SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Surgical Sealant
Device Trade Name:	Progel™ Pleural Air Leak Sealant
Device Procode:	NBE
Applicant's Name and Address:	Neomend, Inc. 60 Technology Drive Irvine, CA 92618
Date of Panel Recommendation:	None
PMA Application Number:	P010047/S036
Date of Notice of Approval:	February 13, 2015

The original PMA (P010047) was approved on January 14, 2010, and 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. The SSED to support the indication is available on the CDRH website and is incorporated by reference here. The current supplement was submitted to expand the indication for the Progel™ Pleural Air Leak Sealant (Progel™ PALS).

II. INDICATIONS FOR USE

Progel™ Pleural Air Leak Sealant is a single use device intended for application to visceral pleura after standard visceral pleural closure with, for example, sutures or staples, of visible air leaks incurred during resection of lung parenchyma.

III. CONTRAINDICATIONS

- Do not use Progel™ PALS in patients who have a history of an allergic reaction to Human Serum Albumin or other device components.
- Do not use Progel™ PALS in patients who may have insufficient renal capacity for clearance of the Progel™ PALS polyethylene glycol load.

- Do not apply the Progel™ PALS 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.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Progel™ Pleural Air Leak Sealant labeling.

V. DEVICE DESCRIPTION

The Progel™ PALS 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™ PALS 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™ PALS 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 disuccinimidyl succinate ((PEG-$(SS)_2$)) as a dried white powder.

- One (1)-Applicator Kit-
  - One (I) - 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

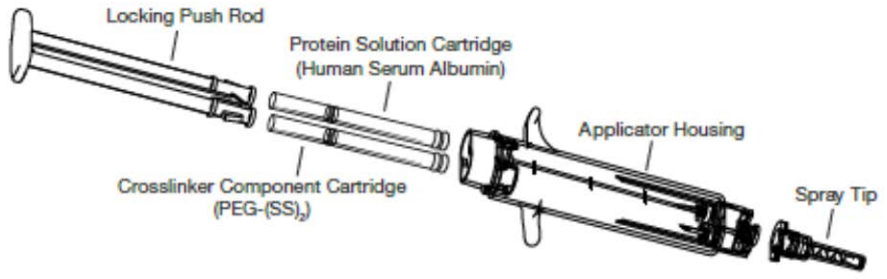
- One (1) - Instructions for Use (Labeling)

Optional replacement and extended spray tips are available for convenience and positioning according to surgeon preference:

- Progel™ PALS Applicator Spray Tips (pack of 2) REF PGST009, 10 units/box with Instructions
- Progel™ PALS Extended Applicator Spray Tip 16 cm REF PGEN005-06, 4 units/box with Instructions

– Progel™ PALS Extended Applicator Spray Tip 29 cm REF PGEN005-11, 4 units/box with Instructions

Figure 1. Progel™ Pleural Air Leak Sealant Delivery System
(Sterile water and syringe not shown)



VI. ALTERNATIVE PRACTICES OR PROCEDURES

A few highly specialized surgical techniques have been utilized for pulmonary air leak (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

Progel™ PALS received premarket approval from the U.S Food and Drug Administration in January of 2010. Progel™ PALS is not marketed outside the U.S.

Progel™ PALS has not been withdrawn from marketing for any reason related to the safety and effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of potential adverse effects (e.g. complications) associated with the use of device in both open thoracotomy and minimally invasive surgery procedures.

- Fever/Pyrexia
- Fibrillation, Atrial
- Dyspnea
- Constipation
- Nausea
- Pneumothorax
- Confusion
- Hypotension
- Anemia
- Pain
- Subcutaneous Emphysema
- Tachycardia
- Death
- Oliguria
- Vomiting
- Pneumonia
- Pulmonary Infiltration
- Chest Pain
- Pleural Effusion
- Urinary Retention
- Ileus
- Tachycardia, Supraventricular
- Abdominal Pain
- Arrhythmia
- Extrasystoles
- Coughing
- Hypoxia
- Renal Failure, Acute
- Adult Respiratory Stress Syndrome
- Hyperkalemia
- Hyponatraemia
- Cardiac Arrest
- ECG Abnormal
- Renal Function Abnormal
- Asthenia
- Influenza-Like Symptoms
- Somnolence
- Abdomen Enlarged/Distension
- Atelectasis
- Postoperative Wound Infection
- Multiple Organ Failure
- Anxiety
- Withdrawal Syndrome
- GI Hemorrhage
- Hypokalemia
- Arrhythmia Atrial
- Respiratory Disorder/distress
- Respiratory Insufficiency
- Sepsis
- Bronchial Obstruction
- Infection Staphylococcal
- Pruritus
- Delirium/mental status changes
- Hypertension
- Angina Pectoris
- Hemoptysis
- Hypoventilation
- Pulmonary Air Leakage
- Urinary tract infection
- Dysuria
- Pneumonia Aspiration
- Pulmonary haemorrhage

IX. SUMMARY OF PRECLINICAL STUDIES

The pre-clinical tests summarized in Table 1 below were leveraged from the original submission to support the application of Progel PALS in all surgical resection of lung parenchyma, regardless of the air leak size. The pre-clinical data reviewed under P010047 was found to be adequate to support the new indication of treatment in the video or robotic-assisted thoracoscopic lung surgery.

Table 1. Preclinical Testing for Progel™

Study	Test Articlc(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
Pyrogenieity-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 Toxicity-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 dav 29.
Subchronic Toxicity-Rat 7 Day study	*In situ* polymerization[1,4]	No systemic effects noted. Enteropathy noted at implantation contact sites. The eneropathy was mitigated by the instillation of saline into the peritoneal cavity post implantation.
Ames Mutagenicity	Extraction[1]	Non-mutagenic
Ames Mutagenicity	Extraction[4]	Non-mutagenic
Ames Mutagenicity	Neat[6]	Non-mutagenic
Mouse lymphoma	Extraction[4]	Non-mutagenic
Chromosome aberration	Extraction[2]	Non-clastogenic
Micronucleus-Rat	*In situ* polymerization[4]	Non-genotoxic
Pilot Mass Balance-Rat	*In situ* polymerization[7]	No gender differences, 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 Handling-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 l14.3 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™ PALS containing human albumin component, gamma sterilized.
[2]Comrnercially available Guinea Pig serum albumin, processed, e-beamed.
[3]Progel™ PALS containing cross-linked low endotoxin prepared Guinea Pig albumin component, e-beamed.
[4]Progel™ PALS containing human albumin component, e-beamed.
[5]Progel™ PALS containing rat albumin component gamma sterilized.
[6]PEG-SS2 crosslinker, e-beamed.
[7] ^{14}C Labeled Progel™ PALS
[8] ^{14}C Labeled Progel™ PALS e-beamed sterilized.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of Progel™ PALS including the Progel™ PALS Extended Applicator Spray Tips as an adjunct to standard closure technique in sealing or reducing visible pleural air leaks in patients undergoing video or robotic-assisted thoracoscopic lung surgery in the US under IDE #G120186. The key secondary objective was to evaluate the efficacy of Progel™ PALS for subjects who remain air leak free following surgery up to one (1) month follow up. Data from this clinical study were the basis for the expansion of indications approval decision. A summary of the clinical study is presented below.

