A Multicenter Observational Study to Evaluate Outcomes of EmboCube Gelatin Embolization to Control Bleeding or Hemorrhaging

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INVESTIGATOR'S SIGNATURE PAGE

Study Title:	A Multicenter Observational Study to Evaluate Outcomes of EmboCube Gelatin Embolization to Control Bleeding or Hemorrhage
Protocol Number & Issue:	3.0
Study Center:	_____ (Print name of study center)

I, the undersigned, have read and understand the protocol specified above and agree with its content. I agree to perform and conduct the Study as described in the protocol, and according to Good Clinical Practice, any local and National Regulations and any requirements specified by the reviewing IRB/EC. In addition, when applicable, I agree to enlist sub-investigators who also agree to perform and conduct the Study as described in the protocol. I will provide copies of this Protocol and all pertinent information to the Study personnel under my supervision and my hospital Institutional Review Board/Ethics Committee. I will discuss this material with them and ensure they are fully informed regarding the conduct of the Study according to applicable Good Clinical Practice (GCP), Declaration of Helsinki, and any local or National regulations.

_____

Principal Investigator – Print Name

_____

Signature

_____

DATE

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VERSION HISTORY

Version and date	Summary of Changes
1.0, 25 JAN 2022	Not applicable – first version
2.0, 09 JUN 2022	Study definitions updated to include Device Failure and Device Malfunction. Estimated Study Duration dates and Study PI were updated.
3.0, 27JUN 2022	Addition of one inclusion and one exclusion criteria applicable to sites in France only.

ABBREVIATIONS

ADE:	Adverse Device Effect
AE:	Adverse Event
(e)CRF	Case Report Form/ Electronic Case Report Form
EC:	Ethics Committee
GCP	Good Clinical Practice
IFU:	Instructions for Use
IPA	Independent Physician Adjudicator
IRB:	Institutional Review Board
ITT:	Intent to Treat
mITT:	Modified Intent to Treat
PI	Principal Investigator
SADE:	Serious Adverse Device Effect
SAE:	Serious Adverse Events
UADE:	Unanticipated Adverse Device Event

PROTOCOL SUMMARY

Study Title:	A Multicenter Observational Study to Evaluate Outcomes of EmboCube Gelatin Embolization to Control Bleeding or Hemorrhage
Study Objective:	To collect clinical safety and performance outcome data associated with the use of EmboCube Embolization Gelatin to control bleeding or hemorrhage.
Study Device:	EmboCube Embolization Gelatin
Study Design:	Multicenter observational post-market clinical follow-up study in subjects treated with EmboCube
Device Regulatory Status:	CE mark approved March 2019 (CE 667862).
Sample size:	A minimum of 100 subjects will be included. This sample size is based on a one-sample non-inferiority analysis of Clinical Success based on the parameters listed below and a 15% loss-to-follow-up: • Reference Clinical Success rate (p_0): 92% • Treatment rate (p): 90% • Non-inferiority margin: 10% • α: 0.05 • Power: 80% The reference Clinical Success rate is based on historical clinical literature data for benchmark gelatin embolic devices.
Subject Population:	Subjects who are treated with EmboCube to control bleeding or hemorrhage in accordance with the current approved CE Mark indication for use as stated in the Instructions for Use (IFU).
Clinical Sites:	Up to 7 centers may be included to allow enrollment of required subjects.
Study Follow-Up:	Data will be collected to 28 days post procedure.
Estimated Study Duration:	First patient enrolled: July 2022 Last patient enrolled: July 2023 Last patient, last visit: August 2023
Primary Endpoints:	The primary performance endpoint will be clinical success defined as cessation of bleeding post-embolization and absence of rebleeding at the treated site requiring reintervention (repeat embolization or additional surgery) within 24 hours. The primary safety endpoint will be absence of unanticipated serious adverse device effects within 24 hours.
Secondary Endpoints:	1. Incidence of adverse events (serious and device and/or procedure-related) to 24 hours post-operative. 2. Incidence of adverse events (serious and device- and/or procedure-related) between 24 hours and 28 days post-operative. 3. Technical success defined as successful occlusion of the target area as seen on post-embolization angiography. 4. Incidence of device observations relating to EmboCube.
Inclusion Criteria:	1. Age ≥18 years 2. Subject requires embolization and is suitable for treatment with EmboCube in accordance with device Instructions For Use for the treatment of bleeding or hemorrhage.

	3. Subject provides written informed consent to study data collection. 4. The subject has Social Security (applicable only in France)
Exclusion Criteria:	1. Bleeding site in the neck, head, or brain. 2. Subject has co-morbidity with survival prognosis of less than 30 days, in the opinion of the treating physician. 3. In the investigator's opinion, participation in the study may not be in the subject's best interest. 4. Pregnant woman, person under guardianship or curatorship, persons under judicial protection, and persons who do not write or speak French (applicable in France only). Refer to the EmboCube Embolization Gelatin IFU for a complete list of device contraindications.

1 INTRODUCTION AND BACKGROUND

1.1 Introduction

This is a multicenter, observational study of the use of EmboCube Embolization Gelatin to control hemorrhaging and bleeding. The study is designed to enable the collection, analysis and reporting of data from “real-world” use of EmboCube used in accordance with the Instructions for Use (IFU) associated with the product’s CE Mark approval.

Data collection will include that relating to safety and effectiveness and the period of observation during which data will be collected will extend from the index procedure through 28 days post procedure. Data collection will be according to the standard follow-up practice of the enrolling institution.

1.2 Literature Summary

Gelatin based embolics are among the earliest materials utilized for therapeutic arterial embolization. Due to absorbability, this material is the preferred device when shorter occlusion time is the objective, a permanent implantable is not desired, or distal super selective targeting is not the goal. A principal use of resorbable embolic material is the management of hemorrhage from spontaneous conditions, instrumentation, or trauma. In each of these uses the goal typically is to achieve an immediate plugging of the source of blood loss without causing permanent ischemia. A large number of publications of case studies and cohort evaluations of comparable gelatin embolics demonstrate clinical success rates of 80-100% (depending on condition) in the control of acute bleeding and massive hemorrhage.

