Protembis

CLINICAL INVESTIGATION PROTOCOL

Cerebral Protection in Transcatheter Aortic Valve Replacement

The PROTEMBO C Trial

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Product Name:
ProtEmbo® Cerebral Protection System

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1. Protocol Synopsis

Title:	**Cerebral Protection in Transcatheter Aortic Valve Replacement: The PROTEMBO C Trial**
Investigational Device:	ProtEmbo Cerebral Protection System (also called 'ProtEmbo System')
Intended Use:	The ProtEmbo System is intended for use as a temporary filter device to deflect embolic material in the aortic arch.
Objective:	The primary objective of this study is to assess the safety and performance of the ProtEmbo Cerebral Protection System used for embolic protection during Transcatheter Aortic Valve Replacement (TAVR) compared to TAVR standard of care (without embolic protection). The Secondary objective is to assess the efficacy of the ProtEmbo system by comparing the median new lesion volume in the brain and the rate of death or all strokes compared to historical data.
Design:	Exploratory, international, multi-center, single-arm study of the safety and performance of using the ProtEmbo System in subjects with severe symptomatic native aortic valve stenosis indicated for TAVR.
Study Treatments:	Subjects included in the study will be undergoing TAVR following placement of the ProtEmbo System for cerebral embolic protection during TAVR.
Number of Patients:	Up to 60 patients who complete the TAVR procedure using the ProtEmbo System.
Duration:	12 months
Primary Endpoints:	*Safety:* Major Adverse Cardiac and Cerebrovascular Events (MACCE) at 30 days defined by VARC-2 including all-cause mortality, all stroke, life-threatening or disabling bleeding, vascular injury and acute kidney injury (stage 2 or 3). Stroke severity will be quantified according to the National Institutes of Health Stroke Scale (NIHSS) score and the occurrence of other Serious Adverse Events up to 30 days. *Performance:* Technical success, defined as ability to safely deliver, deploy, and remove the device, ability to secure positioning and stability of the position throughout the procedure and ability to deflect embolic material, as assessed by adequate coverage, while not impeding blood flow.

Secondary Endpoints: *Efficacy:*

MR Imaging:

Comparison between the median new lesion volume in the brain assessed by diffusion weighted magnetic resonance images (DW-MRI) at 2 to 7 days and historical data; the total new lesion volume is defined as the sum of all diffusion-positive new cerebral lesions in post-procedural DW-MRI relative to the pre-TAVR DW-MRI.

Death or All Stroke:

Death or all stroke according to VARC-2 criteria (to define occurrence and type stroke) within 3 days (72 hours) of the TAVR procedure compared to historical data; Stroke severity will be quantified according to the National Institutes of Health Stroke Scale (NIHSS) score.

Enrollment Criteria: *Inclusion Criteria*:

1. The heart team recommends transcatheter valve aortic valve replace consistent with the 2017 ESC/EACTS Guidelines for the management of valvular heart disease.
2. Compatible left subclavian artery (≥ 4 mm diameter) without significant stenosis (> 70%) and distance between the origin of left subclavian artery and valve plain of ≥ 90mm as determined by Multi-Slice Computed Tomography (MSCT) scan or equivalent imaging modality.
3. The subject and the treating physician agree that the subject will undergo the scheduled pre-procedural testing and return for all required post-procedure follow-up visits.
4. The subject is able to provide informed consent, has been informed of the nature of the trial, agrees to its provisions and has provided written informed consent as approved by the relevant regulatory authority of the respective clinical site.
5. Subject is a minimum of 18 years of age.

Exclusion Criteria:

General:

1. Left upper limb vasculature in the left extremity precluding 6Fr sheath radial / brachial / subclavian access.
2. Inadequate circulation to the left extremity as evidenced by signs of artery occlusion (modified Allen's test) or absence of radial/ brachial pulse.

