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: Evaluation of the efficacy and safety of Kedrion Fibrin Sealant as an adjuvant in the control of haemostasis in patients undergoing minor or major liver resection surgery. A multi-centre, randomized, controlled, open-label Phase II/III study

Investigators: Three principal Investigators in Italy

Study centres: Three centres, all located in Italy

Publication (reference): None

Study period: First patient enrolled: 06/10/2009; Last patient completed: 29/01/2011 | **Phase of development:** II/III

Objectives: The primary objectives of this study were to evaluate the efficacy of the investigational medicinal product (IMP) as an adjuvant in the control of haemostasis at the intra-surgical level, in minor or major liver resection surgeries, and to evaluate the safety of the IMP for the entire duration of the study.

The secondary objectives of this study were to evaluate the efficacy of the IMP in the control of blood loss in the post-surgery phase, to evaluate the efficacy of the IMP in the control of the biliostasis in the post-surgery phase, and to assess data for pharmaco-economy evaluation following the use of the IMP.

Methodology:

This was a multi-centre, randomized, controlled, open-label Phase II/III study to evaluate the efficacy and safety of IMP used as an adjuvant for haemostasis during liver surgery. Eligible patients were randomised to receive Kedrion Fibrin Sealant or standard care.

Number of patients (total and in each arm):

	Randomised	ITT	PP	Safety
Total	119	119	116	119
Fibrin Sealant	62	62	60	61
Standard therapy	57	57	56	58(*)

(*) one patient, randomized to receive the IMP, was actually not treated with Kedrion Fibrin Sealant. He was retained in the ITT population of the treated group, excluded from the PP population, and allocated to the Safety population of the "standard therapy".

Diagnosis and main criteria for inclusion: written informed consent obtained, age > 18 years; patients candidate for anatomic and non-anatomic hepatic resections with a surface of the wedge resection > 20 cm^2.

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 clottable plasma proteins 42 – 78 mg (of which 45-50 mg of human fibrinogen), Factor XIII ≥ 6 U, plasminogen ≤ 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 01LP09CF10 (expiry 12/2010). The dose ranged between a minimum of 10 ml 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 standard care.

Criteria for evaluation:

Efficacy:

The primary efficacy variable of the study was the percentage of patients who reached adequate haemostasis within 10 minutes from the application of the treatment (IMP).

The secondary efficacy variables were:

- Quantity of blood loss during the 3 days after surgery;
- Amount of haemoglobin during the 3 days after surgery
- Amount of bilirubin from the surgery drainage in the first 3 days and on the 5th day (or until removal);
- Need for transfusion (yes/no);
- Quantity of erythrocytes units and/or of transfused plasma (ml) within 30 days post-surgery;
- Duration of post-surgery drainage in days;
- Total drained volume (ml) in post-surgery;
- Need for echo- or CT-guided repositioning of the drains;
- Need for an additional surgery (within 5 days) due to bleeding.

Data for pharmaco-economy assessment:

- Duration of hospitalization (post-surgery hospitalization) in days;
- Post-surgery transfusion treatments; if "yes", the quantity of transfused fluid was evaluated;
- Need for an additional surgery (within 5 days) due to bleeding; if "yes", the "type of surgery" was evaluated.

Safety and Tolerability:

- Percentage of subjects with adverse events associated with the therapy;
- Percentage of subjects who developed antibodies against bovine aprotinin.

Statistical methods:

The following populations were considered for analysis: ITT population, defined as all randomised patients who received the treatment and with at least one efficacy evaluation after the surgery; PP population, defined as all patients included in the ITT population who were evaluable for the primary efficacy variable and did not have any major protocol violation; safety population, defined as all randomised patients who received the treatment.

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 superiority of the Kedrion Fibrin Sealant vs. the standard treatment was evaluated by calculating the confidence interval (CI) at 95% of the difference between the treatments, based on the normal approximation. The superiority was to be declared if the lower limit of the 95% CI of the difference between IMP and standard treatment was to the right of zero. The comparison between groups in primary efficacy variable was also performed using the Cochran-Mantel-Haenszel test. The same test was used in the comparisons between groups of categorical secondary efficacy variables.

The comparison between groups of blood loss during the 3 days after surgery, quantity of erythrocytes units and of transfused plasma during the 30 days after surgery, duration of post-surgery drainage and total drained volume was performed by using an ANOVA model with the centre and the treatment as factors.

