"Prospective, Multicenter, Open-Label, Randomized, Phase III Clinical Trial of Prevention of Prolonged Air Leak After Lung Resection in High-risk Patients, Applying HEMOPATCH®"

CODE: HEMOPATCH/FAP/2014

Promotor: Fundación Instituto de Estudios Ciencias de la Salud de Castilla y León (IECSCYL)-Instituto deInvestigación Biomédica de Salamanca (IBSAL)
Phase: III
National Coordinator:

Dr. Marcelo Jiménez Thoracic Surgery
Hospital Universitario de Salamanca

Version: 2.4.
Date: 17 de Abril de 2017

This protocol will be performed following ICH-GCP (CPMP/ICH/135/95), ethical principles of the Declaration of Helsinki and current Spanish Legislation, including but not limited to RD1090/2015, RD 1591/2009 and MedDEV Guidelines.

1. SUMMARY

0. Type of request: Clinical trial of the use of a new therapeutic strategy in the treatment of patients at risk of postoperative prolonged air leakage through the local application of a patch of Hemopatch®.

1. Promotor: Fundación Instituto de Estudios Ciencias de la Salud de Castilla y León (IECSCYL)-Instituto de Investigación Biomédica de Salamanca (IBSAL)

2. Title: "Prospective, Multicenter, Open-Label, Randomized, Phase III Clinical Trial of Prevention of Prolonged Air Leak After Lung Resection in High-risk Patients, Applying HEMOPATCH®"

3. Code: HEMOPATCH/FAP/2014

4. Coordinator: Dr. Marcelo Jiménez

Servicio de Cirugía Torácica Hospital Universitario de Salamanca

5. Participating centres: Hospital Universitario de Salamanca

Hospital Clínico San Carlos. Madrid

Hospital Clinic de Barcelona

Hospital Virgen del Rocío. Sevilla

Hospital Ramón y Cajal.Madrid

Hospital Marqués de Valdecilla. Santander

6. Institutional Review Board – Ethics Committee:

CEIm del Hospital Universitario de Salamanca

7. Monitor: José Vicente Hernández Madrid (IECSCYL-IBSAL)

8. Experimental Product: Hemopatch®

Pharmaceutical form: Collagen patch derived from bovine skin, coated with NHS-PEG (pentaerythritol polyethylene glycol ether tetrasuccinimidyl glutarate).

9. Clinical trial phase: Phase III.

10. Main Objetive: To analyze the efficacy of the application of Hemopatch® directly on the pulmonary suture line as prevention of postoperative

air leak in patients at high risk after pulmonary resection. Decrease in the postoperative air leak rate (air outflow through the drains on the 5th postoperative day).

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11. **Secundary objetives**: To analyze the effectiveness of the procedure measured in terms of:

-Clinical

- oDuration of postoperative air leakage
- oRate of reinsertion of pleural drainage for symptomatic pneumothorax
- o 30-day postoperative readmission rate for recurrence of symptomatic pneumothorax.
- o Cardiorespiratory related complications.

-Radiologicals:

- o Presence of pneumothorax on chest radiograph.

12. **Desing:** Prospective, multicenter, open-label, randomized.

The study is divided into two phases:

1st- Treatment: intra-operative application of the Hemopatch® patch.

2º- Postoperative follow-up: Daily until drainage removal or hospital discharge, and at 30-90 days postoperatively.

13. **Study disease:** Prolonged postoperative air leak in patients at risk.

14. **Study population:** Patients who are to undergo scheduled anatomic pulmonary resection (excluding pneumonectomy) and D classified, according to the postoperative prolonged air leak risk scale (index > 1.5) (Patient age over 65 years (1 point), body mass index BMI<25 kg/m2 (2 points), FEV1<80% (1.5 points) and presence of pleural adhesions during surgery (1 point). Air leak risk scale. A total of 276 patients were included, 138 in the experimental group and 138 in the control group.

15. **Study duration:** From the inclusion of the first patient to the end of follow-up 18 months. Recruitment period: 18 months from the inclusion of the first patient in the study.

2. ABBREVIATIONS

AA: Adverse events

AAG: Serious Adverse Event

AEMPS: Agencia Española del Medicamento y Productos Sanitarios

ARCO: Association Research Circulation Osseus

GCP: Good Clinical Practice

CEIm: Committee on the Ethics of Research on Medicinal Products.

CRD: Data Collection Notebook

CRO: Clinical Research Organization

PAL: Prolonged Air Leakage

FEV1: First-second exhaled volume

GMP: Good Manufacturing Practice

HUS: University Hospital of Salamanca

ICH: International Conference on Harmonization

IP: Principal Investigator

LPDP: Personal Data Protection Act

WHO: World Health Organization

SOP: Standard Operating Procedure

RNP: Patient-reported records

CT: Computerized axial tomography

WMA: World Medical Association

3. GENERAL INFORMATION:

3.1. Clinical trial Identification: Code: HEMOPATCH/FAP/2014

Title**:** "Prospective, Multicenter, Open-Label, Randomized, Phase III Clinical Trial of Prevention of Prolonged Air Leak After Lung Resection in High-risk Patients, Applying HEMOPATCH®"

3.2. Clinical trial: Phase III

3.3. Investigational producto:

- HEMOPATCH®
- Nature of investigational product: Patch
- Qualitative composition: Collagen patch derived from bovine skin, coated with NHS-PEG (pentaerythritol polyethylene glycol ether tetrasuccinimidyl glutarate).
- Product dossage: 3 units/patient of 4.5x9 cm

3.4. Participating centres: Hospital Universitario de Salamanca

Hospital Clínico San Carlos. Madrid

Hospital Clínic. Barcelona

Hospital Virgen del Rocío. Sevilla

Hospital Ramón y Cajal. Madrid

Hospital Marqúes de Valdecilla. Santander

3.5. Promotor: Fundación Instituto de Estudios Ciencias de la Salud de Castilla y León (IECSCYL)-Instituto de Investigación Biomédica de Salamanca (IBSAL)

3.6. Responsible for investigational product: BAXTER

3.7. Study duration: From the inclusion of the first patient to the end of follow-up 18 months. Recruitment period: 18 months from the inclusion of the first patient in the study.

4. RATIONAL BASIS FOR THE TRIAL, JUSTIFICATION AND OBJECTIVES

INTRODUCTION

Definition, epidemiology and clinical features of postoperative prolonged air leakage

Postoperative prolonged air leak (PAFL) is the outflow of air through the pleural drains after surgery for a prolonged period of time. It is the most frequent technical complication of lung resection (Rice TW, 2002) and, in addition to being a risk for the patient's health (Brunelli A, 2006; Varela G, 2004), it represents a considerable expense for the health system (Varela, G, 2005). An overall incidence has been described in patients with pulmonary lobectomy between 10 and 15% (Cerfolio RJ, 2002; Brunelli A, 2004). Patients with this complication must have an intrapleural drainage for a longer time, which increases pain, anxiety and stress, as well as increasing the risk of other cardiorespiratory complications (Cerfolio RJ, 2002 Okereke I, 2005). On the other hand, it has been demonstrated that this complication is a determining cause of increased hospital stay (Brunelli A, 2006; Varela G, 2004; Bardell T, 2003; Irshad K, 2002).