3. Hemodialysis shunt, graft, or arterio-venous fistula involving the upper extremity vasculature.
4. TAVR conducted via other than transfemoral access (subclavian, axillar, transapical, transaortic, carotid or transcaval).
5. Evidence of an acute myocardial infarction ≤ 1 month before the intended treatment.
6. Aortic valve is a congenital unicuspid or bicuspid valve.
7. Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation >3+).
8. Any therapeutic invasive cardiac procedure resulting in a permanent implant that is performed within 30 days of the index procedure (unless part of planned strategy for treatment of concomitant coronary artery disease).
9. Blood dyscrasias as defined: Leukopenia, acute anemia, thrombocytopenia, history of bleeding diathesis or coagulopathy.
10. Hemodynamic instability requiring inotropic support or mechanical heart assistance.
11. Need for emergency surgery for any reason.
12. Severe hypertrophic cardiomyopathy with or without obstruction.
13. Severe ventricular dysfunction with LVEF ≤30%.
14. Echocardiographic evidence of intracardiac or aortic mass, thrombus, or vegetation.
15. Symptomatic or asymptomatic severe (≥ 70%) occlusive carotid disease requiring concomitant CEA / stenting.
16. Subject has undergone carotid stenting or carotid endarterectomy within the previous 6 weeks.
17. Active peptic ulcer or upper GI bleeding within the prior 6 months.
18. A known hypersensitivity or contraindication to aspirin, heparin, ticlopidine, or clopidogrel, device component material, or sensitivity to contrast media, which cannot be adequately pre-medicated.
19. Recent (within 6 months) CVA or a TIA.
20. Renal insufficiency (creatinine > 3.0 mg / dL or GFR < 30) and / or renal replacement therapy at the time of screening.
21. Life expectancy < 12 months due to non-cardiac co-morbid conditions.
22. Subjects in whom anti-platelet and / or anticoagulant therapy is contraindicated, or who will refuse transfusion.
23. Subjects who have active bacterial endocarditis or other active infections.
24. Currently participating in an investigational drug or another device study.

25. Subjects who have a planned treatment with any other investigational device or procedure during the study follow-up period (30 days).
26. Subjects with planned concomitant surgical or transcatheter ablation for Atrial Fibrillation during the study follow-up period (30 days).
27. Any subject with a balloon valvuloplasty (BAV) within 30 days of the procedure.
28. Subject is a woman of child-bearing potential.
29. Patient with Heparin-Induced Thrombocytopenia Syndrome.
30. Inner diameter of aortic arch is less than 25mm.
31. Brachiocephalic trunk originating from the aortic arch that splits into the bilateral subclavian arteries and a bicarotid trunk (Origin D).
32. Hepatic failure (defined as liver enzyme elevations two times the upper limit of normal) or active infectious hepatitis
33. Cardiogenic shock or severe hypotension (systolic blood pressure < 90 mm Hg) at the time of the index procedure
34. Subjects who have a planned concomitant cardiac surgical or interventional procedure (e.g., coronary revascularization) during the TAVI procedure
35. Subjects who have a pre-existing prosthetic heart valve in any position

Neurological:

1. Subject had active major psychiatric disease.
2. Subject has severe visual, auditory, or learning impairment and is unable to comprehend English or local language and therefore unable to be consented for the study.
3. Subjects with neurodegenerative or other progressive neurological disease or history of significant head trauma followed by persistent neurologic defaults or known structural brain abnormalities.

Angiographic:

1. Excessive tortuosity or severe peripheral arterial disease in the left radial / brachial / subclavian artery preventing ProtEmbo System access and insertion.
2. Subject whose left radial / brachial / subclavian artery reveals significant stenosis, calcification, ectasia, dissection, occlusion or aneurysm, in particular at or within 3 cm of the aortic ostium.
3. Subject with significant stenosis, ectasia, dissection, or aneurysm in the ascending aorta or in the aortic arch, or with abnormal aortic arch angulation or abnormal anatomical conditions of the aorta.

Magnetic Resonance Imaging:

1. Subject Body Mass Index (BMI) precluding imaging in scanner.
2. Contraindications to MRI (subjects with any implantable temporary or permanent pacemaker or defibrillator, metal implants in field of view, metallic fragments, clips, or devices in the brain or eye before TAVR procedure).
3. Subjects who have a high risk of complete AV block after TAVR, with the need of permanent pacemaker (e.g. subjects with pre-existing bifascicular block or complete right bundle branch block plus any degree of AV block).
4. Planned implantation of a pacemaker or defibrillator implantation within the first 4 days after TAVR.
5. Claustrophobia precluding MRI scanning.
6. No scanner hardware, software, coil or protocol changes during the course of the study.

