SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Surgical Sealant
Device Trade Name:	ProGel™ Pleural Air Leak Sealant
Applicant's Name and Address:	NeoMend, Inc 60 Technology Drive Irvine, CA 92618
Date of Panel Recommendation:	June 12, 2008
PMA Application Number:	P010047
Date of FDA Notice of Approval:	January 14, 2010

II. INDICATIONS FOR USE

The ProGel™ Pleural Air Leak Sealant is indicated for application to visceral pleura during an open thoracotomy after standard visceral pleural closure with, for example, sutures or staples, of visible air leaks (≥ 2 mm) incurred during open resection of lung parenchyma.

III. CONTRAINDICATIONS

- Do not use ProGel™ in patients who have a history of an allergic reaction to Human Serum Albumin or other device components.
- Do not use ProGel™ in patients who may have insufficient renal capacity for clearance of the ProGel™ polyethylene glycol load.
- Do not apply the ProGel™ on open or closed defects of main stem or lobar bronchi due to a possible increase in the incidence of broncho-pleural fistulae, including patients undergoing pneumonectomy, any sleeve resection or bronchoplasty.
- Do not apply ProGel™ on oxidized regenerated cellulose, absorbable gelatin sponges or any other surface other than visceral pleura as adherence and intended outcome may be compromised.
- Do not use more 30ml of ProGel™ per patient.

IV. WARNINGS AND PRECAUTIONS

See warnings and precautions can be found in the ProGel™ labeling.

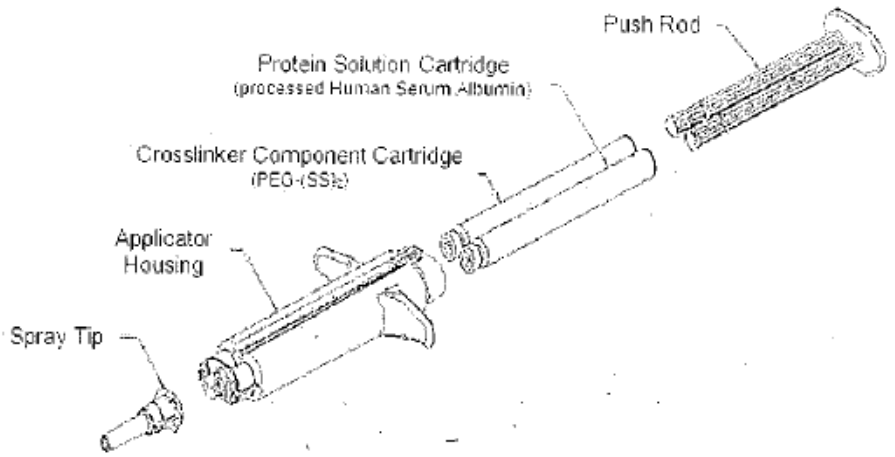
V. DEVICE DESCRIPTION

The NeoMend Inc. ProGel™ Pleural Air Leak Sealant ("ProGel™") is a single-use medical device that is formed as a result of mixing two components: (1) a solution of human serum albumin (HSA) and (2) a synthetic cross-linking component of polyethylene glycol (PEG) that is functionalized with succinate groups. Upon mixing a clear, flexible hydrogel is formed.

ProGel™ is supplied as a sterile, single-use, 2 - component kit which, when mixed makes a 4 ml total volume for application to visceral pleura as an adjunct to standard visceral pleural closure of visible air leaks incurred during resection of lung tissue. As ProGel™ degrades it is metabolized and cleared primarily through the kidneys. The kit includes:

- One (1) - Chemistry Kit —
  - One (1) - pre-loaded cartridge containing 2 ml of Protein solution (processed Human Serum Albumin)
  - One (1) - pre-loaded cartridge containing Polyethyleneglycol di-succinimidyl succinate ((PEG-(SS)2)) as a dried white powder.
- One (1) - Applicator Kit —
  - One (1) - 3 ml plastic syringe with 0.5 inch 26 gauge needle.
  - One (1) - 5 ml vial of USP sterile water for injection (2ml to be used to reconstitute PEG-(SS)2)
  - One (1) - Applicator assembly
  - Two (2) - Spray tips
- One (1) – Instructions for Use (Labeling)

FIGURE 1 ProGel™ PLEURAL AIR LEAK SEALANT DELIVERY SYSTEM (STERILE WATER AND SYRINGE NOT SHOWN)



The Human Serum Albumin (HSA-USP) used to manufacture the ProGel™ is obtained from a U.S. Food and Drug Administration (FDA) licensed supplier and is derived from plasma collected from donors who have been previously screened and tested according to the methods specified by the FDA. These methods are designed to minimize the possibility that blood drawn from donors will contain communicable diseases or viruses such as hepatitis and HIV.

VI. ALTERNATIVE PRACTICES OR PROCEDURES

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

VII. MARKETING HISTORY

The ProGel™ has not been marketed in the United States or any foreign country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device. These events include: Fever, Atrial Fibrillation, Dyspnea, Constipation, Nausea, Pneumothorax, Confusion, Hypotension, Anemia, Pain, Subcutaneous Emphysema, Tachycardia, Death, Oliguria, Vomiting, Pneumonia, Pulmonary Infiltration, Chest Pain, Pleural Effusion, Urinary Retention, Ileus, Supraventricular Tachycardia, Abdominal Pain, Arrhythmia, Extrasystoles, Coughing, Hypoxia, Acute Renal Failure, Adult Respiratory Stress Syndrome, Hyperkalaemia, Hyponatraemia, Cardiac Arrest, Abnormal ECG, Abnormal Renal Function, Asthenia, Influenza-Like Symptoms, Somnolence, Enlarged Abdomen, Atelectasis, Postoperative Wound Infection, Multiple Organ Failure, Anxiety, Withdrawal Syndrome, GI Haemorrhage, Hypokalaemia, Arrhythmia Atrial, Respiratory Disorder, Respiratory Insufficiency, Sepsis, Bronchial Obstruction, Staphylococcal Infection, Pruritus, Delirium, Hypertension, Angina Pectoris and Hemoptysis.