The indication of control of hemorrhaging and bleeding and pre-operative embolization covers a wide range of causes (trauma, postpartum, instrumentation, idiopathic, etc.) in a variety of anatomical locations (limbs, uterus/reproductive tract, viscera, etc.), and in populations ranging from healthy to those with multiple comorbidities or polytrauma. Frequently the bleeding occurs in an emergency situation, requiring rapid medical response and treatment. Although comparable resorbable gelatin embolics have been used to stop bleeding and hemorrhaging and for pre-operative embolization for decades, EmboCube is a more recent product.

1.3 Alternative Treatments / Interventions

There are a number of different hemostatic agent classes and respective methods utilized to mitigate bleeding or hemorrhage. The class and agent(s) a physician chooses are influenced by multiple factors, including how rapidly the bleeding can be controlled, location and type of wound, preference of the medical professional treating the patient, etc.

On a more systemic scale, mechanical agents used to control bleeding and hemorrhage include clamps, tourniquets, sutures, etc. However, for control of acute bleeding and hemorrhage (including intravascular use) temporary mechanical hemostatic agents, like EmboCube Embolization Gelatin are frequently selected. These agents work to obstruct the bleeding site and function temporarily as a scaffold to accelerate the formation of a blood clot and return to homeostasis. Gelatin, collagen, and oxidized regenerated cellulose are three materials that constitute the majority of mechanical agents. (Chiara 2018)

1.4 Device Description

EmboCube Embolization Gelatin consists of biocompatible, hydrophilic, and dry pre-cut cubes of resorbable porcine gelatin packaged in a 10-mL syringe with a standard luer lock tip. Where approved, EmboCube Embolization Gelatin is sold in two sizes (2.5 mm and 5.0 mm) and three weight configurations. Each sterile syringe is intended for single patient use only.

A full description of the device can be found in the Instructions for Use (IFU).

1.5 Study Purpose

The study is designed to enable the collection, analysis, reporting and presentation of data from use of EmboCube in accordance with the Instructions for Use associated with the product’s CE Mark approval.

The intent of this study is to increase the understanding of the performance of EmboCube in 'real world' patient population, encompassing a broad spectrum of causes of bleeding, treated areas, and patient profiles, to confirm the product's performance and safety in general clinical practice. The intended use of EmboCube includes high-risk anatomical sites and conditions, and so the data collected will be used to amplify knowledge about known or estimated risks, clinical and technical performance, and to identify and evaluate any potential unanticipated adverse device effects, and to integrate that information into product risk analysis and update the clinical evaluation report and labeling, if appropriate.

2 STUDY DEVICE

2.1 Intended Use

EmboCube Embolization Gelatin will be used in accordance with the current approved CE Mark indication for use as stated in the Instructions for Use (IFU):

EmboCube Embolization Gelatin is indicated for use in embolization of blood vessels to occlude blood flow to control bleeding/hemorrhaging in the peripheral vasculature.

2.2 Device Regulatory Status

CE Mark was approved March 13, 2019, by BSI (CE 667862).

2.3 Device Preparation and Use

EmboCube Embolization Gelatin will be prepared and used as described in the IFU that accompanies each device.

Procedures for patient treatment and follow-up, including medication, will be according to hospital / institutional standard of care and physician medical judgement.

3 STUDY PLAN

3.1 Study Objective

To collect clinical safety and performance outcome data associated with the use of EmboCube Embolization Gelatin to control bleeding or hemorrhage.

3.2 Design

Multicenter, observational, post-market clinical follow-up study in subjects treated with EmboCube.

This study does not involve submitting subjects to any procedures additional to those performed under normal conditions of use of the device.

3.3 Enrollment

A minimum of 100 subjects undergoing embolization with EmboCube for the treatment of bleeding or hemorrhage will be enrolled in the study. The study will be conducted at up to 7 centers globally**.**

3.4 Study Population

Subjects undergoing embolization with EmboCube for the treatment of bleeding or hemorrhage who meet the inclusion and exclusion criteria are intended to participate in this study. The eligibility criteria are kept to a minimum to better represent the subject profile treated in actual clinical practice without selecting sub-groups of particular low/high risk or excluding certain diseases or anatomies.

3.5 Study Duration and Follow-Up

It is anticipated that enrollment will commence in July 2022 and is expected to continue until July 2023. The last subject visit is expected in August 2023.

Subject follow up visits will be in accordance with standard of care. Data will be collected from available

medical records for baseline (medical history), index hospitalization, up to 24 hours post procedure, and until 28 days post-procedure. If there is no routine clinic visit or follow-up between 4- and 6-weeks post procedure (28 days +14 days), subjects will be contacted by telephone during this time to collect safety follow-up to 28 days.

Start of study is defined as the date of initiation (authorization to start enrollment) of the first site.

Completion of the study is defined as the completion of the last follow-up visit/contact for the last subject.

4 ENDPOINTS AND SUBJECT POPULATION

4.1 Primary Outcome Measures

4.1.1 Primary effectiveness endpoint

The primary performance endpoint will be clinical success defined as cessation of bleeding post-embolization and absence of rebleeding at the treated site requiring reintervention (repeat embolization or additional surgery), within 24 hours.

4.1.2 Primary safety endpoint

The primary safety endpoint will be absence of unanticipated serious adverse device effects within 24 hours.

4.2 Secondary Endpoints

1. Incidence of adverse events (serious and device- and/or procedure-related) to 24 hours post-operative.
2. Incidence of adverse events (serious and device- and/or procedure-related) between 24 hours and 28 days post-operative.
3. Technical success defined as successful occlusion of the treated site as seen on post-embolization angiography.
4. Incidence of device observations relating to EmboCube.