A. Clinical Study Design

This was a prospective, open label, single arm, multi-center clinical study designed to assess the safety and efficacy of the Progel™ PALS product, including the Extended Applicator Spray Tips, against a safety performance goal of 42% when used in video-assisted and robotic-assisted thoracoscopic surgery and efficacy performance goal of 23%. The study was designed to treat approximately 105 subjects in order to obtain 100 evaluable subjects, after allowing for 5% loss to follow-up, at up to 15 U.S. sites. Enrolled subjects who met the initial screening criteria and signed the informed consent form underwent a video or robotic-assisted index study procedure.

1. Clinical Inclusion and Exclusion Criteria

A subject must have met all of the following criteria to be entered in the study:

1. Subject was willing and able to provide written informed consent.
2. Subject was scheduled for video-assisted or robotic-assisted thoracoscopic surgery for lung resection (i.e. lobectomy, bilobectomy, segmentectomy, and wedge resection/lung volume reduction), decortications or biopsy within 45 days of the screening evaluation.
3. Subject was ≥18 years of age.
4. Subject had a life expectancy ≥6 months.

5. Following lung resection, subject had at least one or more visible intraoperative air leaks (IOAL), after standard closure techniques were applied, that required treatment with pleural sealant.
6. Subject was willing and able to comply with the study procedures and complete the entire study as specified in the protocol, including the follow-up visits.

A subject was excluded from study entry if any of the following criteria were met:

1. Subject had undergone previous lung resection or previous use of a sealant for air leaks.
2. Subject had a serum creatinine ≥2.5 mg/dl at baseline or was currently on dialysis.
3. Following lung resection, subject had intraoperative air leaks that required non-standard, visceral pleural closure (e.g. leak was too small or tissue was too fragile to use sutures/staples)
4. Subject had any condition that, in the opinion of the Investigator, would preclude the use of the study device, or preclude the subject from completing the follow-up requirements.
5. Subject had known allergy to human albumin or any component in the Progel™ PALS product.
6. Subject had an active or latent infection which was systemic or at the intended surgery site.
7. Subject had necrotic or friable borders of the defect that would not support secure suture fixation if use of sutures was required.
8. Subject was participating in another investigational drug or device trial.
9. Subject was pregnant or had plans to become pregnant during the study period or was currently breastfeeding.
10. Subject was part of the site personnel directly involved with this study.
11. Subject was a family member of the investigational study staff.

2. Follow-up Schedule

Follow-up through 30 days postoperatively included chest tube air leak assessment, chest tube drainage, time to chest tube removal, patient discharge, physical exam, adverse event assessments, evaluation of chest x-rays, renal function laboratory testing, and quality of life survey. All protocol-mandated chest x-rays were independently reviewed by a radiology core lab and all adverse events were adjudicated by an independent clinical events committee (CEC).

3. Clinical Endpoints

The primary safety endpoint was the rate of device- and/or procedure-related adverse events reported through one (1) month of postoperative follow-up as compared to a performance goal based on literature. Events were adjudicated by an independent CEC. The final study results are presented below.

The key secondary efficacy endpoint was the proportion of subjects without postoperative air leaks following lung surgery up to one (1) month follow-up as measured by observation of air leaks via chest tube.

The other secondary effectiveness endpoints were:

1. The proportion of air leaks that were sealed or reduced, as demonstrated by the air leak test, prior to completion of the lung surgery.
2. The proportion of subjects who were free from air leaks immediately following surgery as measured by the presence of air leaks from the chest tube at the first postoperative time point once the subject is in the recovery room.
3. The duration of postoperative air leaks from the time of surgery until the air leak sealed.
4. The duration of chest tube drainage.
5. The duration of hospitalization (length of stay).
6. Patient reported Quality of Life as measured by the SF-36.

B. Accountability of Subjects

A total of 207 subjects were enrolled and 112 subjects were treated with Progel^{TM}PALS. Of the 112 subjects treated (40 video-assisted surgery and 72 robotic-assisted surgery), 103 subjects completed the study. There were 106 evaluable subjects for the primary endpoint defined as those who completed the 1-month follow-up visit or had a device/procedure related AE before discontinuation.

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

	Total (N=112)
N	112
Gender	
Male	46 (41.1%)
Female	66 (58.9%)
Race	
Asian	3 (2.7)
Other	1 (0.9)
Black or African-American	3 (2.7)
White	105 (93.8)
Age, years	
Mean	67.1
SD	11.21
Median	69
Minimum	34
Maximum	87
Age Category	
<65	39 (34.8%)
>=65	73 (65.2%)
Medical Risk Factors	
Pre-Specified Risk Factors	Total N=112
Hypertension	64 (57.1%)
Diabetes	17 (15.2%)

	Total (N=112)
If Diabetes: Insulin	4 (3.6%)
If Diabetes: Oral agents	10 (8.9%)
Immunosuppression (yes)	2 (1.8%)
Renal Disease (yes)	10 (8.9%)
History of Myocardial Infarction	7 (6.3%)
Cardiovascular Disease (yes)	37 (33.0%)
History of Stroke	4 (3.6%)
History of Transient Ischemic Attack	4 (3.6%)
Congestive Heart Failure	5 (4.5%)
If Congestive Heart Failure: Class I	1 (0.9%)
COPD (yes)	34 (30.4%)
Cancer History (yes)	58 (51.8%)
Previous Thoracic Surgery (yes)	2 (1.8%)
Previous Therapeutic Radiation to Thorax (yes)	6 (5.4%)
Current Systemic Chemotherapy (yes)	3 (2.7%)
Preoperative use of steroids	17 (15.2%)
Weight Loss of >/=10 lbs in last year (yes)	10 (8.9%)
Alcohol Abuse	11 (9.8%)
If Alcohol Abuse: Current	6 (5.4%)
If Alcohol Abuse: Past	5 (4.5%)
Cigarette Smoking	81 (72.3%)
If Cigarette Smoking: Current	21 (18.8%)
If Cigarette Smoking: Past	60 (53.6%)
Drug Abuse	1 (0.9%)
If Drug Abuse: Past	2 (1.8%)
Other Significant Medical History (yes)	77 (68.8%)

Surgery Characteristics and Device Application Parameters

Table 3 presents a summary of primary diagnoses, type of surgery, surgical approach, time in operating room, time to skin closure, intraoperative air leak distribution and size prior to application of Progel™ PALS. Most subjects were indicated for thoracic lung surgery for primary tumors. There were more robotic-assisted procedures than video-assisted procedures. The most frequent type of surgery was lobectomy.