Current treatments for prolonged postoperative air leak.

Various prophylactic measures have been attempted to prevent the complication. Such measures include both surgical techniques such as the "pleural tent" (Brunelli A, 2002) and the use of lung suture supports (Miller JI Jr, 2001) or the use of surgical adhesives (Wain JC, 2001; Fabian T, 2003; Allen MS, 2004). Regarding the latter, there is some controversy in the literature since, in the face of randomized clinical trials demonstrating their effectiveness (Wain JC, 2001; Fabian T, 2003; Allen MS, 2004), a meta-analysis has been published (Belda-Sanchís J, 2010) that advises against their routine use due to two problems: the lack of conclusive demonstration of the effect and the high cost of the products. Modifications to the usual surgical techniques have also been suggested, such as the "Fissure-less technique" (Al Refai M, 2010). The selection of higher risk patients according to a risk scale may justify the routine use of prevention methods.

The base of Hemopatch® is polyethylene glycol, a product that has been widely used in the treatment of air leakage, in fact there are ongoing Phase IV studies (NCT01394978 and NCT01867658), on a collagen base that facilitates the action of the product. The safety of the Hemopatch® product has been demonstrated in multiple studies (Fingerhut 2014, Lewis KM 2014). Hemopatch® is CE marked and is a product that is being used in most hospitals.

We have studies on the use of Hemopatch® for air leak (Lewis KM 2014),

Phase III studies have been conducted with similar collagen patches (NCT00293514) for the treatment of air leak which are the basis for further studies such as the one designed by the investigators.

JUSTIFICATION

Therefore, they justify the performance of this clinical trial:
- The existence of a frequent clinical problem such as prolonged postoperative air leak with no solution so far.
- It is a pathology that causes pain, anxiety, stress, in addition to increasing the risk of other cardiorespiratory complications.
- We can identify the population most at risk of developing this complication.

With this background, we set ourselves the objective of developing a therapeutic alternative in patients at risk of prolonged postoperative air leak based on the topical application of a Hemopatch® collagen patch.)

OBJETIVES

Main objective:
To analyze the efficacy of the application of Hemopatch® directly on the pulmonary suture line as prevention of postoperative air leak in patients at high risk after pulmonary resection. Decrease in the postoperative air leak rate (air outflow through the drains on the 5th postoperative day).

Secondary objectives:
To analyze the efficacy of the procedure measured in terms of:
-Clinical:
oDuration of postoperative air leak.
oRate of reinsertion of pleural drainage for symptomatic pneumothorax
o 30-day postoperative readmission rate for recurrence of symptomatic pneumothorax. oRelated cardiorespiratory complications.
-Radiologicals:
oPresence of pneumothorax on chest radiograph.

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- NCT01867658 Progel® Pleural Air Leak Sealant (PALS) in Video and Robotic Assisted Thoracoscopic Surgery
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5. CLINICAL TRIAL CLASS AND DESIGN

5.1. PHASE

Prospective, multicenter, open-label, randomized, phase III clinical trial of prevention of postoperative air leak after pulmonary resection in high-risk patients by application of HEMOPATCH® directly to the pulmonary suture line.

5.2. GLOBAL DESIGN

5.2.1. DESIGN

Prospective, multicenter, open-label, randomized, prospective study with a control group and an experimental treatment group.

5.2.2. Investigational product. Dose and treatment regimen:

The population will consist of 276 patients undergoing scheduled anatomic lung resection (excluding pneumonectomy) and classified D, according to the postoperative prolonged air leak risk scale (index > 1.5) (Patient age over 65 years (1 point), BMI body mass index<25 kg/m2 (2 points), FEV1<80% (1.5 points) and presence of pleural adhesions during surgery (1 point)).

According to a publication of our group establishing a system for predicting the risk of PAL air leak (Ann Thorac Surg 2010;90:204-9), 21% of the cases in the case cohort and 30% in the validation group are classified as risk D. The median prevalence of PAL in class D is 27%. In this study we have considered a reduction in the rate of PAL of 50%, so the prevalence of PAL in the experimental arm would be around 13.5%.

With this estimated prevalence, we have calculated the number of patients to treat for a 50% reduction in prevalence in the experimental group. We have established an alpha value of 0.05 and beta of 0.80 (two-sided test) and the ratio of experimental/control cases of 1/1. The total number of patients to be treated is 276 (138 in each arm).

With these assumptions, we would obtain the following 2x2 table to estimate the risk ratio:

	Outcome +	Outcome -	Total cases
Cases	21	97	138
Controls	41	117	138

The participating hospitals have been selected by the surgical volume of at least 100 major resections (lobectomy and anatomic segmentectomy) per year, plus at least 100 atypical resections.

Experimental Group: 138 patients who will receive as study treatment the application of Hemopatch® patches applied at the end of the pulmonary resection on the suture lines of the pulmonary parenchyma, once the absence of air leakage has been verified.

However, the study will be stopped if any of the circumstances contemplated as a reason for interruption of the trial occur.

Control group: The usual preventive measures of each center, including suture reinforcement, pleural tent, pericardial plasty or pericardial fat, but not surgical adhesives (Tachosil® or Hemopatch® itself), as this is the type of treatment under study in the experimental group compared to the control group.

5.2.3. Expected duration of participation of the participants. Trial sequence and periods.

The patient inclusion period is 18 months. The follow-up of the patients will be from 1 to 3 months and will be carried out in several visits according to the proposed scheme (see Annex I), therefore the patients will be evaluated longitudinally for all clinical and paraclinical parameters. The study ends with the last follow-up visit of the last patient treated, between 1 and 3 months after the intervention.

5.3. PRE-INCLUSION, TREATMENT AND FOLLOW-UP PERIODS

A. Patients will be provided with a detailed explanation of the technique and its advantages and disadvantages (technical problems and possible complications). They will be provided with the Study Information and Informed Consent Form to sign and date if they agree to participate in the study (Annex VI).

B. Participating hospitals have been selected by surgical volume of at least 100 major resections (lobectomy and anatomic segmentectomy) per year, plus at least 100 atypical resections.

C. Randomization will be carried out according to the order of inclusion against a table of random numbers generated in Excel, this task will be performed by the data manager.

Baseline. Pre-treatment evaluation.

Patients who meet the inclusion criteria will be evaluated by the usual preoperative study.

Treatment.

The experimental group will be administered up to 6 Hemopatch® patches applied at the end of the pulmonary resection on the suture lines of the pulmonary parenchyma, once the absence of air leak or minimum grade 1 according to the Machiarini scale (Annex III) has been verified.

