# Clinical Investigation Plan:

## A Multi-center, Single Arm Post-market Clinical Study to Confirm Safety and Performance of PuraStat® Absorbable Haemostatic Material for the Management of Bleeding In Vascular Surgery

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|---|---|
| **Protocol no.** | **PuraStat-002-VASC** |
| Final Version | 6.0 |
| Date | 19 March 2019 |
| Protocol reference | PuraStat-002-VASC – Final Version 6.0 dated 19 March 2019 |
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# CLINICAL INVESTIGATION PLAN

***PuraStat-002-VASC – Final Version 6.0 dated 19 March 2019***

**PROTOCOL SIGNATURE PAGE**

**PROTOCOL NUMBER: PURASTAT-002-VASC**

Version: 6.0 Date: 19 March 2019

## A Multi-center, Single Arm Post-market Clinical Study to Confirm Safety and Performance of PuraStat® Absorbable Haemostatic Material for the Management of Bleeding In Vascular Surgery

I have read the Clinical Investigation Plan mentioned above and agree to adhere to its requirements.

I have received a copy of the most current version of the IFU.

I will provide copies of the Protocol and access to all information furnished by 3-D Matrix Europe SAS ("Sponsor") to the study personnel under my supervision and involved in carrying out the study. I will discuss this material with them to ensure that they are fully informed about the study device and the conduct of the study.

I have read the Confidentiality Statement of this Protocol. The contents of this Protocol may not be used in any other clinical study and may not be disclosed to any other person or entity without the prior written permission of the Sponsor. The foregoing shall not apply to disclosure required by law or regulation, for example submission to an Ethics Committee; however, I will give prompt notice to the Sponsor of any such disclosure.

Site Number/Name _____

**Printed Principal Investigator Name**_____

Signature: _____Date:_____

**Printed Sponsor Representative Name**: Caroline Leblanc

Signature_____Date_____

# CLINICAL INVESTIGATION PLAN

***PuraStat-002-VASC – Final Version 6.0 dated 19 March 2019***

## PROTOCOL SYNOPSIS

| | |
|---|---|
| **Study Title** | A Multi-center, Single Arm Post-market Clinical Study to Confirm Safety and Performance of PuraStat® Absorbable Haemostatic Material for the Management of Bleeding In Vascular Surgery |
| **Medical device** | PuraStat® |
| **Protocol Reference** | PuraStat-002-VASC Final Version 6.0 dated 19 March 2019 |
| **Objective** | The aim of this clinical study is to confirm the safety and the performance of PuraStat® in the management of bleeding in vascular surgery. |
| **Study design** | Prospective, multi-center, single arm post-marketing study to confirm safety and performance data on PuraStat® for the management of bleeding in vascular surgery |
| **Regulatory Status** | PuraStat® is CE-marked for the management of bleeding in vascular surgery |
| **Planned number of patients and indication** | A total number of 65 patients undergoing elective carotid endarterectomy will be treated with PuraStat®. |
| **Planned number of sites** | Up to 10 sites are expected to be involved in this study. Each site is expected to include no more than 25 patients. |
| **Study timelines** | **Actual start date:** May 2017<br>**Estimated end date:** September 2019 |
| **Study duration** | The study duration at each site is expected to last a maximum of 27 months. The study enrolment phase is expected to last 25 months and subjects treated with PuraStat® will be followed for 1 month (± 15 days) after the operation. |
| **Clinical study follow-up** | Patients will be assessed prior to procedure, 24 hours post-procedure, at discharge and 1 month (± 15 days) after the procedure. |
| **Study Population** | Patients scheduled for elective carotid endarterectomy |
| **Inclusion criteria** | Candidates for the study must meet ALL the following inclusion criteria:<br>1. Male or female patient ≥18 years old<br>2.Subject undergoing elective carotid endarterectomy either with direct closure (without the use of patch) or, patch reconstruction or eversion technique<br>3. Subject who is able to give voluntary, written informed consent to participate in this clinical study and from whom consent has been obtained<br>4. Subject, who, in the opinion of the Clinical Investigator, is able to understand this clinical study, cooperate with the study procedures and is willing to return for the required post-treatment follow-up. |
| **Exclusion criteria** | Candidates for this study will be excluded if ANY of the following conditions are present:<br>1. Presence or sequelae of coagulation disorder<br>2. Known allergy or hypersensitivity to any component of PuraStat®<br>3. Concurrent participation in another clinical trial with a medical device or a medicinal product<br>4. Pregnant or interested in becoming pregnant during the duration of the |

| | |
|---|---|
| | study, or breast feeding |
| **Intra-Operative Criteria** | Intra-Operative Inclusion Criteria:<br>1. Subject requiring the use of PuraStat® for haemostasis during elective carotid endarterectomy either by direct closure (without the use of patch), or by patch reconstruction or eversion technique when haemostasis by ligation or standard means is insufficient or impractical.<br>Intra-Operative Exclusion Criteria:<br>1. Spurting and/or gushing haemorrhage site(s)<br>2. Contaminated or potentially contaminated surgical area<br>3. Fibrin glue and/or topical haemostatic agent used before or concomitantly to the use of PuraStat®<br>4. Persistent major bleeding after conventional haemostasis |
| **Primary endpoint** | Total time-to-haemostasis (min; seconds) |
| **Secondary endpoints** | Performance endpoints will be evaluated by:<br>- Blood Loss (mL)<br>- Drainage volume (mL) (if any)<br>- Rate of transfusion of blood products (if any)<br>- Ease of use of PuraStat®<br>Safety endpoints will be evaluated by:<br>- Rate of revision for bleeding<br>- Adverse events and post-operative complications (AEs, SAEs, Device-related AEs, Unanticipated AEs)<br>- Length of hospital stay |
| **Statistical analysis** | Descriptive statistical analysis for all the parameters recorded during the study (percentage, mean, median and 95% bilateral confidence interval).<br>Safety analysis will be done for all subjects (all patients having signed an Informed Consent Form). If subjects excluded from the Safety population experimented adverse events, a specific summary will be provided (tables and/or listings). In addition, safety will be done on the ITT population. Performance analysis will be done on the ITT population. |
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**Schedule of Assessments / Flow Chart:**

| Parameter/Examination \ Visit | Prior to operation | Surgery | 24 hours post-procedure | Discharge | Post-operative one month follow-up visit (+/- 15 days) (physical or phone call visit) |
|---|---|---|---|---|---|
| Signed Patient informed consent | x | | | | |
| Demography, Medical history | x | | | | |
| Physical exam | x | | | | |
| Blood tests including CBC, Coagulation tests | x | | x | When necessary | When necessary |
| β-hCG test | x | | | | |
| Patient inclusion/exclusion criteria | x | | | | |
| Intra-operative criteria | | x | | | |
| Time-to-hemostasis* | | x | | | |
| Blood loss (mL) | | x | | | |
| Drainage volume (mL) | | | x | x | |
| Transfusion of blood products (if any) i.e blood loss by recording the blood product(s) and/or substitute(s) administered (mL) | | x | x | x | |
| Information regarding the use of PuraStat® including ease of use of PuraStat® | | x | | | |
| Other operative data | | x | | | |
| Surgical revision for bleeding | | x | x | x | x |
| Adverse Event, adverse device effect reaction | | x | x | x | x |
| Concomitant medication related to coagulation disorder(s) | x | x | x | x | x |
| Length of hospital stay | | | | | x |

* Time-to-haemostasis (min, seconds) will be measured from the first application of PuraStat® to a bleeding site after clamp release, until all bleeding at that site has ceased. In case of rebleeding of the treated sites and additional application of PuraStat®, the total time-to-haemostasis (TTH) will be calculated by the addition of TTH1+ $TTH_{(n+1)}$, where TTH1+ $TTH_{(n+1)}$ are the time to haemostasis after each application of PuraStat®.