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

IX. SUMMARY OF PRECLINICAL STUDIES

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

Table 1: Preclinical Testing for ProGel™

Study	Test Article(s) Preparation	Findings
Cytotoxicity	Extraction, Neat[1]	Non-cytotoxic
Irritation, Primary Dermal –Rabbit	*In situ* polymerization[1]	Non-irritant
Irritation, Ocular – Rabbit	*In situ* polymerization[1]	Mild irritant
Irritation (IC) – Rabbit	Extraction[1]	Non-irritant
Irritation (IC)- Rabbit	*In situ* polymerization[1]	Moderate – Severe irritant
Hemolysis	Extraction[1]	Non-hemolytic
Pyrogenicity- Rabbit	Extraction[1]	Non-pyrogenic
Sensitization- Guinea Pig	Extraction[1]	Sensitizer
Sensitization- Guinea Pig	Neat[2]	Sensitizer
Sensitization - Guinea Pig	*In situ* polymerization[3]	Non- sensitizer
Human Repeat Insult Patch Test	*In situ* Polymerization[4]	Non-irritating/Non-sensitizer, when applied topically to 10 subjects
Acute Systemic Toxicity – Mice	Extraction[4]	No systemic toxicity
Subchronic Toxicty – Mice, 7/14 Day	*In situ* polymerization[1,5]	No systemic effects noted. Enteropathy noted at implantation contact sites.
Subchronic Toxicity – Rat 28 Day Study	*In situ* polymerization[1]	No systemic effects noted. Enteropathy noted at implantation contact sites at day 8 but no anatomical findings at day 29.
Subchronic Toxicity – Rat 7 Day Study	*In situ* Polymerization[1,4]	No systemic effects noted. Enteropathy noted at implantation contact sites. The enteropathy was mitigated by the instillation of saline into the peritoneal cavity post implantation.
Ames Mutagenicity	Extraction[1]	Non-mutagenic
Ames	Extraction[4]	Non-mutagenic

Mutagenicity		
Ames mutagenicity	Neat[6]	Non-mutagenic
Mouse lymphoma	Extraction[4]	Non-mutagenic
Chromosome aberration	Extraction[1]	Non-clastogenic
Micronucleus – Rat	*In situ* Polymerization[4]	Non-genotoxic
Pilot Mass Balance – Rat	*In situ* Polymerization[7]	No gender difference, urine was primary route of excretion. Virtually all of the ProGel™ was eliminated 14 days past application.
Full-Scale Mass Balance – Rat	*In situ* Polymerization[8]	No gender difference. Virtually all of the ProGel™ was eliminated 14 days past application.
Histopathology – Pig 7 Day Efficacy	*In situ* Polymerization[1]	No evidence of an immune response
Tissue Healing – Pig 28 Day Study	*In situ* Polymerization[4]	No evidence of an immune response. Wound healing progressed normally.
Efficacy Study-Pig	*In situ* Polymerization[1]	Thoracotomy procedure in 6 pigs. ProGel™ applied to ALs >1000 cc/min. No leaks at day 7, original test sites remained closed.
Gel Time	*In situ* Polymerization[1]	An average gel time of 13.7 sec was measured with two lots of investigational product.
Burst strength	*In situ* Polymerization[1]	An average burst strength of 114.3 mm Hg was determined with two lots of investigational product.
Sterilization		E-Beam sterilization of the device was determined via ANSI/AAMI/ISO 11137, Method 2B. The results demonstrated that the device is sterile with a SAL of 10^{-6}.
Shelf-Life		A shelf life of 12 months was demonstrated by retention of device sterility, protein composition, and device burst strength.

[1]ProGel™ containing human albumin component, gamma sterilized.
[2]Commercially available Guinea Pig serum albumin, processed, e-beamed.
[3]ProGel™ containing cross-linked low endotoxin prepared Guinea Pig albumin component, e-beamed.
[4]ProGel™ containing human albumin component, e-beamed.
[5]ProGel™ containing rat albumin component gamma sterilized.
[6]PEG-SS2 crosslinker, e-beamed.
[7] ^{14}C Labeled ProGel™
[8] ^{14}C Labeled ProGel™, e-beamed sterilized.

Thus, *in vitro* and *in vivo* studies as well as a human repeat insult patch test with 10 volunteers suggest that ProGel™ Pleural Air Leak Sealant is:

- Non-cytotoxic, non-toxic, non-hemolytic, non-pyrogenic, a non-sensitizer, non-mutagenic and non-immunogenic.

- Data from rat and pig studies suggest that the device is rapidly cleared from the body, e.g., 50% of ^{14}C-labeled crosslinker in a polymerized device was excreted by day 1 from rats. While some ProGel™ polymerized on pigs' lungs was present at 7 days after implantation, it was absent by 14 days after implantation.

- 70% of the radioactivity associated with ^{14}C-labeled crosslinker in a polymerized device was recovered in the urine, thus, kidneys appear to be the major pathway for ProGel™ elimination.

- Device polymerization onto the serosal surface of rats' peritoneal cavity resulted in short term slight to moderate inflammation at the implant site. At day 8, but not 29 days after *in situ* device polymerization, enteropathy was observed at the treatment site of both test and control animals with the incidence and severity of these findings being greater in several mid and high dose animals. Animals that underwent *in situ* device polymerization with additional saline instillation in the abdominal cavity displayed a decrease in the incidence and severity of enteropathy.

- The preclinical testing indicated that ProGel™ was safe to be used in humans.

X. SUMMARY OF CLINICAL STUDY

The applicant performed a clinical study to establish reasonable assurance of safety and effectiveness of ProGel™ for application to visceral pleura during an open thoracotomy after standard visceral pleural closure with, for example, sutures or staples, of visible air leaks (≥ 2 mm) incurred during open resection of lung parenchyma in the US under IDE # G980283. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

The study was a prospective, "standard care alone" – controlled, 2 to 1 randomized trial conducted by 5 thoracic surgeon investigators and 5 sub-investigators at 5 centers in the US. Investigators received detailed device use training, which included animal model practice; the sub-investigators received basic bench - top training.

1. Clinical Inclusion and Exclusion Criteria

Qualifying patients were adults who were undergoing open thoracotomy and willing to use birth control up to 6 weeks post-surgery and who had intra-operative air leak (≥ 2mm) following surgery. Patients were excluded if they had a known hypersensitivity to human albumin, were enrolled in the National Emphysema Treatment Trial or any other study involving tissue sealants, or any other study not approved by the sponsor. Subjects were also excluded if pregnant and / or breast feeding, if they had significant clinical disease that might complicate surgery and / or post-operative recovery and in the investigator's opinion would complicate evaluation of device safety and effectiveness.

Enrolled patients were stratified according to pre-operative percent predicted FEV1 (≤40%, >40%). In preparation for open thoracotomy closure, after evaluation per standard protocol with air leak test and initial attempt to close air leaks (AL) with standard care (suture / staples), subjects with at least one clinically significant IOAL (≥ 2

mm in size), were randomized whether or not to receive ProGel™ as an adjunct for visceral pleural air leak closure. 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 mm Hg (30-40 cm water) and looking for air bubbles, which would represent ALs. The size of each AL was estimated. 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 excluded. For enrolled subjects, the size (i.e., < 2 mm, 2-5 mm, and > 5 mm bubbles), location on the lung and source (e.g. staple line, fissure) of the bubbles coming from ALs were recorded. If a subject had more than 5 leaks, the investigator was only required to record data on the first five air leaks. Up to three attempts to seal AL with the ProGel™ were permitted.

2. Follow-up Schedule

Follow-up through 30 days post-operatively, included evaluation of chest x-rays, chest tube air leak, chest tube drainage, laboratory values, and AEs, as well as time to chest tube removal and patient discharge.