4.3 Eligibility Criteria

Subjects are required to meet ALL the following criteria in order to be included in this study:

4.3.1 Inclusion Criteria

1. Age ≥18 years
2. Subject requires embolization and is suitable for treatment with EmboCube in accordance with device Instructions For Use for the treatment of bleeding or hemorrhage.
3. Subject provides written informed consent to study data collection.
4. The subject has Social Security (applicable only in France)

4.3.2 Exclusion Criteria

1. Bleeding site in the neck, head, or brain.
2. Subject has co-morbidity with survival prognosis of less than 30 days, in the opinion of the treating physician
3. In the investigator's opinion, participation in the study may not be in the subject's best interest.
4. Pregnant woman, person under guardianship or curatorship, persons under judicial protection, and persons who do not write or speak French (applicable in France only).

Refer to the EmboCube Embolization Gelatin IFU for a complete list of device contraindications.

5 SCREENING AND ENROLLMENT

5.1 Screening

All consecutive patients who meet the eligibility criteria should be considered for enrollment in the study. Sites should maintain a cumulative log of all screened and enrolled subjects. The Investigator or designee should determine potential eligibility according to Section 4.3. Patients who meet all criteria should be provided with further information on the study in accordance with the procedures in Section 5.2.

5.2 Informed Consent

As bleeding or hemorrhaging requiring embolization occurs in unplanned and/or emergency circumstances, it is anticipated that, in many cases, it will not be possible to obtain written informed consent prior to procedure. This is an observational study and study consent is required for collection and use of patient data, including telephone contact for safety review if required. There are no additional procedures or tests required in addition to routine standard of care. Written informed consent (or non-opposition consent, if applicable), to collect and use data will be collected with the Ethics Committee (EC)/Institutional Review Board (IRB) approved consent form prior to procedure, if feasible. If written consent cannot be collected before the procedure, it should be collected as soon as possible after procedure but no later than time of subject discharge or 7 days post-procedure, whichever occurs first. No data collection can occur until subject has provided written informed consent.

The subject shall be given adequate time to read the Informed Consent form and have the data collection and data transmission procedures explained prior to signing the Informed Consent form. All subjects providing informed consent for data collection are to receive copies of their signed informed consent documentation.

The Sponsor will inform the investigators whenever information becomes available that may be relevant to the subject's confirmed participation in the study. The investigator or designee should inform the subject in a timely manner.

The Sponsor will revise the Informed Consent form whenever new information becomes available that may be relevant to the subject's confirmed participation in the study. The revised information will be sent to the investigator for approval by the EC/IRB. After approval by the EC/IRB, a copy of this information must be provided to the participating subjects, and the informed consent process as described above needs to be repeated.

5.3 Enrollment

All subjects who provide written informed consent for the study, meet all eligibility criteria, and are treated with EmboCube Embolization Gelatin will be considered enrolled in the study.

Subjects who are consented prior to procedure but subsequently do not receive EmboCube Embolization Gelatin will be considered screen failures. These subjects will be entered on the screening log, but no data will be collected on screen failures.

Subjects who are enrolled and treated, but who are later are discovered to not meet all the eligibility criteria will remain in the study for follow-up and a Protocol Deviation form will be completed.

Point of enrollment is the time of informed consent.

5.4 Withdrawal

Subjects may withdraw at any time from the study without prejudice; participation is entirely voluntary. If a subject prematurely terminates from the study, the reason for termination will be recorded in the eCRF.

The Investigator should follow all unresolved serious adverse events until the events are resolved, the subject is lost to follow-up, the subject has withdrawn consent, the subject completes the study follow-up, or the adverse event is otherwise explained.

All reasonable efforts will be made to obtain complete data for all subjects; however, missing observations will occur due to loss to follow-up, withdrawal, or variation in site standard of care assessments.

Sites shall make all reasonable efforts to contact subjects who do not attend for a routine clinic visit between 4 to 6 weeks by telephone to confirm status. In the event subject does not respond to a final contact attempt via certified letter, subject will be documented as lost to follow-up on the Study Exit form. Subjects who withdraw consent after treatment will have their data evaluated until the time of their withdrawal (unless consent for data retention is removed in accordance with local or national regulations). Subjects who withdraw or are lost to follow-up will not be replaced.

6 DATA COLLECTION PROCEDURES

6.1 Visit Schedule

Study participation will last for a total of 28 days (+14 days). Follow-up will be by clinic visit or telephone according to site standard of care. Data will be collected from available medical records for baseline, index hospitalization, and standard of care follow-up until 28 days post-procedure. If there is no routine clinic visit or follow-up between 4 and 6-weeks post procedure (28 days +14 days) subjects will be contacted by telephone during this time to collect safety follow-up to 28 days.

A summary schedule of the data collection for tests and evaluations is in Table 1. Data will only be collected if tests and evaluations are completed per standard of care.

Table 1 Data Collection Schedule

Data	Pre-operative/ baseline	Procedure to 24 hours	28-day follow-up[2] (28 to 42 days)
Informed consent[1]	X		
Demographics	X		
Diagnosis, i.e., cause and location of bleeding or hemorrhage	X	X	
Procedural information		X	
Clinical Success		X	
Technical success		X	
EmboCube use (size, type, and amount)		X	
No/type other adjuvant embolics employed		X	
Device and/or procedure related serious adverse events		X	X
Occurrence of re-intervention to control bleeding at the treated site		X	X
Concomitant antiplatelet and anticoagulant medications	X	X	X

[1] Subject will be asked to provide written informed consent for data collection either preoperatively or prior to hospital discharge.

[2] If subject is not seen by site between 4-6 weeks (28 to 42 days) for clinical visit, subject will be telephoned to collect information on potential device related adverse events and reinterventions.