Medication

Administration of anticoagulant medicines and monitoring of activated clotting time (ACT) per institution guidelines shall be performed throughout the TAVR procedures. A target ACT of at least 250 seconds should be maintained for the duration of the procedure. For those patients not receiving chronic oral anticoagulation prior TAVR, a dual antiplatelet therapy before and after the procedure is recommended.

For those patients with chronic dual antiplatelet therapy (DAPT) use, it is recommended to continue with acetylsalicylic acid and clopidogrel therapy for at least 1 month after TAVR, as per the standard practice of the institution.

For those patients without chronic DAPT use, it is recommended to administer 300 mg of each acetylsalicylic acid and clopidogrel within 24 hours (and at least 2 hours) before the procedure or the equivalent as per the standard of care at the institution.

No modification of the patient's ongoing medical treatment is required as a result of participation in the PROTEMBO C Trial.

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Statistical Assumptions:

	Safety Endpoint	**Performance Endpoint**
Comparator Rate	15%	90%
Delta	10%	15%
Performance goal (PG)	25%	75%
Power	85%	85%
Estimated ProtEmbo rate	10.4%	89%
Sample Size	60	42

2. Introduction and Background

According to the Centers for Disease Control, an estimated 795,000 strokes occur each year in the United States. According to Bergman et al. lifetime direct costs of stroke per patient amount to circa € 33,000 for females and circa € 29,000 for males (Bergman *et al.*, 1995). Approximately 3% of a country's total health expenditure is attributable to all-cause stroke treatment, a figure that typically represents 0.2–0.3% of gross domestic product (Evers *et al.*, 2004). The cost of cerebrovascular diseases to healthcare systems was € 21 billion in 2003 in the 25 EU member states. Eighty-two percent of this figure was due to inpatient care, which represented 2.4% of total healthcare costs (Leal *et al.*, 2006). In 2010, strokes cost in the United States was estimate at $ 53.9 billion dollars (Bendszus & Stoll, 2006). Thus, mitigation of stroke risk has the potential to improve the lives of patients and reduce health care costs significantly.

Stroke can occur in subjects undergoing interventional cardiovascular procedures such as vascular stenting, catheter ablation for atrial fibrillation, endovascular stent grafting, balloon aortic valvuloplasty, and transcatheter aortic valve replacement (TAVR). Procedure-associated cerebrovascular events are usually embolic and embolic protection devices (EPD) are intended to reduce the risk of cerebral embolization. Major adverse events (mortality, stroke, and myocardial infarction) have been reduced during carotid and saphenous vein graft stenting when embolic protection devices were used (Baim *et al.*, 2002; Stone *et al.*, 2003; Gurm *et al.*, 2008).

The advent of transcatheter treatments for valvular heart disease has been a minor revolution in the care of patients, especially for patients with disabilities or intercurrent illnesses that precluded undergoing open cardiac surgical procedures. TAVR was initially introduced to treat patients with severe aortic stenosis who were not candidates for surgical replacement of the aortic valve because of the high risk of morbidity and mortality associated with open heart surgery and cardiopulmonary bypass (Holmes *et al.*, 2012). As TAVR devices have improved and the procedure to place the valves has improved, especially sizing the replacement valve properly, the indications for TAVR have been expanding, and patients with lower preoperative risks, who might actually tolerate an open heart surgery, are nonetheless selecting the TAVR procedure because it offers an acceptable, functional aortic valve replacement, and it is less invasive and causes less morbidity (Eggebrecht & Mehta, 2016; Leon *et al.*, 2016).

Despite the improvements in TAVR procedures and outcomes, the occurrence of stroke represents a significant morbidity of the TAVR procedure. The incidence of stroke or transient ischemic attack (TIA) was 3.3% in a large meta-analysis (Bendszus & Stoll, 2006; Eggebrecht *et al.*, 2012), but may be as high as 10% in some series (Tamburino *et al.*, 2011; Leon *et al.*, 2016), and when stroke occurs, the 30-day mortality following TAVR is increased 3.5 fold (Eggebrecht *et al.*, 2012; Sabate *et al.*, 2013). In a meta-analysis of randomized controlled trials in which embolic protection was used (Giustino *et al.*, 2017), embolic protection was associated with significantly lower risk of death or stroke, and the estimated number needed to treat with embolic protection was 22 patients to prevent 1 death or stroke. Stroke associated with the TAVR procedure may occur when vascular material or debris is dislodged during TAVR so the cerebrovascular events are usually embolic, and the emboli consist of cholesterol particles, air, atherosclerotic plaque material, thrombus and/or calcified valve material (Clark *et al.*, 1995; Barbut *et al.*, 1997; Leon *et al.*, 2010; Eltchaninoff *et al.*, 2011; Nuis *et al.*, 2012; Van Mieghem *et al.*, 2013). Clinically detectable strokes represent only a small fraction of the

