PROGEL™

Pleural Air Leak Sealant

The PROGEL™ Pleural Air Leak Sealant package is provided sterile.

Caution: Federal (USA) law restricts this device to sale by or on the order of a licensed physician or properly licensed practitioner.

Information for the use of PROGEL™ Pleural Air Leak Sealant is provided in this labeling for Physicians. **Before using PROGEL™ Pleural Air Leak Sealant, please read the following information thoroughly.**

1.0 DEVICE DESCRIPTION

PROGEL™ Pleural Air Leak Sealant (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 sealant 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. Each 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 Polyethylene glycol 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 (2 ml to be used to reconstitute PEG-$(SS)_2$)
  - — One (1) Applicator assembly with locking push rod
  - — Two (2) Spray tips
- One (1) – Instructions for Use (Labeling)

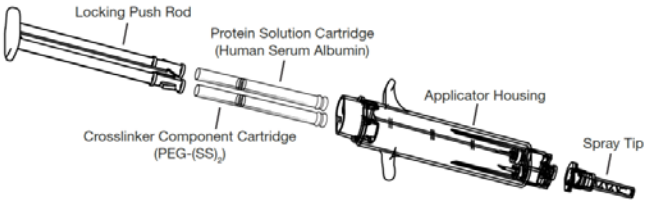
Optional replacement and extended spray tips are available for convenience and positioning according to surgeon preference:

PROGEL™ Applicator Spray Tips (pack of 2) REF PGST009, 10 units/box with Instructions

PROGEL™ Extended Applicator Spray Tip 16 cm REF PGEN005-06, 4 units/box with Instructions

PROGEL™ 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)



2.0 INTENDED USE / 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.

3.0 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 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.

4.0 WARNINGS

Do not apply PROGEL™ PALS on oxidized regenerated cellulose, absorbable gelatin sponges or any other surface other than visceral pleura as adherence and intended outcome may be compromised.

5.0 PRECAUTIONS

- The safety and effectiveness of PROGEL™ PALS has not been established in patients with the following conditions:
  - — Less than 18 years of age, pregnant or nursing women.
  - — Contaminated or dirty pulmonary resection cases.
  - — The presence of an active infection.
  - — In the presence of other sealants, hemostatic devices or products other than sutures and staples used in standard visceral pleural closure.
  - — Visceral pleural air leak due to spontaneous pneumothorax, any non-resective pulmonary tissue trauma, or malignancy as well as congenital or acquired functional or anatomic defect.
  - — Patients receiving PROGEL™ PALS in more than one application session (surgery) before and/or after resorption of PROGEL™ PALS that was applied in any previous surgical session.
  - — In any area or tissue other than the visceral pleural surface as indicated.
  - — FEV1≤ 40% due to small sample size in the clinical study. In the original pivotal study, all 5 PROGEL™ PALS and 4 Control patients with FEV1 ≤40% had post-operative air leak (POAL); whereas in patients with FEV1 > 40%, 59/93 (63.4%) PROGEL™ PALS and 45/53 (84.9%) Control patients had POAL. See Section 7.9 Summary of Primary Clinical Study: Primary Effectiveness Outcome.

- Do not use if sterile package and seal are damaged or open, as sterility may be compromised. Do not re-sterilize the contents.
- PROGEL™ PALS should be refrigerated between 2°C and 8°C (36°F to 46°F). Do not freeze. Store PROGEL™ PALS within the recommended temperature range. Failure to do so may result in poor product performance. Do not use PROGEL™ PALS after the expiration date, as sterility or performance may be compromised.
- Do not use rehydrated cross-linker after 20 minutes, as the performance of PROGEL™ PALS may be compromised.
- Interruption of the application for approximately 10 seconds may result in occlusion of the spray tip. If occlusion occurs, remove the spray tip, wipe the end of the applicator to remove any fluid, and attach a new spray tip (provided) onto the end of the applicator.
- PROGEL™ PALS is intended for single use only. Do not re-sterilize or reuse any component.
- PROGEL™ PALS use with any additive (e.g. antibiotics) to any component has not been studied.
- Discard unused material in accordance to standard practice for PROGEL™ PALS components.
- PROGEL™ PALS resorption time in humans has not been studied. In rats, over 50% of a 14C-labeled device was excreted after 24 hours and virtually all radioactivity was recovered from rats at 14 days post-implant. The PROGEL™ PALS was also largely absent at 4 days with only isolated fragments of the PROGEL™ PALS apparent at 7 days after implantation on pigs' lungs.
  - Human Serum Albumin - HSA (USP) in the PROGEL™ PALS kit is obtained from an FDA licensed supplier and the protein is derived from plasma collected from donors who have been screened and tested according to the methods specified by the FDA. These methods minimize the possibility that drawn blood will contain communicable diseases or viruses such as hepatitis and HIV.
- Do not use more than 30 ml of PROGEL™ PALS per patient.