6.2 Baseline

The following baseline data will be collected:

- Demographic information (age at time of treatment/enrollment, sex, and ethnicity [if permitted by local regulations])
- Relevant medical history
- Diagnosis, i.e., cause and location of bleeding or hemorrhage.
- Height and weight/BMI
- Concomitant anticoagulants and antiplatelet medications

6.3 Procedural Information

All procedures should be conducted in accordance with site standard of care and patient needs, there are no prohibited concomitant treatments. EmboCube Embolization Gelatin shall be used in accordance with the IFU.

Data collected will include the following:

- Procedure type
- Treated vessel and treated area
- Occlusion of the target area as seen on post-embolization angiography
- Time to hemostasis (TTH) post-EmboCube embolization
- EmboCube Embolization Gelatin size, type and number of units used
- Additional embolic agents used in procedure (e.g., coils, glue, microspheres) - number and type and whether used pre- or post EmboCube
- Transfusion/ use of blood products
- Coagulation status (PT, PTT, INR)
- Repeat embolization or additional surgery to address bleeding within 24 hours
    - Rebleeding due to treated vessel
- Serious and device and/or procedure related adverse events
- Device observations – any observations relating to handling and delivery of EmboCube
- Concomitant anticoagulants and antiplatelet medications

6.4 Follow-Up

The following data will be collected by review of all medical records available for the period between index procedure and 28 days. In the event the subject is not seen for routine clinic visit or follow-up between 4- and 6-weeks post procedure (28 days +14 days), subjects will be contacted by telephone during this time to confirm their current status and collect safety information.

- Date of discharge post-index procedure
- Concomitant anticoagulants and antiplatelet medications
- Number, type, and timing of additional interventions to treat bleeding
    - Rebleeding due to treated vessel
- Serious and device and/or index procedure related adverse events

Subjects will continue to be treated according to standard routine practice after completion of study.

7 ADVERSE EVENTS

For the purpose of this Study, all serious and potentially device-related and/or index procedure-related adverse events will be documented to 28 days post-index procedure and reported to Sponsor via the eCRF.

All deaths will be reported to 28 days, regardless of investigator assessment of causality.

The Sponsor shall review all reported adverse events for their relationship to the study device and/or procedures and comparative anticipated safety event rates. The Sponsor will conduct evaluations of any device-related event per standard operating procedures.

An independent Physician Adjudicator will be responsible for review and adjudication of events defined in Section 10.17.

7.1 Adverse Event definitions

Adverse events will be classified according to ISO 14155:2020 definitions. Where the definition indicates "investigational medical device", it refers to the EmboCube Embolization Gelatin used in the index procedure.

Adverse Event (AE): *(ISO14155:2020, 3.2)*
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 the investigational medical device and whether anticipated or unanticipated.
Note 1 to entry: This definition includes events related to the investigational medical device or the comparator.
Note 2 to entry: This definition includes events related to the procedures involved.
Note 3 to entry: For users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators.

Adverse Device Effect (ADE): *(ISO14155:2020, 3.1)*
Adverse event related to the use of an investigational medical device.
Note 1 to entry: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.
Note 2 to entry: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
Note 3 to entry: This includes 'comparator' if the comparator is a medical device.

Serious Adverse Event (SAE): *(ISO 14155:2020 3.45)*
Adverse event that led to any of the following:
a) death,
b) serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:
   1) a life-threatening illness or injury, or
   2) a permanent impairment of a body structure or a body function including chronic diseases, 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) foetal distress, foetal death, a congenital abnormality, or birth defect including physical or mental impairment
Note 1 to entry: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

Serious Adverse Device Effect (SADE): *(ISO 14155:2020 3.44)*
Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

In addition to the ISO14155:2020 definitions, the following study specific definitions apply:

***Procedure-Related Adverse Event**:* an adverse event is considered to be procedure-related when, in the judgment of the Investigator, it is reasonable to believe that the event is associated with the assigned study procedure and is not solely to the device. Other products, surgical techniques, or medications required specifically for the procedure are likely to have contributed to the occurrence of the event.

7.2 Reportable Adverse Events

For the purpose of this study, events which meet the definition of both serious adverse events and that are potentially device-related and/or procedure-related will be reported.

All deaths will be reported as SAE regardless of Investigator assessment of causality.

7.3 Events Not Considered Adverse Events

For purposes of this study, there are no specific events which are not considered adverse events. All events which meet the definition of both serious adverse events and that are potentially device-related and/or procedure-related, and all deaths will be reported.

7.4 Adverse Event Reporting Requirements

7.4.1 General Reporting Requirements

Reportable adverse events should be recorded on the eCRF through 28 days post index-procedure.

The report should include: the description of event, severity, duration, action taken, treatment outcome and relationship of the adverse experience to the study device and/or procedure (refer to section 12 for definitions for causality and severity).

All reportable events should be followed until resolution, or study exit.

7.4.2 Reporting Requirements for Serious Adverse Events

All serious and potentially device and/or procedure-related adverse events, and all deaths must be reported to the Sponsor within 24 hours of knowledge of the event or by the end of the next working day. This may be done via eCRF or by phone, fax, or email using the contact details provided separately to sites.

The Sponsor will review all reported events for potential reporting in accordance the requirements of Regulation (EU)2017/745 of the European Parliament and of the Council of 5 April 2017 on Medical Devices (MDR), and any applicable guidance(s). Sponsor may request medical record documentation (e.g., procedure notes, operative notes, discharge summary, relevant progress notes, imaging, or lab studies) to facilitate this review.

The Sponsor will determine whether all of the local Investigators need to be informed immediately of an SAE, or whether this can be postponed until the next regularly scheduled study update.

The Sponsor will ensure reporting of applicable events to Regulatory Authorities as clinical study safety reports, if required by Local/national regulations.

The Investigator is responsible for reporting applicable serious adverse events to their EC/IRB as required by EC/IRB procedures and local/national regulations. A copy of each EC/IRB safety report will be provided to Sponsor.

Local, specific safety reporting will be specified in a separate safety plan.