Table 3. Primary Diagnosis and Procedure Variables

Primary Diagnosis (postoperatively)	
N	112
Primary Tumor	87 (77.7%)
Metastatic tumor	11 (9.8%)
Benign tumor	4 (3.6%)
COPD	3 (2.7%)
Chronic bronchitis	1 (0.9%)
Emphysema	0 (0.0%)
Other	11 (9.8%)
Operative Procedure*	
Bilobectomy	6 (5.4%)
Lobectomy	61 (54.5%)
Segmentectomy	15 (13.4%)
Wedge Resection	35 (31.3%)
Decortication	2 (1.8%)
Biopsy	5 (4.5%)
Surgery Type	
Video-Assisted	40 (35.7%)

Primary Diagnosis (postoperatively)	
N	112
Robotic-Assisted	72 (64.3%)
Time in OR (mins)	
Mean	225.4
SD	66.25
Median	214.5
Minimum	79
Maximum	433
Time to skin closure (mins)	
Mean	155.4
SD	61.26
Median	143.0
Minimum	47
Maximum	401
IOAL prior to closure	
1	91 (81.3%)
2	20 (17.9%)
3	1 (0.9%)
IOAL size prior to closure	
<2mm	40/133 (30.1%)
2-5mm	88/133 (66.2%)
>5mm	5/133 (3.8%)

*Subjects may be counted more than once in each category if they had multiple procedures in one surgery.

Table 4 reports the actual number of Progel™ PALS applications used per patient and total volume of Progel™ PALS used per air leak.

Table 4. Volume of Progel™ Pleural Air Leak Sealant Used

Volume of Progel™ PALS Used per AL (ml)	
N	133
Mean	4.6
SD	1.99
Median	4
Minimum	0
Maximum	12
Number of Progel™ PALS Applications	
0*	1 (0.7%)
1	108 (80.6%)
2	19 (14.2%)
3	6 (4.5%)

*One air leak became not visible after application of standard procedure, as a result not treated with Progel™ PALS

D. Safety and Effectiveness Results

1. Safety Results

Table 5 presents the incidence of adverse events (AEs) reported for greater than 1% of subjects during the minimally invasive clinical study in 112 subjects treated as compared to the AEs reported in the original pivotal study. Overall, 131 AEs were reported in 59 Progel™ PALS subjects during the minimally invasive study (52.7%; 59/112) as compared to the overall AE rate in the original pivotal study of 65.0% (76/103) for Progel™ PALS and 74.1% (43/58) for the

Control cohort. There were no device related AEs or unanticipated adverse events (UADEs) in this study. The majority of AEs reported were mild (25%) or moderate (18.8%) in severity. Forty SAEs occurred in 28 subjects (25%). The majority of SAEs was pulmonary and expected events as part of a lung resection surgery. Two subjects died during the course of the study, one due to cardiac arrest and another due to multi-system organ failure; neither were considered to be device related or unanticipated.

Table 5. Incidence of AEs reported for Subjects in Minimally Invasive Study as Compared to Original Pivotal Study

Preferred Term	*Open Progel PALS N=103	*Open Control N=58	Minimally Invasive Progel PALS N=112
Number of Subjects with at least one AE	76 (65.0%)	43 (74.1%)	59 (52.7%)
Fever/Pyrexia	22 (21.4%)	12 (20.7%)	12 (10.7%)
Fibrillation, Atrial	12 (11.7%)	7 (12.1%)	NR
Dyspnea	12 (11.7%)	10 (17.2%)	1 (0.9%)
Constipation	11 (10.7%)	6 (10.3%)	NR
Nausea	10 (9.7%)	7 (12.1%)	NR
Pneumothorax	9 (7.8%)	5 (8.6%)	2 (1.8%)
Confusion	8 (7.8%)	5 (8.6%)	NR
Hypotension	8 (7.8%)	6 (10.3%)	5 (4.5%)
Anemia	8 (7.8%)	6 (10.3%)	NR
Pain	7 (6.8%)	4 (6.9%)	3 (2.7%)
Subcutaneous Emphysema	7 (6.8%)	5 (8.6%)	1 (0.9%)
Tachycardia	7 (6.8%)	6 (10.3%)	NR
Death	5 (4.9%)	4 (6.9%)	2 (1.8%)
Oliguria	5 (4.9%)	1 (1.7%)	1 (0.9%)
Vomiting	5 (4.9%)	7 (12.1%)	1 (0.9%)
Pneumonia	5 (4.9%)	7 (12.1%)	3 (2.7%)
Pulmonary Infiltration	4 (3.9%)	0 (0.0%)	NR
Chest Pain	4 (3.9%)	1 (1.7%)	NR
Pleural Effusion	4 (3.9%)	3 (5.2%)	6 (5.4%)
Urinary Retention	3 (2.9%)	0 (0.0%)	2 (1.8%)
Ileus	3 (2.9%)	0 (0.0%)	1(0.9%)
Tachycardia, Supraventricular	3 (2.9%)	0 (0.0%)	NR
Abdominal Pain	3 (2.9%)	0 (0.0%)	1 (0.9%)
Arrhythmia	3 (2.9%)	0 (0.0%)	NR**
Extrasystoles	3 (2.9%)	0 (0.0%)	NR
Coughing	3 (2.9%)	1 (1.7%)	1 (0.9%)
Hypoxia	3 (2.9%)	1 (1.7%)	4 (3.6%)
Renal Failure, Acute	3 (2.9%)	1 (1.7%)	NR
Adult Respiratory Stress Syndrome	3 (2.9%)	1 (1.7%)	2 (1.8%)
Hyperkalemia	2 (1.9%)	0 (0.0%)	1(0.9%)
Hyponatraemia	2 (1.9%)	0 (0.0%)	2 (1.8%)
Cardiac Arrest	2 (1.9%)	0 (0.0%)	1 (0.9%)
ECG Abnormal	2 (1.9%)	0 (0.0%)	NR
Renal Function Abnormal	2 (1.9%)	0 (0.0%)	NR