6.0 POTENTIAL ADVERSE EFFECTS

Below is a list of potential adverse effects (e.g. complications) associated with the device.

- 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
- 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

- Renal Failure, Acute
- Adult Respiratory Stress Syndrome
- Hyperkalemia
- Hyponatraemia
- Urinary tract infection
- Dysuria
- Pneumonia Aspiration
- Pulmonary haemorrhage

7.0 ORIGINAL PIVOTALCLINICAL STUDY

Study Title: A Randomized Study to Evaluate a Polymeric Patch for Sealing Intraoperative Air Leaks Occurring During Pulmonary Resection

7.1 STUDY OBJECTIVES

The primary study objective was to evaluate the safety and effectiveness of the use of PROGEL™ Pleural Air Leak Sealant (PROGEL™ PALS) as an adjunct to standard suture/staple closure of clinically significant (≥ 2 mm in size) intra-operative visceral pleural air leaks incurred during open resection of non-infected pulmonary tissue in adults.

7.2 STUDY DESIGN

The study was a prospective, "standard care alone" – controlled, 2:1 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.

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 (≥ 2 mm) 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™ 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.

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 H_2O) 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.'

7.3 STUDY ENDPOINTS

The primary endpoint for PROGEL™ PALS 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 PROGEL™ PALS measured pre- and post-surgery.

7.4 SUBJECT ACCOUNTING

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™ 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 pre-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.

7.5 DEMOGRAPHICS

The demographics of the subjects enrolled in the study are presented in Table 1.

TABLE 1. Patient Demographics

		PROGEL™ PALS	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%)
	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™ 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 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.

7.6 PRIMARY DIAGNOSIS AND PROCEDURE VARIABLES

Table 2 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 2. Primary Diagnosis and Procedure Variables

	PROGEL™ PALS	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™ PALS and Control groups, the posterolateral thoracotomy was the most frequently used surgical approach for open thoracotomy. Intra-operative 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.

7.7 NUMBER OF PROGEL™ PALS APPLICATIONS

2 ml of PROGEL™ PALS was expected to cover a 20 cm^2 (3 in^2) surface area with 1 mm 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 3 reports the actual number of PROGEL™ PALS applications as well as the number of 2 ml PROGEL™ PALS units used per patient.

TABLE 3. Volume of PROGEL™ Pleural Air Leak Sealant Used

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 (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 4 provides additional information on patient surgeries.

TABLE 4. 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 (min)	N	91	50
	Mean ± SD	156.8 ± 54.9	165.0 ± 62.6
	Median	151.0	143.5
	Minimum	52	81
	Maximum	355	387

7.8 ADVERSE EVENTS (AEs)

Table 5 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 5. Incidence of AEs Reported by > 1% of Subjects by Treatment Group*