embolic events that occur during TAVR – many of the emboli occlude cerebral vessels in 'silent' areas of the brain that, nonetheless, have adverse long-term effects on cognitive and motor function (Gass *et al.*, 2004; Ghanem *et al.*, 2010; Kahlert *et al.*, 2010; Fairbairn *et al.*, 2012). Investigators have turned to diffusion weighted magnetic resonance imaging (DW-MRI) to count the number and assess the volume of new brain lesions following TAVR. DW-MRI is more sensitive to the occurrence of cerebrovascular events than the clinical exam and reflects more accurately the risk of subsequent cognitive decline (Kahlert *et al.*, 2012; Abdul-Jawad Altisent *et al.*, 2016) and was the recommended imaging modality for embolic protection devices in a recent consensus statement (Lansky *et al.*, 2017). DW-MRI obtained in the immediate post-TAVR period (generally within a week of the index procedure) have revealed the extent of embolic events during and following TAVR; new ischemic infarcts, often small, can be identified in almost every patient undergoing TAVR even though the incidence of clinically detectable stroke is 10% or less (Ghanem *et al.*, 2010; Kahlert *et al.*, 2012; Abdul-Jawad Altisent *et al.*, 2016). After 30 days, many of the embolic infarcts have resolved and are no longer detectable by DW-MRI (Lansberg *et al.*, 2001; Gass *et al.*, 2004; Kahlert *et al.*, 2012; Rodes-Cabau *et al.*, 2014), and other MRI imaging sequences (FLAIR MRI) may be preferred (Lansky *et al.*, 2017). Despite the sensitivity of DW-MRI, the current AHA guidelines do not recommend routine acquisition of the DW-MRIs or routine assessment of cognitive function and suggest that clinicians rely on a careful neurological assessment (Sacco *et al.*, 2013).

In summary, there is abundant evidence that TAVR is associated with embolic events in patients. New ischemic lesions can be detected in DW-MRIs in most patients, but the incidence of clinically detectable neurological events is lower (probably between 4 to 7%). Embolic protection devices seem to reduce the number and/or volume of new ischemic events detected by DW-MRI, but the clinical significance of this reduction cannot be assessed because there are too few patients to date treated with embolic protection during TAVR, and the duration of follow-up of patients treated with embolic protection devices during TAVR is too short. Nevertheless, the high frequency of embolic events and the emerging evidence of a consistent reduction in volume of ischemic brain tissue following TAVR when embolic protection devices were used indicate that further work is merited, especially for devices that protect all three of the great vessels, which originate in the arch of the aorta and supply the cerebral circulation. Devices that protect all three vessels provide greater protection of all regions of the cerebral circulation.

2.1. Rationale behind Proposed Research

The ProtEmbo is an adjunctive device used during the TAVR procedure and removed following completion of valve replacement. Based on the Edwards Lifesciences SAPIEN PARTNER A trial, 50% of strokes occurred in the first 24 hours, 96% in the first 9 days, 100% in the first 28 days (Miller *et al.*, 2012). Embolic filters have an established basis of clinical safety and efficacy in carotid filtration. Therefore, carotid filtration during TAVR should also provide benefits.

In addition, new cerebral lesions detected with MRI are reported in 48% of patients after valve surgery and in up to 70 – 80% after TAVR (Ghanem *et al.*, 2010; Kahlert *et al.*, 2012). Most of these lesions have no immediate clinical consequences, but the potential for neurocognitive decline in the long-term remains to be investigated. Several studies have linked (initially subclinical) micro-emboli after heart surgery to neurocognitive outcomes (Clark *et al.*, 1995; Barbut *et al.*, 1997). Vascular cognitive impairment (VCI) could also result from multiple, initially

subclinical, cerebral emboli. Liberation of debris to the cerebrovascular or peripheral vascular systems clearly provides no benefit to the patient and can only cause potential harm.