7.4.3 Device Failures and Malfunctions

All device observations / performance issues, malfunctions, or failures, whether or not associated with an adverse event must be reported to the Sponsor within 24 hours of knowledge of the event or by the end of the next working day. This may be done via eCRF or by phone, fax, or email using the contact

details provided separately to sites.

The Sponsor will review all reported events for potential reporting in accordance with the requirements of Regulation (EU)2017/745 of the European Parliament and of the Council of 5 April 2017 on Medical Devices (MDR), and any applicable guidance(s). The Sponsor may request medical record documentation (e.g., procedure notes, operative notes, discharge summary, relevant progress notes, imaging, or lab studies) to facilitate this review.

8 RISK/BENEFIT ASSESSMENT

8.1 Risks

EmboCube Embolization Gelatin is being used in accordance with the approved CE Mark indication and Instructions for Use.

Vascular embolization is a high-risk procedure. Complications may occur at any time during or after the procedure, and may include, but are not limited to, the following as listed in the device IFU:

- Stroke or cerebral infarction
- Occlusion of vessels in healthy territories
- Vascular rupture
- Neurological deficits
- Infection or hematoma at the injection site
- Allergic reaction, cutaneous irritations
- Transient pain and fever
- Vasospasm
- Death
- Ischemia at an undesirable location, including ischemic stroke, ischemic infarction (including myocardial infarction), and tissue necrosis
- Blindness, hearing loss, loss of smell, and/or paralysis

There are no interactions with concomitant medical treatments identified in the device IFU.

8.2 Risk Minimization

As with any surgical procedure, appropriate safety precautions will be followed. In addition, this Protocol provides additional steps to minimize risk to study subjects. These include the following:

- **Investigator Selection & Training**: All investigators are required to be appropriately qualified by education, training, and expertise in vascular embolization. Embolization with EmboCube Embolization Gelatin should only be performed by physicians who have received appropriate interventional embolization training in the region to be treated.
- **Subject Screening**: Subject selection will be in accordance with the Protocol and the IFU. Subjects with known contraindications to use of embolics should not be enrolled in the study.

8.3 Potential Benefits

There are no specific benefits to the subject from participating in the study and subject treatment is not determined by the protocol.

8.4 Overall Assessment of Risk-Benefits

This is an observational registry using commercially available devices and there are no new risks or benefits to the individual subject associated with study participation.

The additional information obtained on the safety and effectiveness profile of the device may benefit physician understanding of the use of embolics and may support the development of new devices in general. Therefore, Sponsor's assessment is that the potential benefits justify the study.

9 STATISTICAL ANALYSIS

The analysis of the data from this study will be primarily descriptive. Continuous endpoints will be summarized by N, mean, standard deviation, median, minimum, and maximum. Categorical or binary endpoints will be summarized by N and percentage with confidence intervals as appropriate. Kaplan Meier plots will be used to display and summarize time to event data.

The planned sample size for analysis is at least 100 subjects which is believed to be adequate to provide an accurate characterization of EmboCube in a "real-world" clinical setting.

Analysis Population

- Intention-to-Treat (ITT) Analysis Set: includes all enrolled subjects.
- *Per-Protocol (PP) Analysis Set*: includes all enrolled subjects who met all inclusion/exclusion criteria with no major protocol deviations. This is a secondary analysis set for the primary safety and effectiveness endpoints, as well as secondary endpoints.

While ITT is intended as the primary analysis set for all safety and effectiveness endpoints, the primary safety and effectiveness endpoints will additionally be evaluated in the PP analysis sets as supportive information. All subjects excluded from ITT analysis set will be described.

9.1 Population Demographics

The demographics and medical history will be presented in tabular form for all subjects enrolled in this study (ITT analysis set). Means, standard deviations, and sample size will be used to summarize continuous characteristics such as age. Frequencies and percentages will be used to summarize categorical characteristics such as gender. Demographic and medical history data will be additionally tabulated for the ITT and PP analysis sets.

9.2 Primary Endpoint Analysis

Endpoints will be analyzed using the intention-to-treat analysis set. An additional supportive analysis will be conducted in the PP analysis sets for the primary safety and effectiveness endpoints. All available data will be used for each endpoint and no imputations will be done.

The primary endpoint of clinical success will be presented as frequency and percentage.

The primary safety endpoint of absence of SADE within 24 hours, will be presented as frequency and percentage.

9.3 Secondary Endpoint Analysis

All secondary endpoints will be tabulated. Means, standard deviations and sample size will be used to summarize continuous characteristics. Distributions of continuous data will be examined and if non-normality is exhibited, medians and interquartile ranges will be presented. Frequencies and percentages will be used to summarize categorical characteristics. All available data will be used for each endpoint and no imputations will be done.

9.4 Sample Size

The sample size of 100 subjects is based on a one-sample non-inferiority analysis of Clinical Success based on the parameters listed below and a 15% loss-to-follow-up:

- Reference Clinical Success rate (p_0): 92%

- Treatment rate (p): 90%
- Non-inferiority margin: 10%
- α: 0.05
- Power: 80%

The reference Clinical Success rate is based on historical clinical literature data for benchmark gelatin embolic devices.

9.5 Handling of Missing Data

No imputation of missing data is planned.

9.6 Interim Analysis

Interim analyses will be performed to support regulatory submission(s) and may be performed as needed to support conferences, presentations, or publications. No pre-stated study stopping rules are planned.

10 ETHICAL, QUALITY ASSURANCE AND ADMINISTRATIVE ASPECTS

10.1 Good Clinical Practices

This study will be conducted in accordance with ethical principles that have their origins in the Declaration of Helsinki. This study shall be conducted in accordance with ISO14155:2020 and all local or national regulations applicable to this study.

The following ISO14155:2020 requirements do not apply to this study, any additional exceptions from the standard will be justified in the study files:

- Device accountability procedures where commercial products are used.
- Device labelling specific for clinical investigations.
- No Investigator Brochure will be written as sufficient information is available in the commercial IFU and this protocol.
- Reporting to regulatory authorities will be completed only if required by regulations.
- Informed consent will be collected for collection of study data.