Preferred Term	*Open Progel PALS N=103	*Open Control N=58	Minimally Invasive Progel PALS N=112
Asthenia	2 (1.9%)	0 (0.0%)	NR
Influenza-Like Symptoms	2 (1.9%)	0 (0.0%)	NR
Somnolence	2 (1.9%)	1 (1.7%)	NR
Abdomen Enlarged/Distension	2 (1.9%)	1 (1.7%)	1 (0.9%)
Atelectasis	2 (1.9%)	2 (3.4%)	6 (5.4%)
Postoperative Wound Infection	2 (1.9%)	2 (3.4%)	NR
Multiple Organ Failure	2 (1.9%)	1 (1.7%)	1 (0.9%)
Anxiety	1 (1.0%)	1 (1.7%)	1(0.9%)
Withdrawal Syndrome	1 (1.0%)	1 (1.7%)	NR
GI Hemorrhage	1 (1.0%)	1 (1.7%)	NR
Hypokalemia	1 (1.0%)	1 (1.7%)	NR
Arrhythmia Atrial	1 (1.0%)	1 (1.7%)	5 (4.5%)*
Respiratory Disorder/distress	1 (1.0%)	1 (1.7%)	2 (1.8%)
Respiratory Insufficiency	1 (1.0%)	1 (1.7%)	NR
Sepsis	1 (1.0%)	1 (1.7%)	NR
Bronchial Obstruction	1 (1.0%)	1 (1.7%)	1 (0.9%)
Infection Staphylococcal	1 (1.0%)	1 (1.7%)	NR
Pruritus	1 (1.0%)	2 (3.4%)	NR
Delirium/mental status changes	1 (1.0%)	2 (3.4%)	3 (2.7%)
Hypertension	1 (1.0%)	2 (3.4%)	NR
Angina Pectoris	1 (1.0%)	2 (3.4%)	NR
Hemoptysis	1 (1.0%)	3 (5.2%)	NR
Arthropathy	0 (0.0%)	1 (1.7%)	NR
Gall Bladder Disorder	0 (0.0%)	1 (1.7%)	NR
Cachexia	0 (0.0%)	1 (1.7%)	NR
Dehydration	0 (0.0%)	1 (1.7%)	NR
Non-protein Nitrogen Increased	0 (0.0%)	1 (1.7%)	NR
Edema Dependent	0 (0.0%)	1 (1.7%)	NR
Edema Generalized	0 (0.0%)	1 (1.7%)	NR
Fibrillation Ventricular	0 (0.0%)	1 (1.7%)	NR
Cardiac Failure	0 (0.0%)	1 (1.7%)	NR
Hypoventilation	0 (0.0%)	1 (1.7%)	1 (0.9%)
Thrombocytopenia	0 (0.0%)	1 (1.7%)	NR
Allergic Reaction	0 (0.0%)	1 (1.7%)	NR
Fatigue	0 (0.0%)	1 (1.7%)	NR
Rigors	0 (0.0%)	1 (1.7%)	NR
Infection, Fungal	0 (0.0%)	1 (1.7%)	NR
Healing, Impaired	0 (0.0%)	1 (1.7%)	NR
Cramps, Legs	0 (0.0%)	1 (1.7%)	NR
Acidosis, Respiratory	0 (0.0%)	1 (1.7%)	NR
Chyle, Leak	0 (0.0%)	1 (1.7%)	NR
Pulmonary Air Leakage	***	***	10 (8.9%)
Urinary tract infection	0 (0.0%)	0 (0.0%)	5 (4.5%)
Dysuria	0 (0.0%)	0 (0.0%)	2 (1.8%)
Pneumonia Aspiration	0 (0.0%)	0 (0.0%)	2 (1.8%)
Pulmonary haemorrhage	0 (0.0%)	0 (0.0%)	2 (1.8%)

NR= Not Reported

* The data reported in the first two columns were derived from the original PMA pivotal study.
**Term used in VATS/Robotics study was the more specific term of "arrhythmia supraventricular". See Arrhythmia Atrial.
***Pulmonary air leakage was not reported as an adverse event and included as part of the efficacy data for the Open PMA study.

Renal Events

Progel™ PALS degradation products are primarily cleared from the body by the kidneys. Similar to the data presented in the PMA pivotal study, the incidence of Renal AEs along with individual subject data are noted in Table 6 below. Five subjects had renal events all of which were mild in severity, none met serious adverse event (SAE) criteria, and all subjects recovered without sequelae. None of these subjects had preexisting renal disease.

Table 6. Incidence of Adverse Events Related to Renal Function

Renal Adverse Events	Number of Events
N	112
Abnormal renal function	0 (0%)
Urinary retention	2 (1.8%)
Dysuria	2 (1.8%)
Acute renal failure	0 (0%)
Oliguria	1 (0.9%)
Total number of renal adverse events % patients with renal adverse events	5 4.5%

Subject	Surgery Type	Adverse Event	Severity	Serious	Progel™ ml used	BUN (mg/dL)			Creatinine (mg/dL)			GFR (mL/min/1.73^2)		
						Pre-op	D/C	1 MFU	Pre-op	D/C	1 MFU	Pre-op	D/C	1MFU
001-006	Robotic	Urinary retention	Mild	No	4	19	9	16	0.7	0.7	0.8	79.53	79.53	68.17
004-010	Robotic	Oliguria	Mild	No	8	18	7	14	1	1.1	0.9	60	60	60
004-013	Robotic	Dysuria	Mild	No	8	23	19	20	1.2	1.1	1.3	47	51	42
011-005	Video	Urinary retention	Mild	No	4	24	24	22	1.6	1.4	1.4	43	51	51
014-015	Robotic	Dysuria	Mild	No	4	18	17	15	1.1	1	0.9	60	60	81

D/C = discharge from hospital
1MFU = one-month follow-up

Subject Deaths

There were two subject deaths during the study. None of the deaths were considered by the investigators or adjudicated by the CEC to be device-related or Unanticipated Adverse Device Effect (UADE).

Subject 013-006, a 73-year-old white female with a significant medical history of hypertension, bladder cancer, right breast cancer, previous smoker, asthma, depression, hypothyroidism, varicosities, cholecystectomy, cervical spine surgery, sinus surgery, B12 deficiency, and reflux esophagitis underwent robotic-assisted right lower lobectomy on Oct 15, 2013. The subject was treated with Progel™ PALS and was transferred to the post-anesthesia care unit (PACU) in stable condition. The subject remained in the hospital and on post-op day 9, the subject had a drop in the hematocrit (HCT). She was transfused with

packed red blood cells and a bronchoscopy was performed. The bleeding was found with no obvious source as well as a change in the right upper lobe orifice. The perfusion scan was abnormal and the subject was taken back into the operating room. Torsion of the right lung was corrected and a chest tube was inserted. The subject left the operating room (OR) intubated and in guarded condition. The subject remained in the intensive care unit (ICU) on a ventilator. On Oct 28, 2013, post-op day 13, the subject coded and resuscitation efforts were unsuccessful. Twenty (20) minutes following initiation of resuscitation, the subject was pronounced dead due to cardiac arrest. The site reported this event as not related to the device and possibly not related to procedure. The CEC adjudicated this event as not related to the device and definitely related to the procedure.

Subject 014-006, a 77-year-old white male who was a previous smoker with a medical history of COPD, preoperative steroid use, and peripheral vascular disease (abdominal aortic aneurysm) underwent a robotic-assisted right lower lobectomy for a primary tumor on Sept 23, 2013. The subject was treated with Progel™ PALS at the staple line and was transferred from the OR in stable condition. On post-op day 2, the subject experienced nausea and vomiting. The subject developed aspiration pneumonitis. He then went into respiratory distress and Acute Respiratory Distress Syndrome (ARDS) and required intubation and ventilator management. The subject was treated in the ICU and experienced multi-system organ failure. On post-op day 11, the subject experienced cardiopulmonary arrest. The family chose to remove life support and the subject died on Oct 5, 2013, post-op day 12. The site reported this event as not related to the device and not related to the procedure. The CEC adjudicated this event as not related to the device and possibly related to the procedure.

Primary Safety Endpoint

The analysis of the primary safety endpoint was based on 106 evaluable subjects who completed the 1 month follow-up visit or had a device/procedure related AE before discontinuation. The observed incidence of procedure- and/or device-related AEs at one month was 42.5% (90% confidence interval (CI) lower bound 34.3%, upper bound 50.9%), which did not meet criteria for meeting the performance goal of an upper bound less than 42% (p-value=0.5784). There were no device-related adverse events and no unanticipated adverse device effects (UADE) reported in this study through the one-month follow-up. The majority of the procedure-related adverse events were of mild severity and were non-serious, 20.8% (22/106) and 23.6% (25/106), respectively. The most common non-serious procedure-related AEs included fevers/pyrexia (11.3%; 12/106), hypotension (4.7%; 5/106), hypoxia (3.8%; 4/106), and supraventricular arrhythmia (3.8%; 4/106); all of which occurred early in-hospital stay prior to discharge, and are known common post-surgical events.