The ProtEmbo System was developed in an effort to deflect embolic debris during TAVR. Given low peri-procedural complication rates and the lack of reported procedural strokes when using comparable embolic protection devices, an embolic protection device could be highly beneficial for patients undergoing endovascular procedures such as TAVR (Van Mieghem *et al.*, 2013).

2.2. Study Objective

The primary objective of this exploratory study is to assess the safety and performance of the ProtEmbo Cerebral Protection System used for embolic protection during Transcatheter Aortic Valve Replacement (TAVR) compared to TAVR standard of care (without embolic protection). The secondary objective of this study is to assess the efficacy of the ProtEmbo system by comparing the median new lesion volume in the brain and the rate of death or all strokes compared to historical data.

2.3. Background

2.3.1. Previous Clinical Experience

Many devices have been developed to reduce the occurrence of stroke by catching the emboli during endovascular or cardiac valvular procedures or by deflecting the emboli produced during these procedures toward less vulnerable circulations. All embolic protection devices developed to date use a mesh filter of some sort to capture emboli or to cover the orifices of the great vessels supplying the brain. Embolic protection devices have some risks of their own. In the presence of diffuse atherosclerosis in the aorta and great vessels supplying the brain, placement of the embolic protection device may dislodge emboli independent of any embolization associated with TAVR (Steinvil *et al.*, 2016). Investigators in the field are generally skeptical about the benefits of embolic protection devices since existing devices have not shown benefit in cardiac surgery (Banbury *et al.*, 2003) or in carotid artery stenting (Stabile *et al.*, 2014). On the other hand, the sheer number and volume of emboli collected during TAVR has led a variety of companies to develop and test embolic protection devices to be used during TAVR. Using such devices during TAVR has reduced the number and /or volume of infarcts seen in DW-MRIs, but whether the reduction in the number or volume of acute infarcts detected by DW-MRI will translate into a clinically meaningful preservation of cognitive or motor function has not yet been determined. A recent study-level meta-analysis of all randomized control trials for cerebral embolic protection to date found that, as a class, embolic protection devices used during TAVR decreased the risk of stroke and mortality compared to unprotected TAVR, which corresponded to an approximately 4.0 % reduction in absolute risk (Giustino *et al.*, 2017). When patients from the Sentinel US IDE, Clean-TAVI, and Sentinel-Ulm studies were combined, a propensity-matched cohort of patients revealed significant reductions in all-stroke risk and in combined all-cause mortality and all-stroke risk in patients who received treatment with an embolic filter protection device during TAVR compared to those who did not. The relative risk reduction for all-stroke risk was 65% in patients with treated with embolic protection compared to the risk of all-stroke in those without embolic protection during

TAVR and a similar relative risk reduction of 66% in all-cause mortality and all-stroke (Seeger *et al.*, 2019).

The Embrella device (Edwards Life Sciences) is a deflection device that is placed over the orifices of the brachiocephalic trunk and the left common carotid artery. The device is deployed through the right radial or brachial artery using a 6 Fr. delivery sheath. Two 'petals' are opened to cover the orifices of the great vessels once the device is in the aorta. Two published reports using the Embrella are available (Rodes-Cabau *et al.*, 2014; Samim *et al.*, 2016). In the ProTAVI-C study, the Embrella device was implanted in 41 patients and 11 other patients constituted a control group. Samin et al. reported results from a single center in 15 patients treated with the Embrella device and compared results to 37 patients who had previously had TAVR without embolic protection, but in whom DW-MRIs had been obtained after the TAVR (Samim *et al.*, 2015). The Embrella device was feasible to use; it was deployed successfully, and no new problems were introduced in patients undergoing TAVR in whom the Embrella device was also deployed. However, the number of strokes was not reduced. In the ProTAVR-C study, the number of high intensity transient signals detected by transcranial Doppler (an indication of cerebral ischemia) was actually increased in the Embrella treatment group – consistent with the idea that deployment of embolic protection devices may initiate some embolization all by itself. Even though the number of infarcts identified by DW-MRI when the Embrella device was deployed was not different, the volume of ischemic tissue was significantly reduced in the Embrella treated groups.