10.2 Sponsor Responsibilities

The Sponsor is responsible for the overall conduct and quality of the study, including the assurance that the study complies with Declaration of Helsinki, applicable Good Clinical Practices, relevant Data Protection regulations and all relevant international standards and regulations applicable to medical device observational studies.

The Sponsor will ensure that all applicable national regulatory and Data Protection approvals are in place, and that EC/IRB approval is in place prior to commencement of the study at each site.

The Sponsor will obtain and maintain appropriate insurance in accordance with national and local requirements and will provide a copy of the insurance policy to the Investigators, EC/IRB, other national regulatory agencies (as applicable).

The Sponsor will implement systems to select and train investigators, collect data, oversee the quality of the study and monitor investigator compliance with their responsibilities as detailed in this Protocol.

10.3 Investigator Responsibilities

The Investigators are responsible for ensuring that this study is conducted according to this Protocol, Declaration of Helsinki, applicable Good Clinical Practices, relevant Data Protection regulations, and any other applicable local or national regulations and any requirements imposed by the EC/IRB or regulatory authorities .

It is also the Investigator's responsibility to ensure that all sub-investigators and staff assisting with this study have the appropriate qualifications and that they complete training on the Protocol procedures, and that subject confidentiality is respected. Other Investigator responsibilities are detailed throughout Section 10.

10.4 Selection of Clinical Sites & Investigators

The Sponsor is responsible for selection of sites for study participation based upon review of the following criteria:

- Investigator(s) are appropriately qualified by education, training, and expertise in vascular embolization. Embolization with EmboCube Embolization Gelatin should only be performed by physicians who have received appropriate interventional embolization training in the region to be treated.
- Investigator(s) are willing to conduct the study in accordance with this Protocol and all applicable local and national regulatory requirements, including Informed Consent requirements.
- Adequate staff to comply with study data collection and reporting standards.
- Appropriate facilities, resources, and equipment to conduct the study including ability to support EDC requirements.
- Willing to allow access to representatives of the Sponsor and/or regulatory authorities for data monitoring/audit.

10.5 Investigator Training

The Sponsor will ensure that Investigators and site staff are trained in the Study Protocol, including consent requirements and data collection procedures. Training may be completed by on-site visit, WebEx and/or web-based training modules. No additional device training or case support is required for study participation.

10.6 EC/IRB Approvals

The Investigator at each site is responsible for obtaining EC/IRB approval for the Protocol and the Informed Consent documents **prior** to enrollment of the first study subject at site. The Sponsor **must** also review and approve the final Informed Consent documents prior to their use. The Sponsor must receive a copy of EC/IRB final approval letter and the final approved Informed Consent.

The Investigator is responsible for ensuring that all applicable local, national, and Declaration of Helsinki requirements are met when completing the informed consent process. Written, Informed Consent is to be obtained for all subjects **prior** to any data collection.

The Investigator or clinical site staff will not make amendments to this Protocol or the Informed Consent form without **PRIOR** written approval from the Sponsor. All approved amendments must then be submitted to the local EC/IRB, as appropriate for approval.

If the Investigator's IRB or EC withdraws their approval to conduct this study for any reason, the Investigator **must** notify the Sponsor as soon as possible, but in no event later than **five working days** after the withdrawal of the approval.

The Investigator must submit and, where necessary, obtain approval from the EC/IRB for all subsequent significant Protocol amendments and significant changes to the Informed Consent form. The Investigator should notify the EC/IRB of deviations from the Protocol and safety reports in accordance with local procedures.

The Investigator will be responsible for obtaining annual EC/IRB approval and renewal, where applicable, throughout the duration of the study. Copies of the Investigator's reports and the EC/IRB continuance of approval must be sent to Sponsor.

10.7 Required Documentation

The Investigator will maintain all CRFs, source documents and all study documents and correspondence as required by applicable regulatory requirements for the duration of the study.

The following documents should be provided to the Sponsor before the study starts:

- Copy of EC/IRB approval and membership list and any other relevant local approvals.
- Copy of the EC/IRB approved Informed Consent form and any other approved patient information.
- Financial disclosures for the Investigator and sub-Investigator(s).
- Signed and dated Protocol Signature page.
- Current signed and dated curriculum vitae for each Investigator and sub-Investigator.
- Fully executed study agreement, including financial agreement.

10.8 Clinical Data Collection

Standardized electronic case report forms (eCRF) will be used to collect complete and accurate records of the clinical data. The Investigator and/or staff under his/her direction is responsible for accurately recording the clinical data for this study and submitting it to the Sponsor in a timely manner. All data from the trial will be entered into eCRF via a secure, web-based system with password protection. All data should be entered completely and promptly. Data will be remotely reviewed and queried to identify inconsistent or missing data and any adverse events.

Investigators are required to maintain adequate source documents including laboratory results, supporting medical records, and signed Informed Consent forms. These will be used during monitoring visits to verify data contained on the completed eCRF. For source documents, corrections should be made in a manner that does not obscure or eliminate the original error, by striking through the original data with one line, and initialing and dating the change, along with the reason for the change (if not obvious).

The investigator must ensure accuracy, completeness and timeliness of the data reported in the eCRFs and in all other required reports. Data reported on the eCRFs which are derived from source documents must be consistent with the source documents or the discrepancies need to be justified in a documented rationale, signed and dated by the (principal) investigator, to be filed in the subject file.

Only authorized persons can complete an eCRF. An eCRF shall be signed by investigators as specified on the Delegated Tasks List included in the Investigator Site File.

The Electronic Data Capture (EDC) system maintains an audit trail on entries, changes or corrections in eCRFs. If a person only authorized to complete an eCRF makes changes to an already signed eCRF, the investigator shall re-sign this eCRF.