Chest tube management was pre-specified as follows:
The chest tube will be placed on suction (20-25 cm H20) for the first 24 hours. After 24 hours, if there is no air leak, a switch to water seal will be made. If there is still an air leak after 24 hours the switch will be at the discretion of the surgeon; a record of what was done will be noted. The chest tube will be removed when:

1. There is no more air leakage following the switch to water seal,
2. The lung has expanded sufficiently and/or there is no significant increase in the size of a pneumothorax, in the investigators opinion, that would prevent discontinuation, and
3. Drainage has reduced to < 5 cc/kg/ 24 hours or, 2.5 cc/kg/12 hours.

As to Heimlich valve use, the protocol stated that 'occasionally the attending physician will decide to discharge a subject, who still has an air leak, with a Heimlich valve. When this occurs, the subject will be asked to return on a weekly basis until the tube is removed. The date the air leak ceased will be the day the tube is removed.

3. Clinical Endpoints

The primary endpoint for ProGel™ effectiveness was the percent of patients without post-operative air leak (POAL) through one month post-operatively or the duration of hospitalization, whichever is longer.

Secondary effectiveness endpoints were:

1. The proportion of intra-operative air leaks (IOAL) in each group that were sealed or reduced, as demonstrated by the air leak (AL) test, prior to the completion of lung surgery.

2. The proportion of subjects in each group who were free of air leaks immediately following surgery as measured by the presence of air leaks from the chest tube (CT) at the first post-operative time point once the subject was in the recovery room (RR).
3. The duration of post-operative air leaks measured from the time of surgery until the air leak sealed. For patients discharged with a Heimlich Valve (HV) for out-patient management of ongoing air leak, air leak duration was the number of days elapsed from surgery until the subject returned to the clinic with no evidence of an air leak.
4. The duration of chest tube placement. This endpoint included the time that the Heimlich Valve was in place.
5. The duration of hospitalization: post - operative hospital days (POD).

Safety was evaluated by assessment of AEs through 30 days post-operatively and changes in the humoral and cellular responses to the ProGel™ measured pre- and post-surgery.

B. Accountability of the PMA Cohort

A total of 275 subjects were consented and enrolled and 161 subjects were randomized intra-operatively. Of the 161 randomized subjects (i.e., 103 ProGel™ and 58 Control), 148 subjects completed the study. Of the 13 subjects who did not complete the study (i.e., 1 month follow-up information was not available), 9 died, 1 had a post-ProGel™ lung transplant, 1 had a post-ProGel™ lobectomy of the treated lung, and 2 subjects were lost to follow-up. The per-treatment-distribution of these subjects was similar across groups, with 8/103 (7.8%) in the ProGel™ and 5/58 (8.6%) in the Control groups.

C. Study Population Demographics and Baseline Parameters

The demographics of the subjects enrolled in the study are presented below in Table 2.

Table 2 Patient Demographics

		ProGel™	Control
N		103	58
Gender:	Male	66 (64.1%)	36 (62.1%)
	Female	37 (35.9%)	22 (37.9%)
Age, years:	Mean	63.6	65.9
	SD	13.6	11.1
Percent predicted FEV1:	≤ 40%	5 (4.9%)	4 (6.9%)
	> 40%	93 (90.3%	53 (91.4%)
	Missing	5 (4.9%)	1 (1.7%)
Immunosuppression:	No	98 (95.1%)	55 (94.8%)
	Yes	5 (4.9%)	3 (5.2%)
Diabetes:	No	90 (87.4%)	51 (87.9%)
	Yes	13 (12.6%)	7 (12.1%)
COPD:	No	68 (66.0%)	42 (72.4%)
	Yes	35 (34.0%)	16 (27.6%)
Previous Thoracic Surgery:	No	88 (85.4%)	48 (82.8%)
	Yes	15 (14.6%)	10 (17.2%)
Radiation Exposure – Chest:	No	94 (91.3%)	53 (91.4%)

	ProGel™	Control
N	103	58
Yes	9 (8.7%)	5 (8.6%)
Chemotherapy: No	94 (91.3%)	56 (96.6%)
Yes	9 (8.7%)	2 (3.4%)
Steroid Use: No	99 (96.1%)	55 (94.8%)
Yes	4 (3.9%)	3 (5.2%)
Smoking: Never	20 (19.4%)	11 (19.0%)
Current	18 (17.5%)	11 (19.0%)
Former	65 (63.1%)	36 (62.1%)
Pack Years		
N	78	46
Mean ± SD	59.8 ± 36.0	47.6 ± 27.3
Median	50.0	40.5
Minimum	1	1
Maximum	175	120
Hypertension	40 (38.8%)	26 (44.8%)
Immunosuppression	5 (4.9%)	3 (5.2%)
History of Myocardial Infarction	11 (10.7%)	10 (17.2%)
Coronary Artery Disease	21 (20.4%)	19 (32.8%)
Renal Disease	13 (12.6%)	5 (8.6%)
History of Neurological Event	7 (6.8%)	5 (8.6%)
Diabetes	13 (12.6%)	7 (12.1%)
Congestive Heart Failure	4 (3.9%)	3 (5.2%)
Chronic Obstructive Pulmonary Disease	35 (34.0%)	16 (27.6%)
Previous Thoracic Surgery	15 (14.6%)	10 (17.2%)
Radiation Exposure-Chest	9 (8.7%)	5 (8.6%)
Chemotherapy	9 (8.7%)	2 (3.4%)
Steroid Use	4 (3.9%)	3 (5.2%)
Recent Weight Loss	13 (12.6%)	9 (15.5%)
Alcohol Dependency		
No	82 (79.6%)	44 (75.9%)
Current	6 (5.8%)	7 (12.1%)
Past	15 (14.6%)	7 (12.1%)
Prior Cancer	36 (35.0%)	25 (43.1%)
ECOG Score		
0 = Fully active	72 (69.9%)	38 (65.5%)
1 = Ambulatory	23 (22.3%)	18 (31.0%)
2 = In bed <50%	2 (1.9%)	0 (0.0%)
3 = In bed >50%	0 (0%)	0 (0%)
4 = Bedridden	1 (1.0%)	0 (0.0%)
Missing	5 (4.9%)	2 (3.4%)

None of the differences between ProGel™ and Control groups for the reported demographic and risk variables was found to be statistically significant per Wilcoxon Rank Sum Test. The enrollment of patients with percent predicted FEV1 ≤ 40% was less than 6% of each cohort limiting clinical assessment of outcomes for this cohort. There were no clinically notable or statistically significant differences in pre-operative pulmonary function test results.

Surgery Characteristics and Device Application Parameters

Table 3 presents a summary of primary diagnoses, type of surgery, surgical approach, extent of lymphadenectomy, intra-operative air leak (IOAL) distribution and extent of pleural adhesions.

