 (1.7%)
Gall bladder disorder	0	1 (1.7%)
Haemoptysis	0	2 (3.4%)
Hypertension	0	1 (1.7%)
Oedema dependent	0	1 (1.7%)
Oedema generalized	0	1 (1.7%)
Pneumothorax	0	1 (1.7%)
Respiratory disorder	0	1 (1.7%)
Somnolence	0	1 (1.7%)
Subcutaneous emphysema	0	1 (1.7%)
Ventricular fibrillation	0	1 (1.7%)
Withdrawal syndrome	0	1 (1.7%)

The AEs related to renal function were analyzed as a possible indication of an immune response. The results are shown in **Table 38**.

Table 38 Adverse Events Associated with Renal Function

Adverse Event*	Sealant N=103	Control N=58
Abnormal Renal Function	2 (1.9%)	0 (0.0%)
Acute Renal Failure	3 (2.9%)	1 (1.7%)
Oliguria	5 (4.9%)	1 (1.7%)

*One Sealant patient reported with both abnormal renal function and oliguria, and was counted in both renal adverse event categories.

Nine Sealant patients and two control patients experienced adverse events associated with renal function. One Sealant patient reported with both abnormal renal function and oliguria, and was counted in both renal adverse event categories. The differences between the Sealant and Control groups were not statistically significant. Two of the subjects in the Sealant group with oliguria had pre-existing renal disease. Of the remaining subjects with oliguria, 2 were mild and 1 was moderate in the Sealant group compared to 1 mild in the Control group. Detailed information taken from the case report forms relating to the Acute Renal Failures (ARF) for these patients is consolidated in the following.

---------- **(Sealant)**

Surgery Date:---------

Discharge date: ----------

Onset of ARF:----------

Treatment: Hospitalization

Outcome: Resolved 9/29/00

Commentary: ARF judged by investigator as "Other Disease" along with abdominal pain, basilar infiltrate, chest pain, increased cardiac and pancreatic enzymes, syncope episode, and shortness of breath which were reported as Adverse Events (AEs) immediately prior to or on 9/25/00. This subject had continuing AEs following resolution of ARF as late as 12/20/00 which included anemia, bundle branch block, inferior infarct, dyspnea, dysuria/urinary retention, and weakness.

Conclusion: Occurrence of ARF most likely not a result of exposure to Sealant because onset was approximately 3 weeks following its use. It appears most likely that ARF was initialized by accompanying AEs involving the respiratory, cardiac, and pancreatic systems.

---------- **(Sealant)**

Surgery date:---------

Discharge date: ----------

Onset of ARF:---------

Treatment: Medical/Surgical intervention

Outcome: Subject discharged with ongoing ARF and continued on dialysis

Commentary: This subject, similar to Control subject---------- was determined to have pre-existing chronic renal insufficiency resulting in "Anticipated" ARF as a consequence of the surgical procedure. The subject was diagnosed by the clinician as having known renal insufficiency, severe peripheral vascular disease with bilateral renal artery stenosis and questionable solitary functioning of the right kidney.

Conclusion: ARF in this subject likely not a result of exposure to Sealant due primarily to pre-existing chronic renal insufficiency. The precipitating event was judged to be intraoperative hypotension.

----------**(Sealant)**

Surgery Date:----------

Discharge Date: Subject Expired --------

Onset of ARF----------

Treatment: Medication

Outcome: Subject expired

Cause of Death: ARDS & multi-system failure

Commentary: This subject had known alcohol dependency with a past history of delirium tremors and experienced delirium tremors requiring medication along with poor oxygenation beginning on POD1. These were followed by labile blood pressure, sepsis, respiratory distress syndrome, and cardiac arrhythmia, all judged not related to the Sealant, until the subject was transferred to the ICU with ARF, where the subject expired POD6.

Conclusion: ARF in this subject appears not to be a result of exposure to the Sealant but, rather, an anticipated consequence of past health problems leading to deteriorating status because of sepsis, and cardiac and respiratory issues. These events then culminated in ARF and the subject's death.

----------**(Control)**

Surgery Date: ---------

Discharge Date: Subject expired---------

Onset of ARF: ---------

Treatment: Medication

Outcome: Subject expired

Cause of Death: Atrial fibrillation

Commentary: This subject progressively deteriorated from fever, respiratory distress secondary to pneumonia, and tachycardia, to multiorgan system failure, including ARF, and atrial fibrillation, resulting in death ascribed to ARDS and gall bladder obstruction.

Conclusion: Pre-existing renal disease likely contributed to but was not the primary cause of mortality for this subject.

These data suggest that Sealant use was not associated with renal complications.

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 (04-01-206) (see **Section 6.6.5** for narratives). 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.

6.6.3 Deaths

Table 39 presents a summary of subject deaths. There were five deaths among subjects in the Sealant group and four deaths in the Control group. None of the deaths were considered by the investigators to be device related.

Table 39 Summary of Subject Deaths

Subject ID	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	Day of Surgery	Not Related	Ventricular Fibrillation
----------	67/Male	POD38	Not Related	Anoxic Brain Injury

As shown in **Table 39**, the cause of death for Sealant subjects appeared to possibly be pulmonary related events where 1 of the 4 deaths in the Control group (*i.e.*, pneumonia) appeared to be related to a pulmonary event.

Two of the study investigators completed a thorough review of the 9 deaths occurred during the study and concluded that none of the deaths in the Sealant group were caused by a primary pulmonary event. In contrast, two of the Control subjects had a primary pulmonary event that was a significant contributing factor in their cause of death.

Narratives of Deaths

Sealant Group

Subject---------- was a 69 year old male, randomized to the Sealant group with a medical history of renal disease, chronic obstructive pulmonary disease (bronchitis and emphysema) and

who had previously undergone surgery for colon cancer in 1989. Furthermore, 5 days before being randomized to the Sealant group, the patient underwent bilateral lung volume reduction surgery. The patient did well in the initial postoperative period; however, 5 days later he developed a massive AL. Because of ALs, worsened gas exchange, and the inability to keep the lung expanded, surgical intervention was indicated and his sternotomy was reopened. Findings at the time of reoperation included a ruptured bleb, two small punctate holes in the left upper lobe, both below the previous staple lines, as well as some ALs on the right lung. The bleb was excised and suture closed and the punctate holes and other ALs in the right lung were also sutured. Despite suture closure, ALs persisted. At this point, the subject was randomized to the Sealant group. All ALs were sealed upon application of the Sealant. During the surgery, but prior to Sealant application, the patient developed marked hemodynamic instability and his oxygen requirements were substantial.

Following surgery he was transferred to ICU where the patient continued to require a significant amount of hemodynamic support. A CXR showed good expansion of both lungs, but with residual diffuse airspace disease. On the morning of POD7 from the initial surgery, the patient had an unexplained cardiac event and expired. The investigator attributed the cause of death to ongoing airspace disease/ARDS. The investigator considered the event not related to study device.

Subjec---------- was an 82 year old male, randomized to the Sealant Group with a past history of rect---------- enocarcinoma requiring abdominoperineal resection and colostomy in 1976 and melanoma requiring excision of melanomatous lesions in 1968. The patient underwent a right thoracotomy and right middle lobe wedge resection for squamous cell carcinoma on April 27, 2000. Postoperatively, the patient developed a prolonged AL, which was resolved by talc pleurodesis on POD13. The patient also developed a small bowel obstruction requiring exploratory laparotomy, lysis of adhesions, surgical disimpaction, and revision of colostomy on POD18. Following this last surgery, he developed bilateral pneumonias from which he did not recover. The patient expired on POD28. The investigator attributed the immediate cause of death to pneumonia. The investigator considered the event not related to study device.

Subject---------- was a 61 year old male, randomized to the Sealant group with a long history of interstitial lung disease, emphysema, coronary artery disease, and recurrent right upper lobe cancer. On July 14, 2000 the patient underwent a bronchoscopy, followed by a mediastinoscopy and a right thoracotomy. A right upper lobe wedge resection was performed. During the 5 days post-surgery the patient had no evidence of AL and his CTs were removed on POD6. The patient remained in the ICU because of pulmonary toilet. On POD7, the patient sustained a sudden cardiopulmonary arrest. Although the patient responded to resuscitation efforts, he suffered irreversible brain damage. On POD10, following discussion with his relatives, life support was withdrawn and the patient expired. A cardiac evaluation did not reveal a primary cardiac event leading to these events; there was no evidence that a pneumothorax caused the cardiopulmonary arrest, nor did a CT angiogram show a major central pulmonary emboli. The investigator attributed the cause of death to secretions causing acute airway obstruction or to a small pulmonary embolus. The investigator considered the event not related to study device.

