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

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1 STATISTICAL ANALYSIS PLAN APPROVAL

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2 ABBREVIATIONS

CI	Confidence interval
EmboCube	EmboCube Embolization Gelatin
IFU	Instructions for Use
ITT	Intention-to-Treat
PP	Per-Protocol
SD	Standard deviation

3 STUDY SYNOPSIS

Study Title:	A Multicenter Observational Study to Evaluate Outcomes of EmboCube Embolization Gelatin to Control Bleeding or Hemorrhage
Study Objective:	To collect clinical safety and performance outcome data associated with the use of EmboCube Embolization Gelatin (EmboCube) to control bleeding or hemorrhage
Study Device:	EmboCube™ Embolization Gelatin
Study Design:	Multicenter observational post-market[1] clinical follow-up study in subjects treated with EmboCube
Device Regulatory Status:	European Union: CE mark approved March 2019 (CE 667862) Australia: Investigational device
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-based 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 re-bleeding at the treated site requiring re-intervention (i.e., 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 related to EmboCube
Inclusion Criteria:	**French Study Sites**
	1. Age ≥18 years 2. Subject requires embolization and is suitable for treatment with EmboCube in accordance with the device's IFU for the treatment of bleeding or hemorrhage 3. Subject provides written informed consent to participate in the study and allows for data collection 4. The subject has Social Security
	Australian Study Sites
	1. Age ≥18 years 2. Target vessel(s) that require treatment are ≤ 5mm 3. Subject requires embolization and is suitable for treatment with EmboCube in accordance with the device's IFU for the treatment of bleeding or hemorrhage 4. Subject provides written informed consent to participate in the study and allows for data collection
Exclusion Criteria:	**French Study Sites**
	1. Site of bleeding is in the neck, head, or brain 2. Subject has a co-morbidity with survival prognosis < 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, person under judicial protection, and/or person who does not write or speak French (applicable in France only)
	Australian Study Sites
	1. Subject's vascular anatomy precludes correct catheter placement 2. Subject's feeding arteries are too small to accept selected EmboCube 3. Bleeding site in the neck, head, or brain 4. Presence or suspicion of vasospasm 5. High-flow arteriovenous shunts with a diameter greater than the selected EmboCube 6. Use in the pulmonary vasculature 7. Use in pre-operative portal vein embolization 8. Subject has severe atherosclerosis 9. Subject has known allergy to gelatin of porcine origin

	10. Subject has a co-morbidity with survival prognosis of < 30 days, in the opinion of the treating physician 11. In the investigator's opinion, participation in the study may not be in the subject's best interest

[1] Investigational in Australia

4 STUDY OBJECTIVES

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

5 BACKGROUND/INTRODUCTION

This is a multicenter observational study of the use of EmboCube to control bleeding or hemorrhage. Bleeding is defined as the loss of blood from a damaged blood vessel, whereas hemorrhage is defined as massive internal or external blood loss. This study is designed to enable the collection, analysis, and reporting of data from the real-world use of EmboCube when used in accordance with the Instructions for Use (IFU) associated with its CE mark.

Data collection will include outcomes pertaining to the safety and effectiveness of EmboCube from the index procedure through 28 (0/+14) days post-procedure. Data collection will be according to the standard follow-up practices at the enrolling institutions.

5.1 STUDY DESIGN

Multicenter observational post-market clinical follow-up study in subjects treated with EmboCube to control bleeding or hemorrhage. This study does not require subjects to undergo any procedures beyond those performed under normal standard of care associated with the device.

5.2 TREATMENT GROUPS

This will be a single-arm study that will include subjects undergoing embolization with EmboCube for the treatment of bleeding or hemorrhage.

5.3 STUDY POPULATION

Subjects undergoing embolization with EmboCube for the treatment of bleeding or hemorrhage who meet the inclusion and exclusion criteria will be invited to participate in this study. The eligibility criteria are kept to a minimum to better represent the profiles of subjects treated in clinical practice without selecting sub-groups that have low or high risk or excluding subjects with certain diseases or anatomies.