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## List of Abbreviations

| Term | Definition |
|---|---|
| AE | Adverse Event |
| ADE | Adverse Device Effect |
| ASA | American Society of Anesthesiologists |
| BH | Bio-active Haemostatic |
| BMI | Body Mass Index |
| CA | Competent Authority |
| CABG | Coronary Artery Bypass Grafting |
| CBC | Complete Blood Count |
| CRO | Clinical Research Organization |
| DD | Device Deficiency |
| eCRF | Electronic Case Report Form |
| EDC | Electronic Data Capture |
| GI | Gastroinstestinal |
| HAS | Haute Autorité de Santé (French National Authority for Health) |
| hCG | Human Chorionic Gonadotropin |
| IFU | Instructions For Use |
| ITT | Intent-To-Treat |
| LVAD | Left Ventricular Assist Device |
| Min | Minute |
| mL | Millilitre |
| NBH | Non-Bioactive Haemostats |
| NCA | National Competent Authority |
| NSQIP | National Surgical Quality Improvement Program |
| PIC | Patient Informed consent |
| PI | Principal Investigator |
| PMCF | Post-Market Clinical Follow-up |
| PTFE | Polytetrafluoroethylene |
| PTT | Partial Thromboplastin Time |
| s | Second |
| SAE | Serious Adverse Event |
| SADE | Serious Adverse Device Effect |
| SOP | Standard Operating Procedure |
| TTH | Total Time-to-Hemostasis |
| USADE | Unanticipated Serious Adverse Device Effect |

# 1. INTRODUCTION – STUDY RATIONALE

Anastomotic bleeding can be unpredictable, persistent, and occasionally limb and life threatening [1]. This is of particular importance for patients in compromised situations, such as those taking anticoagulants, those with friable vessel, for example, high-risk patients with extensive atherosclerosis or calcified or friable tissue, such as those with diabetes, hypertension, chronic kidney failure, or connective tissue syndromes [2]. Consequently, a plethora of sealants and haemostatic agents have been developed to assist the surgeon in minimizing or controlling anastomotic bleeding, and use of these agents is becoming more widespread in surgical operations [3-5].

Despite the abundance and variety of these agents, an easy-to-use vascular sealant with good risk-benefit, and cost-benefit ratios is still not widely available. Such an agent should be easily applied in a controlled fashion, highly predictable in creating haemostasis, nontoxic, and must not have an adverse effect on anastomotic patency. Additional attributes such as increased anastomotic strength would also be beneficial [6]. Haemostasis in peripheral vascular surgery is made more difficult by the need for direct arterial and arterial graft suturing as well as by systemic anticoagulation to prevent thrombosis during periods of vascular occlusion. Suture line bleeding in arterial surgery is primarily controlled with precise suture technique, including use of fine suture material and needles. To assist with control of residual bleeding after suturing of arterial operative sites, various topical haemostatic aids are in use [7-9].

A *Haute Autorité de Santé* (HAS) (the French National Authority for Health) report “Haemostatic agents and surgery” has been published in 2011. Its conclusions were that “there is evidence only of a mediocre clinical improvement, compared to conventional methods such as cautery and suturing, and that there is a need for large well conducted trials” [10]. Two different haemostatic products have been used: i) bio-active haemostatic (BH) products, which include either fibrin, or some other products of the clotting process, which aim is to speed up the natural clotting process by increasing the concentration of relevant metabolites in the area of bleeding; ii) non-bioactive haemostats (NBH) which work by supplying an artificial matrix bonded to the bleeding surface. This replaces the natural fibrin clot, but allows the healing and resorption processes to go ahead.

3-D Matrix PuraStat® absorbable haemostatic material is a medical device, which falls in the NBH product category, intended to be used intraoperatively in situations where haemostasis is hard to achieve by classical surgical methods such as suturing. It is an absorbable local haemostatic agent consisting of self-assembling polypeptide nano-fibres that form a hydrogel in contact with blood. Haemostasis using PuraStat® results from the physical properties of the gel, which has no bio-active haemostatic components (NBH). Contact between the product and liquid such as blood causes the acidic aqueous peptide solution to be neutralized. In an ionic solution, the peptide molecule, which has a β structure, quickly forms fibres in the aqueous solution, yielding a peptide hydrogel. The hydrogel quickly coats the point of bleeding and, by physically closing the superficial part of the broken blood vessel, causes blood coagulation in the deeper part of the vascular wall, resulting in haemostasis. Any product remaining in the body after haemostasis has been achieved, and the surgical procedure is complete, will be absorbed over time, although some residue may remain for longer than 30 days.

A review on the findings of the HAS report, clinical studies on the safety and performance of surgical haemostatic products were performed in October 2015 [11]. This review concluded that NBH haemostats are clearly effective in achieving rapid haemostasis in a wide range of surgical contexts. Surgeons find them a valuable aid, especially for endoscopic or laparoscopic procedures. Patients report reduced post-operative pain. However the meta-analysis conducted by HAS shows little convincing impact on more quantitative measures such as the need for transfusion or re-operation, and length of hospital stay. Better-designed clinical studies are necessary to demonstrate the effectiveness of haemostatic products.

The below table (Table 1) summarizes the data on Time to haemostasis for Non-Bioactive Haemostats (NBH) products:

Table 1 : Summary of data on Time to haemostasis for Non-Bioactive Haemostats products

| Surgery type | Product | N | Average time to haemostasis (seconds) | Citation |
|---|---|---|---|---|
| Cardiac | CoSeal™ | 74 | 16.5 | 10 |
| Brain tumour resection | Arista™ AH | 33 | 57 | 12 |
| Various | Gelfoam® | 238 | 176 | 13 |
| Liver resection | Sangustop® | 62 | 132 | 14 |
| Hepatic surgery | Veriset™ | 32 | 60 | 15 |
| CABG | Surgicel® | 24 | 432 | 16 |
| | Lyostypt® | 32 | 186 | |
| Weighted mean NBH | | | **144** | |

The below table (Table 2) summarizes the Adverse Events (AE) data for Non-Bioactive Haemostats (NBH) products:

Table 2 : Summary of Adverse Events data for Non-Bioactive Haemostats products

| Surgery type | Product | N | All-cause deaths | Serious adverse events | Device-related adverse events | Citation |
|---|---|---|---|---|---|---|
| CABG | Surgicel® | 72 | 3% | 3% | 0% | 16 |
| Various | Surgicel® | 30 | 3.3% | 50% | 6.7% | 17 |
| Various | Gelfoam® | 238 | 0.8% | 12% | 1.7% | 13 |
| Liver resection | Sangustop® | 62 | 1.6% | 26% | 0% | 14 |
| Hepatic surgery | Veriset™ | 32 | 0% | 31% | 6.3% | 15 |

It is evident that little clinical evidence relevant to haemostasis in vascular surgery has been published since the publication of the HAS report.