Table 3: Primary Diagnosis and Procedure Variables

	ProGel™	Control
N	103	58
Primary Diagnosis, p = 0.620		
Primary Tumor	70 (68.0%)	42 (72.4%)
Metastatic Tumor	19 (18.4%)	8 (13.8%)
Benign Tumor	6 (5.8%)	3 (5.2%)
COPD/Bronchitis/Emphysema	3 (2.9%)	0 (0.0%)
Other	5 (4.9%)	5 (8.6%)
Type of Surgery, p = 0.883		
Bilobectomy	4 (3.9%)	1 (1.7%)
Lobectomy	55 (53.4%)	34 (58.6%)
Segmentectomy	5 (4.9%)	4 (6.9%)
Single Wedge	12 (11.7%)	7 (12.1%)
Multiple Wedge	8 (7.8%)	2 (3.4%)
Lobectomy with Wedge(s)	10 (9.7%)	5 (8.6%)
Lobectomy/Segment./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, p = 0.269		
Median Sternotomy	1 (1.0%)	1 (1.7%)
Posterolateral Thoracotomy	85 (82.5%)	45 (77.6%)
Anterolateral Thoracotomy	3 (2.9%)	6 (10.3%)
Mini-thoracotomy	13 (12.6%)	6 (10.3%)
Other	1 (1.0%)	0 (0.0%)
Lymphadenectomy, p = 0.201		
Not done	30 (29.1%)	11 (19.3%)
Partial	30 (29.1%)	14 (24.6%)
Complete	43 (41.7%)	32 (56.1%)
Pleural Adhesions, p = 0.597		
Missing	1 (1.0%)	1 (1.7%)
No	49 (47.6%)	27 (46.6%)
Yes:	53 (51.5%)	30 (51.7%)
Unspecified	3 (5.7%)	1 (3.3%)
Minimal	28 (52.8%)	14 (46.7%)
Extensive	22 (41.5%)	15 (50.0%)

IOAL prior to closure actual distribution, p = 0.0051		
1	33 (32.0%)	30 (51.7%)
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%)
IOAL statistical distribution, p= 0.134		
Mean	3.0	2.0
SD	9.7	1.4
Median	2.0	1.0
Minimum	1	1
Maximum	100	7

The most frequent type of surgery was lobectomy for both groups. In both the ProGel™ and Control groups, the posterolateral thoracotomy was the most frequently used surgical approach for open thoracotomy. Intra-operative characteristics were similar between the ProGel™ and Control groups for the individual parameters evaluated. Data indicates that the baseline distribution of IOAL was statistically different between treatment groups (p=0.0051); the mean and median were not. Other variables were not statistically different as powered in this study.

Number of ProGel™ Applications:

A 2ml of ProGel™ was expected to cover a 20 cm^2 (3 in^2) surface area with 1 mm thickness of ProGel™, which was expected to be sufficient to treat an average clinically significant visceral pleural AL. Up to three applications of ProGel™ were allowed per individual air leak. Table 4 reports the actual number of ProGel™ applications as well as the number of 2ml ProGel™ units used per patient.

TABLE 4. Volume of ProGel™ Pleural Air Leak Sealant Use

Volume of ProGel™ Used per Patient (ml)	
2	29 (28.2%)
4	37 (35.9%)
6	22 (21.4%)
8	7 (6.8%)
10	4 (3.9%)
12	2 (1.9%)
18	1 (1.0%)
30	1 (1.0%)
Mean ±SD	4.8 ±3.6
Median	4.0
Minimum	2
Maximum	30
Number of ProGel™ Applications Per AL	**ProGel™ - N (%)**
One	125 (59.5)
Two	70 (33.3)
Three	9 (4.3)
Missing/Other	6 (2.9)
Time (minutes) of Application / Unit	
Mean ±SD	3.3 ±4.7
Median	2.0
Minimum	1
Maximum	
Total Application Time (minutes)	
Mean ±SD	7.9 ±8.4
Median	6.0
Minimum	1
Maximum	63

Table 5 provides additional information on patient surgeries.

TABLE 5. Other Operative Details

Treatment		ProGel™	Control
No. of Chest Tubes	1	19 (18.4%)	7 (12.1%)
	2	83 (80.6%)	48 (82.8%)
	≥3	1 (1.0%)	3 (5.2%)
Time in OR (min)	N	102	58
	Mean ± SD	226.7 ± 61.2	236.8 ± 61.5
	Median	225.5	225.5
	Minimum	115	145
	Maximum	455	430
Time to Skin Closure	N	91	50
(min)	Mean ± SD	156.8 ± 54.9	165.0 ± 62.6
	Median	151.0	143.5
	Minimum	52	81
	Maximum	355	387

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

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the cohort of 161 subjects followed for one month after surgery. The key safety outcomes for this study are presented below in tables 6 to 11.

Table 6 presents the incidence of adverse events (AEs) reported for greater than 1% of subjects in either treatment group during a clinical study in 161 subjects randomized in a 2:1 ratio, (i.e., 103 ProGel™ and 58 Control patients).

TABLE 6. Incidence of AEs Reported by > 1% of Subjects by Treatment Group*

Preferred Term	ProGel™ N=103	Control N=58
Fever	22 (21.4%)	12 (20.7%)
Fibrillation, Atrial	12 (11.7%)	7 (12.1%)
Dyspnea	12 (11.7%)	10 (17.2%)
Constipation	11 (10.7%)	6 (10.3%)
Nausea	10 (9.7%)	7 (12.1%)
Pneumothorax	9 (7.8%)	5 (8.6%)
Confusion	8 (7.8%)	5 (8.6%)
Hypotension	8 (7.8%)	6 (10.3%)
Anemia	8 (7.8%)	6 (10.3%)
Pain	7 (6.8%)	4 (6.9%)
Subcutaneous Emphysema	7 (6.8%)	5 (8.6%)
Tachycardia	7 (6.8%)	6 (10.3%)
Death	5 (4.9%)	4 (6.9%)
Oliguria	5 (4.9%)	1 (1.7%)
Vomiting	5 (4.9%)	7 (12.1%)
Pneumonia	5 (4.9%)	7 (12.1%)
Pulmonary Infiltration	4 (3.9%)	0 (0.0%)
Chest Pain	4 (3.9%)	1 (1.7%)
Pleural Effusion	4 (3.9%)	3 (5.2%)
Urinary Retention	3 (2.9%)	0 (0.0%)
Ileus	3 (2.9%)	0 (0.0%)
Tachycardia, Supraventricular	3 (2.9%)	0 (0.0%)
Abdominal Pain	3 (2.9%)	0 (0.0%)
Arrhythmia	3 (2.9%)	0 (0.0%)
Extrasystoles	3 (2.9%)	0 (0.0%)
Coughing	3 (2.9%)	1 (1.7%)
Hypoxia	3 (2.9%)	1 (1.7%)
Renal Failure, Acute	3 (2.9%)	1 (1.7%)
Adult Respiratory Stress Syndrome	3 (2.9%)	1 (1.7%)
Hyperkalaemia	2 (1.9%)	0 (0.0%)
Hyponatraemia	2 (1.9%)	0 (0.0%)
Cardiac Arrest	2 (1.9%)	0 (0.0%)