5.3.1 INCLUSION CRITERIA

French Study Sites

1. Age ≥18 years
2. Subject requires embolization and is suitable for treatment with EmboCube in accordance with the device's IFU for the treatment of bleeding or hemorrhage
3. Subject provides written informed consent to participate in the study and allows for data collection

4. The subject has Social Security

Australian Study Sites

5. Age ≥18 years
6. Target vessel(s) that require treatment are ≤ 5mm
7. Subject requires embolization and is suitable for treatment with EmboCube in accordance with the device's IFU for the treatment of bleeding or hemorrhage
8. Subject provides written informed consent to participate in the study and allows for data collection

5.3.2 EXCLUSION CRITERIA

French Study Sites

1. Site of bleeding is in the neck, head, or brain
2. Subject has a co-morbidity with survival prognosis < 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, person under judicial protection, and/or person who does not write or speak French (applicable in France only)

Australian Study Sites

1. Subject's vascular anatomy precludes correct catheter placement
2. Subject's feeding arteries are too small to accept selected EmboCube
3. Bleeding site in the neck, head, or brain
4. Presence or suspicion of vasospasm
5. High-flow arteriovenous shunts with a diameter greater than the selected EmboCube
6. Use in the pulmonary vasculature
7. Use in pre-operative portal vein embolization
8. Subject has severe atherosclerosis
9. Subject has known allergy to gelatin of porcine origin
10. Subject has a co-morbidity with survival prognosis of < 30 days in the opinion of the treating physician
11. In the investigator's opinion, participation in the study may not be in the subject's best interest

5.4 INTERVENTION

EmboCube will be used in accordance with the currently approved CE mark.

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

5.5 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.[1-12]

5.6 STUDY PROCEDURE

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 [0/+14] days), subjects will be contacted by telephone during this time to collect safety follow-up data to 28 days.

Start of the study will be defined as the date of initiation (i.e., authorization to start enrollment) of the first site.

Study completion will be defined as the completion of the last follow-up visit/contact for the last subject.

5.7 VISIT SCHEDULE

Study participation will last for a total of 28 (0/+14) days (i.e., 28 to 42 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 [0/+14] days) subjects will be contacted by telephone during this time to collect safety follow-up data to 28 days.

A summary schedule of the data collection for tests and evaluations is provided in Table 1. Data from tests and evaluations performed outside of standard of care will not be collected.

Table 1. Data Collection Schedule

Data	Pre-operative/ baseline	Procedure to 24 hours	28 (0/+14) days follow-up[1]
Informed consent[2]	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 (i.e., size, type, and amount)		X	

Data	Pre-operative/ baseline	Procedure to 24 hours	28 (0/+14) days follow-up[1]
No/type of other adjuvant embolic 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] If a subject does not have a clinic visit at the site between 4 and 6 weeks (i.e., 28 to 42 days), the subject will be telephoned to collect information on potential device-related adverse events and re-interventions.

[2] Subject will be asked to provide written informed consent for data collection either pre-operatively or prior to hospital discharge.

6 ANALYSIS POPULATION

The following analysis populations are identified for the study:

- Intention-to-Treat (ITT) analysis set: includes all enrolled subjects.
- Per-Protocol (PP) analysis set: includes all enrolled subjects who meet 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 the ITT analysis set is intended as the primary analysis set for all safety and effectiveness endpoints, the primary safety and effectiveness endpoints will also be evaluated in the PP analysis set as supportive information. All subjects excluded from the ITT analysis set will be described.