Subjec---------- was a 66 year old male, randomized to the Sealant group with a medical history---------- artial glossectomy and radical neck dissection for metastatic squamous cell carcinoma of the tongue and a long history of alcoholic cirrhosis. The patient underwent a right lower lobectomy and complete mediastinal lymphadenectomy on October 2, 2000. On POD2, the patient began experiencing symptoms of delirium tremens. Overnight, the patient became hypotensive, oliguric and hypoxic. The patient was transferred to the ICU and put on a ventilator on POD3. Over the next three days the patient's hemodynamic status deteriorated secondary to bilateral pulmonary infiltrates, ARDS, and multi-system organ failure. The patient expired on POD6. The investigator attributed his death to delirium tremens with subsequent aspiration leading to bilateral pulmonary infiltrates, ARDS, and multi-system failure. The investigator considered the event not related to study device.

Subject----------was a 65 year old male, randomized to the Sealant group with a history of end-stage liver disease, portal hypertension, ascites, esophageal varices, upper GI bleeding due to esophageal varices , COPD, and diabetes. Prior to surgery, the patient underwent an extensive preoperative preparation including nutritional support and control of his acsites with diuretics. The patient underwent a right upper lobe lobectomy for large cell lung cancer on February 6, 2001. The operative procedure was uneventful and the patient's CT was removed early without difficulty. However, his postoperative course was complicated by hepatic failure which occurred on POD7 and renal insufficiency which developed by POD13. The patient also developed a right pneumothorax on POD14 which required CT placement. By POD16, the patient had developed a methicillin-resistant *Staphylococcus aureus* pneumonia which was treated with vancomycin. He also required a tracheostomy due to ventilator dependency. On POD20, the patient developed active GI bleeding which was uncontrollable in spite of endoscopy with sclerosis. He continued receiving blood products and hemodynamic support for the next two days. On POD22, in consultation with the patient's family, support was withdrawn due to liver failure. The patient expired on POD23. The investigator considered the event not related to study device.

Control Group

Subject----------was an 80 year old female, randomized to the Control group with a history of coronary artery disease, a long history of chronic obstructive pulmonary disease, tuberculosis in the right and left upper lobes of the lung, and a previous segmental resection of carcinoma in the left upper lobe of the lung. The patient underwent a left upper lobectomy and chest wall resection for an infiltrating, recurrent carcinoma on January 20, 2000. The patient developed severe postoperative pulmonary complications including respiratory/metabolic acidosis, shortness of breath, hypotension and sinus tachycardia on POD4. The patient was transferred to the ICU and intubated for ventilatory support. The patient developed pneumonia and ultimately expired on POD19 from staphylococci pneumonia.

Subject 02-02-209 was a 71 year old male, randomized to the Control group with a past history of diabetes, renal disease, and cerebral vascular accident. The patient underwent a right lower lobe segmentectomy on March 1, 2000 for excision of a primary lesion. His CT was removed on

POD11. He subsequently developed pneumonia, ARDS, and atrial fibrillation from which he ultimately expired on POD22.

Subject---------- was an 82 year old male, randomized to the Control group with a past medical history of coronary artery disease and prior myocardial infarctions. The patient underwent a right thoracotomy and right lower lobectomy for bronchoalveolar carcinoma on January16, 2001. A preoperative cardiology evaluation and premedication in an attempt to reduce the risk of cardiac event had been provided. At approximately 5:30 pm, on the day of surgery the patient experienced sudden ventricular fibrillation from which he could not be resuscitated and was pronounced dead at approximately 7:00 pm. The investigator attributed the cause of death to ventricular fibrillation of undetermined etiology.

Subject ---------- was a 67 year old male, randomized to the Control group with a recent history of non-small cell lung cancer of the right upper lobe. Six weeks prior to surgery the patient completed concurrent chemotherapy and radiation treatment. On August 1, 2000, he underwent a right upper lobectomy and mediastinal lymph node dissection. The patient did well until POD4, when he experienced recurrent episodes of atrial flutter and atrial fibrillation. These cardiac events were managed by the cardiology service with antihypertensives, antiarrhythmics, diuretics, and anticoagulant therapy. He was discharged on POD8, with follow-up scheduled with his primary care physician for anticoagulant management. Initially, the patient did well, but in late August he developed ankle edema and symptoms of cardiac failure including orthopnea and retention of secretions. On POD38, he was admitted to a local hospital with worsening of respiratory distress, new hemoptysis, and pain in the right chest which was not pleuritic in nature. A CXR revealed consolidation and effusion in the right hemithorax. An ultrasound of the liver reportedly showed multiple masses in the liver which were felt by the treating physician to be representative of rapidly progressive metastatic disease. The treating physician felt the patient probably had a recurrence of his non-small cell lung cancer with endobronchial obstruction causing lung consolidation and hemoptysis and possible pericardial and pleural involvement producing pericardial and pleural effusions and possible progressive liver metastases. The patient was given supportive care and expired shortly after his admission to the hospital.

6.6.4 Other SAEs

In addition to the deaths described above, there were 5 other SAEs: 2 in the Sealant group and 3 in the Control group (**Table 40**). 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 40 Other SAEs

Subject ID	Age/Gender	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

Narratives of Other SAEs

Sealant Group

Subject---------- is a 70 year old female, randomized to the Sealant group with a history of hypertension, coronary artery disease, chronic renal insufficiency, and severe peripheral vascular disease. The patient underwent a left upper lobectomy for a primary lesion on April 6, 2000. She developed acute renal failure requiring dialysis on POD1. Her CT was removed on POD5 and she was discharged from the hospital on maintenance dialysis. The investigator considered the event probably not related to the study device and provided an alternate etiology of concurrent disease or illness.

Subject---------- is a 70 year old male, randomized to the Sealant group with a history of hypertension, myocardial infarction, and coronary artery disease. The patient underwent a left upper lobe bilobectomy for a primary lesion on September 5, 2000. His CT was removed on POD3 and he was discharged from the hospital on POD7. The patient experienced a severe syncopal episode on POD19, which resulted in rehospitalization. This event resolved on POD20. While hospitalized the patient experienced severe abdominal pain and shortness of breath, which began and resolved on POD20. The patient also developed acute renal failure, which began on POD20 and resolved on POD24. In addition, he experienced severe chest pain from POD20-27. A diagnosis of inferior wall myocardial infarction was made on POD28. The patient was treated for these conditions and recovered. The investigator considered these events probably not related to study device and provided an alternate etiology of concurrent disease or illness.

Control Group

Subject ----------is an 83 year old male, randomized to the Control group with a medical history of hypertension, antral ulcers, chronic asthma, coronary artery disease including coronary

artery bypass graft in 1986, aortic valve replacement in 1994, and diabetes. The patient underwent a right upper lobectomy for a primary tumor on February 15, 2000 and had a transient episode of angina while in the hospital. There was no evidence of air leakage from the CT from POD1 through discharge. He was discharged on POD8. The patient was rehospitalized on POD17 with shortness of breath and chest pain. There was some air/fluid posterior to the lung and a pleural tap through the CT was performed to remove the fluid. On POD20, the patient had bloody stools resulting from a GI bleed which was treated with two units of blood. The patient recovered and was discharged on POD22.

Subjec---------- is a 67 year old female, randomized to the Control group with a history of myoca---------- on and coronary artery disease. The patient underwent a right upper lobectomy for a primary tumor on February 23, 2000. The patient developed pneumonia and ARDS leading to severe respiratory distress on POD3. Her CT was removed on POD8. The patient was not discharged from the hospital until POD37. The investigator considered the event a complication of surgery.