Preferred Term	PROGEL™ PALS N=103	Control N=58	Preferred Term	PROGEL™ PALS	Control N=58
Fever	22 (21.4%)	12 (20.7%)	Atelectasis	2 (1.9%)	2 (3.4%)
Fibrillation, Atrial	12 (11.7%)	7 (12.1%)	Postoperative Wound Infection	2 (1.9%)	2 (3.4%)
Dyspnea	12 (11.7%)	10 (17.2%)	Multiple Organ Failure	2 (1.9%)	1 (1.7%)
Constipation	11 (10.7%)	6 (10.3%)	Anxiety	1 (1.0%)	1 (1.7%)
Nausea	10 (9.7%)	7 (12.1%)	Withdrawal Syndrome	1 (1.0%)	1 (1.7%)
Pneumothorax	9 (7.8%)	5 (8.6%)	GI Haemorrhage	1 (1.0%)	1 (1.7%)
Confusion	8 (7.8%)	5 (8.6%)	Hypokalemia	1 (1.0%)	1 (1.7%)
Hypotension	8 (7.8%)	6 (10.3%)	Arrhythmia Atrial	1 (1.0%)	1 (1.7%)
Anemia	8 (7.8%)	6 (10.3%)	Respiratory Disorder	1 (1.0%)	1 (1.7%)
Pain	7 (6.8%)	4 (6.9%)	Respiratory Insufficiency	1 (1.0%)	1 (1.7%)
Subcutaneous Emphysema	7 (6.8%)	5 (8.6%)	Sepsis	1 (1.0%)	1 (1.7%)
Tachycardia	7 (6.8%)	6 (10.3%)	Bronchial Obstruction	1 (1.0%)	1 (1.7%)
Death	5 (4.9%)	4 (6.9%)	Infection Staphyloccal	1 (1.0%)	1 (1.7%)
Oliguria	5 (4.9%)	1 (1.7%)	Pruritus	1 (1.0%)	2 (3.4%)
Vomiting	5 (4.9%)	7 (12.1%)	Delirium	1 (1.0%)	2 (3.4%)
Pneumonia	5 (4.9%)	7 (12.1%)	Hypertension	1 (1.0%)	2 (3.4%)
Pulmonary Infiltration	4 (3.9%)	0 (0.0%)	Angina Pectoris	1 (1.0%)	2 (3.4%)
Chest Pain	4 (3.9%)	1 (1.7%)	Hemoptysis	1 (1.0%)	3 (5.2%)
Pleural Effusion	4 (3.9%)	3 (5.2%)	Arthropathy	0 (0.0%)	1 (1.7%)
Urinary Retention	3 (2.9%)	0 (0.0%)	Gall Bladder Disorder	0 (0.0%)	1 (1.7%)
Ileus	3 (2.9%)	0 (0.0%)	Cachexia	0 (0.0%)	1 (1.7%)
Tachycardia, Supraventricular	3 (2.9%)	0 (0.0%)	Dehydration	0 (0.0%)	1 (1.7%)
Abdominal Pain	3 (2.9%)	0 (0.0%)	Non-protein Nitrogen Increased	0 (0.0%)	1 (1.7%)
Arrhythmia	3 (2.9%)	0 (0.0%)	Edema Dependent	0 (0.0%)	1 (1.7%)
Extrasystoles	3 (2.9%)	0 (0.0%)	Edema Generalized	0 (0.0%)	1 (1.7%)
Coughing	3 (2.9%)	1 (1.7%)	Fibrillation Ventricular	0 (0.0%)	1 (1.7%)
Hypoxia	3 (2.9%)	1 (1.7%)	Cardiac Failure	0 (0.0%)	1 (1.7%)
Renal Failure, Acute	3 (2.9%)	1 (1.7%)	Hypoventilation	0 (0.0%)	1 (1.7%)
Adult Respiratory Stress Syndrome	3 (2.9%)	1 (1.7%)	Thrombocytopenia	0 (0.0%)	1 (1.7%)
Hyperkalaemia	2 (1.9%)	0 (0.0%)	Allergic Reaction	0 (0.0%)	1 (1.7%)
Hyponatraemia	2 (1.9%)	0 (0.0%)	Fatigue	0 (0.0%)	1 (1.7%)
Cardiac Arrest	2 (1.9%)	0 (0.0%)	Rigors	0 (0.0%)	1 (1.7%)
ECG Abnormal	2 (1.9%)	0 (0.0%)	Infection, Fungal	0 (0.0%)	1 (1.7%)
Renal Function Abnormal	2 (1.9%)	0 (0.0%)	Healing, Impaired	0 (0.0%)	1 (1.7%)
Asthenia	2 (1.9%)	0 (0.0%)	Cramps, Legs	0 (0.0%)	1 (1.7%)
Influenza-Like Symptoms	2 (1.9%)	0 (0.0%)	Acidosis, Respiratory	0 (0.0%)	1 (1.7%)
Somnolence	2 (1.9%)	1 (1.7%)	Chyle, Leak	0 (0.0%)	1 (1.7%)
Abdomen Enlarged	2 (1.9%)	1 (1.7%)			

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

ADVERSE EVENTS

Table 6 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 6. 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	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™ PALS-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 PROGEL™ PALS. No other unanticipated adverse events were reported.