10.9 Device Accountability

Device size and lot number will be recorded in the eCRF. Where sites use devices supplied according to standard hospital/clinic procedures for commercial products, no other device accountability procedures will apply.

The Sponsor may provide devices specifically for use in the study, providing this is in accordance with all applicable national laws and regulations. The provision of devices for study specific purposes shall be documented in the clinical study agreement. In such cases, Investigators will be responsible for providing a secure storage location for the devices, separate to any commercial stock, and the disposal and/or return of the devices as instructed by the Sponsor. In addition, Investigators will maintain records to document the receipt, use and disposition of all devices received by their site intended for this study and provide copies to Sponsor. The Sponsor and/or designee will also maintain records of all shipments and disposition of devices. Study specific devices should be available to the monitor for review during on-site monitoring.

10.10 Subject Compensation

Study subjects will not be reimbursed or compensated for their time in participating in the trial.

10.11 Confidentiality

Confidentiality of subjects will be maintained throughout the study. A unique identification code will be assigned to each participating subject. Any data that may be published in abstracts, scientific journals, or presented at medical meetings will reference a unique study code and will not reveal the subject's identity. The Investigator, Sponsor and their representatives will make every reasonable effort to protect subject confidentiality.

10.12 Monitoring

The Sponsor will designate appropriately qualified monitors to review compliance with Protocol and data collection procedures, to assess the accuracy and completeness of eCRF data and record retention. These will primarily be assessed by remote data review. On-site monitoring visits may be undertaken based on review of factors including, but not limited to enrollment rate, adverse event reporting and Protocol compliance.

The Investigator will make available all regulatory documents, completed eCRF, Informed Consent documents, source documentation and other relevant records for enrolled subjects at the site.

It is important that the Investigator and other relevant site personnel are available for consultation with the monitor during on-site monitoring visits and remote review and that sufficient time is devoted at the site to the monitoring process.

A detailed monitoring plan for the study will be maintained separately.

10.13 Audits and Inspections

The Investigator will allow representatives of the Sponsor, EC/IRB and applicable regulatory agencies to inspect all trial records, eCRF, and corresponding portions of the subject's office and/or hospital medical records at regular intervals throughout the trial. These inspections are for the purposes of verifying adherence to the Protocol, completeness and exactness of the data being transcribed into the eCRF, and compliance with regulatory agency regulations.

The Investigator will inform the Sponsor in advance if they are to be audited or inspected by any regulatory agencies. The Sponsor or the Sponsor's designee will also inform the site if they are made aware of a pending audit or inspection by a regulatory agency.

The Investigator and/or designees must be available to respond to reasonable requests by authorized Sponsor, CRO and regulatory agency representatives during the monitoring and inspection process. The Investigator must provide the Sponsor with copies of all correspondence that may affect the review of the current study (i.e., Inspection Observations) or their qualification as an Investigator in clinical studies conducted by the Sponsor. The Sponsor will provide any needed assistance to the clinical site for regulatory audits, if any.

10.14 Amendments to the Protocol

The Sponsor will submit any significant amendment to the protocol, including a justification for this amendment, to the appropriate regulatory authorities and to the investigators to obtain approval from their EC/IRB. The investigator will only implement the amendment after approval of the EC/IRB, regulatory authority (if applicable) and sponsor.

Administrative amendments to the protocol will be submitted to the EC/IRB for notification.

Investigators shall sign any the initial protocol and subsequent approved amendments for agreement.

10.15 Protocol Compliance/ Deviations

The Investigators are responsible for ensuring that this study is conducted according to this Protocol.

All deviations from the Protocol must be reported to the Sponsor.

Investigators shall be required to obtain prior approval from the Sponsor before initiating deviations from the Protocol, except where necessary to protect the life or physical well- being of a subject in an emergency. Such approval shall be documented in writing and maintained in Sponsor and Investigator files.

Investigators will also adhere to procedures for reporting Protocol deviations to their EC/IRB in accordance with their specific EC/IRB reporting policies and procedures.

For reporting purposes, the Sponsor classifies the following as major protocol deviations: Any deviation from subject inclusion and exclusion criteria, failure to obtain subject informed consent and failure to report serious adverse events. Other deviations which occur will be reviewed and classified by Sponsor.

The Sponsor shall report deviations from the approved protocol in the study report.

If the Sponsor and/or their authorized representative become aware that an Investigator is not complying with the study protocol, the Investigator Agreement, the Declaration of Helsinki, applicable privacy standards, or any condition of the study imposed by the IRB / EC, the Sponsor or their authorized representative may immediately secure compliance or suspend or terminate enrollment at site. An inability to secure compliance and/or to complete an investigation into the factors that are inhibiting compliance may result in the Investigator's termination from the study by the Sponsor.

10.16 Investigational Site or Study Termination

The Sponsor reserves the right to terminate an investigational site from the study for any of the following reasons:

- Failure to obtain Informed Consent.
- Failure to comply with safety reporting requirements.
- Repeated Protocol deviations or safety concerns.
- Repeated failure to complete electronic Case Report Forms.
- Failure to enroll an adequate number of subjects.

The Sponsor reserves the right to terminate the study at any stage but intends to exercise this right only for valid scientific or administrative reasons and reasons related to protection of subjects. Investigators, associated IRB/ECs, and regulatory authorities, as applicable, will be notified in writing in the event of study termination. Detailed information on how enrolled subjects will be managed after termination will also be provided. Possible reasons for premature study termination include, but are not limited to, the following.

- Occurrence of unanticipated adverse device effects that present a significant or unreasonable risk to subjects enrolled in the study.
- An enrollment rate far below expectation that prejudices the conclusion of the study.
- A decision on the part of Sponsor to suspend or discontinue development of the device.

10.17 Independent Physician Adjudicator

An independent Physician Adjudicator (IPA) will be responsible for review and adjudication of all serious and potentially device-related adverse events, at minimum. Other events may be reviewed as defined in the IPA Charter.