Preferred Term	ProGel™ N=103	Control N=58
ECG Abnormal	2 (1.9%)	0 (0.0%)
Renal Function Abnormal	2 (1.9%)	0 (0.0%)
Asthenia	2 (1.9%)	0 (0.0%)
Influenza-Like Symptoms	2 (1.9%)	0 (0.0%)
Somnolence	2 (1.9%)	1 (1.7%)
Abdomen Enlarged	2 (1.9%)	1 (1.7%)
Atelectasis	2 (1.9%)	2 (3.4%)
Postoperative Wound Infection	2 (1.9%)	2 (3.4%)
Multiple Organ Failure	2 (1.9%)	1 (1.7%)
Anxiety	1 (1.0%)	1 (1.7%)
Withdrawal Syndrome	1 (1.0%)	1 (1.7%)
GI Haemorrhage	1 (1.0%)	1 (1.7%)
Hypokalaemia	1 (1.0%)	1 (1.7%)
Arrhythmia Atrial	1 (1.0%)	1 (1.7%)
Respiratory Disorder	1 (1.0%)	1 (1.7%)
Respiratory Insufficiency	1 (1.0%)	1 (1.7%)
Sepsis	1 (1.0%)	1 (1.7%)
Bronchial Obstruction	1 (1.0%)	1 (1.7%)
Infection Staphylococcal	1 (1.0%)	1 (1.7%)
Pruritus	1 (1.0%)	2 (3.4%)
Delirium	1 (1.0%)	2 (3.4%)
Hypertension	1 (1.0%)	2 (3.4%)
Angina Pectoris	1 (1.0%)	2 (3.4%)
Hemoptysis	1 (1.0%)	3 (5.2%)
Arthropathy	0 (0.0%)	1 (1.7%)
Gall Bladder Disorder	0 (0.0%)	1 (1.7%)
Cachexia	0 (0.0%)	1 (1.7%)
Dehydration	0 (0.0%)	1 (1.7%)
Non-protein Nitrogen Increased	0 (0.0%)	1 (1.7%)
Edema Dependent	0 (0.0%)	1 (1.7%)
Edema Generalized	0 (0.0%)	1 (1.7%)
Fibrillation Ventricular	0 (0.0%)	1 (1.7%)
Cardiac Failure	0 (0.0%)	1 (1.7%)
Hypoventilation	0 (0.0%)	1 (1.7%)
Thrombocytopenia	0 (0.0%)	1 (1.7%)
Allergic Reaction	0 (0.0%)	1 (1.7%)
Fatigue	0 (0.0%)	1 (1.7%)
Rigors	0 (0.0%)	1 (1.7%)
Infection, Fungal	0 (0.0%)	1 (1.7%)
Healing, Impaired	0 (0.0%)	1 (1.7%)
Cramps, Legs	0 (0.0%)	1 (1.7%)
Acidosis, Respiratory	0 (0.0%)	1 (1.7%)
Chyle, Leak	0 (0.0%)	1 (1.7%)

*There were no statistically significant differences ($p > 0.05$) in the incidence of AEs between the ProGel™ and Control groups.

Table 7 presents those AEs considered by the investigator to be possibly or probably related to the ProGel™. There were 3 subjects in the ProGel™ group with AEs that were considered by the investigator to be possibly or probably related to the device. The AEs reported were: chest pain, constipation, gastroesophageal reflux, nausea, cough, dyspnea; pneumothorax, and subcutaneous emphysema. All were reported as a single occurrence in the ProGel™ group. Two of the AEs, dyspnea and chest pain, were reported as "severe" and "serious", respectively and occurred in the same subject. All others were reported as mild or moderate.

Table 7 Incidence of Adverse Events in ProGel™ Group Considered Possibly or Probably Device - related.

Body System Preferred Term	ProGel™ (N=103)
Body as a Whole	
Chest Pain	1 (1.0%)
Gastrointestinal Systems	
Constipation	1 (1.0%)
Gastroesophageal Reflux	1 (1.0%)
Nausea	1 (1.0%)
Respiratory System	
Coughing	1 (1.0%)
Dyspnea	1 (1.0%)
Pneumothorax	1 (1.0%)
Skin and Appendages	
Subcutaneous Emphysema	1 (1.0%)

UNANTICIPATED ADVERSE DEVICE EVENT

A large, symptomatic pneumothorax that occurred in a 28 year old ProGel™-treated subject at three weeks post open pulmonary metastectomy and required chest tube placement was considered by the investigator to be an unanticipated adverse device effect due to the temporal relationship of the event with the use of the ProGel™. No other unanticipated adverse events were reported.

OTHER SERIOUS ADVERSE EVENTS

Table 8 presents a summary of other serious adverse events (SAEs). There were 5 other SAEs: 2 in the ProGel™ group and 3 in the Control group. Both of the ProGel™ SAEs were considered by the investigator probably not related to the device. All of the events resulted in extended hospital stays or rehospitalization; 4 subjects recovered from these events and 1 subject continued on dialysis.

Table 8 Other Serious Adverse Events

Subject ID	Age/Gender	Relationship To Device	Event	Outcome
ProGel™				
03-02-201	70/Female	Probably Not Related	Acute Renal Failure	Continues on Dialysis
03-01-211	70/Male	Probably Not Related	Myocardial Infarction	Recovered
Control				
01-01-204	83/Male	Not Related	Fluid/Air in Lung & GI Bleed	Recovered
02-02-206	67/Female	Probably Not Related	ARDS	Recovered
03-01-219	70/Male	Not Related	Dehydration	Recovered

PLEURAL AIR LEAK AND AIR SPACE EVENTS

The ProGel™ is a HSA – PEG polymer hydrogel applied to visceral pleura during open thoracotomy and expected to be resorbed within the first week after such application. Upon lung expansion, the ProGel™ interposes between visceral and parietal pleura. It is unknown if interpleural ProGel™ changes post-operative visceral and parietal pleura surface adhesion, changes surface healing and allows air leak sites to re-open upon ProGel™ resorption. Data demonstrated that pneumothorax occurred in 8.7% of the patients and 8.6% of the control patients. In addition ARDS occurred in 2.9% ProGel™ compared to 1.7% control patients; ProGel™ patients with ARDS died. Event incidences are in Table 9.

TABLE 9: Pleural Air Leak and Air Space Events

Pleural Air Leak and Air Space Events	ProGel™	Control
N	102	58
Pneumothorax as an adverse event	9 (8.7%)	5 (8.6%)
Acute Respiratory Distress Syndrome	3 (2.9%)	1 (1.7%)

RENAL EVENTS

ProGel™ degradation products are primarily cleared from the body by the kidneys. The incidence of Renal AEs along with individual subject data are in Table 10.