Subject---------- is a 70 year old male, randomized to the Control group with a history of coronar---------- ease, diabetes, hypertension, peripheral vascular disease, and current alcohol dependency. The patient underwent a left upper lobectomy for a primary lesion on October 13, 2000. His CT was removed on POD3 and he was discharged from the hospital. He was rehospitalized for dehydration from POD10 through POD11.

6.6.5 Unanticipated Adverse Device Effect

The only other significant AE was an unanticipated adverse device effect. Subject---------- was a 28 year old female, randomized to the Sealant group, who experienced a pne---------- weeks post surgery. Due to the temporal relationship to the study device, the investigator considered the event probably related to the device.

Narrative of UADE

Subject---------- is a 28 year old female, randomized to the Sealant group with a history of extra-osseous osteosarcoma with pulmonary metastatic disease diagnosed in December, 1997. The patient had previously undergone local excision of supraclavicular lymph nodes, radiation therapy, several courses of chemotherapy, a right thoracotomy, and wedge resection in August 1998 and a left thoracotomy and wedge resection a month later. From December, 1998 through November, 1999 she received additional chemotherapy. She had some stability of the disease and was scheduled for a redo thoracotomy in early February 2000. This surgery was cancelled due to an upper respiratory infection which resolved following a course of antibiotic therapy. On February 23, 2000 the patient underwent a repeat thoracotomy and removal of three lesions from the left lung, one of which proved to be metastatic osteosarcoma. Upon completion of the lung resection procedure several ALs >5 mm were observed. These areas were suture repaired and then several applications of Sealant were made. Despite suture repairs and repeated application of the Sealant, air leakage continued, although some of the ALs had been reduced from >5 mm to <2 mm. Despite these ALs, the patient had an uneventful postoperative course and by POD2,

the ALs had completely resolved. The patient was discharged from the hospital on POD4. The patient's CXRs at the time of discharge showed expected post surgical changes with apical pleural thickening but no pneumothorax. The patient did well until POD20 when she developed left chest pain and dyspnea. The patient was seen in the emergency room of another hospital and subsequently admitted to that hospital. 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. The investigator attributed the unanticipated AE as probably related to the Sealant due to the temporal relationship of the development of the pneumothorax 3 weeks postoperatively.

6.6.6 Clinical Chemistry and Hematology

Laboratory findings for clinical chemistry and hematology were consistent with the chronic disease status of this study population. In general, there were numerous laboratory values indicative of the pre-existing disease conditions of these subjects. Overall, cholesterol and blood glucose values tended to be high and hemoglobin values low. Creatine values were transient and in a few subjects with underlying renal disease, moved from normal to high and remained elevated. There were no significant between group differences when comparing preoperative and 1MFU laboratory values with respect to changes in and out of the normal ranges.

6.6.7 Humoral and Cell-Mediated Immune Response

6.6.7.1 ELISA

An ELISA was developed to detect antibodies to pulverized Sealant. Subject serum, collected pre- and postoperatively, was analyzed to determine the changes in serum antibody levels in response to the Sealant.

Both pre- and postoperative serum samples were obtained from 71 (69%) of the 103 Sealant subjects and 37 (64%) of the 58 Control subjects. Only 1 subject in each group had a postoperative serum level consistent with the formation of Sealant antibodies. In both cases, the subjects' preoperative serum also showed high values, indicating that their serum contained antibodies that cross-reacted with the Sealant. These results suggest that the use of the Sealant during surgery did not result in the formation of Sealant antibodies. No statistical analysis was performed on these data due to the limited number of positive responses to the assay.

6.6.7.2 LPA

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. The cellular response to mitogens indicated which cell population was 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 both pre- and postoperative samples were included in the analysis. There were 59 Sealant subjects and 34 Control subjects for mitogen analysis, and 69 Sealant and 32 Control subjects for recall antigen and Sealant analyses. The only significant difference observed was the lower preoperative value for tetanus in the Control group than Sealant group. The higher preoperative values in the Sealant group were not clinically meaningful since the results 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 the cell's response to antigenic stimuli.

6.6.8 Vital Signs

Vital signs including temperature, blood pressure, respiratory rate, and heart rate were measured at screening, during POD1-7, at discharge, and at 1MFU. There were statistical differences between treatment groups in mean preoperative vital sign measurements for pulse and respiration; however, these differences were not considered clinically meaningful.

Changes in vital signs during the first 7 postoperative days were also analyzed. There were significant within group differences in mean systolic blood pressure, diastolic blood pressure, pulse, respiration and temperature. In addition, there were statistically significant differences in pulse rate between groups, however, these differences where not considered clinically meaningful.

Mean changes from preoperative vital signs to discharge and 1MFU measurements showed significant within group differences for systolic blood pressure, diastolic blood pressure, pulse, and temperature. Differences were observed in both treatment groups for all but diastolic blood pressure. Vital signs outside the specified limits were reviewed by the sponsor's medical monitor and two investigators (Drs. Wood, UWMC, and Allen, Mayo); none of the observed differences were considered clinically meaningful by the reviewers.

6.6.9 Chest X-rays

6.6.9.1 Investigators' Assessment

Chest X-rays (CXRs) were obtained prior to surgery, in the recovery room, before and after chest tube removal, and at the 1MFU visit. There were no clinically significant differences in CXR findings between treatment groups. As part of the safety evaluation, the 1MFU CXR findings were subsequently reviewed by the sponsor's medical monitor and the investigator for evidence of pneumothorax or residual air space. There were no clinically significant findings at one month with the exception of one subject in the Sealant group, who presented with a pneumothorax three weeks postoperatively (see **Section 6.6.5** UADE). In addition, neither the Sealant nor the Control subjects required hospitalization or treatment for symptoms relating to postoperative pneumothorax. **Table 41** below presents a summary of the CXR results at 1MFU.

Table 41 Summary of CXR Results at 1MFU

1 MFU CXR	Sealant N=96	Control N=53
Complete Expansion	49 (51.0%)	34 (64.2%)
Partial Expansion[1]	32 (33.3%)	12 (22.6%)
Other	9 (9.4%)	5 (9.4%)
Missing[2]	6 (6.3%)	2 (3.8%)

[1] Considered within normal limits for postoperative thoracotomy.
[2] CXRs were not performed.

As shown in **Table 41**, the investigators' assessments of 1MFU CXRs indicated that 33% (32/96) of the Sealant and 23% (12/53) of the Control patients had partial lung expansion at 30 days post surgery. This difference was not statistically significant (p=0.17) nor was it clinically significant since there was no event among the subjects with partial lung expansion post CT removal that required any medical attention.

It is important to note that partial lung expansion is not atypical after major pulmonary resection. It is expected to see a residual air space, or "partial lung expansion" after a lobectomy or bilobectomy due to the inability of the remaining lung to completely fill the residual chest cavity. This is a geometric consequence of pulmonary resection and does not represent an adverse outcome or evidence of device failure. If device failure occurred after CT removal this would be clearly evident by the new development of an enlarging pneumothorax and/or subcutaneous emphysema, which would be symptomatic and clinically significant, resulting in the need for treatment, *e.g.*, CT replacement.

6.6.9.2 Independent CXRs Review

FDA raised a question about the somewhat higher proportion of Sealant patients than Control patients (33% vs. 23%; p=0.17) with partial lung expansion based on the investigators' assessment of CXRs. The Agency recommended that the CXRs taken in the study be read by an independent masked radiologist to permit an objective evaluation of this aspect of device safety. Such an evaluation was undertaken in three of the five investigational sites. The three sites were selected on the basis of the fact that they had digital CXRs which would make it convenient for retrieval and processing and they represented high enrollment of both Sealant and Control subjects. These sites also had the highest percentage of subjects with "partial expansion with normal limits" at the one-month follow-up visit in both groups. It was felt that limiting the random selection of subjects to these three sites was reasonable approach for investigating the clinical importance of the difference between the Sealant and Control groups with respect to this parameter. A random sample of 60 patients (40 Sealant and 20 Control) in these three sites, representing approximately one third of the patients in the study (103 Sealant and 58 Control), was reviewed by an independent radiologist masked to the treatment assignment. As shown in **Table 42**, the incidence of complete lung expansion for both groups was similar when subjects were in the recovery room (RR) and somewhat better for Sealant patients than Control patients at the time of chest tube pull (51% vs. 40%). The results of the evaluation demonstrated that there

was no evidence of any investigator bias in classifying CXR results based on the treatment assignment and thereby assured the objectiveness of the original interpretation of the CXR results.