OTHER SERIOUS ADVERSE EVENTS

Table 7 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 rehospitalization; 4 subjects recovered from these events and 1 subject continued on dialysis.

TABLE 7. 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

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 post-operative 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 8.

TABLE 8. 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 9.

TABLE 9. 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*	10	2
% patients with renal adverse events	9/95 (9.5%)	2/53 (3.8%)
*1 PROGEL™ PALS patient was reported to have 2 events: abnormal renal function and oliguria		

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

*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™ PALS and 1 control patients who had a renal AE, and no pre-existing 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 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.

Urinary system disorders occurred in 12 patients in the PROGEL™ PALS group (11.7%), and 2 patients in the Control group (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 pre-existing renal disease is unknown.

SUBJECT DEATHS

Table 10 presents a summary of subject deaths. 5/103 (4.9%) PROGEL™ PALS 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 = 5 ml) and median (2.0 Units = 4 ml) 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, or 30 ml total volume) 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 10. Summary of Subject Deaths

Age , Gender Pre-op ECOG Score, Pre-op 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
82/Male ECOG=0, FEV1>40	POD28	Not Related	Pneumonia	4 ml
61/Male ECOG=1, FEV1>40	POD10	Not Related	Acute Airway Obstruction or Pulmonary Embolism	2 ml
66/Male ECOG=1, FEV1>40	POD6	Not Related	ARDS & Multisystem Failure	6 ml
65/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

7.9 EFFECTIVENESS

Primary Effectiveness Outcome

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

TABLE 11. Primary Endpoint Results

Air Leak Status Through 1MFU Visit	PROGEL™ PALS 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™ PALS and Control groups for the primary endpoint analysis.

As to stratification for pre-op FEV1 ≤ 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 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 12. 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 12. 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 post-operative time point once the subject was in the recovery room (RR) is presented in Table 13. 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 13. 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 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 post-operative day (POD) on which the AL was noted. Time to no air leak is presented in Table 14.

TABLE 14. Duration of Post-Operative 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

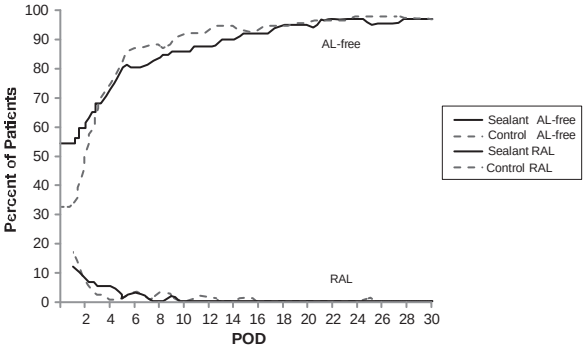
*Differences were not statistically significant as determined by a Wilcoxon Rank Sum Test comparing PROGEL™ PALS and Control groups based on all available data (N=157).

Data demonstrate that overall the mean duration of Post-Operative Air Leaks was 1.1 days longer for the PROGEL™ 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 had 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 post-operative 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 pre-op FEV1 ≤ or > 40%, mean (median) air leak duration for patients with FEV1 ≤ 40% was 6.3 (4.0) days for PROGEL™ PALS 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™ PALS 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™ 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 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.