Perioperative Protocol.

They will be admitted to hospital the day before surgery and will receive standardized postoperative care; this care includes extubation of the patient in the operating room at the end of the operation, postoperative analgesia according to the protocol of each center, and the usual respiratory care. The type of surgical approach will not be standardized and will be at the discretion of the surgeon, who in all cases will be an investigator of this project. The suture of the pulmonary parenchyma will be performed with mechanical staplers or resorbable manual suture material; in no case will adhesives or prosthetic material for reinforcement other than that contained in the Investigational Product be added for the experimental group. The use of surgical adhesives (Tachosil® or Hemopatch® itself) is also excluded in the control group, since the intervention under study will be used in the experimental group.

The pleural space will be drained with one or two 24-28 French caliber multifenestrator tubes. Once the intervention has been completed, the drainage tube or tubes will be connected to a bottle with a valve system connected or not to aspiration according to the uses of each center.

FOLLOW-UP AND EVALUATIONS

The follow-up will be done daily during the time the patient is admitted. A daily visit will be made until the patient is discharged from the hospital.:

Clinical parameters

- o Assessment of the existence of air leakage.
- o Amount of air leak.
- o Existence of cardiorespiratory complications.
- o Need for placement of pleural drainage due to symptomatic pneumothorax.

Radiological parameters

o Presence of pneumothorax in the chest X-ray.

The duration of admission will depend on the clinical evolution. This will take into account:

Clinical parameters:

- The patient is capable of self-care
- Afebrile
- Does not require opioids for pain control.

- Absence of significant effusion or pneumothorax

Analytical parameters:

- Normal blood count, coagulation and biochemistry.

Subsequent follow-up will be carried out in consultation within 1-3 months post-operatively, collecting the following evolutionary data:

- Evaluate the clinical evolution especially related to the appearance of complications.

- Data collection: special attention to the clinical situation of the patient.

- Radiological parameters: chest X-ray, BP and L projections.

The trial sponsor will provide all patients included in the study with a follow-up card identifying that these patients have been treated with Hemopatch® patches.

6. PARTICIPANT SELECTION

6.1. TARGET POPULATION

The population will consist of patients undergoing scheduled anatomic lung resection (excluding pneumonectomy) and classified D, according to the postoperative prolonged air leak risk scale (index > 1.5) (Patient age over 65 years (1 point), BMI body mass index<25 kg/m2 (2 points), FEV1<80% (1.5 points) and presence of pleural adhesions during surgery (1 point)).

6.2. INCLUSION CRITERIA

- Age between 18 and 80 years
- Patients who are going to undergo scheduled anatomical lung resection (excluding pneumonectomy).
- Patients class D on the air leak risk scale.

Patients included in the study must meet all inclusion criteria.

6.3. EXCLUSION CRITERIA

Patients who present any of the following exclusion criteria cannot be included in the clinical trial:

- Those who in the judgment of the investigator are not in an adequate situation to tolerate the procedure.
- Clinical and anesthetic criteria that contraindicate surgery (e.g. ASA IV-V).
- Severe uncontrolled disease
- Pregnant women
- Individuals who are taking a clinical research drug or have participated in a clinical research study (with an authorized or unauthorized product) in the 30 days prior to randomization.
- Lack of informed consent or revocation of consent.
- Postoperative mechanical ventilation or thoracic surgical reintervention in the month of follow-up.

6.4. WITHDRAWAL CRITERIA AND EXPECTED ANALYSIS OF WITHDRAWALS AND DROPOUTS

Patients will discontinue the clinical trial if at least one of the following occurs:

- When the patient is uncooperative or fails to comply with the requirements of the study.

- When the investigator considers that the patient's health is compromised.

- Serious adverse event(s) that in the investigator's judgment necessitates withdrawal. (Toxicity grade IV on the WHO scale of adverse effects).

- Serious protocol violation.

- Withdrawal of consent by the patient.

- Loss of follow-up.

Patients will be informed that they can leave the clinical trial at any time they wish without any detriment to their subsequent medical care. The investigator may also, at his discretion, suspend treatment in patients in whom any of the following reasons appear:

- Refusal to receive treatment.

- Concomitant illness.

- Major protocol violations.

- Requirement of the patient.

- Non-compliance with the established visits.

- Administrative reasons.

- Loss of patient follow-up.

- Specific or general changes in the patient.

Patients who drop out of the trial for any reason are not eligible for re-inclusion.

At the time of leaving the trial, the primary cause for withdrawal from the trial should be collected and, if possible, the patient should be re-evaluated with the required tests at the End-of-Treatment visit. In the event that the cause is due to the patient's own decision, the patient will not be required to provide any explanation for this.

It should be noted that once the patient has received the administration of the investigational product (a single dose is administered), withdrawal from the study will not provide any safety benefit, so continuation of the study will be recommended.

When the investigator no longer hears from a patient, every attempt should be made to contact him/her (unless the patient has clearly expressed a wish not to be contacted) to obtain the date on which the patient was discontinued from follow-up, to establish the reason for discontinuation, to ask the patient to resume study procedures or to attend at least one last visit, and to suggest that the patient provide the contact details of the physician who will be following his/her case. If all attempts to contact the patient fail, all actions taken will be requested to be documented in the medical record, and if key study data cannot be obtained before the final visit, the investigator will then declare the patient as "lost to follow-up".

In the event of premature discontinuation of the study, the investigator should note in the CRD the reason(s) for discontinuation. If more than one reason is given, the investigator should give the primary reason.

According to good clinical practice, all patients who prematurely drop out of the study will have to be recommended for alternative treatment. If withdrawal is due to a significant adverse event, patients will be monitored by the investigator until appropriate termination, i.e., until the adverse event disappears or is determined to be permanent.

6.5. CLINICAL TRIAL DISCONTINUATION

The clinical trial may be discontinued in the view of any serious adverse event related to the investigational product ori f any of the following circunstances arise:

1. Response < 20%
2. Severe infections > 50%
3. Failure to include a minimum of 10% of patients in the first 18 months after approval and distribution.

6.6. EXPECTED PATIENT ENROLLMENT

A total of 276 pacients are expected to be enrolled.

6.7. PARTICIPANT IDENTIFICATION

Patients will be identified with the acronym HEMFAP plus a sequential numerical identification code, which will be assigned to each patient in sequential order of inclusion when they give their informed consent. In the event that a patient is included in the study, i.e. signs the informed consent, and once the procedures of the screening visit have been carried out, he/she is considered ineligible to continue in the study or the patient withdraws his/her consent, the number assigned to that patient cannot be reused for another patient.

The sponsor will only be able to identify the subjects by the number assigned to them, their date of birth and their sex. The investigator should keep a record of the names of the patients and the assigned identification number.

