

ANESTHESIOLOGY AND RESPIRATORY THERAPY DEVICES PANEL

Gaithersburg, Maryland

June 12, 2008

NeoMend Inc. ProGEL™ Surgical Sealant

PMA P010047

SPONSOR'S EXECUTIVE SUMMARY

SPONSOR'S EXECUTIVE SUMMARY

Background

Approximately 100,000 lung resection surgeries are performed annually in the U.S. to treat lung cancer and emphysema. During lung resection surgery a portion of diseased lung is removed and the remaining lung is sutured or stapled to seal the wound and prevent leakage of air into the chest cavity.

Both suturing and stapling approaches to sealing the lung can exacerbate rather than remedy the situation and it is recognized that air leaks (ALs) are still one of the most common complications of pulmonary surgery. ALs can develop from suture/staple lines and other types of surgical manipulation, or ALs can develop simply due to the fragile state of the diseased lung tissue. Without prompt and effective treatment, ALs can lead to increased morbidity (e.g., pneumonia or infection) and extended hospitalization.

Consequently, there has been a recognized clinical need to seal intraoperative air leaks during pulmonary surgery. Surgeons often use a variety of products to seal or prevent air leaks during pulmonary surgery, including fibrin sealants and other patch type materials as an adjunct to suturing/stapling. However, these efforts have met with limited success due to difficulty of use, ineffective closure of ALs, poor adhesion, or poor cost/benefit. While tissue sealants are emerging as another important adjunct to surgical procedures, there are no products currently marketed in the U.S. for sealing ALs in lungs.

ProGEL™ Surgical Sealant

ProGEL™ Surgical Sealant (“Sealant”) was originally developed by 3M Corporation as a lung air leak sealant. 3M completed the product design and originally sponsored this clinical study. In 2007 NeoMend became the Sponsor of this study when it acquired the Sealant from 3M.

The Sealant is a hydrogel polymer consisting of two components: human serum albumin USP and a cross-linking component of polyethylene-glycol (PEG) functionalized with succinate groups. Both components are widely used in the pharmaceutical industry and hospital setting and have well established biocompatibility profiles.

The cross-linker component is provided as a powder, which is reconstituted with sterile water. Following reconstitution of the cross-linker, the two liquid components are housed in an applicator that mixes them within a spray tip, initiating a polymerization reaction. The PEG cross-linker component reacts with the albumin component to form a clear, pliant hydrogel. Polymerization is essentially completed within 30 seconds, and does not generate any heat. The Sealant is designed to withstand 30 mmHg air pressure within two minutes and 90 mmHg in less than ten minutes. After application, the Sealant forms a flexible seal over the surface of the tissue around the AL, and it remains soft and compliant. The Sealant then degrades and is completely resorbed.

Preclinical Studies

Three series of tests were performed to characterize the Sealant's burst strength, polymerization rate and pyrogenicity. The Sealant performed satisfactorily across all three categories.

Biocompatibility was evaluated through multiple tests: cytotoxicity, subchronic toxicity, systemic toxicity, genotoxicity, irritation, hemolysis, pyrogenicity, sensitization, and mutagenicity. The Sealant performed satisfactorily for all aspects of biocompatibility.

A number of animal tests were performed to assess the efficacy of the product for closing air leaks. Robust testing demonstrated that the product was effective in a variety of *in vivo* models. Additional tests confirm the expectation that resorption will extend beyond the necessary healing time.

Clinical Trial and PMA Timeline

The IDE for the pivotal clinical study was conditionally approved by FDA in June 1999. Following amendments to the IDE, enrollment for the study at five U.S. centers commenced in December 1999 and concluded in March 2001. The original PMA was submitted by 3M in August 2001 and was supplemented by a series of Amendments to address FDA questions. In March 2004 prior to a scheduled Advisory Panel meeting, 3M notified FDA of its decision, based upon an internal shift in strategic priorities, to put the PMA on Directed Hold. In June 2007 NeoMend completed the acquisition of the Sealant from 3M and promptly requested that the directed hold be lifted.

ProGEL™ Pivotal Clinical Study

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

Methodology: This was an open-label, randomized (2:1 ratio), controlled, multi-center study. Thoracotomy patients who met the initial screening criteria and who had at least one clinically significant IOAL (≥ 2 mm in size) following surgery, as determined by a saline submersion test (*i.e.*, "air leak test"), were enrolled. Investigators used standard techniques to close air leaks. Subjects were then randomized into either the Sealant or Control group.