Table 42 Comparison of Sealant and Control Groups Assessment of Lung Expansion by the Independent Radiologist[1]

Lung Expansion	Sealant[1]	Control	P-value[2]
RR			
Complete	26 (72%)	14 (70%)	1.000
Partial	10 (28%)	6 (30%)	
CT Pull			
Complete	20 (51%)	8 (40%)	0.582
Partial	19 (49%)	12 (60%)	
1MFU			
Complete	30 (83%)	20 (100%)	0.078
Partial	6 (17%)	0 (0%)	

[1]Four patients, 1 patient and 4 patients had missing Ptx measurement at RR, CT pull, and 1MFU, respectively.

[2]Fisher's exact test.

In the CXR evaluation there were 6 Sealant patients with unresolved residual air space (radiologically appears as a pneumothorax, or "Ptx") at "one month follow up" post-surgery (1MFU) whereas all Ptx in Control patients had resolved. While none of these observed differences were statistically significant, the Sponsor performed a more in-depth analysis of those 6 Sealant patients with Ptx at 1MFU.

In the CXR evaluation, as shown in **Table 43**, among patients with Ptx noted at CT pull, the median change (decrease) in Ptx size from CT pull to 1MFU was similar in both groups, namely 17.5 mm and 14 mm in the Sealant and the Control groups, respectively.

Table 43 Change in Pneumothorax Size from CT Pull to 1MFU Among Patients with Pneumothorax at CT Pull

Change in Pneumothorax (mm)	Result	Sealant	Control
Difference (1MFU-CT Pull)	**N**	18*	12
	Mean ± SD	-15.1 ± 14.4	-17.8 ± 11.5
	Median	-17.5	-14.0
	Range	-50, 23	-39, -5

*N of 19 was reduced by the one patient who did not have pneumothorax measurement at 1MFU.

Of the 6 Sealant patients with Ptx at 1MFU, Ptx size also decreased from CT pull to 1MFU in 4 of the 6 patients, and increased in only one patient. A change in Ptx size could not be determined for one patient because no Ptx measurement was available at CT pull for this patient.

Sponsor was able to obtain from the study centers post-study follow up information for 5 of the 6 Sealant patients with Ptx at 1MFU. For 4 of the 5 patients where the company was able to obtain information, all data indicated that these patients did not have clinically significant Ptx and that no treatment was required for this observation on CXR.

Only one patient whose Ptx size increased at 1MFU was found to have a clinically important Ptx. However, this patient had numerous risk factors for prolonged air leak and was found to be notable in several ways: (1) this is the only patient in the Sealant group during the entire study who had an adverse event requiring re-hospitalization to place a chest tube for recurrent Ptx; (2) this patient had previously received radiation therapy and chemotherapy, and underwent a redo throracotomy to resect metastatic osteogenic sarcoma[6]; (3) this patient had bilobectomy (right upper and right middle lobe) surgery, creating a very large post-operative pleural space, and so was obviously of higher risk for PAL and Ptx; and (4) this patient had multiple air leaks and, after application of the sealant, still had 2 intraoperative air leaks (IOAL).

There was one patient for whom Sponsor could not obtain post-study follow up information. A review of the study records for this patient was conducted with the assistance of the Principal Investigator which did not reveal any events or characteristics that would suggest the possibility of anything other than an uneventful recovery. Further, this patient had a respiration rate postoperatively and at 1MFU of not more than 20 per minute, suggesting that the observed Ptx was not clinically significant.

Sponsor then evaluated other factors among the Sealant and the Control groups in the CXR evaluation and found several important issues that likely contributed to the findings. First was the type of procedure performed and their risk factors that may contribute to a radiologic Ptx finding at 1MFU. A number of studies have conclusively shown that upper lobe resections (UL) are a major risk factor for persistent air leaks (PAL) and an apical pleural space (which can appear as a Ptx on a CXR) when compared to lower lobe resections[7,8,9,10,11]. Similar results were also observed in this study.

A review of the surgical procedures performed revealed a progressive imbalance in the type of surgery between the Sealant and Control patients, with Sealant patients slightly more likely to have UL than Control patients when considering the total study population, increasing to almost twice the percentage of Sealant patients having UL than Control patients for the independent CXR evaluation subset. This imbalance likely contributed to the larger Ptx size observed in the

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6 Allen, M. S. et al. Prospective Randomized Study Evaluating a Biodegradable Polymeric Sealant for Sealing Intraoperative Air Leaks That Occur During Pulmonary Resection. Ann Thorac Surg 2004; 77: 1792-1801

7 Robinson, LA and Preksto, D. Pleural Tenting During Upper Lobectomy Decreases Chest Tube Time And Total Hospitalization Days. *J Thorac Cardiovasc Surg* 1998; 115:319-327.

8 Abolhoda, A. et al. Prolonged Air Leak Following Radical Upper Lobectomy: an Analysis of Incidence and Possible Risk Factors. *Chest* 1998; 113:1507-1510.

9 Okereke, I. et al. Characterization and Importance of Air Leak After Lobectomy. *Ann Thorac Surg* 2005; 79:1167-1173.

10 Cerfolio, RJ. Recent Advances in the Treatment of Air Leaks. *Curr Opin Pulm Med* 2005; 11:319-323.

11 DeCamp, MM et al. Patient and Surgical Factors Influencing Air Leak After Lung Volume Reduction Surgery: Lessons Learned From the National Emphysema Treatment Trial. *Ann Thorac Surg* 2006; 82:197-207.

Sealant patients and the apparent longer time to Ptx resolution, as compared to the Control patients. As shown in **Table 44**, more Sealant patients had UL surgery than Control patients in the CXR evaluation subset, and for patients with Ptx at CT pull the proportional difference grew to almost 50% more Sealant patients with UL surgery compared to Control patients (47% vs. 33%). Notably, 5 of 6 Sealant patients with Ptx at 1MFU had a right UL.

Table 44 Proportion of Patients Having Upper Lobectomy (UL)

Study Populations	Sealant	Control
Total Study	48/103 (47%)	24/58 (41%)
Independent Radiologist CXR Subset	17/40 (43%)	5/20 (25%)
CT Pull CXR Subset	9/19 (47%)	4/12 (33%)
1MFU CXR Subset	5/6 (83%)	0/0 (N/A)

Another factor among the Sealant and the Control groups in the CXR evaluation that likely contributed to the findings were the actual number of days to 1MFU. The average follow-up for the 6 Sealant patients with unresolved Ptx at 1MFU was found to be shorter than other patients in the Sealant and Control groups who had Ptx at CT pull. Only one-third (2/6) of the Sealant patients had their 1MFU visit more than 5 weeks after surgery compared with two-thirds (8/12) of Control patients with Ptx at CT pull. Moreover, none of the 6 Sealant patients had their 1MFU visit more than 6 weeks after surgery, where 25% of the 12 Control patients with Ptx had an extended time to their 1MFU. The longer follow-up time in the Control group permitted a longer time for resolution of Ptx in these patients, another factor contributing to the lower incidence of Ptx at 1MFU in Control patients.

In conclusion, the independent CXR evaluation demonstrated the objectiveness of the investigators' original assessments of the CXR results. Although the results in this small study suggested a higher incidence of Ptx in the Sealant group than control group at 1MFU, further review of the risk factors and patient outcomes suggests that the CXR findings of Ptx in the Sealant group could be anticipated as simply residual air space that are not clinically significant, and, in any case were not statistically significant.

6.6.9.3 Discussion of Lung Expansion and Pneumothorax

A perspective on risk factors associated with upper lobectomy and the clinical significance of lung expansion, collectively taken from peer reviewed publications, is provided in the following section and in more detail in **Appendix A**.

The precise definition and use of various terms is important to this discussion. Especially, the terms *air space* or *pleural space, partial lung expansion,* and *pneumothorax* all have different meanings and they must not be used interchangeably.