7. TREATAMENT DESCRIPTION

7.1. INVESTIGATIONAL PRODUCT

Investigational product: Hemopatch®

Pharmaceutical form: Collagen patch derived from bovine skin, coated with NHS-PEG (pentaerythritol polyethylene glycol ether tetrasuccinimidyl glutarate).

7.2. INVESTIGATIONAL PRODUCT IDENTIFICATION

The identification and labeling of the product under investigation is detailed in Annex IV.

7.3. INVESTIGATIONAL PRODUCT STEWARDSHIP

In the experimental group, at the end of the pulmonary lobectomy, up to 6

Hemopatch® patches are applied on the suture lines of the pulmonary parenchyma, once the absence of air leakage or minimum grade 1 according to the Machiarini scale (Annex III) has been verified. The use of the investigational product will be done in the same tissue, same location and same type of patient in which it is usually administered with the indication of hemostasis. The only difference is that in the patients participating in the clinical trial the post-surgical air leak parameter will be measured to evaluate the efficacy of HEMOPATCH® in this new indication.

They will be admitted to hospital the day before surgery and will receive standardized postoperative care; this care includes extubation of the patient in the operating room at the end of the operation, postoperative analgesia by epidural catheter with local anesthesia and fentanyl supplemented with NSAIDs, and respiratory care by physiotherapists exclusively dedicated to patients undergoing cardiothoracic surgery. The type of surgical approach will not be standardized and will be at the discretion of the surgeon, who in all cases will be an investigator of this project. The suture of the pulmonary parenchyma will be performed with mechanical staplers or resorbable hand suture material; in no case will adhesives or prosthetic material for reinforcement other than that contained in the Investigational Product be added. The pleural space will be drained with one or two 24-28 French caliber multifenestrating silicone tubes. At the end of the procedure, the drainage tube(s) will be connected to a bottle with a valvular system connected or not to aspiration according to the uses of each center.

7.4. PERMITTED AND PROHIBITED CONCOMITANT TREATMENTS

7.4.1. PERMITTED CONCOMITANT TREATMENTS

All drugs that, in the opinion of the principal investigator, are considered necessary for the patient's well-being and that do not interfere with the investigational product will be admitted, although they must be listed in the corresponding section of the CRD.

7.4.2. PROHIBITED CONCOMITANT TREATMENTS

The following medications and supportive treatments as well as procedures are prohibited during the trial:

- Any other agent under investigation
- Any surgical adhesive (Tachosil® or Hemopatch) in the control group, as well as any surgical adhesive other than Hemopatch in the experimental group.

7.4.3. ADVERSE EVENT'S MANAGEMENT

Complications arising from the procedure will be treated as standard, and always at the discretion of the investigator. They should be recorded in the data collection notebook as adverse events and the treatments required as concomitant medication.

8. TRIAL DEVELOPMENT AND RESPONSE EVALUATION

8.1. RESPONSE EVALUATION

A- Hospital follow-up: daily visit until hospital discharge. A daily visit will be made until hospital discharge:

Clinical parameters

- Duration of postoperative air leakage
- Reinsertion rate of pleural drainage for symptomatic pneumothorax.
- 30-day postoperative readmission rate due to recurrence of symptomatic pneumothorax.
- Cardiorespiratory related complications

Radiologic parameters

- Presence of pneumothorax on chest x-ray

B- Follow-up one month-3 months after hospital discharge: FIRST POSTOPERATIVE VISIT IN CONSULTATION

- To evaluate the clinical evolution, especially in relation to the appearance of complications. Data collection: special attention to the patient's clinical situation.
- Radiological: Chest Rx, PA and L projections.

8.2. CLINICAL TRIAL DEVELOPMENT

The Hemopatch product administration procedure (day 0 of the study) and the rest of the study visits and procedures will take place in each of the participating hospitals.

-Visit 1: Selection: The selection of candidate patients will be made by the Thoracic Surgery Department of each participating hospital. During this visit, and once the usual evaluation has been carried out, in response to the demand for care for which he/she attends, the patient potentially suitable for the study will be informed of the objectives of the study and the overall requirements. Informed consent will be obtained prior to any study-specific assessment. The patient will then undergo a clinical evaluation to ensure compliance with the inclusion and exclusion criteria.

The patient's medical record should record how the patient agrees to participate in the HEMOPATCH/FAP/2014 clinical trial, date of consent signature, assigned patient

number and study sponsor.

The date of the visit shall be recorded and collected:

- Presentation of written informed consent.
- Medical history, including concomitant diseases and medication, supportive treatment and baseline medical conditions.
- Complete physical examination.
- Serum pregnancy test in fertile women.
- Respiratory functional evaluation
- Chest CT scan.

Once the results of all the above-mentioned procedures have been obtained, and it has been verified that all the inclusion criteria have been met and none of the exclusion criteria have been met, the patient may continue in the study and be randomized. If, on the other hand, the patient does not meet the inclusion criteria, he/she will not be able to continue in the study and the reason for the patient's non-selection must be recorded in the CRD.

- Visit 2: Product administration
According to the description above.

- Perioperative visits: Day +1 to the day of discharge from hospital
In order to analyze the efficacy of the administration, the patient's general condition will be assessed. In the patient's clinical history and CRD, the following will be collected:
- AA and concomitant medications from the previous visit.
- Vital signs (blood pressure, heart rate, respiratory rate).

Follow-up and assessment of variables:
Clinical:
- Efficacy Variables:
  - Technical success (air leak yes/no).
- Safety variables:
  - Morbidity (absence/presence).
  - Absence of mortality (yes/no) Radiological:
  - Presence of pneumothorax

End of follow-up visit

Patients who have completed the treatment period and, if possible, those who have discontinued prematurely regardless of the reason, should have follow-up visits between 1 and 3 months after the intervention. The following evaluations will be performed:

- Anamnesis and complete physical examination.
- Documentation of the patient's condition
- X-ray

8.3. TASK DSTRIBUTION

- Dr. Jimenez will be in charge of the supervision and coordination of the trial.
- The principal investigators of each center and their collaborators included as sub-investigators of the study will be responsible for patient selection and post-treatment evaluation, as well as surgical procedures.
- General laboratory tests: will be performed in the central laboratory of each center,
- Microbiological studies will be performed in the Microbiology Service of each center.

9. ADVERSE EVENTS*

All adverse events (AEs) will be recorded in the data collection notebooks from the moment the patient signs the informed consent. The investigator will decide whether these events are related to the treatment received (unrelated, unlikely, possible, probable, safe, not assessable) and his/her decision will be recorded on the sheets for all adverse events. Adverse events unrelated to treatment (i.e., reported as unrelated or unlikely to be related) will not be considered as side effects or toxicity; these will be reported separately in the analysis.

* *Note: No adverse effects different from those expected for the other indications are expected.*

9.1. DEFINITIONS

An **Adverse Reaction** (AR): An AR is any unintended, harmful reaction to an investigational product, regardless of the dose administered. The reactions produced as a consequence of the procedures of the study such as the surgical intervention or application of anesthesia necessary for its implantation should also be considered.