For subjects in the Control group, a second air leak test was conducted following randomization to determine the success of the standard technique in sealing or reducing leaks. For subjects in the Sealant group, the Sealant was applied to the air leak sites that were first closed with standard technique. Up to three applications of Sealant per air leak were permitted. Following the application of Sealant, a second air leak test was conducted on the Sealant subjects to assess IOALs. Following the second air leak test, if

air leaks were observed in either group, the investigators could use other surgical techniques (*e.g.*, pleural flap/tent, pneumoperitoneum) to close the air leak.

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

During the postoperative hospital stay, until the subjects' CT was removed or upon discharge, the following assessments were performed daily: 1) measurement of vital signs measurement; 2) measurement of CT drainage; 3) determination of air leak status; and 4) occurrence of adverse events (AEs). In addition, CXRs were obtained prior to and following CT removal and as clinically indicated.

Number of Subjects and Centers: Enrolled: 275; Randomized: 161; 5 U.S. centers

Key Eligibility Criteria:

Inclusion Criteria

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

Exclusion Criteria

- Significant clinical disease or condition that might complicate the surgery and/or postoperative recovery
- Known hypersensitivity to human albumin

Endpoints:

Primary Efficacy Endpoint: Proportion of subjects who remained air leak free through the one month follow-up (1MFU) period or the duration of hospitalization, whichever was longer.

Secondary Efficacy Endpoints:

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

Safety Measures: Clinical assessment was based on the investigators' assessment of AEs related to the device reported during the postoperative hospitalization through the 1MFU period. Laboratory assessment was based on two immunologic assays performed preoperatively and at one month postoperatively.

Results: 275 subjects were enrolled at 5 clinical sites. 114/275 (41.5% of subjects) were not randomized, principally because they were not found to have IOALs. 161 subjects were randomized: 103 to the Sealant group and 58 to the Control group.

For the primary efficacy endpoint, a significantly greater proportion of Sealant subjects (35%) remained air leak free following surgery through the 1MFU visit or the duration of hospitalization, whichever was longer, compared to the Control subjects (14%), (p=0.005). Sealant patients were thus more than twice as likely to avoid an air leak following surgery compared to the Control subjects. (See, Sponsor's Summary of Clinical Data (SSCD) § 6.5.1).

For the secondary efficacy endpoints, a significantly greater proportion of Sealant subjects had their IOALs sealed (71%) compared to the Control subjects (10%). Of 318 individual IOALs tracked, a significantly greater proportion were sealed in the Sealant group (161/210, or 77%) compared to the Control group (17/108, or 16%), (p<0.001). Significantly more Sealant subjects (54%) were air leak free at the recovery room observation period compared to Control subjects (33%), (p=0.002). Length of hospital stay was also significantly shorter (p<0.05) for subjects in the Sealant Group compared with subjects in the Control group (median = 6 and 7 days, respectively). (See, SSCD § 6.5.3).

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

There was no statistically significant difference in the incidence of AEs between the Sealant and Control groups. A total of 14 serious AEs (SAEs) were reported: 9 deaths (5 Sealant, 4 Control), and 5 other SAEs (2 Sealant, 3 Control), all considered not device related. One SAE in the Sealant group (pneumothorax 3 weeks post surgery), was considered by the investigator to be an adverse device effect due to the temporal relationship of the event with the use of the Sealant. There were no significant changes observed in humoral and cellular immune responses between the Sealant and Control groups. (See, SSCD § 6.6).

Additional Findings:

There were several additional findings in the study worth noting, some of which respond to questions issues by FDA. None of these additional findings were statistically significant.

Sealant residence time

The Sealant was tested in rats and pigs prior to the clinical study. Those tests demonstrated that while most of the Sealant cleared within a few days, the Sealant was effective in sealing lung air leaks in those animal models. In the clinical study, the Sealant demonstrated statistical superiority over standard therapy for sealing lung air

leaks through 1MFU (35% for Sealant vs. 14% for Control, $p=0.005$). (See, SSCD § 6.5.1).