For instance, a post-operative lobectomy patient will commonly have a pleural space where the lobe was removed (see below), and the term *partial lung expansion* is often used to describe evidence of that pleural space on postoperative chest x-rays. Unfortunately the term *partial lung expansion* can also imply that the remaining non-resected lobe(s) of lung have not fully

expanded. In fact the patient's remaining lung may have only *partially* filled the space formerly occupied by the resected lobe yet the remaining lobes are *completely* expanded. This confusing use of the term *partial lung expansion* is why thoracic surgeons more consistently use the term *pleural space*.

The term *pneumothorax,* which literally means air in the chest, is important from the clinical perspective to evaluate whether there is ongoing air leak. If no air leak is present, the more accurate term is *pleural space.*

In our study, after resolution of the air leak, any pleural space was managed by removing the chest tube. This approach is routinely used by thoracic surgeons and is summarized by Cerfolio[12]:

> "If there is no air leak but there is residual air in the pleural space, additional suction can be applied. First, the physician must ensure that the tubes are patent and connected properly. The lung should have been mobilized completely at time of surgery. If these conditions are met, increased suction rarely resolves the residual pleural space problem, because the patient's remaining lung does not fill the space, regardless of the amount of suction applied to the tubes. In this case, and when the space is not infected, removing the tubes is acceptable despite the presence of a pneumothorax. This space, however, should not be called a pneumothorax because the term implies that the lung can re-expand to fill it; calling it a fixed pleural space is probably more appropriate. Regardless, this condition presents no clinical problem unless the tubes are left in too long unnecessarily increasing the chances of infection. As previously described, after the tubes are pulled out, fluid usually fills this space without sequelae."

Residual air space is an expected outcome after upper lobectomy as observed by Robinson[7]:

> "Resection of the upper lobe of the lung leaves behind a very irregular lung surface, which rarely conforms to the apex of the pleural cavity. Therefore, despite the compensatory mechanisms, the net result is the very high incidence of residual postresection apical pleural air spaces especially after upper lobectomy. With modern radiographic techniques, it is apparent that virtually all patients undergoing an upper lobectomy will have an anterior and apical residual air space to some extent."

There is agreement in the literature reports that PAL is the more important condition to treat with no emphasis to aggressively treat residual air spaces. Further, at least one author recommends that any residual pleural space not be over-treated and, in fact, should be left to resolve spontaneously by filling with fluid following chest tube removal.

Studies reported in the literature universally focus on the frequency, duration, and management of air leaks, as prolonged air leaks can lead to such complications as infection, subcutaneous

[12] Cerfolio RJ. Chest tube management after pulmonary resection. Chest Surg Clinic North Am 2002; 12: 507-527.

emphysema, dyspnea, and pneumonia which often result in an extended hospital stay. It is of significance to note that the published findings/positions do not recognize "lung expansion" and "non-expanding pneumothorax" as clinically significant events.

The literature supports the following conclusions of the study:

- Upper lobectomy presents a higher risk for PAL, and PAL has been linked to more complications and longer hospital stays. In our study, the Sealant demonstrated statistical superiority for subjects remaining air leak free through 1MFU (Sealant = 35% vs. Control = 14%, p = 0.004). Moreover, the study demonstrated no statistical difference in adverse events between the Sealant and the Control groups (indeed, the Sealant group had a much lower frequency of pneumonia) and the Sealant demonstrated a shorter hospital stay ($p<0.05$) when compared to the Control group.

- No concerns expressed in the literature about the clinical consequences of "partial lung expansion" in the absence of PAL. Instead, studies of other lung sealants and studies of lobectomy surgery issues universally identify prolonged air leak, especially when symptomatic, as a complication to be treated. Again, in our study, the Sealant group demonstrated superior sealing of air leaks to 1MFU and no elevation in the frequency of complications symptomatic of PAL.

In conclusion, the literature consistently identifies prolonged air leak as a clinically significant complication and our study demonstrated significant superiority over standard therapies for sealing air leaks and for achieving a shorter hospital stay.

6.6.10 Potential Sequelae Related to Partial Lung Expansion

Clinical symptoms and sequelae that may potentially be related to residual air space (partial lung expansion) were identified by two of the study investigators. The specific AEs were selected from the list of all the AEs that occurred in the study population and included fever, dyspnea, pneumothorax, subcutaneous emphysema, atelectasis, respiratory disorder, and sepsis.

Table 45 summarizes these events as they occurred in the Sealant and Control groups. There were more Control subjects than Sealant subjects who had pulmonary-related events. None of the between group differences in the incidence of AEs were statistically significant.

Table 45 Adverse events potentially related to residual airspace by treatment group

Adverse Event	Sealant N=103	Control N=58	p-value
Fever	22 (21.4%)	12 (20.7%)	1.000
Dyspnea	12 (11.7%)	10 (17.2%)	0.346
Pneumothorax	8 (7.8%)	5 (8.6%)	1.000
Subcutaneous emphysema	7 (6.8%)	5 (8.6%)	0.758
Atelectasis	2 (1.9%)	2 (3.4%)	0.620

Adverse Event	Sealant N=103	Control N=58	p-value
Respiratory disorder	1 (1.0%)	1 (1.7%)	1.000
Sepsis	1 (1.0%)	1 (1.7%)	1.000

In the overall study population, both the Sealant and Control groups had similar AE profiles (see **Section 6.6.2**). None of the events reported for either group was considered inconsistent with the diagnoses of the patients and the operative procedures performed. Of the severe AEs reported, only one, dyspnea, is considered potentially related to residual air space.

Partial lung expansions that were identified via CXRs at 30 days were all considered clinically insignificant by the investigators. There were no symptoms or sequelae that required treatment. As discussed earlier, partial lung expansions viewed on a CXR are not "air leaks" but rather caused by anatomical issues related to the extent and type of surgery performed. The critical factors are whether or not the patient was symptomatic at the time, the size of the air space/Ptx, the course of events for that patient, and whether or not the air space enlarges, requires treatment or prolongs hospitalization. The presence of small air spaces, as seen in this study, is typically not considered an AE unless it is unanticipated, alters the patient management due to symptoms or complications that require treatment, or occurs late in the patient's treatment course.

6.6.11 Safety Discussion and Conclusion

The safety evaluation of the Sealant included both clinical and laboratory assessments. The clinical assessment was based on the incidence of AEs that were reported during the study period. The laboratory assessment was based primarily on two immunologic assays: the LPA, used to detect changes in cell-mediated immune response, and an ELISA that detects the presence of circulating IgG antibodies directed against the Sealant and serves as a specific marker for changes in the humoral immune response. Significant changes in blood chemistry and hematology values or vital signs were also reviewed.

Subjects in both the Sealant and Control groups had similar AE profiles. The events reported for both groups were consistent with the diagnoses of the patients and the operative procedures performed. 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. There was no significant difference in the incidence of any AE between treatment groups.

There was a total of 15 SAEs reported during this study: 9 deaths, 5 other SAEs, and 1 UADE. None of the deaths were considered device related. All 5 other SAEs (2 Sealant, 3 Control) resulted in extended hospital stays or rehospitalization. Four subjects recovered from these events and 1 subject continues on dialysis.

The change in cell-mediated immune response, as determined by the LPA, was not significantly different between the Sealant and Control groups, indicating that the Sealant did not alter the ability of the subjects' cells to respond to the antigenic stimulus and that the cells had not been sensitized specifically to the Sealant. The humoral immune response, as detected by ELISA, was negative in both groups, indicating that the use of the device did not result in the formation of antibodies to the Sealant.

Overall, the AE profile of both the Sealant and Control groups was similar and not atypical of the patient population studied. There were no laboratory values, humoral or cell-mediated immune response results, vital signs or other physical findings of statistical or clinical concern. In general, the Sealant was well tolerated by the subjects in this study population.

7 RISK-BENEFIT ANALYSIS

7.1 Benefits of the Sealant

The clinical study results showed that the sealant was significantly more successful in sealing intraoperative air leaks (IOALs) and in reducing the incidence of POALs compared to the Control. The sealant was found by the investigators to be easy to use, clinically effective as an adjunct to standard methods of air leak closure, and without any significant safety issues in the population studied.