The TriGuard device (Keystone Heart, now Venus Medtech) is also a deflection device placed across the orifices of the great vessels. The TriGuard device is mechanically more complex, but it covers the brachiocephalic, the left common carotid *and* the left subclavian artery orifices consistently (the Embrella device does not consistently cover the opening of the left subclavian artery). The TriGuard device is introduced through the femoral artery and requires a 9 Fr. delivery sheath. The TriGuard device was studied in the DEFLECT I trial, a single arm, multicenter observational trial (Baumbach *et al.*, 2015), and a CE mark was obtained based on results from the first 20 patients. In a subsequent, randomized, controlled trial, the DEFLECT III Trial, there were 39 patients in the control group (TAVR without embolic protection) and 26 patients in the TriGuard plus TAVR treatment group (Lansky *et al.*, 2015). The TriGuard was deployed successfully to cover all three orifices of the great vessels in ~90% of the patients. The number of strokes and the clinically detected neurological impairment did not differ between groups. The volume of new lesions detected by DW-MRI was significantly less in the TriGuard treatment group (although the number of large ischemic lesions was not different between groups). Many subjects were lost to follow-up in one endpoint or another, and so the assessment of neurological outcomes was incomplete.

The Sentinel device (Claret Medical, now Boston Scientific) is an embolic capture device that protects the brachiocephalic and left common carotid arteries (there is no filter or embolic collection placed within or across the opening of the left subclavian artery). The Sentinel device is placed through the right radial brachial artery through a 6 Fr. sheath. The Sentinel device has been studied more extensively than the other devices using a variety of TAVR devices in 3 randomized controlled trials (CLEAN-TAVI, MISTRAL-C, SENTINEL). The CLEAN-TAVI Trial was completed on an earlier generation of the device (Montage device), there were 50 patients in the device plus TAVR group and 50 patients in the TAVR alone, control group) (Haussig *et al.*, 2016). The device was deployed successfully ~90% of the time. The contents of the filter / capture device confirmed the ubiquity of emboli associated with TAVR. There were

no significant differences in neurological symptoms between the TAVR alone and TAVR plus Sentinel device, and no reduction in the incidence of new lesions detected by DW-MRI. However, the number of new lesions in each patient was reduced in the Sentinel device group compared to the TAVR alone group. The MISTRAL-C Trial also reported both a reduction in the number and volume of new brain lesions on DW-MRI 5 days post-procedure, and a smaller decline in cognitive function measured at 3 months post-procedure in Sentinel device treatment group. The SENTINEL Trial was a large multicenter randomized control trial, and in this trial as well, debris was captured in the devices in 99% of the cases, and patients treated with the Sentinel device had a lower volume of new cerebral lesions. Moreover, the MACCE rate was slightly lower in the Sentinel treatment group, and the incidence of strokes was reduced compared to unprotected TAVR procedures. It was demonstrated for the first time, that there is a correlation between new lesion volume and neurocognitive decline (Demir *et al.*, 2018), and on the individual device level, the Sentinel demonstrated a significantly higher rate of stroke-free survival when the Sentinel device was used during TAVR compared to unprotected TAVR (Seeger *et al.*, 2019).

2.3.1.1. Previous Clinical Experience with the ProtEmbo Device

The Sponsor completed a First in Human study, 'Cerebral Protection in Transcatheter Aortic Valve Replacement – The PROTEMBO SF Trial,' in October 2018. The primary objective of The PROTEMBO SF Trial was to evaluate the safety and feasibility of the ProtEmbo Cerebral Protection System used for embolic protection during TAVR. The indication for use of the ProtEmbo device was identical to the current study – the ProtEmbo device is indicated as a temporary intra-aortic filter placed within the arch of the aorta to deflect embolic material in patients undergoing cardiovascular procedures. Five (5) subjects with severe symptomatic native aortic valve stenosis, selected by the Heart Team at each study center, who met the approved indications for TAVR and complied with the inclusion/ exclusion criteria, were enrolled in the trial. The trial was a prospective, observational, multi-center, intention-to-treat clinical investigation of the safety and feasibility of the ProtEmbo used in subjects with severe symptomatic native aortic valve stenosis indicated for TAVR. The inclusion and exclusion criteria were identical (the wording of the inclusion and exclusion criteria were changed for the PROTEMBO C Trial, but the patients included and excluded were not altered by these editorial changes).