7 OUTCOME VARIABLES

7.1 PRIMARY OUTCOMES

7.1.1 PRIMARY EFFECTIVENESS ENDPOINT

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

7.1.2 PRIMARY SAFETY ENDPOINT

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

7.2 SECONDARY OUTCOMES

The secondary outcomes will include the following safety and performance measures:

- Incidence of adverse events (serious and device- and/or procedure-related) to 24 hours post-operative
- Incidence of adverse events (serious and device- and/or procedure-related) between 24 hours and 28 (0/+14) days post-operative

- Technical success defined as successful occlusion of the treated site as seen on post-embolization angiography
- Incidence of device observations related to EmboCube

7.3 DEMOGRAPHY AND BASELINE CHARACTERISTICS

The following demographic and baseline data for study subjects will be collected and reported:

- 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, weight, body mass index
- Concomitant anticoagulants and antiplatelet medications

Data collected for the embolization procedure with EmboCube will also be reported.

7.4 SUBJECT DISPOSITION

A tabulation of study subject disposition will be presented including the number of subjects treated and the number of subjects that do not complete the study, the reasons for study incompletion will be described as documented in the case report form.

8 STATISTICAL METHODOLOGY

8.1 GENERAL METHODOLOGY

Final analyses will be performed after all study subjects have completed the final follow-up visit, defined according to the protocol as 28 (0/+14) days.

For continuous variables, outputs will be presented with mean, standard deviation (SD), median, minimum, and maximum values. Mean and median values will be rounded to a single decimal place while SD will be rounded to two decimal places. When appropriate, a corresponding 95% confidence interval (CI) will be calculated. Categorical variables (e.g., sex, race) will be reported using frequencies and percentages. All percentages will be rounded to one decimal place. If percentages do not add up to 100% due to rounding, a footnote explanation will be provided accordingly.

When the mean is not an appropriate measure of central tendency, alternative statistics will be considered (e.g., median). When the distribution of a variable does not support the use of parametric statistics, nonparametric approaches or data transformations may be implemented. If data transformations are used, they will be specified in the final clinical report.

Correlation analyses will be used to analyze relationships for continuous variables. Independent t-tests will be conducted to test differences for continuous variables between binary groups. A Fisher's exact test will be used to analyze the relationships between categorical variables. P-values less than or equal to 0.05 will be considered significant. All p-values will be rounded to 3 decimal places and will be presented as "<0.001" if less than 0.0005.

Time-dependent response variables will be expressed using the Kaplan-Meier curve, and the hazard ratio and the 95% CI will be reported.

Data for all categorical endpoints are shown with the number of patients, percentage, and Clopper-Pearson's exact 95% CI.

Descriptive statistics will be used to examine demographic and baseline characteristics and to perform other efficacy analyses.

Each table generated will have headers that include the total sample size (N). Frequencies and percentages for categorical variables will be calculated using the number of subjects (n) with non-missing values.

8.1.1 DATA SOURCE

All data will be extracted from Medrio, which is the electronic data capture (EDC) used for data collection in this study. Datasets will be merged and cleaned prior to data analysis. Data processing procedures will be documented to ensure replicability and support error checks. All analyses and codes will be uploaded to Merit Medical Affairs Share (SharePoint) drive.

8.1.2 REPORTING OUTPUTS

SAS software Version 9.4 (SAS Institute Inc., Cary, NC, USA), or other widely accepted statistical or graphical software as required, will be used for all statistical analyses and in the generation of exhibits. Tables will be formatted using SAS software and Microsoft Office.

8.1.3 HANDLING OF MISSING DATA

No imputation of missing data is planned.

8.1.4 CLASSIFICATION OF PROTOCOL VIOLATION

Protocol deviations will be summarized in the final clinical study report. 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
- Failure to report serious adverse events

Other deviations that occur will be reviewed and classified by the Sponsor.

8.1.5 INTERIM ANALYSIS

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

8.2 PRIMARY DATA ANALYSES

Endpoints will be analyzed using the ITT analysis set. Additional supportive analyses 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 of data are planned.

The primary endpoint of clinical success (defined as cessation of bleeding post-embolization and absence of re-bleeding at the treated site requiring re-intervention [i.e., repeat embolization or additional surgery], within 24 hours) will be presented as frequency and percentage.