### 1.1. Literature clinical data

A total of 6 randomized, controlled studies focusing exclusively on vascular surgery were selected (not counting aortic surgery) in the HAS report to evaluate the usefulness of surgical haemostatic agents in vascular reconstruction and arteriovenous surgery with the implantation of a prosthesis made of PTFE [6, 7, 18-21] [10]. Two of them were specifically dedicated to carotid endarterectomy with patch reconstruction [20,21]. Among synthetic materials used for patch angioplasty, Polytetrafluoroethylene (PTFE) and Dacron patches are commonly used after endarterectomy [22,23]. Patching with autologous venous tissue is also a commonly used option for arterial patching during endarterectomy.

Beside patch reconstruction after carotid endarterectomy (often considered as the "conventional technique"), eversion technique is also performed in surgical centers [24]. The 2012 carotid endarterectomy-targeted American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database has recently been analyzed (n=3845 patients) [25]. Patient, disease, and surgical characteristics of patients undergoing carotid endarterectomy were assessed in univariate and multivariate analyses. In univariate analysis the principal endpoint (30-day combined postoperative stroke or death rate) rate in asymptomatic patients was 2.2% in patients treated by patch reconstruction and 1.9% in patients treated by the eversion technique, and in symptomatic patients 4.7% and 2.2% respectively. In the multivariate logistic regression analysis there was no statistical relationship in the results according to the type of surgical procedure (i.e. patch reconstruction or eversion carotid endarterectomy) [25].

The following endpoints were used in these trials, as either primary or secondary endpoints [6, 7, 18-21]:

- Time-to-hemostasis, endpoint in five studies out of the six [6, 7, 18, 20, 21] (with extreme varying between 25 s and 22 min).
- Successful hemostasis within 1, 4, 5, or 10 min was assessed in four studies [6, 7, 18, 19].
- Blood losses were assessed in five studies [7, 18-21].

In some studies, sites of the anastomoses were accounted for confounding variables. For example, in femoral bridges in which more than one anastomotic site was treated, the site that took the longest to obtain hemostasis was the one evaluated for the time-to hemostasis endpoint [6].

### 1.2. Available Clinical Testing of PuraStat®

The aim of this study is to confirm safety and performance of the CE-marked PuraStat® in the management of bleeding in vascular surgery. This has already been tested in two previous studies. The first was a cohort study conducted in Japan [26], and the second was a post-market study conducted in Germany.

In the Japanese cohort study, efficacy and safety endpoints were collected. The primary efficacy endpoint was a qualitative (non-quantitative) measure of haemostasis, which was visually evaluated and ranked in 4 categories:

- Very effective: Complete haemostasis seen at the target site.
- Effective: Complete haemostasis was temporarily seen at the target site, but during the course of the surgery a secondary haemorrhage, which required treatment, occurred at the application site, and complete haemostasis was seen after re-application of Purastat®.
- Somewhat effective: Complete haemostasis was temporarily seen at the target site, but during the course of the surgery a secondary haemorrhage, which required treatment, occurred at the application site, and complete haemostasis was seen after treatment other than PuraStat® application.
- Ineffective: Bleeding from the target site was reduced, but haemostasis could not be achieved.

Successful haemostasis, in this Japanese cohort study, was defined by a score of "Effective" or "Very effective". For the angiostomy cohort, there were 82 application sites, with a successful haemostasis rate of 91.5%.

In comparison to the qualitative measure of the Japanese cohort study, the HAS report defines success of hemostasis in quantitative measures: time (time-to-haemostasis); blood loss; need for blood transfusion; adverse events and complications; duration of operation or hospital stays.

In the post-market study conducted in Germany, the objective was to confirm safety and performance of PuraStat® for the management of bleeding after left ventricular assist device (LVAD) implantation. The primary efficacy endpoint for this study was more in line with definitions in the HAS report. For each surgical site treated with PuraStat®, total time-to-haemostasis was measured. Fifteen patients with 29 anastomotic bleeding sites were analysed. Data for 26 bleeding sites were available, which reported a mean time-to-haemostasis of 0.32 minutes. There were 0% reported device-related serious adverse events (SAEs), device-related adverse events (AEs), or unanticipated device-related SAEs in this post-market study.

Collective data from the Japanese cohort study, and the post-market German study, yields performance results in a total of 108 vascular (angiostomy and anastomotic) application sites.

### 1.3. Justification of the PMCF study in vascular surgery (Elective Carotid Endarterectomy):

Based on the available clinical data and on the current PMCF plan of PuraStat®, a multicentre, single arm post-market clinical study is designed in order to assess the safety and the performance of PuraStat® for the management of bleeding in vascular surgery (Carotid Endarterectomy either by direct closure (without the use of patch), or by patch reconstruction or eversion technique).

The duration of the follow-up is defined according to the current institution's practices: at 24 hours post-procedure, at discharge and at 1-month postoperatively (± 15 days).

In the present study, the choice of the primary endpoint, TTH, is consistent with studies presented in the HAS Report, and with the post-market German study, which evaluated PuraStat® in 15 subjects during LVAD implantation.

In addition, the following secondary criteria (blood loss, rate of transfusion of blood products, rate of revision for bleeding as well as adverse events and post-operative complications (AEs, SAEs, Device-related AEs, Unanticipated AEs) and length of hospital stay will be assessed, which is also consistent with endpoints included in the above mentioned studies.

Other performance endpoints (Drainage volume and ease of use of PuraStat®) will be also evaluated.

## 2. STUDY DEVICE

### 2.1. Description of the medical device:

PuraStat® is a Class III medical device and is CE-marked since January 2014. PuraStat® is a synthetic haemostatic material in the form of a prefilled syringe, filled with a clear, 2.5% concentration aqueous peptide solution, sterilized by aseptic filtration. The outer surface of the syringe and inner surface of the blister pack are sterilized by ethylene oxide (see current version of the IFU).

PuraStat® is presented as a sterile prefilled syringe with supplied optional nozzle for direct application to the site of bleeding (see Figures 1 and 2). Three fill volume variants exist: 1 mL, 3 mL, and 5 mL.

