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: Efficacy and safety evaluation of Kedrion Fibrin Sealant in patients undergoing to middle ear microsurgery. Monocentric, two parallel arms randomized, controlled, single blind, phase II/III study.

Investigator: Prof Stefano Berrettini – Pisa, Italy

Study centres: Single centre - Azienda Ospedaliero-Universitaria Pisana, Pisa, Italy

Publication (reference): None

Study period: First patient enrolled: 16/03/2011; Last patient completed: 12/01/12 | **Phase of development:** II/III

Objectives: The primary objective of this study was to demonstrate the sealant/adhesive efficacy of Kedrion Fibrin Sealant in restoring normal tympanic anatomy (closure of tympanic perforation within 3 weeks ± 3 working days of surgery) after middle ear microsurgery.

The secondary objectives of this study were: to evaluate the efficacy of the investigational medicinal product (IMP) in terms of recovery of hearing loss and need for topical treatments (cortisones and/or antibiotics); and to evaluate the safety and tolerability of the IMP for the entire duration of the study.

Methodology:

This was a single-centre, parallel-group, randomised, controlled, single-blind, phase II/III study for the evaluation of the efficacy and safety of Kedrion Fibrin Sealant in patients undergoing middle ear microsurgery (type I tympanoplasty). Eligible patients were randomised to receive Kedrion Fibrin Sealant or standard care. The duration of participation of a subject was of approximately 9 weeks from surgery.

Number of patients (total and in each arm):

	Randomised	ITT	PP	Safety
Total	48	47	47	47
Fibrin Sealant	25	24	24	24
Standard therapy	23	23	23	23

Diagnosis and main criteria for inclusion: written informed consent obtained, age > 18 years; patients undergoing ear microsurgery for chronic otitis media (perforation of the tympanic membrane).

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. In the study only one batch of Kedrion Fibrin Sealant was used, namely 10LP10CF10 (expiry 12/2012). The amount of IMP ranged between a minimum of 0,2 ml to a maximum of 1 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:

Efficacy:

The primary efficacy variable of the study was the closure of the tympanic perforation within 3 weeks (± 3 working days) of surgery.

The secondary efficacy variables were:

- Restoration of hearing impairment;
- Need for topical treatments (cortisones and/or antibiotics).

Safety and Tolerability:

- 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);
- Blood and blood chemistry parameters.

Statistical methods:

The following populations were considered for analysis: safety/ITT population, defined as all randomised patients who received the treatment; PP population, defined as all patients included in the ITT population who did not have any major protocol violation.

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 number and percentage of patients experiencing closure of tympanic membrane perforation at 3 weeks from surgery was presented for each treatment group. The superiority of the IMP over standard treatment was evaluated using Fisher's exact test and superiority was to be declared if the following conditions were verified: higher success rate in the group treated with the IMP than in the control group; p-value ≤ 0.05.

The number and percentage of patients with tympanic perforation closure at 6 and 9 weeks from surgery were presented for both treatment groups.

For each treatment group, the mean changes from screening in pure tone audiometric (PTA) air conduction (AC), PTA bone conduction (BC) and air bone gap (ABG) at each follow-up visit were presented with their 95% confidence intervals (CI). The changes from screening in ABG was also analysed using an ANCOVA model for repeated measures including the following fixed effects: baseline value, treatment, visit, interaction between treatment and visit, interaction between baseline value and visit. An unstructured covariance matrix was assumed for each patient for the measurements performed at the different visits. The mean difference between treatments at 9 weeks after surgery was calculated with its CI and p-value.

The number and percentage of patients requiring topical treatments (cortisones and/or antibiotics) were presented for both treatment groups.

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. The mean change from screening to surgery in vital signs (blood pressure, body temperature, heart and respiratory rate) was presented with their 95% CI. Laboratory parameters were listed for each patient.

Study population:

A total number of 48 patients were randomised: 25 were randomised to receive Kedrion Fibrin Sealant (named Treated group hereinafter) and 23 were randomised to receive the standard care (named Control group hereinafter). One patient allocated to the Treated group did not receive treatment with the IMP. All patients in the safety/ITT population in both groups regularly completed all follow-up visits at 3, 6 and 9 weeks post-surgery, and none of them prematurely discontinued the study.

Extent of exposure and compliance:

Treatment was administered in single application following appropriate procedures.

Efficacy results:

Primary efficacy variable:

All 24 patients in the Treated group (100.0%) reached closure of tympanic membrane perforation at 3 weeks from surgery, compared to 13 patients (56.5%) in the Control group: the difference between groups was statistically significant ($p<0.001$ in the Fisher's exact test).

Secondary efficacy variables (ITT population):

Closure of tympanic membrane perforation at 6 and 9 weeks from surgery:

The closure of tympanic membrane perforation at 6 and 9 weeks from surgery was reached (or maintained) by all patients in the two groups.

Recovery of hearing loss:

Air conduction

The mean air conduction threshold decreased from baseline to any follow-up visit in both groups. The extent of the decrease was higher in the Treated group than in the Control group at any time point.

Bone conduction

The mean bone conduction threshold did not substantially change from baseline to any follow-up visit in both groups.

Air bone gap (ABG)

The mean ABG decreased from baseline to any follow-up visit in both groups. The extent of the decrease from baseline to the follow-up visits at 6 and 9 weeks after surgery was slightly higher in the Treated group than in the Control group.

The comparison between groups showed that the adjusted means at the follow-up visit at 9 weeks after surgery were -12.19 dB (95% CI: -15.02 to -9.37) in the Treated group and -11.39 dB (95% CI: -14.28 to -8.50) in the Control group. The treatment difference between the Treated group and the Control group was -0.80 dB (95% CI: -4.85 to 3.25), thus showing that the difference between groups was not statistically significant ($p = 0.692$ in the ANCOVA model).

Need for topical treatment prescription:

None of patients in both groups needed for a prescription of a topical treatment (cortisones and/or antibiotics) during the entire study period.

Safety results:

Adverse events:

One adverse event was reported in 1 patient (4.3%) in the Control group. The event was a serious adverse event (SAE) and consisted in pre syncope as preferred term (verbatim term: lipothymia; SOC: nervous system disorders).

Formation of antibodies against bovine aprotinin:

The formation of bovine aprotinin antibodies was reported in a total of 7 patients (29.2%) in the Treated group.

Conclusions:

The results of the present study have shown that treatment with Kedrion Fibrin Sealant is highly effective in achieving a rapid closure of tympanic membrane perforation in patients with chronic otitis media undergoing ear microsurgery compared to the standard treatment. A significantly higher percentage of patients treated with the IMP (100% of patients) reached closure of tympanic membrane perforation at 3 weeks after surgery compared to standard treatment (56.5% of patients). Treatment with Kedrion Fibrin Sealant was also associated with a rapid and sustained recovery of hearing loss.

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.