The AE rate of 42.5% is higher than expected because the AEs that were adjudicated included many minor events that were not included in the literature-derived performance goal. An additional analysis of the adverse event data was performed to evaluate the data with respect to the pre-specified performance goal excluding several of the non-serious AEs reported in the VATS/Robotics study such as: fevers/pyrexia, hypotension, hypoxia, catheter site cellulitis, hypoesthesia, pleural effusion, procedural pain, productive cough, and abdominal distension. When these events were excluded from the primary endpoint analysis, the

observed incidence of procedure-and/or device related AEs at one month was 24.5% which met the primary endpoint performance goal (p=0.0003) (Table 7).

Table 7. Rate of AEs Related to the Study Device and/or Procedure Through the 1-Month Follow-up (mITT Population) and Identified in the Literature Used to Set the Performance Goal for the Primary Endpoint.

	Subjects N=112	90% CI	One Sided P-value
Rate of AEs Related to the study device and/or procedure	26/106 (24.5%)	(17.8%, 32.4%)	0.0003
Rate of AEs Related to the study device	0/106 (0%)		
Rate of AE's Related to the study procedure	26/106 (24.5%)	(17.8%, 32.4%)	0.0003

Table 8 summarizes the rate of AEs related to the study device and/or procedure for the Video and Robotic treatment group through the 1-month follow-up. There was an observed difference between the video-assisted and robotic-assisted groups in the rates of procedure-related AEs (p=0.0047). While the proportion of subjects with any procedure-related AE was higher in the robotic-assisted group, the majority of these subjects had mild and non-serious events.

Table 8. Rate of AE Related to the Study Device and/or Procedure Through the 1-Month Follow-up by Surgery Type (mITT Population)

	Subjects N=112	90% CI
Video Assisted		
Rate of AEs Related to the study device and/or procedure	10/ 40 (25.0%)	(14.2%, 38.7%)
Rate of AEs Related to the study device	0/ 40 (0.0%)	(0.0%, 7.2%)
Rate of AEs Related to the study procedure	10/ 40 (25.0%)	(14.2%, 38.7%)
Robotic Assisted		
Rate of AEs Related to the study device and/or procedure	35/ 66 (53.0%)	(42.2%, 63.6%)
Rate of AEs Related to the study device	0/ 66 (0.0%)	(0.0%, 4.4%)
Rate of AEs Related to the study procedure	35/ 66 (53.0%)	(42.2%, 63.6%)
Comparison between Video and Robotics: P-value	0.0047	

Relatedness is based on the CEC adjudicated outcome.
P-value is from chi square test.
The denominator is the number of subjects who have completed 1-month follow-up visit or had device/procedure related AE before discontinuation.

Table 9 shows the rate of procedure-related SAEs and Moderate/Severe AEs by surgery type. The difference in procedure-related AEs between the two surgery types was reduced when SAEs or moderate to severe AEs were analyzed. The rate of procedure related SAEs was 17.5% in video-assisted procedures as compared to 20% in the robotic-assisted procedures. The rate of moderate/severe AEs was 17.5% in video-assisted procedures as compared to 24.6% in the robotic-assisted procedures.

Table 9. Rate of SAEs and Moderate/Severe AEs Related to the Study Device and/or Procedure Through the 1-Month Follow-up <u>by Surgery Type</u> (mITT Population)

	Video Assisted		Robotic Assisted	
	Rates(n/N)[1]	90% CI	Rates(n/N)[2]	90% CI
Rate of SAEs Related to the study device and/or procedure	7/ 40 (17.5%)	(8.5%, 30.4%)	13/ 65 (20.0%)	(12.3%, 29.9%)
Rate of Moderate/Severe AEs Related to the study device/procedure	7/ 40 (17.5%)	(8.5%, 30.4%)	16/ 65 (24.6%)	(16.1%, 35.0%)

Relatedness is based on the CEC adjudicated outcome.
[1]The denominator is the number of subjects who have completed 1-month follow-up visit or had device/procedure related SAE before discontinuation.
[2]The denominator is the number of subjects who have completed 1-month follow-up visit or had device/procedure related moderate or severe AE before discontinuation.

Overall, when the results were analyzed for the clinically relevant events of serious or moderate/severe adverse events, the observed complication rate was lower than the Performance Goal of 42% with 19.0% (serious) or 21.9% (moderate/severe) procedure-related adverse events.

Table 10. Rate of SAEs and Moderate/Severe AEs Related to the Study Device and/or Procedure Through the 1-Month Follow-up (mITT Population)

	Subjects N=112	90% CI	One Sided P-value
Rate of SAEs Related to study device and/or procedure	20/105 (19.0%)	(13.0%, 26.5%)	<0.001
Rate of Moderate/Severe AEs Related to the study device and/or procedure	23/105 (21.9%)	(15.5%, 29.6%)	<0.001

Relatedness is based on the CEC adjudicated outcome.
The p-value is based on comparison to a Performance Goal of 42%.
The denominator 105 is the number of subjects who have completed 1-month follow-up visit or had device/procedure related SAE before discontinuation.

2. Key Effectiveness Results

The key secondary efficacy endpoint of the proportion of subjects without postoperative air leaks (POAL) following surgery through the 1 month follow-up is presented in Table 11. There was no observed difference between the video-assisted and robotic-assisted groups in postoperative air leak (p=0.5924) (Table 12).

Table 11. Percentage of subjects who remained air leak-free through the 1 MFU

Air Leak Status through IMFU	Total n=112	P-value*
No POAL	55 (49.1%)	<0.001
With POAL	57 (50.9%)	

*As compared to a 23% Performance Goal based on the PMA Pivotal thoracotomy study Progel™ group.

Table 12. Proportion of Subjects without Postoperative Air Leaks Following Lung Surgery Through 1- month Follow-up by Surgery Type (mITT Population)

	Proportion of subjects with no air leak		
Surgery Type	n/N(%)	90% CI	One sided p-value[1]
Surgery type: Video Assisted	21/ 40 (52.5%)	(38.5%, 66.2%)	<.0001
Surgery type: Robotic Assisted	34/ 72 (47.2%)	(37.1%, 57.5%)	<.0001

	Proportion of subjects with no air leak		
Surgery Type	n/N(%)	90% CI	One sided p-value[1]
Comparison between Video and Robotics p-value [2]	0.5924		

[1] p-value is computed compared with Performance Goal = 23% on exact binomial test
[2] p-value computed using Chi-square test

Secondary Effectiveness Outcomes

- Table 13 presents a summary of IOALs sealed or reduced. There were 107 of 133 air leaks sealed immediately after Progel™ PALS application, and an additional 21 were considered reduced, with a total of 128 (96.2%) air leaks sealed or reduced after Progel™ PALS application and before completion of lung surgery.

