2 SYNOPSIS

Name of Company: Kedrion S.p.A, 55051 Castelvecchio Pascoli (Lucca), Italy **Name of Active Ingredient:** Fibrinogen, Bovine Aprotinin, thrombin, Calcium chloride **Name of Finished Product: Kedrion Fibrin Sealant**	**Individual Study Table Referring to Part V of the Dossier** **Volume: NA** **Page: NA**	***(for National Authority Use only)***

Title of the study: Multicentre, randomised, controlled, prospective, open label Phase II/III study to evaluate the efficacy and safety of Kedrion Fibrin Sealant as an adjuvant for air leak control in patients undergoing surgical lung resection

Investigators: 3 Investigators – Ferruccio Santini (Principal Investigator), Giuseppe Cardillo, Achille Lococo

Study centres: 3 centres, all located in Italy: Careggi University Hospital, Florence; S. Camillo Forlanini Hospital, Rome; Pescara Hospital.

Publication (reference): None

Study period: First patient enrolled: 24/09/2008; Last patient completed: 15/12/2009	**Phase of development:** II/III

Objectives: The main objective of this study was to assess the efficacy and safety of Kedrion Fibrin Sealant used in the control of aerostasis in lung resection surgery.

Methodology: This was a multi-centre, randomised, controlled, prospective, open-label Phase II/III study to evaluate the efficacy and safety of Kedrion Fibrin Sealant as an adjuvant for air leak control in patients undergoing surgical lung resection. Eligible patients were randomised to receive Kedrion Fibrin Sealant or no treatment (i.e. standard care).

Number of patients (total and in each arm):

	Randomised	ITT	PP	Safety
Total	185	185	165	185
Fibrin Sealant	91	91	81	91
No treatment	94	94	84	94

Diagnosis and main criteria for inclusion: written informed consent obtained; age between 18 and 75 years; primary or secondary neoplastic pulmonary pathology or any parenchymal pathology to be treated with lung resection; patient candidates for anatomic lung resection or atypical lung resection (lobar resection, bilobectomy, typical segmentary resection, wedge resection; open surgical access (standard thoracotomies, mini-thoracotomies, muscle-sparing thoracotomies); life expectancy $\geq$ 6 months.

Test product, dose and mode of administration, batch no:

Kedrion Fibrin Sealant consists of two components: component 1 (powder and solvent for reconstitution) - 1 ml reconstituted containing coagulable plasma proteins 42 – 78 mg (of which 45-50 mg of human fibrinogen), Factor XIII $\geq$ 6 U, plasminogen $\leq$ 0.2 U, and aprotinin 0.74 – 1.1 PEU; component 2 (powder and solvent for reconstitution) - 1 ml reconstituted containing approximately 2 mg of human proteins, of which thrombin (Factor IIa of coagulation) 1000-1562 IU, and calcium chloride 0.275mM. Kedrion Fibrin Sealant was administered by using a sterile applicator. Kedrion Fibrin Sealant batches were: 17LP08CF10, expiry 12/2009, and 18LP08CF5, expiry 12/2009. The dose ranged between a minimum of 5ml to a maximum of 20 ml for patient.

Duration of treatment: single application. Epilesional use

Reference therapy, dose and mode of administration, batch no: not applicable. The control group of patients received no treatment (i.e. standard care).

Criteria for evaluation:

The aerostatic efficacy of the IMP was evaluated in terms of the management of post-surgery air leaks for the entire duration of the study.

The evaluation of the aerostatic efficacy of the IMP in connection with any type of surgery procedures involved a monitoring of post-surgery air leaks by measuring duration and characteristics both in quantitative and qualitative terms (inspiratory/expiratory/forced expiratory).

The primary efficacy variable was the duration of drainage.

The secondary efficacy variables were: percentage of patients without air leakage for the entire hospitalisation time; percentage of patients without air leaks at the end of the surgery; duration of post-surgery hospitalisation.

Note: The number and percentage of patients who required drainage repositioning was also presented even if not requested in the protocol.

Safety:

Safety variables were: percentage of subjects with adverse events associated with the therapy; formation of antibodies against bovine aprotinin; vital signs (blood pressure, body temperature, heart and respiratory rate); laboratory parameters (haematology and blood chemistry).

Statistical methods:

The following populations were considered for analysis: ITT population, defined as all randomised patients; PP population, defined as all patients in the ITT population who were evaluable for the primary efficacy assessment and did not have any major protocol violation; safety population, defined as all randomised patients (i.e. the ITT population).

Summary statistics (mean, standard deviation, median, minimum, maximum) were provided for continuous variables, and the number and percentage of patients in each category were provided for categorical data.

The comparison between groups of primary variable duration of drainage was performed by means of the Mann-Whitney U test. The analysis of overall duration of air leakage and the duration of post-surgical hospitalisation were performed as for the primary efficacy variable. The number and percentage of patients without air leakage for the entire hospitalisation time and at the end of the surgery were compared between groups by means of Chi-square test or Fisher exact test. The qualitative and quantitative assessment of air leakage was performed by means of frequency distributions at any time point. The number and percentage of patients who required drainage repositioning was also presented.