Reduces POALs. The occurrence of POALs is a common problem following pulmonary surgery and is the most common postoperative condition that causes a prolonged hospital stay for these patients in the United States. The sealant provides the surgeon with an effective device to help reduce the incidence of POALs. The proportion of subjects who remained air leak free throughout the study was significantly greater ($p=0.005$) in the Sealant group (35%) compared with the Control group (14%). The control of IOALs and the potential to decrease the incidence of POALs are clinically significant factors in reducing the morbidity and length of hospital stay of patients undergoing lung resection surgery.

Seals Intraoperative Air Leaks. The clinical results showed that the sealant, when used as an adjunct to standard methods, was statistically more successful in eliminating IOALs than standard methods (sutures and staples) ($p<0.001$). IOALs were sealed in 71% of Sealant subjects compared with only 10% of Control subjects. The results showed that the sealant was most successful with small to medium size air leaks ($\leq$5 mm) and when fewer IOALs were identified in surgery. The sealant was always associated with a higher proportion of sealed IOALs than the Control, regardless of the number, size or source of IOALs. Intraoperative success in sealing air leaks is an important step toward managing POALs, which is significant because persistent POALs are associated with increased morbidity, hospitalization and costs. The clinical importance of POALs is clearly related to lengthened hospital stay.

Potential to Reduce Air Leak Duration. Prolonged or persistent POALs remain a common problem for patients undergoing lung resection surgery. The duration of POALs was comparable

for both treatment groups, with the majority of POALs in both groups lasting less than three days. The Sealant subjects were shown to have a greater opportunity to be discharged earlier with a HV compared to Control subjects with prolonged air leaks due to diminished fluid drainage from their chest tube, fewer adverse outcomes, and a stable CXR. Early discharge with a HV is viewed as a favorable outcome as it allows patients with a persistent air leak to be managed on an outpatient basis.

Potential to Reduce Chest Tube Duration. CT duration is directly related to air leak duration and was comparable for both treatment groups (the median duration was 5 days in both groups). As stated above, more Sealant subjects had isolated air leaks without major fluid drainage, without adverse events requiring extended hospital care, and a stable CXR that allowed consideration of early discharge for those patients. This result is important, as there is a strong clinical, psychological and financial benefit to patients of being able to be managed as outpatients, even though a CT may still be required.

Reduced Length of Stay. The median LOS for Sealant subjects was significantly shorter ($p=0.04$) compared to the Control subjects (the median LOS was 6 and 7 days, respectively). Since this difference could not be attributed to reduced air leak or CT durations, other factors were considered. The incidence of prolonged air leaks that resulted in hospital stays >10 days was similar between the two groups (5% of Sealant group vs. 3% of Control group). The frequency of other complications appeared to be comparable, with the exception of a higher frequency of pneumonia in the Control group than in the Sealant group (12% vs. 5%), which may partially explain the difference in LOS. More Sealant subjects were considered candidates for outpatient management with a HV, as mentioned above, which may also be a contributing factor to a shorter LOS in the Sealant group.

7.2 Potential Risks of the Sealant

While several issues have been raised by the FDA as potential risks of the sealant, the following discussions highlight some key information from the clinical study that support NeoMend and the study investigators' belief that the risk associated with the sealant is minimal.

Similar Adverse Event Profile. It is important to emphasize that there was no difference in the AE profile of the Sealant and Control subjects and there was no statistical difference in the incidence of any of the AEs reported. This further supports that there is no increased risk associated with the use of the sealant as an adjunct to standard methods of sealing air leaks. All of the AEs reported for both groups were consistent with the diagnoses of the patients and the operative procedures performed. Most of the AEs were mild to moderate in severity. There were no AEs suggesting an immune response to the sealant. Of the 15 SAEs reported, none of the deaths or other SAEs were considered to be device-related by the investigators. There was one unanticipated adverse device effect observed during the study.

Prolonged Air Leak Duration/Chest Tube Duration. Chest tube duration is directly related to air leak duration. There were a total of 22/102 (21.5%) of the Sealant subjects and 11/58 (19%) of the Control subjects who had an air leak beyond postoperative day 5 (POD5). This difference is

not statistically significant. Within this subset of subjects, 55% (6/11) of the Control subjects had more adverse events that were a predominant factor prolonging hospitalization compared to 27% (6/22) in the Sealant subjects. The differences in air leak and chest tube durations between the Sealant and Control groups were directly affected by the increased opportunity for Sealant subjects to be discharged with a HV (10 Sealant vs. 1 Control) due to diminished fluid drainage and/or fewer AEs requiring extended hospital stay and a stable CXR compared to the Control group. While the use of HV was advantageous to the patient, the physician, and the hospital system, the use of HV skewed the incidence of prolonged air leaks (>11 days) to a greater degree in the Sealant group. Following discharge from the hospital, subjects with HVs would return to the clinic on a weekly basis only to have their HV checked for air leaks. Therefore, a conservative ascertainment of the end date of air leaks was made for these subjects. It should be noted that the proportion of patients with CT placement >11 days excluding patients discharged from the hospital with a HV was similar in the Sealant and Control groups, 4.3% (4/93) and 3.5% (2/57), respectively. NeoMend and the study investigators believe that this result demonstrates the beneficial outcome of outpatient CT management with a HV, and does not suggest any adverse outcomes associated with the use of the Sealant.

Development of New POALs. FDA raised a concern regarding the difference in the development of new POALs (on POD1 or after, that persisted beyond POD5) in 27% (6/22) of the Sealant subjects compared to 9% (1/11) of the Control subjects. It is not statistically valid to make this comparison based on a subset of patients according to their response to treatment. It is rather necessary to compare the development of POAL, on POD1 or after, based on the total study population randomized to treatment. In this comparison, there were 19.4% (20/103) Sealant subjects and 18.9% (11/58) Control subjects who developed a POAL on or after POD1. There is no statistical difference between the Sealant and Control group with respect to the development of POALs on or after POD1, and this nominal difference is not considered clinically significant by the study investigators.

These POALs may be "new" ALs or they may represent the re-opening of leaks that had been sealed during surgery. It was not possible to distinguish between these two sources of POALs in this study. As stated above, the development of new ALs is common after major pulmonary resection and it is not expected that the sealant would be successful in preventing these new ALs. There was no evidence to suggest that the new POALs in the clinical study represent any sealant-related failure. Some of the discrepancy may lie in the fact that 90% of Control subjects still had ALs at the end of surgery that were not sealed, leaving little opportunity to detect new ALs in this group. Conversely, since most of the Sealant subjects had their IOALs sealed at surgery; the chances of documenting the development of a new AL was potentially greater. There is no suggestion that the development of new ALs was device related.

Short Sealant Residence Time. Information from the rat study suggested to the agency that some of the clinical outcomes may have occurred because the sealant resorbed so that the sealed ALs may re-open before the lung tissue was able to fully heal. The resorption time in humans is expected to be longer than in rats because the surface area to volume ratio is smaller in humans. Therefore, the relatively quick resorption time observed in rats cannot be directly linked to clinical outcomes.

The issue of critical residence time of the sealant is a function of the rate at which extracellular matrix from fibroblasts replaces the sealant. The literature on wound healing indicates that normal healing leads to an influx of fibroblasts by four days and collagen deposition begins shortly thereafter. As the deposition of extracellular matrix increases, the need for the sealant decreases. Based on surface area to volume considerations, it is anticipated that the sealant will have a dissolution time that is sufficient to seal ALs until normal healing takes place.

Preclinical evidence supports that the residence time of the sealant is sufficient to seal ALs during the healing process. To evaluate the effect of the sealant in the lung on wound healing, the study Sponsor conducted a study in a model that most closely resembles the healing rate of humans, an experimental pig model. In the study, the presence or absence of the sealant was also noted. At four days there was residual sealant present and the ingrowth of extracellular matrix was sufficient to provide the closure necessary to maintain the seal initiated by the sealant. These preclinical results provide evidence that the sealant is able to perform as a mechanical seal for a period of time until sufficient natural wound healing has occurred.