Partial Lung Expansion

Sealant subjects had a higher proportion of partial lung expansion compared to Control subjects (33% vs. 22%, respectively). (See, SSCD § 6.6.9). The study's primary and secondary endpoints were prospectively identified to evaluate the effectiveness of the Sealant to seal lung air leaks. Lung expansion was not chosen as an endpoint because: (1) lung expansion is a subjective determination based upon reading of chest x-rays and due to the removal of significant lung tissue in a resection, oftentimes the remaining lung will fully expand, but not enough to fill the newly created space ("fixed pleural space deficit"); and (2) no clear link is established in the literature between partial lung expansion and surgical morbidity. Lung air leaks are the primary concern of lung resection surgery as they can directly lead to increased morbidity and hospital stay for the patient. Study results showed the Sealant's superiority in sealing lung air leaks and resultant benefit of a shorter hospital stay.

Late air leaks

The incidence of late air leaks was higher in the Sealant group (8/103, or 8%) versus the Control group (1/58, or 2%). Late air leaks were those leaks that occurred after surgery and became evident only for those patients who were previously air leak free. Following surgery, 72/103 Sealant subjects were air leak free immediately following surgery, compared to 6/58 Control subjects. Thus, there were only a small number of Control subjects previously air leak free who could have subsequently developed a measurable air leak, where in contrast many Sealant subjects could have developed a post-surgical air leak. (See, SSCD § 6.5.3)

Pneumothorax

Four (4) Sealant subjects and no Control subjects with AL >5 days were reported to have had a pneumothorax. Only 1 of the 4 Sealant subjects required management of their pneumothorax and this subject had multiple morbidities. The other 3 subjects did not require any management of a pneumothorax because they were not new or enlarging pneumothorax which would indicate a serious AL. The presence of an air space or residual pleural space (appearing as a "pneumothorax" on a CXR) is an expected finding following lung resection surgery and will normally resolve on its own without clinical management. (See, SSCD § 6.6.9.2).

Hospital stay

In one subgroup of patients, the hospital stay for 16/21 (76%) of Sealant subjects compared to 5/11 (46%) of Control subjects was prolonged due to post-operative air leak. This comparison is based on a selective subset of patients and not on a randomized patient population. In the entire randomized study population, the Sealant group demonstrated a statistically significantly shorter hospital stay than did the Control group. (See SSCD § 6.5.3.7).

Air leak status at 1 month

67/103 Sealant subjects were not air leak free at 1MFU compared to a higher proportion of Control subjects (50/58; 86.2%) who were not air leak free at 1 month. Throughout the surgical recovery period and especially during the first few post surgical days, a higher proportion of Sealant subjects were air leak free compared to Control subjects, contributing to the finding that Sealant subjects had a shorter hospital stay. (See, SSCD § 6.5.1).

Impact on renal function

Urine was the primary route of excretion in rats, with most of the Sealant clearing within a few days. The Sealant is designed to break down after the healing process is capable of sustaining the seal of an air leak. One of the Sealant's components, polyethylene glycol (or PEG), is widely used with a well established biocompatibility profile. The other Sealant component, human serum albumin, is commonly used as a blood expander during cardiopulmonary bypass surgery and also has a well established biocompatibility profile. Additionally, and at the request of FDA, Sponsor collected data from two assays (ELISA and LPA) specifically designed to identify any immunological or humoral reaction to the Sealant and its components. Study results based on both blood tests showed no difference between the Sealant and the Control groups.

Clinical study results showed certain adverse associated with renal function (10/103 Sealant adverse events per total number of subjects (9.7%) versus 2/58 in the Control group (3.4%)). 5/10 Sealant subjects had oliguria, a mild type of abnormal renal function. 3 Sealant subjects and 1 Control subject had pre-existing renal disease. 3 Sealant subjects had acute renal failure compared to 1 Control subject (not dissimilar proportions noting the study's 2:1 randomization). (See, SSCD § 6.6.2).

Pneumonia

The rate of pneumonia was lower among Sealant subjects (4.9%) than among Control subjects (12.1%). Pneumonia is a serious complication of lung resection surgery often causing significantly greater morbidity and mortality, and a longer hospital stay and the study results indicated that the Sealant may help reduce the incidence of pneumonia. (See, SSCD § 6.6.2).

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