Table 10: Incidence of Adverse Events Related to Renal Function (n, %)

RENAL Adverse Events	ProGel™	Control
N, patients through 1MFU	95	53
Abnormal renal function	2 (1.9%)	0
Acute renal failure	3 (2.9%)	1 (1.7%)
Oliguria	5 (4.9%)	1 (1.7%)
Total number of renal adverse events* % patients with renal adverse events *1 ProGel™ patient was reported to have 2 events: abnormal renal function and oliguria	10 9/95 (9.5%)	2 2/53 (3.8%)

Subjects with renal function (RF) adverse events

Treatment	Adverse Event	BUN		Creatinine		ProGel™	Severity
		Pre-op	1 MFU	Pre-op	1 MFU	ml used	
ProGel™	Abnormal RF	25	26	1.1	1.8	6	Severe
ProGel™	Abnormal RF, oliguria	23	84**	0.7	1.8**	4	Severe
ProGel™	Acute renal failure	21	24	1.4	1.7	2	Severe
ProGel™	Acute renal failure*	54	14	3.8	5.0	2	Severe
ProGel™	Acute renal failure.	8	***	1.0	***	6	Severe
ProGel™	Oliguria*	13	17	1.1	1.3	4	Moderate
ProGel™	Oliguria*	33	39	1.7	2.2	8	Moderate
ProGel™	Oliguria	12	8	0.9	1.0	6	Mild
ProGel™	Oliguria	10	11	0.9	0.8	2	Mild
Control	Acute renal failure*	15	***	1.0	***	na	Severe
Control	Oliguria	12	11****	1.2	1.0****	na	Mild

*Pre-existing renal disease
**at discharge; no 1MFU as patient died
***no discharge or 1MFU as patient died
****at discharge; no 1MFU data

Data demonstrated pre-existing renal disease in 3 ProGel™ and 1 control patients who had a renal AE, and no pre-existing renal disease in 6 ProGel™ and 1 control patients who had a renal AE. Severe renal AEs occurred in 4 ProGel™ patients without pre-existing disease and 2 of those patients died. Severe renal AE occurred in 1 control device patient with pre-existing disease and that patient died.

All urinary system disorders occurrence was ProGel™: 12 (11.7%), Control: 2 (3.4%). Reasons for the difference between cohorts in the incidence of renal AEs are unclear; the potential of ProGel™ to exacerbate renal dysfunction in patients with pre-existing renal disease is unknown.

SUBJECT DEATHS

Table 11 presents a summary of subject deaths. 5/103 (4.9%) ProGel™ and 4/58 (6.9%) control subjects died during this study. None of the deaths were considered by the investigators to be device-related. Death in 2 ProGel™ and 1 control patient was associated with multi-organ failure. 1 control treated patient reported to have multi-organ failure was not reported to have died. Death in 2 of 3 ProGel™ patients with ARDS was associated with more than the mean (2.5 Units = 5ml) and median (2.0 Units = 4ml) amount of ProGel™ used in clinical study.

The single patient who received the maximum volume of ProGel™ used in this clinical trial (15 Units (30ml) was a 71 year old male who, about five days after bilateral lung volume reduction surgery, developed significant ALs that were repaired with ProGel™ application. ARDS was noted 0-6 hours Post-op ProGel™ application. The patient developed pulseless ventricular fibrillation and flutter and died on POD 2 after ProGel™ application; autopsy findings bilaterally included moderate pleural cavity adhesions on gross exam, congestion on cut lung surface, and fibrinous pleuritis microscopically.

TABLE 11. Summary of Subject Deaths

Age , Gender Preop ECOG Score , Preop FEV1 ≤ or > 40%	Day of Death	Relationship to Device	Cause of Death	Amount of ProGel™ used
ProGel™				
71yo Male ECOG=4, FEV1≤ 40%	POD2	Not Related	ARDS	30 ml
82/Male ECOG=0, FEV1>40	POD28	Not Related	Pneumonia	4 ml
61yo Male ECOG=1, FEV1>40	POD10	Not Related	Acute Airway Obstruction or Pulmonary Embolism	2 ml
66yo Male ECOG=1, FEV1>40	POD6	Not Related	ARDS & Multisystem Failure	6 ml
65yo Male ECOG=2, FEV1>40	POD22	Not Related	ARDS & Multisystem Failure	4 ml
Control				
80/Female ECOG=0/FEV1>40	POD19	Not Related	Pneumonia	N/A
70/Male ECOG=1/FEV1>40	POD22	Not Related	Atrial Fibrillation	N/A
82/Male ECOG=0/FEV1>40	POD0	Not Related	Ventricular Fibrillation	N/A
67/Male ECOG=unknown/FEV1>40	POD38	Not Related	Anoxic Brain Injury	N/A

N/A = Not Applicable

HUMORAL AND CELL-MEDIATED IMMUNE RESPONSE

Both pre- and post-operative serum samples were obtained from 71/103 (69%) ProGel™ and 37/58 (64%) Control subjects. Seventy (70) of the ProGel™ and 36 of the Control subjects showed no immune reaction to the ProGel™. One (1) subject in each group had

pre-operative and post-operative serum levels consistent with the presence of ProGel™ antibodies prior to device exposure.

The response of peripheral blood mononuclear cells to various concentrations of mitogens (i.e., Con A, PHA, and PWM), recall antigens *(Candida* and Tetanus), and ProGel™ was tested by mixed lymphocyte proliferative assay (LPA) in pre- and postoperative whole blood samples. Mitogen analyses were compared in pre- and postoperative samples of 59 ProGel™ and 34 Control subjects and recall antigen and ProGel™ analyses were performed in 69 ProGel™ and 32 Control subjects. No clinically significant differences were observed in the pre and postoperative blood samples for either Control or ProGel™ subjects.

2. Effectiveness Results

The analysis of effectiveness was based on the 161 evaluable patients at the 1 month time point. Key effectiveness outcomes are presented in tables 12 to 17.

Primary Effectiveness Outcome

Percentage of subjects who remained air leak-free through the 1 MFU visit is presented in Table 12.

TABLE 12 Primary Endpoint Results

Air Leak Status Through 1MFU Visit	ProGel™ N (%)	Control N (%)	P-value[a]
No POAL	36 (35.0%)	8 (13.8%)	0.005
With POAL	67 (65.0%)	50 (86.2%)	

[a]Logistic regression analysis comparing ProGel™ and Control groups for the primary endpoint analysis.

As to stratification for pre-op FEV1 ≤ or > 40%, all 5 ProGel™ and 4 Control patients with FEV1 ≤ 40% had POAL; whereas 59/93 (63.4%) ProGel™ and 45/53(84.9%) Control patients with FEV1 > 40% had POAL.

Secondary Effectiveness Outcomes

- Proportion of intra-operative air leaks (IOAL) in each group that were sealed or reduced, as demonstrated by the air leak (AL) test, prior to the completion of lung surgery is presented in Table 13. Of the 210 ALs tracked in the ProGel™ group, 76.7% were sealed after the application of ProGel™ compared with 15.7% of the 108 ALs in the Control group. IOALs were sealed in 70.9% of the ProGel™ and 10.3% of the Control subjects following the final AL test.