The results of adverse events were analysed in a descriptive manner, reporting the type and absolute and relative frequency of all adverse events, investigational medicinal product (IMP)-related adverse events, IMP-non related adverse events, and serious adverse events. Adverse events were categorised by system organ class (SOC) and preferred term (PT) by using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of patients that presented at least one complication among the following was presented: fever, bleeding, haematological complications, pulmonary embolism, infections, and lymphatic exudation.

The number and percentage of patients that developed antibodies against bovine aprotinin was presented only for the group of patients treated with the IMP. Vital signs and laboratory parameters were listed for each patient.

Study population:

A total number of 185 patients were randomised: 91 were included in the group Treated with Kedrion Fibrin Sealant (named Treated group hereinafter) and 94 were randomised to receive the standard care (named Control group hereinafter).

Extent of exposure and compliance:

Treatment was administered in single application following appropriate procedures.

Efficacy results:

Primary efficacy variable:

The mean duration of drainage in the ITT population was slightly lower in patients in the Treated group (143 hours) than in the Control group (157 hours); median duration was 119.4 and 118.5 hours, respectively in the two groups. The comparison between groups did not show statistically significant differences (p = 0.992). The results in the PP population were consistent with those observed in the ITT population.

According to the primary objective and the primary assessment criteria of this trial, stated in the protocol, the mean duration of leakage from the end of surgery as well as quantitative and qualitative assessment of air leakage were evaluated.

Mean duration :

The duration was of 43.1 hours in the Treated group and 66.6 hours in the Control group. The comparison between groups showed a statistically significant difference (p<0.005), in favour of the Treated group.

Quantitative assessment:

An overall significantly higher rate of patients with air leakage score equal to 0 (i.e. absence of air leakage) was observed in the Treated group than in the Control group in the first period between the end of treatment and Day 2 post surgery. There were no important differences between the two groups in rate of patients with absence of air leakage from Day 3 to Day 5. From Day 6 to day 9, there was a progressive decrease of rate of patients with absence of leaks and an increase of patients with score 1 (small countable bubbles). The rate of patients with absence of leakage in this time range was again higher in the Treated group than in the Control group, with reversed rates of patients with score 1. Only few patients in both groups had no countable form of air leakage (score = 2) and continuous and massive stream of air leakage (score = 3).

Qualitative assessment:

The expiratory and forced expiratory air leakage resulted the most common characteristics, with an overall prevalence of expiratory leaks in the Control group and of forced expiratory leaks in the Treated group at the examined time points.

Secondary efficacy variables (ITT population):

Percentage of patients without air leakage at the end of surgery and for the entire hospitalisation time:

The number and rate of patients without air leakage at the end of surgery was 17 (18.9%) in the Treated group and 0 (0.0%) in the Control group. The comparison between groups showed a statistically significant difference (p<0.001).

The number and rate of patients without air leakage in the entire study duration was 15 (17.2%) in the Treated group and 10 (11.1%) in the Control group. The comparison between groups did not show statistically significant differences (p = 0.242).

Duration of post-surgery hospitalization:

The mean duration of post-surgery hospitalisation was 7.64 days in the Treated group and 7.58 days in the Control group. The comparison between groups did not show statistically significant differences (p = 0.712).

Percentage of patients with drainage repositioning :

Only 2 patients (2.13%) in the Control group and none in the Treated group required drainage repositioning.

Safety results:

Adverse events:

The number and rate of patients with adverse events was 20 (22.0%) in the Treated group and 22 (23.4%) in the Control group. The number and rate of patients with serious adverse events was 7 (7.7%) in the Treated group and 10 (10.6%) in the Control group. None of the adverse events was considered as treatment-related. Atrial fibrillation (5 patients in the Treated group and 4 in the Control group) and hyperpyrexia (5 and 7 patients, respectively in the two groups) were the most common adverse events. Wound dehiscence was reported in 3 patients in the Control group and in none of the Treated group. Bacterial infection was reported in 4 patients in the Control group and in 1 in the treated group.

Adverse events were fatal in 1 patient in the Treated group and in 5 in the Control group. Fatal or otherwise serious adverse events generally consisted of complications due to the underlying respiratory disease or to concomitant non-pulmonary diseases.

Formation of antibodies against bovine aprotinin:

The formation of bovine aprotinin antibodies was reported in a total of 34 patients (37.4%) in the Treated group.

Conclusions:

The results of the present study have shown that:

- No statistical significant difference was found in the mean time of chest tube removal because the chest drains were removed only if the pleural fluid was less than 100 ml/day even if the latter variable was not linked to the efficacy of the IMP.
- The overall mean duration of leakage was significantly shorter in the treated group compared to the control group, as also the percentage of patients without air leakage at the end of surgery was significantly higher in the treated group than in the control group. Although the rate without air leakage in the entire study duration was still higher in the treated group than in the control group, the difference between groups was not statistically significant. Such result may have been influenced by the current clinical practice of reinstituting aspiration also in absence of pneumothorax.
- The quantitative assessment of air leakage showed that, overall, the rate of patients with absence of leakage was higher in the treated group than in the control group.
- The duration of post-surgery hospitalization was similar in the two groups.
- Kedrion Fibrin Sealant was well tolerated and was not associated with any increased risk of serious and non-serious adverse events, and of surgical complications, compared to the untreated controls. The proportion of treated patients that developed bovine aprotinin antibodies was in compliance with literature data.