The comparison between treatment groups of haemoglobin during the 3 days after surgery, bilirubin (from vacuum and from laboratory analysis separately) during the 3 days and on the 5th day after surgery (or until removal) was performed by using an ANOVA model for repeated measures with treatment, time, interaction between treatment and time and centre as effects. A sensitivity analysis, based on two separate analyses, one on data related to days 1 to 3 using the same mixed model for repeated measurements and one on the 5th day data using an analysis of variance model, was also performed on bilirubin values (both from vacuum and from laboratory analysis).

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 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 119 patients were randomised: 62 to the Kedrion Fibrin Sealant group (Treated group hereinafter) and 57 to the standard care group (Control group hereinafter).

Extent of exposure and compliance:

Treatment was administered in single application following appropriate procedures.

Efficacy results:

Primary efficacy variable:

The results of primary variable percentage of patients who reached adequate haemostasis within 10 minutes in the ITT and the PP population are shown in the table below:

ITT population		
	IMP N=62	**Standard treatment N=57**
Number (%) of patients reaching haemostasis within 10 minutes	61 (98.4%)	32 (56.1%)
Treatment difference: IMP – standard treatment	42.2%	
95% confidence interval	29.0% to 55.5%	
Cochran-Mantel-Haenszel test: p value	<0.001	
PP population		
	IMP N=60	**Standard treatment N=56**
Number (%) of patients reaching haemostasis within 10 minutes	60 (100.0%)	31 (55.4%)
Treatment difference: IMP – standard treatment	44.6%	
95% confidence interval	31.6% to 57.7%	
Cochran-Mantel-Haenszel test: p value	<0.001	

In the ITT population, the rate of patients reaching haemostasis within 10 minutes was significantly higher in the Treated group (98.4%) than in the Control group (56.1%): the difference in rates between group was 42.2% (95% CI: 29.0% to 55.5%, p<0.001).

The results in the PP population were consistent with those observed in the ITT analysis, with 100.0% of patients in the Treated group and 55.4% in the Control group that reached haemostasis within 10 minutes: the difference in rates between group was 44.6% (95% CI: 31.6% to 57.7%, p<0.001).

Secondary efficacy variables (ITT population):

Quantity of blood loss:

The mean blood loss on day 1 was slightly lower in the Treated group (137.9 ml) than in the Control group (154.7 ml), while the mean blood loss on day 2 was slightly lower in the Control group (152.8 ml) than in the Treated group (176.4 ml). There were no substantial differences between groups on day 0, on day 3 and in the total day 0-3 period. The comparison between groups in the overall 3 days post-surgery did not show statistically significant differences (p = 0.998).

Haemoglobin amount in the drainage during the 3 days post-surgery:

The mean haemoglobin amount was lower in the Treated group than in the Control group on day 0 (1.18 vs. 3.53 g/dl), day 2 (0.69 vs. 0.84 g/dl) and day 3 (0.39 vs. 0.90 g/dl), while there were no substantial difference between groups on day 1. The comparison between groups in the overall 3 days post-surgery did not show statistically significant differences (p = 0.107), as well as there were no significant differences between groups in any day (p = 0.152 on day 0, p = 0.925 on day 1, p = 0.548 on day 2 and p = 0.056 on day 3).

Amount of bilirubin (vacuum, drainage) in the 3 days and in the 5th day post-surgery or until removal:

The mean bilirubin levels were lower in the Treated group than in the Control group in all the 3 days post-surgery and on the 5th day. Few patients in both groups had assessment after day 5. The comparison between groups in the overall 3 days and in the 5th day post-surgery did not show statistically significant differences (p = 0.147), as well as there were no significant differences between groups in any day (p = 0.235 on day 0, p = 0.093 on day 1, p = 0.914 on day 2, p = 0.418 on day 3 and p = 0.341 on day 5). The sensitivity analysis also did not show statistically significant differences between groups in the overall 3 days post-surgery (p = 0.233), as well as in the comparisons between groups in any day (p = 0.237 on day 0, p = 0.093 on day 1, p = 0.920 on day 2, p = 0.420 on day 3), and in the 5th day (p = 0.097).