In order to enhance objectivity and reduce the potential for bias, the IPA shall be independent of the Sponsor as well as the investigational sites and investigators. The methodology for performing these responsibilities shall be developed and outlined in the IPA Charter. Operational provisions shall be established to minimize potential bias.

10.18 Measures to Minimize bias

The following measures will be implemented to minimize the potential for bias in this single arm Registry:

- Sites are requested to screen and enroll consecutive subjects, as far as possible, and enrollment activities will be documented in a screening/enrollment log.
- Multiple sites will be included to ensure a representative sample of physicians performing the procedure and to provide a reasonable enrollment period.
- Site selection will be performed using predefined parameters to ensure Investigators are appropriately qualified to conduct registry.
- Only physicians that are trained and experienced in vascular embolization can participate.
- Site training will be performed to assure full understanding and engagement to comply with the study design and all protocol requirements.
- A sample of adverse events will be reviewed and assessed by an independent Physician.
- Any known or foreseeable factors that may compromise the outcome of the Registry or the interpretation of results are covered by the Inclusion and Exclusion criteria.
- Financial disclosures will be collected from all investigators to document any potential for bias or conflict of interest.

11 RECORDS, REPORTS AND PUBLICATION

11.1 Record Retention

Sponsor and Investigators will maintain their study records until two (2) years after the final report is completed, or longer if required by local, national or international regulatory agencies. The Sponsor will notify each site regarding the regulatory requirements for record retention at the time of study close-out.

11.2 Reporting Timelines

The Investigator will report information and events according to the timelines below:

Form/Report	Submission Timeframe
eCRF	Completion within 10 working days of visit/follow-up, or chart review.
All serious and potentially device-related events and all deaths	Submit notification to Sponsor within 24 hours of the site becoming aware of the event, or by the end of the next working day; submit to the local EC/IRB as required according to local and national regulations.
All device observations / performance issues, malfunctions or failures	Submit notification to Sponsor within 24 hours of the site becoming aware of the event, or by the end of the next working day; submit to the local EC/IRB as required according to local and national regulations.
Major deviations	Submit notification to Sponsor within 24 hours of the site becoming aware of the event, or by the end of the next working day; submit to the local EC/IRB as required according to local and national regulations.
Progress Reports	As required by the local EC/IRB
Final Report to the EC/IRB	As required by the local EC/IRB

11.3 Study Reports

All information and data generated in association with the study will be held in strict confidence and remains the sole property of the Sponsor. The Investigator agrees to use this information for the sole purpose of completing the study and for no other purpose without prior approval of the Sponsor.

The Sponsor will submit all required reports to regulatory authorities throughout the study.

Upon receipt of the final study data and the final reports from each center, the Sponsor will complete a final study report. Copies of the final report will be provided to each Investigator.

11.4 Publication Policies

Publications and presentations will be coordinated by Sponsor to allow the use of all available data. The following publication policy will have to be adhered to by all participating investigation sites:

Authorship on any publication(s) will be assigned according to substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content and final approval of the version to be published. This is in accordance with the International Committee of Medical Journal Editors' "Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals (ICMJE Recommendations)", December 2019, as agreed upon by the editors of all major medical journals. The number of authors will be dependent on the regulations of the concerning journal with a maximum of 10 authors. Names of all participating investigators will appear in the Acknowledgment of the paper.

Based on the principle that Sponsor owns the study data, a single investigation site may access and use the data provided by itself for scientific publications following prior approval by Sponsor.

Pooling data from several investigation sites for publication purposes, national projects and international projects all require prior approval by Sponsor.

Sponsor as the owner of the data can use the data and/or any results derived from the data or publications based on that data for marketing purposes, further research and development of devices or educational use.

Participating subjects will not be identified by name in any published reports about the study. This study will be registered with www.clinicaltrials.gov. including requirements to make results publicly available.

12 STUDY DEFINITIONS

ADVERSE EVENT CAUSALITY

The sponsor and the investigators will use the following definitions to assess the relationship of the serious adverse event to the study device, or the investigation procedure[1].

1. Not related: Relationship to the device, or procedures can be excluded when:

- the event has no temporal relationship with the use of the study device, or the procedures related to application of the study device;
- the serious adverse 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 adverse event;

[1] Definitions derived from "MDCG 2020-10/1 Safety reporting in clinical investigations of medical devices under the Regulation (EU) 2017/745" May 2020.

- the event involves a body-site or an organ that cannot be affected by the device or procedure;
- the serious adverse 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);

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 adverse event.

2. Possible: The relationship with the use of the study device, or the relationship with procedures, 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 where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.

3. Probable: The relationship with the use of the study device, or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.

4. Definitely related (*Causal relationship*): the serious adverse event is associated with the study 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 study device use/application or procedures;
- the event involves a body-site or organ that
    - the study device or procedures are applied to;
    - the study device or procedures have an effect on;
- the serious adverse 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 adverse 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;

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 adverse event.

ADVERSE EVENT SEVERITY

The following definitions for rating severity of adverse events will be used:

Mild:	Awareness of signs or symptoms, but easily tolerated; are of minor irritant type; causing no loss of time from normal activities; symptoms would not require medication or a medical evaluation; signs or symptoms are transient.
Moderate:	Interferes with the subject's usual activity and/or requires symptomatic treatment.
Severe:	Symptom(s) causing severe discomfort and significant impact of the subject's usual activity and requires treatment.

Device Failure: A device that is used in accordance with the Instructions for Use, but the device does not perform according to the Instructions for Use and negatively impacts the treatment.

Device Malfunction: A malfunction of a device is an unexpected change to the device that is contradictory to the Instructions for Use and may or may not affect device performance.

13 REFERENCES

1. Chiara, O., Cimbanassi, S., Bellanova, G. et al. A systematic review on the use of topical hemostats in trauma and emergency surgery. BMC Surg 18, 68 (2018).

[redacted]