An **Unexpected Serious Adverse Reaction** (SUSAR): Any adverse reaction whose nature, intensity or consequences do not correspond to the safety reference information for the drug.

An **Adverse Event** (AE) is defined as any untoward medical episode or experience in a patient or clinical trial participant receiving an experimental treatment, in this study Hemopatch implantation, regardless of dose or causal relationship. This may include any sign (such as a rash or hepatomegaly) or symptom (such as nausea or chest pain) that is unfavorable or unintended, an abnormal laboratory finding (including blood tests, x-rays or scans), an illness temporally associated with the use of the study treatment, or a worsening of a pre-existing condition.

In addition, any event associated with an overdose of the product will also be considered an adverse event.

A **persistent disorder** is a clinical condition (including a disorder that is being treated) that was diagnosed before the participant signed the informed consent and is documented in the participant's medical record.

A **Serious Adverse Event** (SAE) is defined as any unwanted experience that affects a patient, whether or not it is considered related to the protocol treatment. Serious adverse events are those that result in:

- Death.
- A life-threatening event (i.e., there was a risk of immediate patient death at the time the reaction was observed).

- Hospitalization or prolonged hospitalization.
- Persistent or significant disability/disability.
- A congenital anomaly or birth defect.
- Any other significant medical condition (i.e., significant adverse reactions that are not immediately life-threatening and do not result in death or hospitalization but may endanger the patient or may require intervention to prevent another of the outcomes listed above) based on appropriate medical judgment.

Toxic death is defined as death secondary to toxicity. This should be specified on the death report form: the cause of death should be listed as "toxicity". The assessment of toxic deaths is independent of the response assessment (patients may die from toxicity after a full assessment of response to treatment).

Hospitalization is defined as official admission to a hospital. Hospitalization and prolongation of a hospitalization are criteria for severity of an AA; however, they are not by themselves considered an AAG. If an AA does not exist, the investigator should not report hospitalization or prolonged hospitalization as an AAG. This is the case in the following situations:

- Hospitalization or prolonged hospitalization is needed to perform a procedure required by the protocol.

- Hospitalization or prolonged hospitalization that is part of a routine procedure of the facility.

- Hospitalization due to a pre-existing condition that has not worsened.

A **protocol-related adverse event** is an AE that occurs during a clinical trial that is unrelated to the investigational product but, in the opinion of the investigator, is related to the investigational requirement(s) under investigation. For example, a protocol-related AE may be a harmful event that occurs during a washout period or is related to a medical procedure required by the protocol. AAs and AAGs suffered by the subjects from the signing of the informed consent until the end of their participation in the study should be recorded and reported.

The investigator or his/her collaborator will question and/or examine the patient for signs of adverse events. Patient questioning regarding the possible occurrence of adverse events will be done in a general manner (e.g., "How have you been feeling since the last visit?"). The patient should not be questioned about the presence or absence of specific adverse events.

SERIOUS ADVERSE EVENTS SHOULD BE REPORTED IMMEDIATELY,

WITHIN 72 HOURS, TO THE SPONSOR AND THE STUDY MONITOR ACCORDING TO THE PROCEDURE DETAILED IN THIS PROTOCOL.

9.2. RRECORDING AND REPORTING OF ADVERSE EVENTS

9.2.1. NON-SEVERE ADVERSE EVENTS

All adverse events should be recorded in the patient's medical record and in the data collection notebook using standard medical terminology, avoiding the use of ambiguous or colloquial expressions. The dates of onset and resolution and the severity of any adverse event, as well as its relationship to the study drug, should be noted.

The severity of the adverse event (mild, moderate, severe) and the relationship to the procedure (unrelated, unlikely, possible, probable, safe, or not assessable) should be assessed according to the guidelines specified below. Actions taken and outcomes (e.g., hospitalization, treatment withdrawal, etc.) of any adverse events should also be noted. AEs that are likely to be unrelated to the procedure (i.e., reported as unrelated) will not be considered as adverse reactions to treatment in the toxicity analyses and will be reported independently.

9.2.2. SEVERE ADVERSE EVENTS

For the reporting of serious adverse events, the definitions and provisions of the document MEDDEV 2.7/3 of December 2010 will be followed. "Guidelines on medical devices: Clinical investigations: Serious adverse event reporting under Directives 90/385/EEC and 93/42/EEC".

The AEMPS will be informed of all those AGEs and unexpected events that have a causal relationship with the treatment under study, or that are possible, probable or unknown, in the manner foreseen in the current legislation on clinical research with medical devices, including the document MEDDEV 2.7/3 Clinical investigations: Serious adverse event reporting under Directives 90/385/EEC and 93/42/EEC.

The investigator should notify the sponsor of any AAG detected, whether or not it is considered to be related to the investigational product, as soon as possible, within a maximum of 3 days from the time the event becomes known, according to the MEDDEV 2.7/3 Clinical investigations: Serious adverse event reporting under Directives 90/385/EEC and 93/42/EEC. Notification should be made using the AAG notification form included in the CRD. If the report is made by telephone, the telephone report should include a detailed description of the event and its sequelae, in addition to the investigator's causality relationship to the study drug. The source of the report (investigation, spontaneous, other) should always be specified. The date and signature of the responsible investigator or one of the authorized members of his staff

should appear on all reports.

For its part, the sponsor should make the AAG communication to the AEMPS as soon as possible:

- Within the first 48 hours after knowledge of said AAG by the sponsor in the case of AAGs that pose an imminent risk to the patient's life, or a severe injury or illness that requires immediate action on the patient and is extensible all those who have been treated with the study medical device in the indication of the study.
- Within 7 days after the sponsor's knowledge of the AAG in the case of the rest of the AAG.

The sponsor should periodically report all serious and/or unexpected adverse events to the Safety Committee. With this information, the Safety Committee, at its discretion, may interrupt or modify the treatment or even terminate the patient's participation in the study. Likewise, reports of serious adverse events should be communicated as soon as possible to the IRB/IEC, in accordance with current legislation.

Notification of pregnancies: although they are not considered serious adverse events, if a woman becomes pregnant during the course of a clinical trial, the principal investigator or a collaborator must notify the monitor.

The AEMPS will be informed of all those AAGs and Unexpected AAGs that have a causal relationship with the treatment under study, or this is possible, probable or unknown, in the manner provided for in the Spanish legislation on clinical trials, using the official form.

It should be noted that AGEs that have not been previously documented in the Investigator's manual, or that occur in a more severe form than expected (i.e., that are "unexpected"), are subject to prompt communication to the Regulatory Authorities by the Sponsor. This also applies to reports from spontaneous sources and from any type of clinical or epidemiological investigation, regardless of its design or purpose. The source of the report (research, spontaneous, other) should always be specified.

THE DATE AND SIGNATURE OF THE RESPONSIBLE INVESTIGATOR OR ONE OF HIS OR HER AUTHORIZED STAFF MEMBERS MUST APPEAR ON ALL REPORTS.