- Table 15 presents a summary of the duration of chest tube placement in number of post-operative 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 15. Duration of CT Placement[a]

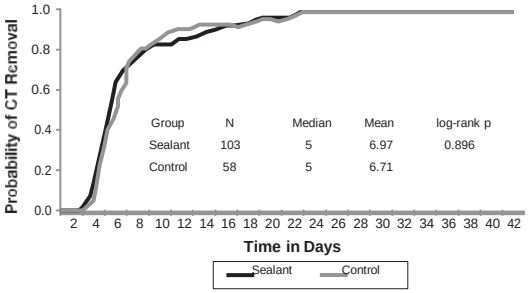
CT Duration	PROGEL™ PALS N (%)	Control N (%)
N	103	58
Missing[b]	3 (2.9%)	3 (5.2%)
N	100	55
0-2 days	2 (1.9%)	0 (0.0%)
3-4 days	34 (33.0%)	19 (32.8%)
5-6 days	37 (35.9%)	21 (36.2%)
7-9 days	11 (10.7%)	9 (15.5%)
10-11 days	3 (2.9%)	3(5.2%)
> 11 days	13 (12.6%)	3 (5.2%)
Mean	6.8	6.2
SD	5.5	3.5
Median	5.0	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 & 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 a 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 were 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 3 below.

As to stratification for pre-op FEV1 ≤ or > 40%, mean (median) chest tube placement duration for patients with FEV1 ≤ 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.

FIGURE 3. Time to Chest Tube (CT) Removal



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

- Table 16 presents the duration of hospitalization or post-operative hospital days (POD).

TABLE 16. Duration of hospitalization POD

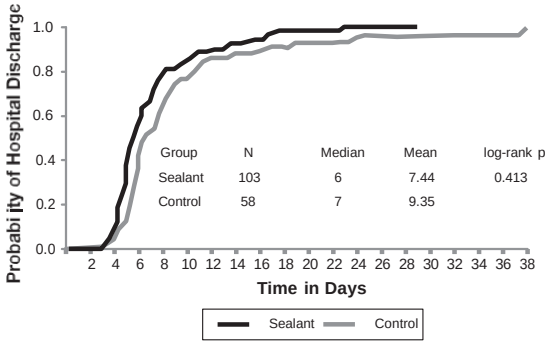
Hospital stay, days	PROGEL™ PALS N (%)	Control N (%)	P-Value[a]
N	103	58	
Missing[b]	5 (4.9%)	3 (5.2%)	0.0413
N	98	55	
3-4 days	11 (10.7%)	4 (6.9%)	
5-6 days	49 (47.6%)	23 (39.7%)	
7-9 days	22 (21.4%)	16 (27.6%)	
10-11 days	7 (6.8%)	5 (8.6%)	
> 11 days	9 (8.7%)	7 (12.1%)	
Mean	7.44	9.35	
SD	3.4	5.6	
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=161) and treated patients with missing time of hospital discharge as censored observations. The results of the survival analysis are shown in Figure 4.

FIGURE 4: Time to Hospital Discharge



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

7.10 OTHER SAFETY ASSESSMENT

Humoral and Cell-Mediated Immune Response

Both pre- and post-operative 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 pre-operative and post-operative 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 post-operative whole blood samples. Mitogen analyses were compared in pre- and post-operative 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 post-operative blood samples for either Control or PROGEL™ PALS subjects.

8.0 RESULTS OF THE VATS/ROBOTICS SUPPORTING CLINICAL TRIAL

8.1 PRIMARY OBJECTIVE

The primary objective of this study was to evaluate the safety of PROGEL™ PALS including the PROGEL™ Extended Applicator Spray Tip 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. The 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.

8.2 STUDY DESIGN

The study was a prospective, multi-center, single arm study. Eligible patients were adults undergoing video or robotic-assisted thoracic lung resection surgery that had intra-operative air leak(s) of any size after standard visceral pleural closure techniques were applied. Patients were excluded if they had undergone previous lung resection or previous use of a sealant for air leaks, had a serum creatinine of greater than or equal to 2.5mg/dl or on dialysis, had a known hypersensitivity to human albumin, had necrotic or friable borders that will not support secure suture fixation if use of sutures is required, if pregnant and/or breast feeding, or any condition that in the investigator's opinion would preclude the use of the study device or from completing the follow-up.

A total of 112 subjects were treated in this study at 15 U.S. sites with a split of 40 video and 72 robotic-assisted procedures to have at least 100 evaluable subjects. Follow-up assessment was scheduled 30 days post-operative.

The safety assessment 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 from the published literature. Events were adjudicated by an independent Clinical Events Committee (CEC). The final study results are presented below.