*Figure 1:* Unlabeled syringe and nozzle

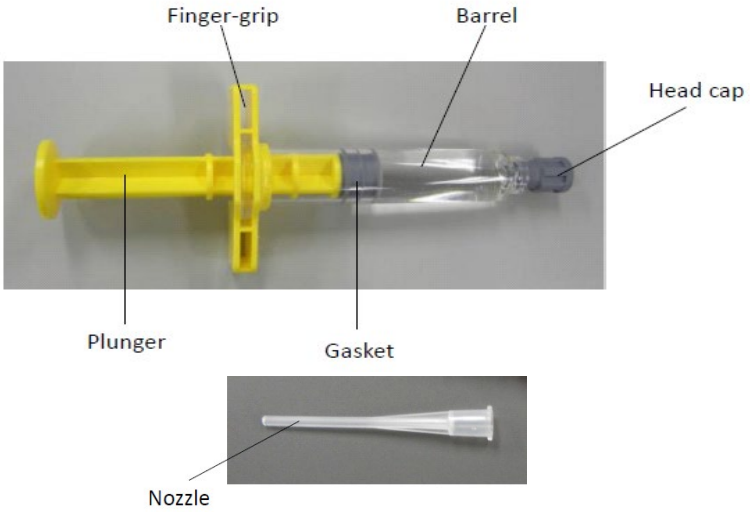


*Figure 2:* 3 mL prefilled PuraStat® syringe


Contact between the product and liquid with a physiological pH, such as blood causes the acidic aqueous peptide solution to be neutralized and, as a result, the peptide molecule, which has a β structure, quickly forms fibres in the aqueous solution, yielding a peptide hydrogel. The hydrogel quickly coats the point of bleeding and, by physically closing the superficial part of the broken blood vessel, causes blood coagulation in the deeper part of the vascular wall, resulting in haemostasis. Any product remaining in the body after haemostasis has been achieved, and the surgical procedure is complete, will be absorbed over time although some residue may remain for longer than 30 days.

### 2.2. Indications for use:

(See current version of the IFU)

PuraStat® is indicated for haemostasis in the following situations encountered during surgery, when haemostasis by ligation or standard means is insufficient or impractical:

- Bleeding from small blood vessels and oozing from capillaries of the parenchyma of solid organs
- Oozing from vascular anastomoses
- Bleeding from small blood vessels and oozing from capillaries of the GI tract following surgical procedures

Circumstances and examples of these situations include the following (Table 3):

Table 3 : Circumstances and examples of situations where PuraStat® could be applied

| Indication | Relevant clinical circumstances | Examples |
|---|---|---|
| Bleeding from small blood vessels and oozing from capillaries of the parenchyma of solid organs | Bleeding point is from blood vessels or parenchyma of a solid organ resection surface.<br><br>Any partial resection of such organs or removal of any organ attached to them. | Partial hepatectomy, Splenectomy; nephrectomy or pancreatectomy, Prostatectomy, Myomectomy |
| Oozing from vascular anastomoses | Any vascular anastomosis, vessel to vessel or graft to vessel, or arteriotomy closure.<br>Blood with low clotting function (e.g. due to anticoagulation) | Anastomosis to native or artificial vessel; surgery of the aorta or any peripheral arteries; coronary bypass; femoral bypass |
| Bleeding from small blood vessels and oozing from capillaries of the GI tract following surgical procedures | Bleeding point is the mucosal resection site.<br>Laparoscopic or endoscopic procedure (transcatheter application).<br>Low pressure bleeding and oozing following endoscopic surgical procedures such as non-variceal or non-arterial bleeding and oozing. | Endoscopic mucosal resection (EMR) of GI tract; Endoscopic submucosal dissection (ESD) of GI tract; Laparoscopic resection of GI tract organs |

PuraStat is also indicated for the reduction of delayed bleeding following gastrointestinal endoscopic submucosal dissection (ESD) procedures in the colon.

Each syringe bears a lot number which allows traceability of the product to be achieved.
PuraStat® is a class III CE-marked medical device. PuraStat® is to be used by medical personnel in hospital setting only.

Note: For the needs of the study, “standard means” are methods such as: suture, compression.

### 2.3. Application of PuraStat®

PuraStat® must be applied according to the current IFU.

### 2.4. Storage

PuraStat® is stored according to the current IFU:

- PuraStat® should be stored in a refrigerator (from 2°C to 8°C).
- Keep dry.

## 3. STUDY OBJECTIVES

The objective of this post-market clinical follow-up study is to collect medical information on patients implanted with PuraStat®, according to each participating institution’s procedures and standards of care. Analyses of the observational data collected will include an analysis of safety and effectiveness.

# 4. STUDY DESIGN AND PATIENT POPULATION

This is a prospective, multi-center single arm post-market clinical study, to confirm safety and performance data on PuraStat® for the management of bleeding in vascular surgery.

Up to 10 clinical sites are expected to be involved in this post-market clinical study.

During 25 months, sixty-five (65) patients undergoing elective carotid endarterectomy either by direct closure (without the use of patch), or by patch reconstruction or eversion technique will be enrolled. Each site is expected to include no more than 25 patients.

PuraStat® will be used in accordance with its current IFU.

Participating investigators will be asked to provide their observations collected during routine care for patients treated with PuraStat®. Informed consent of the patients for the use of their clinical records for study purposes will be obtained before their data will be collected in the post-market clinical study.

Patients will be evaluated according to the routine care and after their consent has been obtained.

The expected duration in each site is a maximum of 27 months.

# 5. STUDY ENDPOINTS

## 5.1. Primary Endpoint

Primary endpoint will be the Total Time-to-Haemostasis (min, seconds), measured from the first application of PuraStat® to a bleeding site after clamp release, until all bleeding at that site has ceased.

N.B: The area of bleeding to be studied will be identified after the vessel clamps are removed.
Counting the time-to-haemostasis begins when the surgeon starts applying PuraStat® on the area of bleeding. Several application of PuraStat® might be needed to obtain the initial haemostasis.
Haemostasis will be considered successful when there is no visible bleeding on the treated area.

In case of rebleeding of the treated sites and additional application of PuraStat®, the total time-to-haemostasis (TTH) will be calculated by the addition of TTH1+ $TTH_{(n+1)}$, where TTH1+ $TTH_{(n+1)}$ are the time to haemostasis after each application of PuraStat®.

The total Time of haemostasis will be measured thanks to a stopwatch.

## 5.2. Secondary Endpoints

Performance endpoints will be evaluated by:
- Blood Loss (mL)
- Drainage volume (mL) (if any)
- Rate of transfusion of blood products (if any)
- Ease of use of PuraStat®

Safety endpoints will be evaluated by:
- Rate of revision for bleeding
- Adverse events and post-operative complications (AEs, SAEs, Device-related AEs, Unanticipated AEs)
- Length of hospital stay.

# 6. INCLUSION AND EXCLUSION CRITERIA

## 6.1. Inclusion Criteria

Candidates for the study must meet ALL the following inclusion criteria:

1. Male or female patient ≥18 years old
2. Subject undergoing elective carotid endarterectomy either by direct closure (without the use of patch),or by patch reconstruction or eversion technique
3. Subject who is able to give voluntary, written informed consent to participate in this clinical study and from whom consent has been obtained
4. Subject, who, in the opinion of the Clinical Investigator, is able to understand this clinical study, cooperate with the study procedures and is willing to return for the required post-treatment follow-up.

## 6.2. Exclusion Criteria

Candidates for this study will be excluded if ANY of the following conditions are present:

1. Presence or sequelae of coagulation disorder
2. Known allergy or hypersensitivity to any component of PuraStat®
3. Concurrent participation in another clinical trial with a medical device or a medicinal product
4. Pregnant or interested in becoming pregnant during the duration of the study, or breast feeding

## 6.3. Intra-operative criteria

Intra-Operative Inclusion Criteria:

Candidates for the study must meet ALL the following inclusion criteria:

1. Subject requiring the use of PuraStat® for haemostasis during elective carotid endarterectomy either by direct closure (without the use of patch), or by patch reconstruction or eversion technique when haemostasis by ligation or standard means is insufficient or impractical.