Endpoint Derivation:

- "Was there a re-intervention to treat bleeding?" is checked NO, **AND**
- "Was occlusion of the treated area (as seen on post-embolization angiogram) successful?" is checked YES, **AND**
- "Did subject have any re-interventions post-procedure through 24 hours post-procedure?" is checked NO

The primary safety endpoint of absence of serious adverse device effect within 24 hours will be presented as frequency and percentage

Endpoint Derivation:

- "Did any serious and device- and/or procedure-related adverse events occur during the procedure or up to 24 hours post-procedure?" is checked NO

8.3 SECONDARY DATA ANALYSES

All secondary endpoints will be tabulated. Means, SDs, and sample size will be used to summarize continuous variables. 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 variables. All available data will be used for each endpoint and no imputations will be performed.

Incidence of adverse events to 24 hours post-operative (serious and device- and/or procedure-related)

Endpoint Derivation:

- Serious adverse events as reported by the site, **AND**
- "Seriousness" is checked as anything other than "Not Serious", **AND**
- Relationship to study device **AND/OR** relationship to study procedure is "Definitely related"

Incidence of adverse events between 24 hours and 28 days post-operative (serious and device- and/or procedure-related)

Endpoint Derivation:

- "Were there any serious and device- or procedure-related adverse events since the 24-hour contact visit?" is checked YES, **AND**
- Serious adverse events as reported by the site and in which "Seriousness" is checked as anything other than "Not Serious", **AND**
- Relationship to study device **AND/OR** relationship to study procedure is "Definitely related"

Technical success defined as successful occlusion of the treated site as seen on post-embolization angiography

Endpoint Derivation:

- "Was occlusion of the treated area (as seen on post-embolization angiogram) successful?" is checked YES

Incidence of device observations related to EmboCube

Endpoint Derivation:

- "Was procedure aborted due to device observation?" is checked YES

8.4 SAFETY SUMMARY

All device or procedure-related adverse events collected will be summarized cumulatively throughout the follow-up period. The frequency count of adverse events and the unique number of subjects who had the adverse events will be presented. Also, the frequency and percentage of patients who had a serious adverse event, or a device- or procedure-related serious adverse event will be tabulated separately. If a patient experienced multiple adverse events, only the most severe event or the most intense relationship to the study device will be counted within an adverse event code. The following information will be reported as listings about each adverse event:

- Start date
- Stop date
- Severity
- Relationship
- Action taken
- Outcome

9 TABLES, LISTINGS, AND FIGURES

9.1 PLANNED TABLES

The planned tables are provided below. Additional tables may be added to the reporting at the discretion of the Biostatistician in consultation with the Project Manager.

- Demographics and baseline characteristics (ITT)
- Medical history (ITT)
- Medications (ITT)
- Blood tests/coagulation status (ITT)
- General procedure characteristics (ITT)
- Embolization procedure characteristics (ITT)
- General re-intervention procedure Information (ITT)
- Primary endpoints—Clinical success and absence of unanticipated serious adverse device effect within 24 hours (ITT)
- Primary endpoints—Clinical success and absence of unanticipated serious adverse device effect within 24 hours (PP)

- Secondary endpoints—Incidence of adverse events, technical success, and incidence of device observations related to EmboCube (ITT)
- Secondary endpoints—Incidence of adverse events, technical success, and incidence of device observations related to EmboCube (PP)
- Safety summary (ITT)
- Subject disposition (ITT)
- Protocol deviations (ITT)
- Device observations (ITT)

9.2 PLANNED LISTINGS

The planned listings are provided below. Additional listings may be added to the reporting at the discretion of the Biostatistician in consultation with the Project Manager.

- Demographics and baseline characteristics
- Medical history
- Medications
- Blood tests/coagulation status
- General procedure characteristics
- Embolization procedure characteristics
- General re-intervention procedure information
- Clinical success and technical success
- Adverse events
- Subject disposition
- Protocol deviations
- Device observations

9.3 PLANNED FIGURES

There are no figures planned; any figures generated will be added to the reporting at the discretion of the Biostatistician in consultation with the Project Manager.

10 REFERENCES

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