TABLE 17. 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	
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%)
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%)
Pre-operative 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%)

TABLE 18. Primary Diagnosis and Procedural Characteristics

Primary Diagnosis (post-operatively)	
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%)
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 19. 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.

8.3 ADVERSE EVENTS

Overall, 131 AEs were reported in 59 PROGEL™ subjects during the minimally invasive study (52.7%; 59/112) as compared to the overall AE rate in the original pivotal study of 65% (76/103) for PROGEL™ and 74.1% (43/58) for the Control cohort. There were no device related adverse events or unanticipated adverse events 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 were pulmonary and expected events as part of a lung resection surgery. Two patients died during the course of the study, one due to cardiac arrest and another due to multi-system organ failure; neither were device related or unanticipated.

TABLE 20. 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
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%)*

Preferred Term	Open Progel PALS N=103	Open Control N=58	Minimally Invasive Progel PALS N=112
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

*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.

8.4 PRIMARY SAFETY ENDPOINT

Out of 106 evaluable subjects, the observed incidence of procedure- and/or device-related AEs at one month was 42.5% (90% CI 34.3%, 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. When the results were analyzed for the clinically relevant events of serious or moderate/severe, the observed complication rate was 19.0% (20/105) (serious) or 21.9% (23/105) (moderate/severe) procedure-related adverse events.

An additional analysis was performed on the performance goal studies 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 criteria (p=0.0003).

Table 21. 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	P-value
Rate of AEs Related to the study device and/or procedure	26106 (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

8.5 KEY SECONDARY EFFICACY ENDPOINT

The key secondary efficacy endpoint of the proportion of subjects without postoperative air leaks (POAL) following surgery through the 1 month follow-up was 49.1% ($p < 0.001$), providing strong evidence suggesting the use of PROGEL™ PALS in minimally invasive procedures is as effective in preventing POALs as in open surgeries.

TABLE 22. 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™ PALS group.

8.6 OTHER SECONDARY EFFECTIVENESS ENDPOINTS

TABLE 23. IOAL Closure Summary

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

TABLE 24. 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%)

TABLE 25. Duration of Post-Operative 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 26. 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.

TABLE 27. 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
Mean	4.6
Std	3.48
Median	3.0
Min-Max	1.0 - 20

9.0 PATIENT COUNSELING INFORMATION

The physician should discuss the following with patients potentially receiving PROGEL™ PALS:

- The Indication for PROGEL™ PALS Use
- The risk/benefit issues associated with PROGEL™ PALS use.
- The presence of HSA prepared from pooled human plasma donors in the final product. Use of this product presents some risk of transmitting infectious agents. While this risk is deemed remote, it cannot be totally excluded. This also applies to pathogens that are as yet unknown.

The Human Serum Albumin (HSA-USP) used to manufacture the PROGEL™ PALS 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.

10.0 INSTRUCTIONS 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.

Assess Air Leaks after Standard Suture/Staple Closure

After applying standard suture/staple closure methods to seal air leaks, assess for persistent air leaks from the visceral pleura. If visible air leaks from the visceral pleura are observed, consider applying the PROGEL™ PALS.

If a patient is a candidate for PROGEL™ PALS use, perform the following steps:

Inspect Packaging

The PROGEL™ PALS kit consists of two sealed, sterile packages. Contents:

- One (1) – Chemistry Kit, e-beam sterilized
- One (1) – Applicator Kit, ethylene oxide sterilized
- One (1) – Instructions For Use insert (Labeling)

Inspect the packages before opening. Do not use PROGEL™ PALS after the Expiration date, because sterility or performance may be compromised. If package and/or product integrity have been compromised (i.e. damaged package seal, or broken glass), do not use or resterilize the contents. Refer to other precautions as listed in the beginning of this labeling.