9.3. ASSESSMENT OF CAUSALITY AND SEVERITY OF ADVERSE EVENTS

The investigator will make the causality assessment using the following definitions:

UNRELATED: There is no evidence of any causal relationship.

IMPROBABLE: There is little evidence to suggest a causal relationship (e.g., the event did not occur within a reasonable period of time after administration of the study treatment). There is another reasonable explanation for the event (e.g., the patient's clinical condition, other concomitant treatments).

POSIBLE: There is evidence to suggest a possible causal relationship (e.g., because the event occurred within a reasonable time after administration of the study treatment). However, the influence of other factors may have contributed to the event (e.g., the patient's clinical condition, other concomitant treatments).

PROBABLE: There is evidence to suggest a causal relationship and the influence of other factors is unlikely.

RELATED: There is clear evidence to suggest a causal relationship and a possible contribution of other factors can be ruled out.

NOT EVALUABLE: There is insufficient or incomplete evidence to make a clinical judgment about a causal relationship.

The Investigator will also evaluate the intensity of the event according to the following classification:

MILD: AE is appreciated by the patient but does not interfere with his/her life.

MODERATE: AE causes discomfort and interferes with daily life.

SERIOUS: AE severely limits the patient's ability to perform usual tasks and requires symptomatic treatment. OSA directly endangers the patient's life.

Actions to be taken in response to the adverse event

The actions to be taken in the event of an adverse event are described on a numerical scale, from 0 to 3, covering different possibilities. One or more of them should be selected.

0 =	None
1 =	Concomitant medication administration
2 =	Non-pharmacological treatment administration
3 =	Hospitalization/prolongation

10. ETHICAL ASPECTS

10.1. GENERAL CONSIDERATIONS

This study should be conducted in accordance with the protocol following the standard operating procedures of the sponsor or the designated company.

The trial will be conducted in accordance with the recommendations for Clinical Trials and Investigational Product Evaluation in Man, contained in the Declaration of Helsinki, as revised at successive World Assemblies (WMA, 2004) (see Annex VII),

and the current Spanish Legislation on Clinical Trials, specifically that applicable to Research with Medical Devices, including but not limited to RD 1090/2015, RD 1591/2009 and the MEDDEV 2.7/3 document of December 2010. ICH-GCP (CPMP/ICH/135/95) shall be followed.

The IRB/IEC should review and approve the protocol and informed consent before proceeding with the inclusion of subjects. Prior to performing any of the procedures specified in the protocol, the participant must sign and date the informed consent document approved by the IRB/IEC.

10.2. INFORMATION TO BE PROVIDED TO THE PARTICIPANTS AND TYPE OF CONSENT TO BE SOUGHT IN THE TRIAL

The consent of the subject participating in the trial will always be obtained in writing (see Annex VI). The subject will sign and date the informed consent form before being included in the study, i.e., before undertaking any study procedure. The investigator will explain the nature of the study, its purpose, the procedures involved, the anticipated duration, the possible risks and benefits involved and any discomfort that may be involved, and will give the participant a copy of the signed patient information and consent form. The investigator will inform the subject that participation in the study is voluntary and that he/she has the right to withdraw from the study at any time without having to give explanations and without his/her withdrawal resulting in any liability or prejudice, affecting his/her subsequent medical treatment or the relationship with the treating physician. Sufficient time will be given to consider the study before deciding whether the participant will participate in the trial or to withdraw at any time.

In the event that amendments are made to the final protocol that may directly affect the subject's participation in the study (e.g., a change in any procedure), the information sheet and informed consent form should be changed to incorporate this modification and the subject should sign the amended form to indicate that he/she maintains his/her consent to participate in the study.

The investigator will be responsible for providing each subject or the subject's legal representative with a patient information sheet and informed consent form, which will be those approved by the appropriate IRB/IEC.

The subject will express his or her consent in writing. The informed consent form must be completed by the participant himself/herself. Once signed and dated by the participant (or his/her representative) and by the investigator, a copy will be given to the subject. The original of this document will be kept at the center together with the rest of the study documentation. No patient will be allowed to participate in the trial until he/she has signed the informed consent form.

10.3. ACCESS TO THE DATA OF THE STUDY

In order to guarantee the confidentiality of the trial data, the original data will be kept at the hospital and only the investigator and his team of collaborators, the trial monitor and the Clinical Research Ethics Committee of the corresponding center or the one supervising the trial will have access to them. The investigator will allow audits and inspections by the Spanish or European Health Authorities.

10.4. PROTECTION OF THE DATA OBTAINED IN THE STUDY

The content of the data collection notebooks (CRD), as well as the confidentiality of each patient's data will be respected at all times. Appropriate procedures will be followed to ensure compliance with the provisions of Law 15/99 of December 13, 1999 on the Protection of Personal Data.

The documents generated during the study will be protected from unauthorized use by persons outside the research and, therefore, will be considered strictly confidential and will not be disclosed to third parties except to those specified in the previous section.

The investigator will inform the study participants that the data obtained in the present trial will be stored and analyzed by computer and that the Spanish regulations on the handling of computerized data will be followed.

The investigator agrees that the sponsor has the right to use the results of the clinical trial including CRD sheets or copies thereof. To allow the use of the information obtained in the clinical trial, the investigator understands that he/she is obliged to provide the full test results and all information developed during the study to the sponsor.

The anonymity of the participants in the trial will be maintained at all times.

The results or conclusions of the clinical trial will be communicated as a priority in scientific publications before being disclosed to the non-health public. Procedures of not yet determined feasibility will not be prematurely or sensationally disclosed.

10.5. STUDY INSURANCE

The IBSAL as promoter of the study, has, in accordance with Spanish legislation, a civil liability insurance policy. This policy covers all possible damages that the participant may suffer as a result of the administration of the product under study, according to current legislation (RD1090/2015, article 9).

The insurance policy or civil indemnity subscribed and its characteristics are attached (Annex VIII).

10.6. MASTER FILE AND PRESERVATION OF TEST DOCUMENTATION

The Sponsor and the study investigators will retain the Clinical Trial records for a minimum period of time of five years after the completion of the clinical investigation, including the Subjects' references, informed consents, Clinical Trial Protocol, subsequent modifications, data collection sheets, authorizations, memoranda and correspondence related to the Clinical Trial.

11. PRACTICAL CONSIDERATIONS

11.2. RESPONSIBILITIES OF TRIAL PARTICIPANTS

11.3. CLINICAL.

The trial sponsor, monitor, and investigators will fulfill the responsibilities established, respectively in Articles 39, 40, and 41 of RD 1090/2015.

The responsibilities of the PRINCIPAL INVESTIGATOR will be:

1. sign together with the sponsor the trial protocol.

2. To have a thorough knowledge of the properties of air leak therapy.

3. ensure that the informed consent is collected in accordance with the provisions of RD 1090/2015.