Table 13. IOAL Closure Summary

		Total
After Progel™ Sealant IOAL size	No IOAL	107/133 (80.5%)
	<2mm	24/133 (18.0%)
	2-5mm	2/133 (1.5%)
	>5mm	0/133 (0.0%)

- Proportion of subjects 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 postoperative time point once the subject was in the recovery room (RR) is presented in Table 14. No ALs were observed in the RR in 60.7% of the Progel™ PALS subjects.

Table 14. Summary of POALs in the Recovery Room

Response	Total n=112
No AL	68 (60.7%)
Occasional Intermittent Bubbles	22 (19.6%)
Frequent Bubbles, Not continuous	12 (10.7%)
Continuous Bubbles	8 (7.1%)
Missing	0 (0.0%)

- Duration of postoperative air leaks was measured from the time of surgery until the air leak sealed. If the subject was discharged with a portable chest tube (e.g. Heimlich valve), the day the air leak ceased was recorded as the day the portable chest tube was removed. The majority of POALs lasted less than 3 days and was similar for both video-assisted and robotic-assisted groups. Time to no air leak is presented in Table 15. The mean (SD) duration of postoperative air leaks was 2.8(6.75) days and median was 1.0 day. Of the 11 subjects that had postoperative air leak duration >7 days, 6 were discharged with a portable chest tube

Table 15. Duration of Postoperative Air Leaks (POAL)

Duration POAL (Days)	Total n=112
0 day	55 (49.1%)
1-2 days	32 (28.6%)
3-4 days	7 (6.3%)
5-7 days	6 (5.4%)
>7 days	11(9.8%)
Missing	1 (0.9%)
n	111
Mean	2.8
SD	6.75
Median	1.0
Minimum	0.0
Maximum	46

- Table 16 presents a summary of the duration of CT placement in number of postoperative days. The median duration of CT placement was 2.0 days.

Table 16. Summary of Chest Tube Duration (mITT Population)

Chest Tube Duration (days)*	Total (N=112)
1-2 days	56 (50.0%)
3-4 days	30 (26.8%)
5-7 days	12 (10.7%)
>7 days	13 (11.6%)
Missing	1 (0.9%)
N	111
Mean	4.3
Std	6.02
Median	2.0
Min-Max	1.0 - 46

*If the leak stop date was missing, then the chest tube removal date was regarded as leak stop date.

- A summary of hospital duration is provided in Table 17. The median hospital duration was 3.0 days. The majority of subjects (83.9%) were discharged from the hospital by postoperative Day 7. Eight subjects were discharged with a portable chest tube. Two subjects died prior to discharge and are not included in the hospital duration calculations.

Table 17. Summary of Hospital Duration (mITT Population)

Hospital Stay Duration (days)	Total (N=112)
1-2 days	30 (26.8%)
3-4 days	40 (35.7%)
5-7 days	24 (21.4%)
>7 days	16 (14.3%)
Missing	2 (1.8%)
N	110

Hospital Stay Duration (days)	Total (N=112)
Mean	4.6
Std	3.48
Median	3.0
Min-Max	1.0 – 20

- Quality of life was measured using the SF-36v2 questionnaire, and the absolute change from baseline for the component summary scores is provided in Table 18. Baseline values were collected before surgery, and since the SF-36 has a 30-day recall period and subjects were administered the survey at the 1-month follow-up visit, a decrease in SF-36 scores is not unexpected.

Table 18. Summary of SF-36v2 Norm-Based Scores at Baseline and at One Month Follow-up (mITT Population)

		Baseline	1 Month Follow Up	Change From Baseline
Mental Component Summary	N	110	95	93
	Mean	49.2	49.0	-0.2
	SD	12.08	11.87	9.20
	Median	52.7	50.1	0.7
	Minimum	9.2	16.0	-30.8
	Maximum	69.9	70.3	21.2
Physical Component Summary	N	110	95	93
	Mean	45.3	38.8	-6.5
	SD	10.97	9.99	9.98
	Median	47.0	40.1	-6.9
	Minimum	16.6	10.5	-33.7
	Maximum	65.5	58.7	21.4

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 15 initial principle investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Original Pivotal Clinical Study

The applicant had previously performed a pivotal clinical study to establish a 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 (≥2mm) incurred during open resection of lung parenchyma in the US

under IDE #G980283. Data from this pivotal clinical study were the basis for the original PMA approval decision for its original intended use. A summary of the clinical study is presented below.

A. Pivotal Study Design – (G980283)

This was 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 intraoperative 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 postoperative recovery and in the investigator's opinion would complicate evaluation of device safety and effectiveness.

Enrolled patients were stratified according to preoperative percent predicted FEV 1 (≤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™ PALS 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™ PALS were permitted.

2. Follow-Up Schedule

Follow-up through 30 days postoperatively, 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™ PALS effectiveness was the percent of patients without postoperative air leak (POAL) through one month postoperatively or the duration of hospitalization, whichever is longer.

Secondary effectiveness endpoints were:

1. The proportion of intraoperative air leaks (IOAL) in each group that were sealed or reduced, as demonstrated by the air leak (AL) test, prior to completion of the surgery.
2. The proportion of subjects in each group who were air leak-free immediately following surgery as measured by the presence of ALs from the chest tube (CT) at the first postoperative time point once the subject was in the recovery room (RR).
3. The duration of postoperative air leaks measured from the time of surgery until the AL sealed.
4. The duration of chest tube placement. This endpoint included the time that the Heimlich Valve was in place.
5. The duration of hospitalization: postoperative hospital days (POD).

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

B. Accountability of PMA Cohort

A total of 275 subjects were consented and enrolled and 161 subjects were randomized intraoperatively. Of the 161 randomized subjects (i.e.; 103 Progel™ PALS 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™ PALS lung transplant, 1 had a post-Progel™ PALS 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™ PALS and 5/58 (8.6%) in the Control groups.

C. Study Population Demographics and Baseline Parameters

The demographic characteristics of the enrolled subjects are presented in Table 19.

Table 19. 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 FEVl:		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%)
	Yes	9 (8.7%)	5 (8.6%)
Chemotherapy:	No	94 (91.3%)	56 (96.6%)
	Yes	9 (8.7%)	2 (3.4%)
Steroid Use:		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		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 = Ambulatorv	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	I (1.0%)	0 (0.0%)
Missing	5 (4.9%)	2 (3.4%)

None of the differences between Progel™ PALS 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 FEVl 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 preoperative pulmonary function test results.

Surgery Characteristics and Device Application Parameters

Table 20 presents a summary of primary diagnoses, type of surgery, surgical approach, extent of lymphadenectomy, intraoperative air leak (IOAL) distribution and extent of pleural adhesions.

Table 20. 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.l %)
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 Sterrnotomy	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™ PALS and Control groups, the posterolateral thoracotomy was the most frequently used surgical approach for open thoracotomy. Intraoperative characteristics were similar between the Progel™ PALS 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™ PALS Applications:

A 2ml of Progel™ PALS was expected to cover a 20 cm² (3in²) surface area with 1mm thickness of Progel™ PALS, which was expected to be sufficient to treat an average clinically significant visceral pleural AL. Up to three applications of Progel™ PALS were allowed per individual air leak.

Table 21 reports the actual number of Progel™ PALS applications as well as the number of 2ml Progel™ PALS units used per patient.