Importantly, the clinical evidence is consistent with the preclinical findings, *i.e.*, that the rate of extracellular matrix replacement is sufficient for sustained closure. This is demonstrated by the statistically significant difference seen in the study's primary endpoint. After surgery, the proportion of subjects who remained air leak free was significantly greater in the Sealant group, suggesting that the Sealant, when used as an adjunct to sutures and staples, maintained its adherence properties over time. In addition, there was no significant difference in the occurrence of late ALs between the two groups. While the Sealant may not seal all ALs, it does offer an adjuctive method for the surgeon to use that can help improve the results of standard AL closure methods alone.

Partial Lung Expansion/Pneumothorax 30 days After Surgery. The clinical study showed a slight trend toward more Control subjects with complete lung expansion 30 days after surgery than Sealant subjects. This nominal difference between the two groups is not considered clinically significant. Partial lung expansion and radiologic pneumothorax are often used to describe a residual air space after major pulmonary resection. It is important to distinguish the radiological observation of an air space from the condition of a clinically significant pneumothorax. The radiological observation of an air space supports a clinical diagnosis of pneumothorax, but is insufficient by itself to diagnose a clinical AE associated with pneumothorax. Only when the patient becomes symptomatic or requires intervention, does air in the pleural space become a pneumothorax AE. It is expected that a residual air space will be present after lung resection due to the inability of the remaining lung tissue to completely fill the chest cavity. This observation has been categorized in this study as partial lung expansion, but it represents a geometric consequence of surgery and does not suggest sealant failure or an adverse outcome. The presence of an air space is not an AE but rather an expected outcome of thoracic surgery, particularly with patients who have undergone upper lobectomy. If device failure occurred after CT removal, this would be clearly evident by the new development of an enlarging pneumothorax and/or subcutaneous emphysema. These sequelae would be symptomatic and clinically significant, resulting in the need for CT replacement, which did not occur in the study.

In addition, an analysis of the incidence of AEs that were considered indicative of clinically meaningful ALs was conducted between subjects with partial lung expansion and complete lung expansion. No significant differences were observed that would suggest that there was any association between the presence of the partial lung expansion and relevant AEs.

7.3 Conclusion

Based on the outcomes of the clinical study, no clinically significant safety or performance issues were observed that would preclude use of the Sealant as an adjunct to standard methods of AL closure. The intraoperative results of the clinical study demonstrated that the Sealant adhered, expanded with the lung, and was able to significantly seal more IOALs compared to the Controls. The use of the Sealant also significantly reduced the incidence of POALs compared to the Control. Moreover, the length of hospital stay was significantly shortened in the Sealant patients compared to Controls. The study investigators found the Sealant to be easy to use and perceived a clinical benefit of the Sealant without significant device-related AEs. In summary, the Sealant achieved the intended performance as a soft tissue reinforcement to be used for sealing or reducing air leaks that occur during pulmonary surgery.

8 OVERALL CONCLUSIONS

POALs continue to be one of the most common complications of pulmonary surgery. Consequently, there is a recognized need for a product that effectively seals IOALs. The objective of this study was to evaluate the safety and efficacy of the Sealant to seal IOALs in patients undergoing a thoracotomy and thereby reduce the incidence of POALs. To better assess the Sealant's ability to seal IOALs, the protocol required that subjects randomized into the study had at least one clinically significant IOAL, defined as ≥2 mm in size.

The results of this study demonstrated a significantly greater proportion of Sealant subjects (35%) remained air leak free following surgery through 1MFU (or the duration of hospitalization, whichever was longer) compared to the Control subjects (14%) ($p=0.005$).

The results of this study also demonstrated a significantly greater proportion of IOALs were sealed in Sealant subjects (71%) compared to Control subjects (10%) and of the 318 individual IOALs tracked, 161/210 (77%) were sealed after the application of Sealant compared to 17/108 (16%) in the Control group. The differences between Sealant and Control groups were statistically significant ($p<0.001$).

The results of this study also demonstrated a significantly greater proportion of Sealant subjects (54%) were air leak free during the observation period in the recovery room compared to Control subjects (33%). The duration of ALs was comparable for both treatment groups with the majority of ALs lasting less than 3 days (the median duration was 2 days in both groups). The duration of CT placement was also comparable with a median duration of 5 days for both groups. The median length of hospital stay was significantly shorter for subjects in the Sealant Group compared with subjects in the Control group.

The results of this study demonstrated no statistically significant difference in the incidence of AEs between the Sealant and Control groups. A total of 14 SAEs was recorded: 9 deaths (5 Sealant, 4 Control), and 5 other SAEs (2 Sealant, 3 Control) and none was considered device related. There was 1 other SAE in the Sealant group (pneumothorax three weeks post surgery) considered by the investigator to be an UADE due to the temporal relationship of the event with the use of the Sealant. There were no significant changes observed in humoral and cellular immune responses between the Sealant and Control groups, indicating the lack of immune response to the Sealant.

These results support the safety and effectiveness of the Sealant when used as an adjunct to standard closure of ALs incurred during pulmonary surgery.

APPENDIX A

Discussion of Lung Expansion and Pneumothorax

1. Terminology

The precise definition and use of various terms is important to this discussion. Especially, the terms *air space* or *pleural space, partial lung expansion,* and *pneumothorax* all have different meanings and they must not be used interchangeably.

For instance, a post-operative lobectomy patient will commonly have a pleural space where the lobe was removed (see below), and the term *partial lung expansion* is often used to describe evidence of that pleural space on postoperative chest x-rays. Unfortunately the term *partial lung expansion* can also imply that the remaining non-resected lobe(s) of lung have not fully expanded. In fact the patient's remaining lung may have only *partially* filled the space formerly occupied by the resected lobe yet the remaining lobes are *completely* expanded. This confusing use of the term *partial lung expansion* is why thoracic surgeons more consistently use the term *pleural space*.

The term *pneumothorax,* which literally means air in the chest, is important from the clinical perspective to evaluate whether there is ongoing air leak. If no air leak is present, the more accurate term is *pleural space.*

In the Neomend Clincial Study, after resolution of the air leak, any pleural space was managed by removing the chest tube. This approach is routinely used by thoracic surgeons and is summarized by Cerfolio in the following.

> "If there is no air leak but there is residual air in the pleural space, additional suction can be applied. First, the physician must ensure that the tubes are patent and connected properly. The lung should have been mobilized completely at time of surgery. If these conditions are met, increased suction rarely resolves the residual pleural space problem, because the patient's remaining lung does not fill the space, regardless of the amount of suction applied to the tubes. In this case, and when the space is not infected, removing the tubes is acceptable despite the presence of a pneumothorax. This space, however, should not be called a pneumothorax because the term implies that the lung can re-expand to fill it; calling it a fixed pleural space is probably more appropriate. Regardless, this condition presents no clinical problem unless the tubes are left in too long unnecessarily increasing the chances of infection. As previously described, after the tubes are pulled out, fluid usually fills this space without sequelae"[1].

2. Review of Lung Resection Literature

2.1 Risk Associated with Upper Lobectomy

The incidence of pleural space or air space is frequent in the early postoperative period after pulmonary resection, particularly after upper lobe resection. In 1998, Robinson and co-workers[2] conducted a retrospective review of 48 patients undergoing isolated upper lobectomy at their institution with the objective of assessing the effectiveness of pleural tenting in these procedures. Robinson reported that "By standard chest radiography, 20-40% of all patients having major lung resection will initially have a pleural space. But with more sophisticated imaging, it is apparent that most patients will have a space and virtually all undergoing an upper lobectomy will have an anterior and apical space."

Robinson explained the compensatory response to the pleural space in the following:

> "Mechanisms for physiologic compensation seen initially after a partial lung resection that tend to obliterate the free pleural space include: (1) hyperexpansion of the remaining lung and some remodeling of the lung shape to fit the space; (2) shift of the mediastinal structures to the operated side; (3) elevation of the ipsilateral diaphragm; and (4) narrowing of the ipsilateral intercostal spaces if the chest wall is not involved with restrictive disease."
>
> "Most patients undergoing a lung resection have some degree of chronic obstructive lung disease and their lungs are already hyperexpanded, which negates the effectiveness of the first compensatory mechanism. Prior mediastinal radiation therapy or chest surgery such as coronary artery bypass grafting, which is exceedingly common in the lung cancer population, often results is a relatively immobile mediastinum, thereby diminishing the effect of the second space-decreasing mechanism listed above. Finally, the most common definitive operative procedure for lung cancer is an upper lobectomy because most primary lung cancers arise in the upper lobes. Resection of the upper lobe of the lung leaves behind a very irregular lung surface, which rarely conforms to the apex of the pleural cavity. Therefore, despite the compensatory mechanisms, the net result is the very high incidence of residual postresection apical pleural air spaces especially after upper lobectomy. With modern radiographic techniques, it is apparent that virtually all patients undergoing an upper lobectomy will have an anterior and apical residual air space to some extent."