4. Collect, record and report data correctly and ensure its veracity.

5. Follow the instructions regarding the reporting of adverse events established in the protocol.

6. Immediately report serious non-compliance with the protocol to the sponsor.

7. To ensure that all persons involved will respect the confidentiality of any information about the trial participants, as well as the protection of their personal data.

8. To report regularly to the IRB/IEC on the progress of the trial.

9. To be jointly responsible, together with the sponsor, for the preparation of the final report of the trial, giving their agreement to it with their signature.

The responsibilities of the PROMOTOR shall be:

1. Establish and maintain a system of quality assurance and quality control, with written standard operating procedures, so that the trials are conducted and the data generated, documented and communicated in accordance with the protocol, the standards of good clinical practice and the provisions of RD 1090/2015.

2. Sign, together with the corresponding investigator, the protocol and any of its modifications.

3. Select the most appropriate investigator according to his/her qualifications and available means, and ensure that he/she will carry out the study as specified in the protocol.

4. Provide the basic and clinical information available on the investigational product and update it throughout the trial.

5. To request the opinion of the CEIm and the authorization of the Spanish Agency of Medicines and Health Products, as well as to inform them of the start of the trial, serious breaches of the protocol, and other necessary information, seeking the appropriate authorizations, without prejudice to the communications that must be made to the autonomous communities, in accordance with article 19 of RD 1090/2015.

6. Supply free of charge the product under investigation and guarantee that the rules of correct elaboration have been complied with and that the samples are adequately packaged and labeled. It is also responsible for the conservation of samples and their manufacturing and control protocols, for the registration of the samples delivered and for ensuring that in the center where the assay is performed there will be a correct procedure for the handling, conservation and use of these samples.

7. To ensure that the participation of a participant in the clinical trial will not entail an additional cost for him/her in addition to that which he/she would have had to face in the context of usual clinical practice.

8. To designate the monitor who will oversee the progress of the trial.

9. To report suspected serious and unexpected adverse reactions in accordance with the provisions of Articles 49 to 53 of RD 1090/2015 (failing this, with the provisions of the legislation applicable to medical devices, in the specific case of this clinical trial).

10. To provide the investigator, the Spanish Agency of Medicines and Medical Devices and the CEIM, immediately, with any information of importance related to the clinical trial to which he/she has access during the clinical trial.

11. Comply with the obligations of compensation for damages under the terms provided in Article 9 of RD 1090/2015. Provide the investigator with legal and economic coverage in these cases except when the injury is a consequence of negligence or malpractice of the investigator.

12. Agree with the investigator on the obligations regarding data processing, reporting and publication of results. In any case, the sponsor is responsible for preparing the final report and the annual reports of the trial as well as for communicating them to whom it may concern.

13. The sponsor should have a point of contact where the trial participants can

obtain further information about the trial, which may be delegated to the investigator as an option.

14. To comply with the obligations imposed by the Spanish Clinical Trials Register for the publication of the trials of which he/she is the sponsor.

15. To agree with the investigator, the address of the center and the alternative distribution methods in those cases in which the center does not have a Pharmacy Service. In this case, it will be possible the shipment of the products under investigation by the sponsor to the research center assuming the investigator of said center the responsibilities related to the correct administration, custody and delivery of said products under investigation, according to what is specified in the protocol of the study.

The responsibilities of the MONITOR will be to:

1. work in accordance with the sponsor's SOPs (in the absence of SOPs, the SOPs of the company designated for this purpose will be followed in this study), visit the investigator before, during and after the trial to check compliance with the protocol, ensure that data are recorded correctly and completely, as well as ensure that informed consent has been obtained from all subjects prior to their inclusion in the trial.

2. Ensure that the investigators and the site where the research will be conducted are suitable for the purpose during the period of the trial.

3. Ensure that both the principal investigator and his or her collaborators have been adequately informed and ensure prompt communication between the investigator and sponsor at all times, especially in the area of trial safety monitoring.

4. Verify that the investigator complies with the protocol and all approved amendments to the protocol.

5. Verify that the storage, distribution, return, and documentation of the investigational product is safe and adequate.

6. Submitting to the sponsor reports of monitoring visits and all relevant contacts with the investigator.

11.4. MONITORING

The trial monitors should monitor the trial on a periodic basis to ensure that the rights and welfare of patients are safeguarded, that the protocol, applicable regulatory and ethical requirements are met, that the necessary documentation is available, and that the data collected accurately reflect the CRF data.

11.5. AMENDMENTS OR MODIFICATIONS TO THE PROTOCOL

Once a protocol has been approved by the CEIm and authorized by the Spanish Agency of Medicines and Health Products, neither the investigator nor the sponsor can make modifications or alterations without the written consent of both parties. If it is necessary to make a modification or alteration to the protocol, this modification should be discussed and agreed between the principal investigator and the sponsor and signed by both parties. Amendments to the protocol will form an integral part of the original protocol. Any modification in the authorized conditions for the trial that is considered relevant, because it affects the safety of the subjects, cannot be carried out without the prior favorable opinion of the IRB/IEC and the authorization of the AEMPS.

11.6. Publication of test results and use of the information.

The results of this clinical trial will be reported at scientific congresses and published in a scientific journal of the highest possible impact. The results of the trial and any proposal for publication will be sent to the sponsor at least 30 days prior to submission for publication.

11.7. **Basic trial regulation**.

The Principal Investigator and/or the HOSPITAL undertake not to use or transmit to third parties, nor to divulge and/or publish the results obtained in this Trial without the prior written consent of the IBSAL, the sole promoter of the trial. In any case, the following conditions must be respected:

a) The results of the present study may not be published until the completion of the trial or earlier, if agreed by both parties.

b) The sponsor will not cite the name of the investigators without their authorization, except in the case of references to previously published work.

c) The sponsor will allow the publication of the data obtained in this trial in journals of recognized scientific prestige and its dissemination in seminars and conferences within the medical professional field, provided that the provisions of paragraph a) of this section are respected and that the final draft of the article is reviewed by the sponsor

within a minimum period of thirty days.

12. STATISTICAL ANALYSIS

The data collection notebooks will be processed by a pre-set and validated Clinical Data Computer System. After double data recording, resolution of all inconsistencies and coding using the medical dictionaries, a final quality control process will be applied and in case of compliance the database will be considered free of errors and will proceed to freeze and perform the statistical exploitation of the data. The results of the clinical trial will be analyzed in the intention-to-treat population.

12.1. Population for analysis

The efficacy and safety analysis will include all patients enrolled in the study. Efficacy analyses will be performed on data from the intention-to-treat population.

The term "treatment period" used for efficacy and safety analyses refers to the period from cell administration and the end-of-treatment week (+/-7 days). This period will form the basis for the efficacy and safety summaries.