Table 21. Volume of Progel™ Pleural Air Leak Sealant Use

Volume of Progel™ PALS 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™ PALS Applications Per AL	Progel™ PALS- N (%)
One	125
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 22 provides additional information on patient surgeries.

Table 22. Other Operative Details

Treatment		Progel™ PALS	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

ı 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 23 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™ PALS and 58 Control patients).

Table 23. Incidence of AEs Reported by > 1% of Subjects by Treatment Group*

Preferred Term	**Progel™ PALS 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%)

Preferred Term	Progel™ PALS N=103	Control N=58
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%)
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%)

Preferred Term	Progel™ PALS N=103	Control N=58
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™ PALS and Control groups.

Table 24 presents those AEs considered by the investigator to be possibly or probably related to the Progel™PALS. There were 3 subjects in the Progel™ PALS 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™ PALS 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 24. Incidence of Adverse Events in Progel™ PALS Group Considered Possibly or Probably Device-related.

Body System Preferred Term	Progel™ PALS (N=103)
Body as a Whole	
Chest Pain	1(1.0%)
Gastrointestinal Systems	
Constipation	1(1.0%)
Gastroesophageal Reflux	1 (1.0%)
Nausea	l (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™ PALS-treated subject at three weeks post open pulmonary mastectomy 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™PALS. No other unanticipated adverse events were reported.

OTHER SERIOUS ADVERSE EVENTS

Table 25 presents a summary of other serious adverse events (SAEs). There were 5 other SAEs: 2 in the Progel™ PALS group and 3 in the Control group. Both of the Progel™ PALS SAEs were considered by the investigator probably not related to the device. All of the events resulted in extended hospital stays or re-hospitalization; 4 subjects recovered from these events and 1 subject continued on dialysis.

Table 25. Other Serious Adverse Events

Subject ID	Age/Gender	Relationship To Device	Event	Outcome
Progel PALS				
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™ PALS 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™ PALS interposes between visceral and parietal pleura. It is unknown if interpleural Progel™ PALS changes postoperative visceral and parietal pleura surface adhesion, changes surface healing and allows air leak sites to re-open upon Progel™ PALS 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™ PALS compared to 1.7% control patients; Progel™ PALS patients with ARDS died. Event incidences are in Table 26.

Table 26. Pleural Air Leak and Air Space Events

Pleural Air Leak and Air Space Events	Progel™ PALS	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™ PALS degradation products are primarily cleared from the body by the kidneys. The incidence of Renal AEs along with individual subject data are in Table 27.

Table 27. Incidence of Adverse Events Related to Renal Function (n, %)

Renal Adverse Events		Progel PALS				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 PALS 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 PALS	Severity
		Pre-op	1 MFU	Pre-op	1 MFU	ml used	
Progel PALS	Abnormal RF	25	26	1.1	1.8	6	Severe
Progel PALS	Abnormal RF, oliguria	23	84**	0.7	1.8**	4	Severe
Progel PALS	Acute renal failure	21	24	1.4	1.7	2	Severe
Progel PALS	Acute renal failure*	54	14	3.8	5.0	2	Severe
Progel PALS	Acute renal failure	8	***	1.0	***	6	Severe
Progel PALS	Oliguria*	13	17	1.1	1.3	4	Moderate
Progel PALS	Oliguria*	33	39	1.7	2.2	8	Moderate
Progel PALS	Oliguria	12	8	0.9	1.0	6	Mild
Progel PALS	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

*Preexisting renal disease
**at discharge; no l MFU as patient died
***no discharge or IMFU as patient died
****at discharge; no lMFU data

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

All urinary system disorders occurrence was Progel™PALS: 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™ PALS to exacerbate renal dysfunction in patients with preexisting renal disease is unknown.

SUBJECT DEATHS

Table 28 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™ PALS 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™ PALS patients with ARDS was associated with more than the mean (2.5 Units = 5ml) and median (2.0 Units = 4ml) amount of Progel™ PALS used in clinical study.

The single patient who received the maximum volume of Progel™ PALS 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™ PALS application. ARDS was noted 0-6 hours post-op Progel™ PALS application. The patient developed pulseless ventricular fibrillation and flutter and died on POD 2 after Progel™ PALS application; autopsy findings bilaterally included moderate pleural cavity adhesions on gross exam, congestion on cut lung surface, and fibrinous pleuritis microscopically.

Table 28. 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 PALS Used
Progel PALS				
71/Male ECOG=4, FEV1≤ 40%	POD2	Not Related	ARDS	30 ml
66/Male ECOG=1, FEV1>40	POD6	Not Related	ARDS & Multisystem Failure	6 ml
61/Male ECOG=1, FEV1>40	POD10	Not Related	Acute Airway Obstruction or Pulmonary Embolism	2 ml
65/Male ECOG=2, FEV1>40	POD22	Not Related	ARDS & Multisystem Failure	4 ml
82/Male ECOG=0, FEV1>40	POD28	Not Related	Pneumonia	4 ml
Control				
82/Male ECOG=0/FEV1>40	POD0	Not Related	Ventricular Fibrillation	N/A
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
67/Male ECOG=unknown/FEV1>40	POD38	Not Related	Anoxic Brain Injury	N/A

NIA= Not Applicable

HUMORAL AND CELL-MEDIATED IMMUNE RESPONSE

Both pre and postoperative serum samples were obtained from 71/103 (69%) Progel™ PALS and 37/58 (64%) Control subjects. Seventy (70) of the Progel™ PALS and 36 of the Control subjects showed no immune reaction to the Progel™PALS. One (1) subject in each group had preoperative and postoperative serum levels consistent with the presence of Progel™ PALS 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™ PALS 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™ PALS and 34 Control subjects and recall antigen and Progel™ PALS analyses were performed in 69 Progel™ PALS and 32 Control subjects. No clinically significant differences were observed in the pre and postoperative blood samples for either Control or Progel™ PALS subjects.

2. Effectiveness Results

The analysis of effectiveness was based on the 161 evaluable patients at the l 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 29.

Table 29. Primary Endpoint Results

Air Leak Status Through lMFU Visit	Progel™ PALS N(%)	Control N(%)	P-value
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 FEVl ≤ or > 40%, all 5 Progel™ PALS and 4 Control patients with FEV1 ≤ 40% had POAL; whereas 59/93 (63.4%) Progel™ PALS and 45/53(84.9%) Control patients with FEVI > 40% had POAL.

Secondary Effectiveness Outcomes

- Proportion of intraoperative 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 30. Of the 210 ALs tracked in the Progel™ PALS group, 76.7% were sealed after the application of Progel™ PALS compared with 15.7% of the 108 ALs in

the Control group. IOALs were sealed in 70.9% of the Progel™ PALS and 10.3% of the Control subjects following the final AL test.

Table 30. IOAL Closure Summary

Parameter	Response	Progel PALS 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 postoperative time point once the subject was in the recovery room (RR) is presented in Table 31. 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™ PALS 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™ PALS and 33% of the Control subjects.

Table 31. Summary of POALs in the Recovery Room

Observation Period	Response	Progel PALS 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 postoperative 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 32.