TABLE 13. IOAL Closure Summary

Parameter	Response	ProGel™ N (%)	Control N (%)	P-value[a]

Sealed IOAL/Individual AL	No IOAL	161 (76.7%)	17 (15.7%)	< 0.001
	<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	No IOALs	73 (70.9%)	6 (10.3%)	< 0.001
	With IOALs	30 (29.1%)	51 (87.9%)	
	Missing	0 (0.0%)	1 (1.7%)	

[a]p-value associated with Fisher's Exact Test for categorical data.

- Proportion of subjects in each group who were free of air leaks immediately following surgery as measured by the presence of air leaks from the chest tube (CT) at the first post-operative time point once the subject was in the recovery room (RR) is presented in Table 14. After surgery, subjects were transferred to the recovery room where chest tubes (CTs) were placed on suction and the subjects' air leakage was determined by observing air bubbles in the CT drainage system. A statistically significant number of ProGel™ subjects were air leak-free in recovery room compared to Control subjects. No ALs were observed in the recovery room in 54% of the ProGel™ and 33% of the Control subjects.

TABLE 14. Summary of POALs in the Recovery Room

Observation Period	Response	ProGel™ N (%)	Control N (%)	P-value[a]
Recovery Room	No AL	56 (54.4%)	19 (32.8%)	0.002
	Occasional Infrequent Bubbles	30 (29.1%)	20 (34.5%)	
	Frequent Bubbles	7 (6.8%)	16 (27.6%)	
	Continuous Bubbles	8 (7.8%)	3 (5.2%)	
	Missing	2 (1.9%)	0 (0.0%)	

[a]P-value associated with Fisher's Exact Test of categorical data.

- Duration of post-operative air leaks measured from the time of surgery until the air leak sealed. For patients discharged with a Heimlich Valve (HV) for out-patient management of an ongoing air leak, air leak duration was the number of days elapsed from surgery until the subject returned to the clinic with no evidence of an air leak. Duration of POAL was defined as the first postoperative day (POD) on which the AL was noted. Time to no air leak is presented in Table 15.

Table 15: Duration of Post-Operative Air Leaks*

	Post-op		
Duration POAL	ProGel™	Control	
N (%)			
Missing	2 (1.9%)	2 (3.4%)	
0-2 days	54 (52.4%)	29 (50.0%)	
3-4 days	18 (17.5%)	14 (24.1%)	
5-6 days	7 (6.8%)	6 (10.3%)	
7-9 days	6 (5.8%)	1 (1.7%)	

10-11 days	3 (2.9%)	3 (5.2%)
> 11 days	13 (12.6%)	3 (5.2%)
Mean	4.7	3.6
SD	6.8	3.9
Median	2.0	2.0
Minimum	0.5	0.5
Maximum	42	22
N	101	56

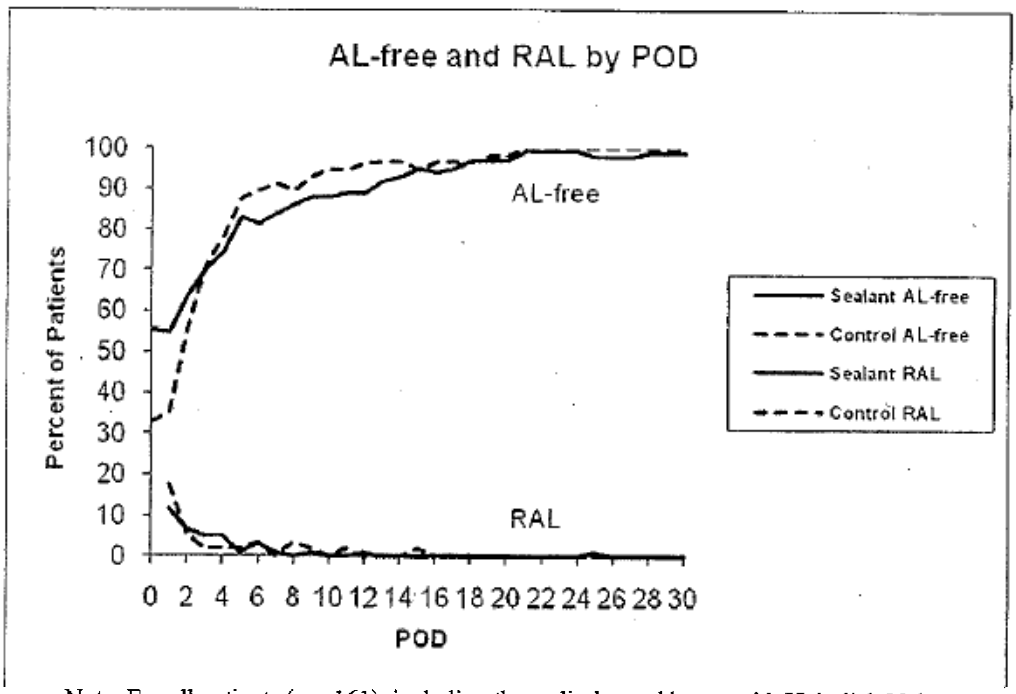
*Differences were not statistically significant as determined by a Wilcoxon Rank Sum Test comparing ProGel™ and Control groups based on all available data (N=157).

Data demonstrate that overall the mean duration of Post-Operative Air Leaks was 1.1 days longer for the ProGel™ cohort than the control cohort, with no difference in the median duration (2 days in each cohort). Data also indicate that while 2.4% more ProGel™ patients had no air leak at 0-2 days, 10.1% more control patients had no air leak at 3-6 days, and that 7.4% more ProGel™ patients' air leak continued through more than 11 days.

It is clinically notable that ten (10%) subjects in the ProGel™ group and one (2%) subject in the Control group were discharged from the hospital with a Heimlich valve [the difference was not statistically significant as powered in this study]. Since patients discharged with a HV valve were re-evaluated weekly rather than daily, patient discharge from the hospital with a HV confounded determination of the true duration of post-operative air-leaks, which may in part explain the higher proportion of ProGel™ patients with air leak that continues through more than 11 days.

As to stratification for preop FEV1 ≤ or > 40%, mean (median) air leak duration for patients with FEV1 ≤ 40% was 6.3 (4.0) days for ProGel™ and 4.3 (3.0) days for Control subjects; for patients with FEV1 > 40% the mean (median) air leak duration was 4.7 (2.0) days for ProGel™ and 3.6 (2.0) days for the Control cohorts.

Figure 2. Air-leak Free and Recurrence of Air Leak by Post-operative Days (POD)



Note: For all patients (n = 161), including those discharged home with Heimlich Valve.

Recurrence of air leak (RAL) is defined as chest tube documented air leak following one or more air-leak free days. One ProGel™ patient experienced a late pneumothorax on POD25 was also counted as having a recurrence of air leak. Overall, data demonstrates that the duration of POALs was comparable for both treatment groups with a majority of POALs lasting less than three days: median duration was two days in both groups. For each post-operative day, patients were excluded from the analysis if they were dead, lost to follow-up, had no air-leak assessment, received lung transplant, or completed 1MFU. Patients who were discharged with a Heimlich valve were counted as having AL on the post-operative days between the date of discharge and the date of chest tube removal.