Intra-Operative exclusion criteria:

Candidates for this study will be excluded if ANY of the following conditions are present:

1. Spurting and/or gushing haemorrhage site(s)
2. Contaminated or potentially contaminated surgical
3. Fibrin glue and/or topical haemostatic agent used before or concomitantly to the use of PuraStat®

4. Persistent major bleeding after conventional haemostasis

### 6.4. Enrolment

During 25 months, 65 patients will be consecutively enrolled according to the eligibility criteria.

A unique patient identification number will be assigned to any patient at inclusion. This number serves as the patient's identifier in the study as well as in the study database. The patient number will consist of the centre number followed by a consecutive number for each patient at that centre starting from 01 onwards.

The Sponsor will not impose requirements that limit health care professionals from exercising their best medical judgment for treatment. Therefore, patient selection, diagnostic imaging and treatment interventions will be determined by physicians based on clinical practice standards.

### 6.5. Withdrawal and discontinuation

Each patient shall remain in the study until completion of the required follow-up period; however, a patient's participation in any clinical study is voluntary and the patient has the right to withdraw at any time without penalty or loss of benefit.

#### 6.5.1. During procedure

In the event that PuraStat® is not used to treat the patient during the procedure, the patient will be considered a drop out. A study termination form will be completed. Any patient who exits the study for this reason will be replaced until the required treated study population is attained.

Other conceivable reasons for discontinuation may include but not limited to:

- Voluntary withdrawal
- Clinically indicated withdrawal by the physician
- Lost to follow-up (= if the patient misses two consecutive scheduled follow up time-points, and attempts at contacting the patient are unsuccessful, then the patient is considered lost to follow-up)

#### 6.5.2. After device use

Due to the limited study duration, no patient withdrawal is anticipated in the study.
Nevertheless, subjects have the right to withdraw from the clinical study at any time and for any reason without prejudice to their future medical care by the study team or study site.
In case of withdrawal,

1) Investigator will ask reason(s) to the patient(s) for their withdrawal and will record all information regarding the patient discontinuation in the eCRF.
2) Up to the date of withdrawal, data will be completed in the eCRF. No additional data will be needed and will be recorded from patients once withdrawn from the study.

Patients will not be replaced.

# 7. STUDY PROCEDURES

## 7.1. Surgical procedures

Elective carotid endarterectomy is performed either by direct closure (without the use of patch), or by patch reconstruction or eversion technique in accordance with the standard of care of the institution.

## 7.2. Device procedure/ Procedure handling

The device procedure / procedure handling is described below:

After the vascular clamps are removed:

1. Remove as much blood as possible from haemorrhagic site (from the suture lines and anastomosis) by for example applying adequate pressure.

2. If oozing bleeding occurs at suture lines or anastomosis, PuraStat® will be applied via the syringe to the bleeding area (no clamps) according to its current instructions for use :

    a. Apply an adequate quantity of PuraStat® to the haemorrhagic site.

    For best results:

- The nozzle should be as close as possible to the bleeding point.

- Do not disturb the self-assembled PuraStat gel until sufficient time has been allowed for haemostasis to occur.

    b. If necessary, repeat the application of PuraStat® several times until haemostasis is achieved.

    c. After haemostasis is confirmed, excess PuraStat® may be left in place.

3. After use: If the optional dedicated nozzle has been used with the syringe, ensure that it remains connected on completion of the procedure. Dispose of the syringe, nozzle and any unused PuraStat® by placing into an appropriate container as clinical waste.

4. Time to haemostasis will be measured with a stopwatch. One person will be assigned to start the stopwatch and to stop it, upon investigator's decision. Once the investigator starts applying PuraStat® on the bleeding point, the stopwatch will start. The stopwatch will stop once hemostasis is achieved, i.e. when there is no bleeding coming from the suture lines or anastomosis.

    Note 1: Complete haemostasis with PuraStat® could be observed relatively quickly (less than 1 minute). Several applications of PuraStat® might be needed to obtain the initial haemostasis. The investigator will inform the person in charge of the stopwatch once haemostasis is observed.

    Note 2: In case of rebleeding of the treated sites and additional application of PuraStat®, the total time-to-haemostasis (TTH) will be calculated by the addition of $TTH1+TTH_{(n+1)}$, where $TTH1+TTH_{(n+1)}$ are the time to haemostasis after each application of PuraStat®.

5. If a treated site does not achieve hemostasis within 5 minutes, the investigator may use other available methods to achieve hemostasis according to usual clinical practice and this is going to be considered as a failure of PuraStat® in the respective surgical site.

## 7.3. Study visit assessments

### 7.3.1. Informed consent form

Patient Informed consent form (PIC) must be provided to each site. Each site and/or sponsor shall submit the informed consent document to the Ethics Committee for approval when applicable.

The physician will exercise his normal duties to inform the patient about the treatment (carotid endarterectomy) that he/she is going to receive. The treatment-related information must be given independently of information about the study. During the preoperative visit, the investigator informs the patient and answers all his questions concerning the objective, the nature of the constraints, the predictable risks and benefits expected from the clinical study. The investigator also specifies the rights of the patient during the clinical study.

After this information session, the patient is provided time to think and then make a decision about participating in the protocol. The investigator is responsible for obtaining of written consent by the patient.

The informed consent form must be signed by the subject before the procedure. A copy of the informed consent form or addendum to an existing informed consent form must be provided to the subject. No major deviations should be made from the informed consent form.

### 7.3.2. Prior to operation

Prior to enrolment and treatment of a given study subject, a medical history will be obtained and a clinical evaluation will be performed in accordance with the standards of care at the involved sites. The purpose of these pre-procedural assessments will be to identify possible contraindications and to assess the patient's overall state of health with regard to undergoing carotid endarterectomy.

The following examinations and tests will be completed prior to the surgery (it is recommended to have the baseline results within 1 or 2 days before the procedure). The preoperative visit is performed by the investigator or a designee.

The following data will be collected:

- Date of the preoperative visit
- Blood tests:
    - Complete Blood Count (CBC)
    - The following coagulation tests will be performed as per hospital standard of care : Quick prothrombin time (PT) test, Fibrinogen or Partial Thromboplastin time (PTT)
    - β-hCG test
- Demography (including age, gender, height, weight and BMI),
- Medical history (including at least smoking and diabetes status, patient histories, ASA score),
- Physical exam
- Concomitant medication related to coagulation disorder(s) is defined as any medication related to coagulation disorder(s) that is taken during the clinical study by the patient.

### 7.3.3. Surgery

The surgery procedure is performed according to the standard of care of the institution by the investigator or a designee. Intra-operative criteria are verified before the application of PuraStat® in accordance with its current IFU.

PuraStat® will be applied to the bleeding site after the vessel clamps are removed; if there is still oozing

bleeding from suture lines or anastomosis lines, a sufficient quantity of PuraStat® will be applied in order to cover the bleeding point (see section 7.2. Device procedure/ procedure handling).