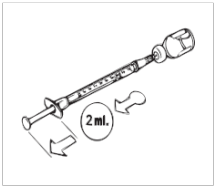
Prepare PROGEL™ Pleural Air Leak Sealant

Using aseptic technique, open the sterile package and pass the following contents into the sterile field. Cartridges may be assembled into the delivery system in any order. Load each cartridge as follows:

- One (1) - pre-loaded cartridge containing 2 ml of processed Human Serum Albumin
  - — Note: This cartridge can be identified by examining the differences between the two contents. The Human Serum Albumin cartridge is in liquid form and has a slight yellow tint to the solution.
- One (1) - pre-loaded cartridge containing 260 mg of Polyethylene glycol di-succinimidyl succinate (PEG-$(SS)_2$) as a dried white powder.
  - — Note: This cartridge can be identified by examining the differences between the two contents. The cross-linker cartridge containing the Polyethylene glycol di-succinimidyl succinate (PEG- $(SS)_2$) is in the form of a white powder.
- One (1) - 3 ml plastic syringe with 0.5 inch 26 gauge needle
- One (1) - 5 ml vial of USP sterile water for injection (Used for reconstitution of the PEG-$(SS)_2$)
- One (1) - Applicator assembly with locking push rod

Step 1

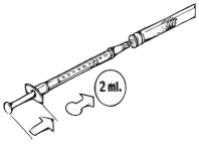
Using the 3 ml syringe, draw 2 ml of sterile water into the syringe and express all air in the syringe (syringe and sterile water are provided in the Applicator Kit).



Draw 2 ml Sterile Water

Step 2

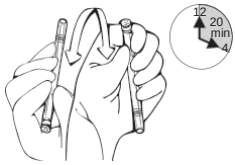
Inject the 2 ml of sterile water into the cartridge containing the cross-linker, (white powder cartridge provided in the Chemistry Kit). Note: The Human Serum Albumin cartridge contains a yellow liquid. Water is only to be injected in to the cross-linker (white powder) cartridge.



Inject 2 ml sterile water into the white powder Crosslinker Cartridge

Step 3

Mix water and the cross-linker in the cartridge by gently rocking the cartridge from end to end (generally 1-2 minutes) until the solution contains no undissolved powder. When all powder is dissolved, the cross-linker is ready for use. Note: The PROGEL™ PALS should be used within 20 minutes after dissolving the cross-linker in water.



Mix

Step 4

Without the spray tip attached, point the applicator injection tip up and load each cartridge into the twin-chambered applicator housing. Gently press the cartridges to seat them into place.

NOTE: When properly loaded the chemistry cartridges should sit flush with the end of the applicator housing.


Load HSA and Crosslinker Cartridges into Applicator

Step 5

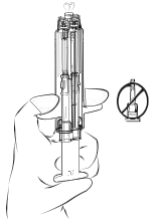
Without the spray tip attached, point the applicator injection tip straight up to allow any air in the chemistry to rise to the top of the cartridges. Insert the locking push rod into the openings in the rear of the cartridges until it snaps into place.

NOTE: During applicator assembly, the PROGEL™ push rod is designed to lock in to the applicator housing. Forced removal of the locking push rod from the applicator housing may result in potential damage to the applicator system or the chemistry cartridges.


Insert the Locking Push Rod

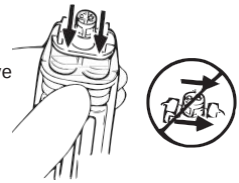
Step 6

With the tip of the applicator pointed upward, briskly flick the applicator to free any air bubbles. Express the air by gently but firmly pushing up on the push rod until the stoppers in each cartridge are aligned with one another. Take care to express as little fluid as possible during this process.


Express Air

Step 7

Wipe the applicator tip with clean, sterile gauze to remove any liquid that may have been expressed with the air. Avoid mixing of components: do not wipe from one cartridge opening across to the other – wipe each opening separately.



Wipe Nose Clean

Step 8

Place a spray tip on the tip of the applicator and rotate the spray tip clockwise 1/4 turn until locked. Alternatively, a PROGEL™ Extended Applicator Spray Tip may be used (sold separately). For complete instructions on use of the PROGEL™ Extended Applicator Spray Tip, please reference complete labeling included with the product. REF PGEN005-06, PGEN005-11.

Attach Spray Tip

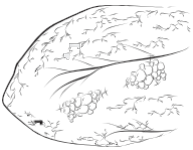
Step 9

The PROGEL™ PALS is ready for application.