- **Duration of Chest Tube Placement**

Table 16 presents a summary of the duration of CT placement in number of postoperative days. The duration of chest tube placement was comparable for both treatment groups. The median duration of CT placement for both groups was five days.

TABLE 16. Duration of CT Placement[a]

CT Duration	ProGel™ N (%)	Control N (%)	
N	103	58	
Missing[b]	3 (2.9%)	3 (5.2%)	
N	100	55	
0-2 days	2 (1.9%)	0 (0.0%)	
3-4 days	34 (33.0%)	19 (32.8%)	
5-6 days	37 (35.9%)	21 (36.2%)	
7-9 days	11 (10.7%)	9 (15.5%)	

10-11 days	3 (2.9%)	3(5.2%)	
> 11 days	13 (12.6%)	3 (5.2%)	
Mean	6.8	6.2	
SD	5.5	3.5	
Median	5.0	5.0	
Minimum	2	3	
Maximum	42	22	

[a] Differences were not statistically significant as determined by a Wilcoxon Rank Sum Test comparing ProGel™ and Control groups based on all available data (N=155).
[b]"Missing" subjects were either censored (incomplete, i.e., entered the study late and didn't have chance to complete the whole study, lost-to-follow-up, or other causes). The time-to-event survival analyses included all subjects into the analyses and used all subject information up to the time they censored.

Consistent results were observed using a survival analysis, which included all randomized patients (N=161) and treated patients with missing time of CT removal as censored observations. The results of the survival analysis are shown in Figure 1.

As to stratification for preop FEV1 ≤ or > 40%, mean (median) chest tube placement duration for patients with FEV1 ≤ 40% was 8.3 (7.0) days for ProGel™ and 5.8 (4.5) days for Control subjects; for patients with FEV1 > 40%, the mean (median) chest tube placement duration was 6.8 (5.0) days for ProGel™ and 6.2 (5.5) days for the Control cohorts.

- **Duration of hospitalization: post - operative hospital days (POD)**

Table 17 presents the length of hospital stay in days.

Table 17 Duration of hospitalization POD

Hospital stay, days	ProGel™ N (%)	Control N (%)	P
N	103	58	
Missing[b]	5 (4.9%)	3 (5.2%)	0.0413
N	98	55	
3-4 days	11 (10.7%)	4 (6.9%)	
5-6 days	49 (47.6%)	23 (39.7%)	
7-9 days	22 (21.4%)	16 (27.6%)	
10-11 days	7 (6.8%)	5 (8.6%)	
> 11 days	9 (8.7%)	7 (12.1%)	
Mean	7.44	9.35	
SD	3.4	5.6	
Median	6.0	7.0	
Minimum	3	4	
Maximum	23	38	

[a]P-value associated with Wilcoxon Rank Sum Test comparing ProGel™ and Control groups based on all available data (N-155)

[b] "Missing" subjects were either censored (incomplete, i.e., entered the study late and didn't have chance to complete the whole study, lost-to-follow-up, or other causes). The time-to-event survival analyses included all subjects into the analyses and used all subject information up to the time they censored.

Consistent results were observed using a survival analysis, which included all randomized patients (N=161) and treated patients with missing time of hospital discharge as censored observations.

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

A. Panel Meeting Recommendation

At the advisory meeting was held on June 12, 2008 and the Anesthesiology and Respiratory Therapy Devices Advisory Panel recommended that the NeoMend PMA for ProGel™ be conditionally approved. The panel recommended the following conditions:

- The product label should limit the amount of device used to "no more than 30 ml."
- A post approval study should evaluate cardiac, renal, and ARDS adverse events. The study should have a comparison group hopefully within the same institution and will go for at least 30 days, but hopefully for a longer period than that perhaps 90 days. In lieu of the randomized control trial, the Society of Thoracic Surgeons, thoracic surgical database may be considered. Data evaluation should include a standard criteria for ARDS (e.g., by the European-American consensus criteria with PF ratios). Re-admission rate should also be collected as part of the PAS. The post marketing study should have a different primary outcome than the studies that have been presented us today, and should include a time to event analysis.
- The label should limit device use to the surface of the lung.
- A precautions statement that the sealant is effective for short-term closure of air leaks, and maybe associated with delayed air leaks.

B. FDA'S POST-PANEL ACTION

CDRH agreed with the Panel's recommendations, and is approving the PMA with a condition of a Post Approval Study (PAS) to evaluate the long-term safety of the device.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Safety Conclusion

The adverse effects of the device are based on data collected in a clinical study conducted to support PMA approval as described above. There were no statistically significant differences in the incidence of AEs between the ProGel™ and Control groups. There

were no significant changes observed in humoral and cellular immune responses between the ProGel™ and Control groups, indicating the lack of systemic changes in the immune system following use of the ProGel™ in surgery.

B. Effectiveness Conclusions

The results of this study demonstrated a significantly greater proportion of ProGel™ subjects were air leak-free at the end of the surgical procedure and remained air leak-free through the one month follow-up when compared to Control subjects. In addition, a statistically significant difference in the closure of IOALs was observed ($p < 0.001$) in the ProGel™ group compared to the Control group.

C. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. These results demonstrate the safety and effectiveness of the ProGel™ when used as an adjunct to standard closure of ALs incurred during pulmonary surgery.

XIII. CDRH DECISION

CDRH issued an approval order on January 14, 2010. The final conditions of approval cited in the approval order are described below.

The PAS will be a non-randomized, sequential-enrollment controlled, multi-center 90-day follow-up trial on 400 subjects (i.e., 267 device and 133 control patients) from the pivotal study centers and up to 20 other expert centers. Study subjects will be consecutively enrolled in two sequential non-overlapping phases under a common protocol at each center, first into the control group and then into the device group. All subjects will be followed for 90 days. The control subjects will receive current standard of care for an air leak following pulmonary surgery. The proposed study is a safety study with twelve adverse events of interest:

1. Pulmonary:
    a. Pneumothorax
    b. Air leak, persistent
    c. Air leak, late onset
    d. Residual pleural space
    e. ARDS

2. Post-surgical renal abnormalities

3. Cardiovascular
    a. Myocardial infarction
    b. Atrial arrhythmia
    c. Ventricular arrhythmia
    d. Cardiac arrest

4. Death (all-cause)

5. Hospital readmission

Summary descriptive statistics will be reported for all baseline and demographic parameters and each outcome endpoint will be evaluated by the differences in proportions of cases compared to controls with upper one-sided 95% confidence bounds. Event rates for power calculations were estimated based on prior IDE studies or published literature. Sample size calculations used a non-inferiority model with one-sided significance of .05 and statistical power of 80%.

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

XIV. Approval Specifications

DIRECTIONS FOR USE: See product labeling (Information for Use).

HAZARDS TO HEALTH FROM USE OF THE DEVICE: See Indications, Contraindications, Warnings and Precautions, and Adverse Events in the product labeling.

Post-approval Requirements and Restrictions: See Approval Order.