Table 32. Duration of Postoperative Air Leaks*

	Post-op	
Duration POAL	**Progel™ PALS**	**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

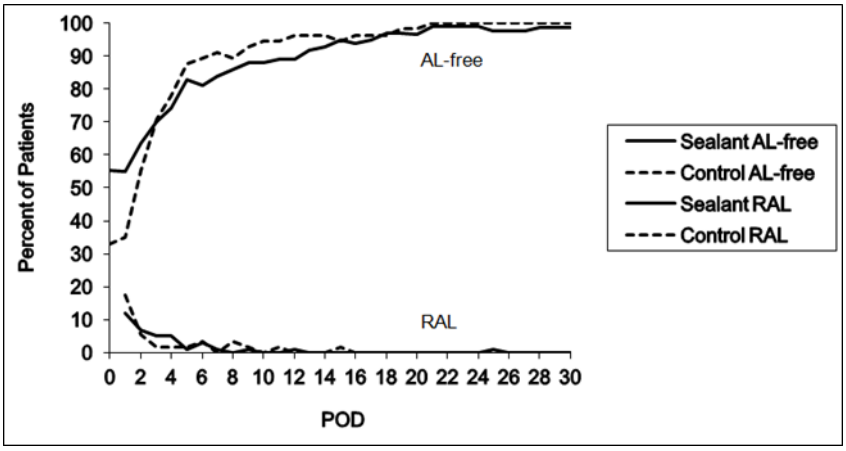
*Differences were not statistically significant as determined by a Wilcoxon Rank Sum Test comparing Progel™ and Control groups based on all available data (N=157).

Data demonstrate that overall the mean duration of postoperative air leaks was 1.1 days longer for the Progel™ PALS 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™ PALS patients had no air leak at 0-2 days, 10.1% more control patients bad no air leak at 3-6 days, and that 7.4% more Progel™ PALS patients' air leak continued through more than 11 days.

It is clinically notable that ten (10%) subjects in the Progel™ PALS 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 postoperative air-leaks, which may in part explain the higher proportion of Progel™ PALS patients with air leak that continues through more than 11 days.

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

Figure 2. Air-leak Free and Recurrence of Air Leak by Postoperative 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™ PALS 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 postoperative 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 lMFU. Patients who were discharged with a Heimlich valve were counted as having AL on the postoperative days between the date of discharge and the date of chest tube removal.

- **Duration of Chest Tube Placement**

Table 33 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 33. Duration of CT Placement[a]

CT Duration	Progel PALS 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™ PALS and Control groups based on all available data (N=l55).
[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 FEVl ≤ or > 40%, mean (median) chest tube placement duration for patients with FEVI ≤ 40% was 8.3 (7.0) days for Progel™ PALS 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™ PALS and 6.2 (5.5) days for the Control cohorts.

- **Duration of hospitalization: postoperative hospital days (POD)**

Table 34 presents the length of hospital stay in days.

Table 34. Duration of hospitalization POD

Hospital stay, days	Progel PALS N (%)	Control N (%)	P-Value[a]
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™ PALS 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=l61) and treated patients with missing time of hospital discharge as censored observations.

XII. PANEL MEETING RECOMMENDATION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Device Act of 1990, this PMA was not referred to the Anesthesiology and Respiratory Therapy Devices Advisory Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

Overall efficacy is equal to that reported in the approved Progel™ PALS application for open thoracotomy and the benefit is translatable to the video-assisted and robotic-assisted thoracoscopic surgery populations without an increase in SAE rate. The benefit-risk profile is acceptable as there is a high efficacy of air leak closure, which results in earlier chest tube removal, less pain and earlier discharge from the hospital. Though these parameters were not studied via control group the efficacy results are equal to that in the P010047 study, which showed significant improvement versus a control group.

B. Safety Conclusions

The risks of the device are based on the data and information collected from a clinical study conducted to support the expansion of indications approval as described above. The sponsor submitted safety and effectiveness data to support its label change in removing surgery procedure restriction (i.e. to include minimally invasive surgery applications such as video- and robotic-assisted thoracoscopic surgeries), as well as removing air leak size restriction. The safety data did not meet the pre-specified performance goal of an upper bounded confidence interval of 42% as it reported a mean AE rate of 42.5% with an upper bound of 50.9%. However, this result is confounded by the lack of device related AEs (0% reported), and thus the failure of the safety endpoint is entirely related to procedure related AEs, of which the majority are reported in the robotically assisted cohort. Furthermore, in reviewing the type of AEs, it is found that these are primarily AEs that are of minor clinical importance, which is evident because the SAE rate (clinically important) is below the performance goal and the safety event differences between the video-assisted thoracoscopic surgery and robotic-assisted thoracoscopic surgery disappear. It is concluded that the overall AE rate is higher due to the increased surveillance found in an IDE study and that the pre-specified performance goal was likely constructed from the literature that reflects primarily SAEs and does not include the many minor AE that were reported in the robotic-assisted thoracoscopic surgery arm. The overall SAE rate is acceptable for approval and demonstrates that there is not a difference between procedure cohorts and that the more labor intensive robotic-assisted thoracoscopic surgery procedure results in an increase in minor AEs that do not affect the overall patient safety. The study included patients with air leaks less than 2 mm in size and demonstrated that it was safe and effective in this population of subjects.

C. Benefit-Risk Conclusions

The probable benefits of the device are also based on data collected in a clinical study conducted to support the expansion of indications approval as described above. The clinical data taken in its totality supports Progel™ PALS labeling change and expanded indications. The data showed initially that it did not meet the pre-specified performance goal of an upper bounded confidence interval of 42% as it reported a mean AE rate of 42.5% with an upper bound of 50.9%. However, this is confounded by there being no device related AEs and because SAE rate, which is more clinically important, is below the performance goal. In addition, there are no SAE differences between the video-assisted thoracoscopic surgery and robotic-assisted thoracoscopic surgery groups. This is relevant since the AE rate is significantly higher in the robotic-assisted thoracoscopic surgery group and is composed primarily of low hazard, high signal safety events. Overall efficacy is equal to or greater than that reported in the market-approved application for open thoracotomy and is translatable, and the benefit is significantly higher than the risk posed. It should be taken into consideration that this is a tool or an adjunct to a much larger procedure of surgical resection of lung and that Progel™ PALS is already approved for an open procedure and its use in a closed procedure should not affect the procedure's hazard risk to the patient differently than an open surgery. The benefits outweigh the risks by twice fold of not using the sealant as compared to an open thoracotomy control group. In addition, the benefit of early chest tube removal is a significant benefit in regards to reduction in patient suffering and the decrease in use of hospital resources.

In conclusion, given the available information above, the data support that for application to visceral pleura after standard visceral pleural closure with, for example, sutures or staples, of visible air leaks incurred during resection of lung parenchyma using the Progel™ PALS, the probable benefits outweigh the probable risks.

D. Overall Conclusions from Clinical Data

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™ PALS when used as an adjunct to standard closure of ALs incurred during pulmonary surgery and extends the indicated use to subjects undergoing pulmonary resection to include less invasive procedures video and robotic assisted surgery with air leaks smaller than 2mm.

XIV. CDRH DECISION

CDRH issued an approval order on February 13, 2105.

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

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.