Apply PROGEL™ PALS

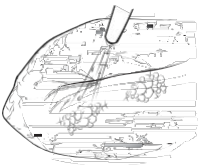
Step 10

After applying standard suture/staple closure methods to seal identified air leaks, assess for persistent visible air leaks from the visceral pleura. If visible air leaks from the visceral pleura, note location of leak and consider applying PROGEL™ PALS. Do not use more than 30 ml of PROGEL™ PALS per patient.



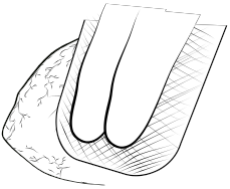
Step 11

Rinse the visceral pleural surface to be treated with sterile saline to remove any pooled blood or blood clots with irrigation and/or suction.



Step 12

IMPORTANT: Blot the target tissue area with a sponge or gauze to remove excess moisture.



Step 13

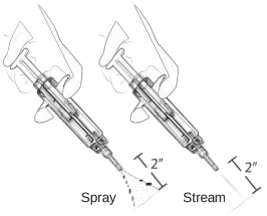
Ventilation to the affected area should be stopped. If ventilation needs to be maintained, reducing the tidal volume is recommended to minimize air leakage and lung movement during application of the sealant. In procedures where CO^2 insufflation is being used, consider reducing or discontinuing CO^2 pressure during PROGEL™ PALS application and for the duration of the sealant set time.

Step 14

Select the target site to be sealed. Note: Each 4 ml applicator will supply enough PROGEL™ PALS to cover an area 40 cm^2 (6 in^2) and 1 mm thick.

Step 15

Hold the spray tip approximately 5 cm (2 in) from the tissue to be sealed, and apply firm, steady pressure to the push rod to dispense the gel to the target location. Note: The gel can be applied in either a spray pattern or a stream depending upon the amount of pressure applied to the push rod. Applying a light pressure will cause the gel to be dispensed in a stream. Applying slightly more pressure to the push rod will cause the stream to convert to a spray.

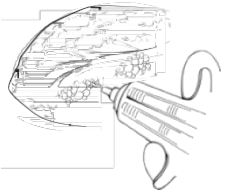


Interruption of the application for approximately 10 seconds may result in occlusion of the spray tip. If occlusion occurs, remove the spray tip, wipe the end of the applicator to remove any fluid, and attach a new spay tip (provided) onto the end of the applicator as described in step 8 of the PROGEL™ PALS Preparation section.

Keep the applicator tip approximately 5 cm (2 in) away from the target area to avoid creating bubbles in the sealant material and apply with a smooth sweeping motion. The formation of bubbles may compromise the adherence and/or mechanical properties of the Progel PALS.

Step 16

Maintain firm pressure on the push rod and move the spray tip from side to side along the margin of the tissue surface to be sealed.



Step 17

Allow the PROGEL™ PALS to cure for 15-30 seconds, forming a flexible hydrogel. Two minutes after application, the sealant's success in sealing the target site(s) can be tested using the saline submersion test or by irrigating the site to check for air bubbles.

Step 18

PROGEL™ PALS application over an air leak site that leaks despite standard methods of closure may be repeated up to a total of 3 applications per site if necessary to seal the air leak. Thereafter, other methods for sealing an air leak should again be considered.

Step 19

If the applicator's contents are not entirely used in the first application, immediately remove the spray tip and wipe residual PROGEL™ PALS components from the applicator tip with clean dry gauze to prevent the remaining material from activating. Repeat application requires spray tip replacement with an unused, sterile tip. An additional spray tip is provided in the kit. PROGEL™ Extended Applicator Spray Tips are sold separately.

Step 20

If more than one kit is needed, additional kits should be prepared and applied as needed.

11.0 HOW SUPPLIED

STERILE: PROGEL™ Pleural Air Leak Sealant is supplied sterile, with total reconstituted component volume of 4 ml per PROGEL™ PALS unit. It is intended for single use only. Non-pyrogenic. Do not use if package is opened or damaged.

12.0 STORAGE

PROGEL™ PALS should be refrigerated between 2°C and 8°C (36°F to 46°F). Do not freeze.

Note: Store PROGEL™ PALS within the recommended temperature range. Failure to do so may result in poor product performance.

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