The following data will be collected:

- Date of the surgery
- Start time and end time of the surgery
- Type of technique used: direct closure (without the use of patch), patch reconstruction (including type of patch) or eversion
- Quality of vessel (at suture/anastomosis site)
- Type and time of clamp (if any)
- Type of haemostasis used before PuraStat® (if any)
- Information regarding the use of PuraStat®.
    - For each application of the product:
        - Type of syringe used,
        - Estimated amount of product used (mL),
        - Haemostasis,
        - Time-to-Haemostasis (TTH) (min, seconds)
        - Other application(s) necessary at the same site,
    - Number of syringe(s) used, total amount used (mL)
    - Total Time to haemostasis (min, seconds)
- Blood loss (mL)
- Transfusion of blood products (if any) i.e blood loss by recording the blood product(s) and/or substitute(s) administered (mL)
- Any persistent or recurrent bleeding after haemostasis with PuraStat®
- Need of another action to stop the bleeding
- Report information on ease of use of the product
- Report of any need of surgical revision for bleeding, of any adverse events or adverse device effect including intra-operative complications
- Concomitant medication related to coagulation disorder(s)

#### 7.3.4. 24 hours post-procedure visit

The 24 hours post-procedure visit is performed by the investigator or a designee.

The following data will be collected:

- Date of the visit
- Blood tests (CBC, coagulation tests (coagulation tests to be performed as per hospital standard of care))
- Drainage volume (mL) (if any) until drain removal.
- Transfusion of blood products (if any) i.e blood loss by recording the blood product(s) and/or substitute(s) administered (mL)
- Presence of hematoma (if any)
- Report of any need of surgical revision for bleeding, of any adverse events or adverse device effect including post-operative complications
- Concomitant medication related to coagulation disorder(s)

#### 7.3.5. Discharge visit

The discharge visit is performed by the investigator or a designee.

The following data will be collected:

- Date of the visit
- Blood tests (CBC, coagulation tests (coagulation tests to be performed as per hospital standard of care)): at discharge, blood tests will be performed according to the Investigator judgment.
- Drainage volume (mL) (if any) until drain removal.
- Transfusion of blood products (if any) i.e blood loss by recording the blood product(s) and/or substitute(s) administered (mL)
- Presence of hematoma (if any)
- Report of any need of surgical revision for bleeding, of any adverse events or adverse device effect including post-operative complications
- Concomitant medication related to coagulation disorder(s)

#### 7.3.6. 1-month post-operative visit (±15 days)

The 1-month post-operative visit (± 15 days) is performed by the investigator or a designee, either physically or by a phone call.

Note: The completion of the 1-month post-operative follow-up will be done according to the standard of care of the institution.

- Date of the visit
- Length of hospital stays (days)
- Blood tests (CBC, coagulation tests (coagulation tests to be performed as per hospital standard of care)). Blood tests will be performed according to the Investigator judgement.
- Report of any need of surgical revision for bleeding,
- Events related with 1 month post-operative adverse events, adverse device effect reactions including complications due to postoperative bleeding
- Concomitant medication related to coagulation disorder(s)

## 8. RISK-BENEFIT ANALYSIS

Risks associated with PuraStat® include those risks associated with the routine haemostatic products and mentioned in the current IFU:

**The following residual risks have been identified and may result in adverse events when the product is used:**

- irritation/inflammation, or disruption of blood components, due to the low pH of the product
- thromboembolism following migration of thrombus resulting from haemostatic effect
- embolization of gelled product following migration into blood vessels before or after gelation

Other problems and/or adverse events, not yet experienced and/or reported here, may occur.

**The expected benefits of treatment with PuraStat® are:**

- Shorter bleeding time
- Blood transfusion reduction
- Less perioperative and postoperative complications
- Transparency which allows seeing the bleeding site.

# 9. ADVERSE EVENT MANAGEMENT

## 9.1. Definitions as per EN ISO 14155:2011 and MEDDEV 2.7/3 revision 3

**Adverse Event (AE):**
Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to PuraStat®.
NOTE 1: This definition includes events related to PuraStat®.
NOTE 2: This definition includes events related to the procedures involved.
NOTE 3: For users or other persons, this definition is restricted to events related to PuraStat®.

**Adverse Device Effect (ADE):**
Adverse event related to the use of PuraStat®.
NOTE 1- This includes any adverse event resulting from insufficiencies or inadequacies in the instructions for use, the deployment, the implantation, the installation, the operation, or any malfunction of PuraStat®.
NOTE 2- This includes any event that is a result of a use error or intentional abnormal use of PuraStat®.

**Serious Adverse Event (SAE):**

Adverse Event that:
a) Led to death,
b) Led to serious deterioration in the health of the subject, that either resulted in
    1) A life-threatening illness or injury, or
    2) A permanent impairment of a body structure or a body function, or
    3) In-patient or prolonged hospitalization, or
    4) Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
c) Led to foetal distress, foetal death or a congenital abnormality or birth defect.
NOTE 1: Planned hospitalization for pre-existing condition, or a procedure required by the Clinical Investigation Plan, without a serious deterioration in health, is not considered a serious adverse event.

**Serious Adverse Device Effect (SADE):**
Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

**Unanticipated Serious Adverse device Effect (USADE):**
Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report of PuraStat®.
NOTE: Anticipated SADE (ASADE): an effect which by its nature, incidence, severity or outcome has been previously identified in the risk analysis report.

**Device Deficiency (DD):**

Inadequacy of PuraStat® with respect to its identity, quality, durability, reliability, safety or performance. This may include malfunctions, use error, or inadequacy in the information supplied by the manufacturer.

## 9.2. Recording and Reporting of Adverse Events and Device Deficiencies (DD)

### 9.2.1. Recording and Reporting of Adverse Events

AE will be reported in the eCRF. Each reported AE will be assessed by the Investigator for its primary suspected relationship to the device or procedure following the below definitions (MEDDEV 2.7/3) – see section 9.2.2 for "relationship definitions".

### 9.2.2. Recording and Reporting of Serious Adverse Events

The information for the event will include the date of onset and resolution, the action taken, the corrective treatment and how the patient recovered with or without sequelae. In case of death, whether the death is related to the study device and/or the study procedure will be well documented. The date on which patient expired, what attempts were made to treat the event that led to death, the performance and functioning of PuraStat® during the event will be noted.

Each reported SAE will be assessed by the Investigator for its primary suspected relationship to the device or procedure following the below definitions (MEDDEV 2.7/3):

**1) Not related:** relationship to the device or procedures can be excluded when:

- The event is not a known side effect of the product category the device belongs to or of similar devices and procedures;

- The event has no temporal relationship with the use of the investigational device or the procedures;

- The serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;

- The discontinuation of medical device application or the reduction of the level of activation/exposure – when clinically feasible – and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event;

- The event involves a body-site or an organ not expected to be affected by the device or procedure;

- The serious event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);

- The event does not depend on a false result given by the investigational device used for diagnosis, when applicable;

- Harms to the subject are not clearly due to use error;

In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

**2) Unlikely:** the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.

**3) Possible** the relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.

**4) Probable** the relationship with the use of the investigational device seems relevant and/or the event cannot reasonably be explained by another cause, but additional information may be obtained.