Amount of bilirubin (laboratory, blood) in the 3 days and in the 5th day post-surgery or until removal:

The mean bilirubin levels were higher in the Treated group than in the Control group in all the 3 days post-surgery and on the 5th day, while fewer patients in both groups had assessment after day 5. The comparison between groups in the overall 3 days and in the 5th day post-surgery did not show statistically significant differences (p = 0.098), as well as there were no significant differences between groups in any day (p = 0.060 on day 1, p = 0.084 on day 2, p = 0.197 on day 3, and p = 0.197 on day 5 in the ANOVA model). In the comparison between groups limited to the 3 days post-surgery, the comparison between groups did not show statistically significant differences overall (p = 0.078) and in any day (p = 0.052 on day 1, p = 0.072 on day 2 and p = 0.182 on day 3). The sensitivity analysis on the 5th day also did not show statistically significant differences between groups (p = 0.205).

Patients needing for transfusion:

The number of patients needing for transfusion was 6 (9.68%) in the Treated group and 8 (14.0%) in the Control group (p = 0.367 between groups).

Quantity of erythrocytes units and of transfused plasma within 30 days post-surgery:

Although only few patients in both groups required post-surgery transfusions, the mean total quantity of erythrocytes units was lower in the Treated group (2.83 units) than in the Control group (4.14 units). The comparison between groups did not show statistically significant differences (p = 0.408).

Only one patient in the Treated group and 4 in the Control group received plasma transfusions.

Duration of post-surgery drainage:

The mean duration of post-surgery drainage was comparable in the Treated group (5.59 days) and in the Control group (5.72 days). The comparison between groups did not show statistically significant differences (p = 0.938).

Total drained volume in post-surgery:

The mean total drained volume in post-surgery was comparable in the Treated group (938.2 ml) and in the Control group (1014.1 ml). The comparison between groups did not show statistically significant differences (p = 0.729).

Patients needing for Echo- or CT-guided repositioning of the drains:

The number of patients needing for Echo- or Cat-guided repositioning of the drains was 2 (3.23%) in the Treated group and 3 (5.26%) in the Control group. The comparison between groups did not show statistically significant differences (p = 0.540).

Patients needing for an additional surgery within 5 days due to bleeding:

Only one patient (1.61%) in the Treated group and none in the Control group needed an additional surgery within 5 days due to bleeding. The comparison between groups did not show statistically significant differences (p = 0.371).

Other economic evaluation parameters:

The mean duration of post-surgery hospitalization was comparable in the Treated group (10.6 days) and in the Control group (12.0 days).

Safety results:

Adverse events:

The number and rate of patients with adverse events was 21 (34.4%) in the Treated group and 24 (41.4%) in the Control group (p = 0.434 between groups). The number and rate of patients with serious adverse events was 7 (11.5%) in the Treated group and 7 (12.1%) in the Control group (p = 0.920 between groups).

None of the adverse events was considered as treatment-related.

Pyrexia was the most common adverse event and was reported in similar rates in the two groups (9.8% in the Treated group and 13.8% in the Control group). Among post-surgery complications, biliary fistula was reported in 4 patients in the Control group and in none in the Treated group, localised intra-abdominal fluid collection was reported in 2 patients in the Treated group and ascites was reported in 1 patient in the Treated group and in 1 patient in the Control Group. Only 1 patient in the Treated group and in 2 in the Control group had infective complications.

Fatal adverse events occurred in 2 patients in the control group and the other serious adverse events generally consisted of complications due to the surgical procedure or to the underlying disease.

Formation of antibodies against bovine aprotinin:

The formation of bovine aprotinin antibodies was reported in a total of 40 patients (65.6%) in the Treated group.

Conclusions:

The results of the present study show that treatment with Kedrion Fibrin Sealant is effective and safe in the control of haemostasis in minor or major liver resection surgeries. A significantly higher percentage of patients (98.4%) reached adequate haemostasis within 10 minutes from the application of the IMP, compared to standard treatment (56.1%), confirming the primary efficacy end-point. Although no statistically significant differences between the Treated group and the Control group was observed, the results showed a positive trend for IMP treatment regard to the secondary efficacy end-points.

Kedrion Fibrin Sealant was well tolerated and was not associated with any increase of risk of serious and non-serious adverse events, and of surgical complications, compared to standard treatment. The proportion of treated patients that developed bovine aprotinin antibodies was in compliance with literature data.