Abolhoda, et al[8], performed a retrospective review of 100 consecutive patients in 1998 who had right upper lobectomy and mediastinal lymph node dissection with the objective of examining incidence and clinical significance of prolonged air leak (PAL), and to determine clinical risk factors for PAL in the group of patients. In their series of right upper lobectomies, they found that an "alarmingly large percentage of patients required prolonged chest tube drainage for PALs." Most importantly, Abolhoda concluded that upper lobectomies often result in large apical air spaces with poor visceral-parietal pleural apposition, and that this pre-disposed these

patients to longer PAL, thus establishing a link between upper lobectomies, large apical air spaces, and PAL.

More recently, Okereke et al[13], performed a prospective study of 319 patients undergoing isolated anatomic lobectomy, with the objectives of determining the prevalence of an air leak and identifying its risk factors, characterizing the duration of air leak and discovering its correlates, and evaluating the importance of air leak to patient recovery. Okereke reported that 70% of recorded air leaks followed either right or left upper lobectomy surgeries, while the remainder was associated with left lower, right lower, and right middle lobectomies.

Cerfolio[11] authored in 2006 a literature review of air leak treatment. Similar to Abolhoda, he linked risk factors for air leaks to large resections that leave a large pleural space deficit and states that a pleural space need not be over-treated in preference to air leaks. Again, Cerfolio stated that an upper lobectomy and bilobectomy are factors that increase the risk of a PAL, where removal of a large amount of pulmonary parenchyma leaves a very large pleural space with little chance of parietal pleural-to-visceral pleural apposition. Most importantly, Cerfolio also pointed out that some patients have a fixed pleural space deficit, defined as a non-resolving pneumothorax in a patient with a fully expanded lung and patent chest tubes that are on suction and in the pneumothorax, and advises such a space is best left alone and not over-treated. If the patient does not have an air leak, the tubes should be removed, and the space will fill with fluid.

DeCamp et al[12] conducted a review of 552 patients in the National Emphysema Treatment Trial (NETT) to identify risk factors for air leak occurrence and duration following Lung Volume Reduction Surgery (LVRS). Similar to the results of Okereke et al, De Camp reported that 73% of air leaks following LVRS were following surgery to treat predominantly upper lobe disease. Further, upper lobe and diffuse disease presented a higher risk of longer air leaks (correlation coefficient = 0.89).

In summary, there is abundant scientific evidence that upper lobectomy is a know risk factor for pleural space and prolonged air leak.

2.2 Clinical Significance of Lung Expansion.

A comprehensive literature search was conducted on lung resection surgery to identify the outcomes and complications that are considered clinically significant. This search included the topics of air leak and chest tube management following lobectomy, management of pneumothorax, management of complications following pulmonary resection and lung volume reduction surgery, and lung expansion following lobectomy.

The literature search identified at least 14 relevant publications, in addition to the publication of NeoMend Clinical Study results by Allen et al, as follows:

- 5 randomized studies (minimum 50 patients each) of lung sealants (fibrin glues, CoSeal, FocalSeal-L/AdvaSeal) with an aggregate of 635 patients from U.S. and foreign centers[3,4,5,6,7].
- 9 studies of various lung surgery topics (e.g. air leaks, chest tube management, surgical complications) with an aggregate of 3,475 patients from U.S. and foreign centers[8,9,10,11,12,13,14,15,16].

General Findings

The literature search revealed that all of the randomized studies of various lung sealants were designed to compare the frequency and duration of air leaks of the sealant group to a control group during lobectomy. None of the lung sealant studies listed lung expansion or pneumothorax as an efficacy or safety endpoint. Moreover, none of the lung sealant studies reported any data comparing lung expansion or pneumothorax between the sealant and the control groups.

The literature search also revealed numerous studies or articles of complications of lung resection surgery. These studies universally focus on the frequency, duration, and management of air leaks, while none of the studies reported any data regarding lung expansion or provided any substantive discussion of the clinical importance of lung expansion following lung resection surgery.

Citing specific publications

Abolhoda et al[8], in a study of 100 consecutive right upper lobectomy patients, concluded "PAL (prolonged air leak) represents a major source of morbidity and is the most frequent cause of an extended length of hospitalization in patients undergoing upper lobectomy." Abdolhoda further reported "as evidenced in our series, patients with even mild-to-moderate pulmonary dysfunction are at risk to develop PAL, and that preventive strategies should include all patients undergoing upper lobectomies."

Regarding pneumothorax, Cerfolio[16] stated that "quantifying the size of a pneumothorax on a portable CXR is difficult to do." Cerfolio further stated that "Although we believe that parietal pleura to visceral pleura apposition is an important factor for the healing of air leaks, this study has shown it is not a necessary component. Some patients have fixed pleural space deficits after pulmonary resection. The elasticity and/or compliance of the remaining lung, chest wall, and diaphragm are such that the remaining lung cannot fill the pleural space. This residual space will fill with non-infected fluid over time if the tubes are removed quickly."

Okereke's[13] study of air leaks stated that "presence of air leak (regardless of duration) predicts a worse outcome (longer hospital stay and more complicated postoperative course). Thus, we now consider any air leak as a surgical complication, not simply those lasting 7 days or more. This emphasizes the importance of preventing air leak at the time of operation. A comprehensive strategy for air leak must include both prevention and effective management."

Cerfolio[11] clarified management of air leaks by stating that "A pneumothorax is not an indication for suction. . . . patients can safely go home with an air leak and with chest tubes. The tubes can be managed on an outpatient basis and then removed, even if the patient still has an air leak, as long as there is no subcutaneous emphysema or a symptomatic pneumothorax."

Schmidt[15] reported on a study of 470 patients that "residual postoperative pneumothorax was observed in 20.7% of the patients at discharge after removal of the chest tubes," and concluded "there is no need for treatment of residual postoperative pneumothorax . . ."

Misthos[14] in 2005 reported on a study of 966 patients following lung resection to determine frequency and sequelae of residual pleural spaces. His finding was that 92 (9.5%) of patients had residual pleural space "which developed frequently ($p<.001$) after upper lobectomies, malignant disease, at an apical location, and on the right side." Misthos concluded that "postresectional residual pleural spaces of small size without any associated complications should not prolong hospitalization time."

Murthy[17] reported on the problem of air leak and the potential complications, namely infection or empyema. He states "Patients with air leakage have an increase in other complications and a protracted hospital stay. Consequently, prevention and effective management are critical." Murthy further states that "Reoperation for intractable air leakage is uncommon and should be considered only after other options have been exhausted or discounted. The main risk of continued conservative expectant management of air leak is empyema."

3. Conclusion

Studies found in the literature consistently state that upper lobe resections increase the risk and duration of post operative air leaks and residual air spaces. It is also notable that there is universal agreement that PAL is the more important condition to treat with no emphasis to aggressively treat residual air spaces. Further, at least one author recommends that any residual pleural space not be over-treated and, in fact, should be left to resolve spontaneously by filling with fluid following chest tube removal.

With regard to partial lung expansion, it is of considerable significance to note that the published findings/positions do not recognize "lung expansion" and "non-expanding pneumothorax" as clinically significant events nor do any studies link partial lung expansion to any clinically significant complications or outcomes and no studies of lung sealants use these outcomes for safety or efficacy endpoints.

Instead, all of the studies emphasize avoidance or management of air leaks, as prolonged air leaks can lead to such complications as infection, subcutaneous emphysema, dyspnea, and pneumonia which often result in an extended hospital stay.

In conclusion, the literature consistently identifies prolonged air leak as a clinically significant complication and NeoMend Clinical Study clearly demonstrated significant superiority over standard therapies for sealing air leaks and for achieving a shorter hospital stay.

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