**5) Causal relationship**: the serious event is associated with the investigational device or with procedures beyond reasonable doubt when:

- The event is a known side effect of the product category the device belongs to or of similar devices and procedures;
- The event has a temporal relationship with investigational device use/application or procedures;
- The event involves a body-site or organ that
    - the investigational device or procedures are applied to;
    - the investigational device or procedures have an effect on;
- The serious event follows a known response pattern to the medical device (if the response pattern is previously known);
- The discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible);
- Other possible causes (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;
- Harm to the subject is due to error in use;
- The event depends on a false result given by the investigational device used for diagnosis, when applicable;

In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

All SAE irrespective of potential causal relationship to the study will be reported to the Sponsor within 24 hours of the Investigator's first knowledge of the event via the eCRF. Suspected SAE also should be reported.

The Investigator will forward information about the event promptly and complete the SAE report form provided by the Sponsor, even if the information is incomplete or it is obvious that more data will be needed to form any conclusions. Additional information regarding the event will be recorded on the follow-up SAE form forwarded to the Sponsor. The Investigator and/or the Sponsor will be responsible for forwarding initial and follow-up information as per relevant local regulatory requirements to his/her Ethics Committee.

As per relevant local regulatory requirements, the Sponsor will notify SAE information to the appropriate regulatory agencies in a timely manner. The Sponsor will inform all the investigators within a timeframe based on the perceived risk.

#### 9.2.3. Recording and Reporting of PuraStat® Device Deficiencies

All PuraStat® device deficiencies (i.e. malfunctions, use errors, and inadequate labelling) will be documented on the eCRF and reported to sponsor.

Inadequacy of PuraStat® with respect to its identity, quality, durability, reliability, safety or performance will also be reported.

The Investigator and/or the Sponsor will be responsible for forwarding initial and follow-up information as per relevant local regulatory requirements to his/her Ethics Committee. As per relevant local regulatory requirements, the Sponsor will notify device deficiency information to the appropriate regulatory agencies in a timely manner. The Sponsor will inform all the investigators within a timeframe based on the perceived risk.

### 9.3. Follow-Up of Adverse Events

Any AE or ADE will be followed until it has resolved, has a stable level of sequelae or in the Investigator's opinion is no longer clinically significant.

## 10. STATISTICAL CONSIDERATIONS

### 10.1. Sample Size

The aim of this trial is to confirm the safety and the performance of PuraStat® in the management of bleeding in vascular surgery.

No formal statistical hypothesis has been conducted to derive the sample size since studies on peripheral vascular surgery selected in the French National Authority for Health (Haute Autorité de Santé) (HAS) report shows an extreme variability in Time-to-Hemostasis (reported results being between 25 s to 22 min). As a result, the establishment of an objective performance criterion is difficult and matter of discussion.

With a sample size of 65 treated subjects at the time of statistical reporting, an acceptable accuracy will be reached for all criteria, and in particular for the primary endpoint. Indeed, such a sample should ensure that all theoretical assumptions necessary to derive asymptotic 95% confidence intervals will be verified.

### 10.2. Study Population Definition

Safety population is defined as all patients having signed an Informed Consent Form.
ITT population is defined as all patients from the safety population compliant with the inclusion/exclusion criteria of the protocol and treated with PuraStat®.

Safety analysis will be done for all subjects (all patients having signed an Informed Consent Form). If subjects excluded from the Safety population experimented adverse events, a specific summary will be provided (tables and/or listings). In addition, safety will be done on the ITT population. Performance analysis will be done on the ITT population.

### 10.3. Analysis Method

Statistical analyses will be conducted using SAS System®, Version 9.4. No replacement of missing data will be performed.

Continuous variables will be summarized using standard quantitative statistics: mean, standard deviation, median, quartiles and range (minimum and maximum observed values). The number of missing observations, if any, will also be summarized. The 95% 2-sided confidence intervals around the median and/or the mean will be presented for primary and secondary endpoints, when appropriate.

Categorical variables will be summarized using classical frequency statistics: number of non-missing observations and percentages by categories.

For all presence/absence endpoints, the 95% 2-sided exact binomial confidence intervals will be presented.

All safety data will be presented and reported as follows:

- Rate of revision for bleeding
- Total number of AE reported
- Number of SAE reported
- Number of device related AE reported
- Number of device related SAE reported
- Number of unanticipated device related SAE reported
- Number and percentage of Subjects AE with at least one AE reported
- Number and percentage of Subjects AE with at least one SAE reported
- Number and percentage of Subjects AE with at least one device related AE reported
- Number and percentage of Subjects AE with at least one device related SAE reported
- Number and percentage of unanticipated device related SAE reported
- Length of hospital stay

# 11. GENERAL STUDY CONDUCT

## 11.1. Ethical and Regulatory Considerations

The study will be performed in accordance with the standard EN ISO 14155:2011 on clinical investigation with medical devices on human subjects and recommendations guiding physicians in biomedical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964 and later revisions.

The clinical investigational plan, informed consent, any other specific study documents and all amendments to these study documents will be reviewed and approved by the appropriate Ethics Committees and Competent Authority before enrolment if any (depending on the national regulation). Incidents' reporting is under the responsibility of the sponsor. Incidents will be reporting to NCAs as per the European regulations.

## 11.2. Clinical Investigation Plan Changes / Amendments

Neither the Sponsor nor the Investigators can modify this clinical investigational plan without obtaining written concurrence from each other.

As appropriate, the Investigator or the Sponsor, as per local requirement, will submit changes/amendments in the clinical investigational plan to the Ethics Committee for approval and to Competent Authority if any.

### 11.3. Study Early Termination

Both the Sponsor and Investigator reserve the right to terminate the study at any time. If necessary, and after review and consultation with Principal Investigator, Sponsor will make a final determination on whether to terminate the study.

### 11.4. Clinical Investigation Plan Deviations

Any deviations from the clinical investigational plan undertaken to protect the life or physical well-being of a subject in an emergency situation must be reported to MedPass within 48 hours of occurrence and if applicable the respective Ethics Committee as soon as possible, but in no event later than five working days after the emergency occurs.

In addition, the following protocol deviations/site non-compliance will be identified by the monitors:

- Patient not consented prior to enrolment
- Patient Informed consent (PIC) form not fully executed
- Use of non-approved PIC
- Clinical site personnel signing an PIC on behalf of a patient
- Non respect of Inclusion/Exclusion Criteria
- Missing Baseline examination
- Missing data for Endpoint evaluation
- Non-PI or designated Co-Investigator completed surgery/procedure
- Missing or Inadequate source documentation.

The complete list of deviations will be determined at the moment of the statistical analysis.

The Sponsor and the Coordinating Investigator are responsible for analysing the deviations and assessing their significance.

### 11.5. Data collection and Data handling

Data for this study will be collected via an electronic data capture system (EDC). All data will be entered into the eCRF by the sites. Monitors will source verify the entry of the data and all queries resolution will be performed. The investigator must maintain and update the electronic case report form (eCRF) throughout the course of the study. At each follow-up interval, the investigator or designee must complete the relevant section of the eCRF. It is the responsibility of the investigator to maintain all relevant clinical study documentation and to notify the CRO (MedPass) of any issues as soon as possible.

Data queries will be generated via the Electronic Data Capture (EDC) system. The study monitors and the clinical data management may also generate data queries for resolution by the investigator or appropriate qualified study personnel.

### 11.6. Device accountability

Purastat® medical devices are currently commercialized in Europe. Nevertheless, as the products launch is recent, PuraStat® will be provided for free by the Sponsor.