The primary efficacy data set will consist of all patients in the study who have completed all treatment. Events occurring in patients who have been withdrawn early will also be included if the patients meet the withdrawal criteria.

For the primary endpoints, an analysis will be conducted using the evaluable patient data set as well as the primary efficacy data set. Summaries of the safety data will include all patients treated in the study. The primary and secondary data set will be defined in a statistical analysis plan.

12.2. Procedures for handling non-existent, unused and confusing data

All available safety and efficacy data will be included in the data lists and tables. No imputation of values will be made for unavailable data.

Potentially confusing or erroneous data will be reviewed in accordance with standard data control procedures.

Analyses of patient-reported records (PNRs) will impute missing data using the last observation carried forward. The missing pattern will be examined prior to any imputation. If the missing pattern is obviously informative, the impact of non-random missing data will be assessed using sensitivity analyses.

For RNP analyses, if one item of a subscale is missing from several subscales, the average of the remaining items will be used as the scale score, provided that at least half of the items of that scale are available.

12.3. Statistical methods

Those commonly used in biomedicine (i.e., Student's t-test and Mann-Witney U test for quantitative variables and Chi-square for categorical variables; comparative analysis for paired samples will be performed by repeated measures ANOVA).
In principle, no intermediate statistical analyses will be performed.

The analysis will be performed at the University Hospital of Salamanca.

12.4. Safety análisis

Safety assessments will depend on the incidence, intensity and type of adverse events as well as clinically significant changes in the patient's physical examination findings. Safety variables will be included in a table and provided for all patients.
All adverse events occurring during the study will be included in data lists organized by patient. Those events that are considered treatment-related (possibly, probably or definitely related to treatment) will also be included in a table. A table listing adverse events by maximum intensity will also be provided. Deaths, serious adverse events and adverse events involving discontinuation of treatment will also be classified in another table.

12.5. Procedures for reporting deviations from the original statistical plan.

All deviations from the original statistical analysis plan are included in the final clinical study report.

ANNEX I: SUMMARY OF FOLLOW-UP

A-Hospital follow-up: daily visit until hospital discharge, the duration of which depends on the clinical evolution. For this purpose, the following are taken into account:

Clinical parameters:

- The patient is capable of self-care
- Afebrile
- Does not require opioids for pain control.
- Absence of significant effusion or pneumothorax Analytical parameters:
- Normal blood count, coagulation and biochemistry.

B-Follow-up at one month-3 months after hospital discharge: FIRST POST-OPERATIVE VISIT IN CONSULTATION

To evaluate the clinical evolution especially related to the appearance of complications.

Data collection: special attention to the patient's clinical situation Radiological: Chest X-ray, PA and L projections.

ANNEX II: POSTOPERATIVE PROLONGED AIR LEAK RISK SCALE

Variables	PUNCTUATION
AGE > 65 (years)	1
BMI < 25.5 m/kg^2	2
FEV_1 < 80%	1.5
Presence of pleural adhesions	1

BMI = body mass index; FEV_1 = forced expiratory volume in one second;

PAL risk scale

Class A (punctuation 0)

Class B (punctuation 1)

Class C (punctuation 1.5–3)

Class D (punctuation > 3)

Brunelli A, Varela G, Refai M, Jiménez MF, Pompili C, Sabattini A, et al. A scoring system to predict the risk of prolonged air leak after lobectomy. Ann Thorac Surg 2010;90:204-9

ANNEX III: MACCHIARINI INTRA-OPERATIVE AIR LEAK SCALE

After performing the lung sutures, the parenchyma is immersed in saline and the lung is progressively ventilated with a pressure of 25 cm H2O.

Grade 0 no bubble output
Grade 1 a countable number of bubbles are formed
Grade 2 if there is a small stream of bubbles
Grade 3 if they are coalescing bubbles

Macchiarini P, Wain J, Almy S, Dartevelle P. Experimental and clinical evaluation of a new synthetic, absorbable sealant to reduce air leaks in thoracic operations. J Thorac Cardiovasc Surg 1999;117(4):751- 8.

ANNEX IV: IDENTIFICATION OF THE PRODUCT IN RESEARCH LABELING

HEMOPATCH hemostatic sealant ("HEMOPATCH") consists of a soft, thin, pliable and flexible patch of bovine-derived collagen coated with NHS-PEG (pentaerythritol polyethylene glycol ether tetrasuccinimidyl glutarate). The white side, which is applied to the tissue, is coated with a thin layer of NHS-PEG providing a firm adhesion to the tissue, thus sealing the bleeding surface and inducing hemostasis at the same time. Due to its flexible structure, the application of HEMOPATCH to the site where hemostasis is desired is easily controlled. The uncoated side is marked with blue squares of a biocompatible dye to differentiate it from the coated side.

For the HEMOPATCH/FAP/2014 clinical trial, HEMOPATCH 4.5 x 9 cm patches will be used. They come in boxes of 6 packs with 3 patches inside each of the packs, including each patch inside 2 envelopes: one sealed aluminum outer and a second cellulose inner, to maintain the sterility of the device.

Since the sponsor of the clinical trial is not the owner of the patent of the product under investigation, an agreement has been reached with the same (Baxter España), so that the Hemopatch® patches will be supplied by said company, at no additional cost to the study sponsor, in their usual marketing format. This means that each package (containing 3 patches) will bear the CE marking. The product under investigation is currently marketed for the indication of hemostasis control in surgical procedures, with CE marking. The reason for its experimental use in this study is its use in the indication of prevention of prolonged air leak in patients at risk, an indication not approved at present and not covered by the CE marking. This marking will be removed by the developer before supplying the product to the centers, by means of an opaque marker. Also, following the indications of RD 1591/2009 and Directive 93/42/CE, the container will be relabeled, adding an adhesive label with the study protocol code and the legend "Exclusive use for clinical research".

Once relabeled, its distribution and storage will be made directly by the sponsor to the operating room warehouse provided in each center for that purpose, accessible only to the investigators participating in the study and in boxes containing 6 Hemopatch® containers each, also labeled with the study protocol code and the legend "Exclusive use for clinical research".

ANNEX V: DATA COLLECTION BOOKLET

Rules for filling in the CRD

Each investigator agrees to:

- Register the patient as soon as the patient is included in the study.
- Fill in the data collection sheets for each patient.

For the correct completion of the sheets, the following should be taken into account:

- The sheets on which it is indicated, must be dated and signed by the authorized principal investigator.
- All the boxes must be filled in. If you do not have the requested data, you should write ND (not available).
- Unusual or extreme results, or those that do not agree with the expected sequence, should be checked. They will be corrected by initialing, signing and explaining.
- Laboratory results that exceed the normal ranges established by the center's laboratory should be checked by the investigator and their meaning should be noted next to the data, initialed and signed.
- He/she will try to write the open questions in legible handwriting, otherwise it will be considered as missing information.
- The investigator will perform a final check or review of each and every CRD.
- The data should be collected with a black ballpoint pen.