The devices used in this study and the volume applied during procedures will be documented.

### 11.7. Financing and Insurance

For any injuries which can be traced to the study, patients participating in the study are covered by insurance policies, as required by regulation for clinical studies. A product liability insurance policy taken out by 3-D Matrix Europe SAS will cover liability for possible injury to the patient, provided the investigator and his/her staff have followed the instruction of sponsor in accordance with this protocol and any amendments thereto, that the product administered to the patient in this study have been supplied by sponsor and that the investigator and his/her staff have in general performed this study in accordance with scientific practice and currently acceptable techniques and know how.

### 11.8. Publication Policy

Any written or oral communication of the results of the clinical study has to receive the preliminary agreement of the Coordinating Investigator and of the Sponsor.

The publication of the global results mentions the name of the Sponsor (3-D Matrix Europe SAS, France) and all the Investigators having included or followed at least one subject:

- The publication is written by the Coordinating Investigator (first author).

- The main authors are quoted according to the number of subjects enrolled.

This policy does not affect any applicable legal publication obligations of the Sponsor.

## 12. STUDY RESPONSIBILITIES

### 12.1. Sponsor Responsibilities

Sponsor has the overall responsibility for its conduct, including assurance that the study meets the regulatory requirements of the Standard EN ISO 14155:2011 on Clinical Investigations with medical devices on human subjects. Sponsor or its representative will ensure adherence to the EN ISO 14155:2011 standard and Sponsor's general duties, selection of Investigators, monitoring, supplemental applications, maintaining records, and submitting periodic and final reports.

After Site Qualification Visits performed by MedPass International, Sponsor will select qualified Investigators experienced in the field of application and trained in the use of the device with consideration of familiarity with the background and requirements of the clinical study methodology.

Sponsor will provide devices only to participating Investigators, obtain a signed Investigator's Agreement and provide the investigator with the information necessary to conduct the study.

The training of appropriate clinical site personnel will be the responsibility of the Sponsor. To insure uniform data collection and Clinical Investigation Plan compliance, the Sponsor will present a formal educational session to study site personnel which will review the Clinical Investigational Plan, techniques for the identification of eligible patients, instructions on in hospital data collection, methods for soliciting data from alternative sources, schedules for follow-up with the study site coordinators, and regulatory requirements.

Sponsor will maintain copies of correspondence, data, SADEs and other records related to the study, as per national requirements. Sponsor will maintain records related to the signed Investigator Agreements.

The Sponsor will review significant new information, including unanticipated AEs, and ensure that such information is provided to the Investigators, and to the Ethics Committees, and Competent Authorities (CA) as appropriate.

### 12.2. Patient Confidentiality

The confidentiality of patients must be maintained. Enrolled patients will be identified in the eCRFs and other study documents by a sequential patient number. Documents that identify the patient (e.g., the signed informed consent) are not submitted to the Sponsor AND must be maintained in strict confidence by the Investigator. Patient medical information obtained in this study will be confidential. Only authorized personnel will have access to this confidential information.

The Sponsor's representatives, CRO representatives (monitors), Ethics Committees and the local regulatory authorities may review subjects' medical records.

### 12.3. Investigator Responsibilities

Study Investigators will ensure that all work and services they provide will be conducted in compliance with the standards of good clinical and research practice guidelines, EN ISO 14155:2011 and current national regulation(s).

The investigator will ensure that the study is conducted in compliance with the current clinical approved documents (e.g. Clinical Investigation Plan, informed consent form etc.) and the Investigator's Agreement.

The Investigator will be responsible for the day to day conduct of the study as well as for the safety and well-being of the human subjects involved in the clinical study.

The Investigator will have the resources to conduct the clinical study properly and obtain from the sponsor information which he judges essential about the device and be familiar with this information.

The Investigator must ensure that the study has received a written Ethics Committee and/or CA approval(s) (depending on the national requirements) prior to including any patient in the study. The Investigator will be provided by the Sponsor with a sample patient informed consent form (PIC) that may be modified to meet individual Ethics Committee requirements. Any modifications of the PIC must be submitted to the Sponsor or Sponsor representative for approval prior to submission to the Ethics Committee. The Investigator shall ensure that adequate information is given to the subject both in oral and written form, on the nature of the study. This information shall be easily understandable by the subject. This information shall include the aims, expected benefits for him/her and/or others, risks and inconveniences and an explanation of any alternative methods, and of possible consequences of any withdrawal from the study. Subjects shall be allowed sufficient time to decide whether or not they wish to participate. The subjects shall be informed that his/her participation in the clinical study is confidential. Patients shall be made aware that the data relating to the study may be made available to third parties while maintaining anonymity. Patients shall sign the PIC form prior to their inclusion in the study. A copy of the approved PIC along with a copy of each patient's signed consent form will be maintained by each Investigator in a designated clinical study administrative file. A copy of the signed consent form must be given to each patient.

Electronic case report forms (eCRF) to be completed for all enrolled patients into the study will be provided to the Investigator. Completion of eCRF should be accurate and must record of patient's data collected during the study according to EN ISO 14155:2011 recommendations. It is the responsibility of the Investigator to ensure the quality of the data collected and recorded.

The Investigator will maintain study records for an appropriate time, as per national requirements, and the patient's identity shall not be released to third parties without the patient's prior consent. Record retention periods will be provided to all concerned by Sponsor. All information and data concerning patients or their participation in this study will be considered confidential. Only authorized personnel will have access to this confidential information. All data used in the analysis and reporting of this evaluation will be without identifiable reference to individual patients.

### 12.4. Monitor Responsibility

The Sponsor has appointed MedPass International SAS as Clinical Monitor for this study. MedPass personnel are qualified by training and experience to oversee the conduct of the study. MedPass will fulfil the responsibilities identified in its standard operating procedures (SOPs), available for review at MedPass. These responsibilities include collecting and tracking data forms and study compliance.

Under the supervision of the Sponsor, monitors will conduct initiations, site monitoring and close-out visits to ensure that all Investigators are in compliance with the regulatory requirements of the Standard EN ISO 14155:2011 and recommendations guiding physicians in biomedical research involving human subjects adopted by the 18$^{th}$ World Medical Assembly, Helsinki, Finland, 1964 and later revisions, with the Clinical Investigation Plan and with the Investigator's Agreement. Sites will be monitored to ensure completed eCRFs match the investigator's records and to resolve any discrepancies. The monitors and Sponsor will evaluate circumstances where an Investigator deviates from the Clinical Investigation Plan.

The Monitor's responsibilities include: maintaining regular contact with each investigational site, through telephone contact and on-site visits, to ensure that the investigational plan is followed; ensure that complete, timely and accurate data are submitted; ensure that problems with inconsistent and incomplete data are addressed; and that the site facilities continue to be adequate. Any questions regarding these matters should be addressed to MedPass International.

Data will be collected by study Investigators and reported in the eCRF. Data entry will be performed in a manner that ensures accuracy. The entered data will be audited for verification and validation purposes. The eCRFs will be reviewed for errors, omissions, internal consistency, and to ensure that the investigator has signed and dated the appropriate sections.

## 13. BIBLIOGRAPHY/REFERENCES

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