This First in Human trial demonstrated that the ProtEmbo System and, specifically, the ProtEmbo device were safe for use in humans. There were no Serious Adverse Events attributable to the ProtEmbo device. There were no MACCE and no new strokes and no cognitive decline among the patients in the trial. TAVR was successfully performed in all patients. The ProtEmbo did not limit or interfere with the capacity to perform TAVR successfully. A ProtEmbo was successfully implanted and deployed in four of five subjects in the study. One patient was unable to receive the ProtEmbo as excessive calcification of the left radial artery precluded insertion of a commercially available guiding sheath through which the ProtEmbo device must be delivered. The PROTEMBO SF Trial was not designed to evaluate the effectiveness of embolic protection, but the study design did successfully model the neurological evaluations and MR images that will be required for a formal evaluation of the ProtEmbo when used during TAVR procedures. The number of pre-existing lesions was relatively large in this particular group of patients compared to the studies summarized above, and the MR images indicated that new cerebral lesions followed each TAVR (as other studies have also demonstrated). Although new lesions were apparent in MR images following each

TAVR, there were no new strokes and no changes in cognitive function in any of the subjects following TAVR performed using the ProtEmbo. Thus, the safety and feasibility of the ProtEmbo was demonstrated in four subjects enrolled in the PROTEMBO SF Trial. Moreover, the responses of the four patients treated within the PROTEMBO SF Trial did not lead to identification of any new or unanticipated risks.

2.3.2. Summary: Previous Experience with Embolic Protection Devices in TAVR

In summary, embolic protection devices consistently reduce the volume or number of new emboli ischemic lesions on DW-MRI images of the brain and appear to reduce the incidence of stroke and MACCE events following TAVR. The clinical findings are only trends thus far (the studies were not powered for some of these endpoints). Nevertheless, embolic protection devices used during the TAVR procedure appear to be safe and feasible, and the early surrogate and clinical efficacy measures suggest that there will be clinical benefit when sufficiently large numbers of subjects are studied. The benefits of embolic protection appear to outweigh the risks of using these devices based on the data available at this time. Thus, there is good justification for the Sponsor to move forward with the PROTEMBO C Trial.

2.3.3. Preclinical Experience with the ProtEmbo Device

The ProtEmbo Cerebral Protection System has been subjected to a comprehensive pre-clinical testing program to verify design, safety, and performance against pre-specified engineering, mechanical and system requirements. Pre-clinical testing included bench, biocompatibility, animal, and sterilization testing. In addition to evaluation against internal specifications and international standards, the ProtEmbo System was also tested in accordance with the US Food and Drug Administration Center For Devices and Radiological Health's Embolic Protection Device (EPD) guidance document - Guidance for Industry and Staff – Coronary and Carotid Embolic Protection Devices – Premarket Notification [510(k)] Submissions (February 15, 2008) where applicable.

Bench testing included embolic filter performance (deflection efficiency, flow characteristics, resistance to rupture), simulated use (deployment and retrieval forces, TAVR system and accessory device compatibility, kink resistance, tensile strength). All required bench testing was successfully completed and demonstrated compliance with the predetermined performance specifications.

Acute animal studies have been performed to further support the safety and performance of the ProtEmbo System. Multiple developmental studies and a verification study were performed to verify the safety and feasibility of deployment and retrieval of the device and histopathological responses of the device. The device elicited no adverse blood or tissue response, and no gross vascular injuries were associated with the placement or removal of the device, thereby demonstrating the safety and feasibility of the device in an animal model. In summary, pre-clinical animal studies have been conducted and support the safety and performance of the ProtEmbo System through simulated use under in-vivo conditions in a porcine model.

Complete biocompatibility testing was performed for the ProtEmbo System according to ISO-10993, Biological Evaluation of Medical Devices Part 1: Evaluation and Testing requirements for externally communicating devices in limited contact with circulating blood, and Good Laboratory Practices. These tests include cytotoxicity, sensitization, irritation, acute system toxicity, hemocompatibility (hemolysis, complement activation, in-vivo thromboresistance), and pyrogenicity. All required biocompatibility tests for the ProtEmbo System were performed and the results met the testing requirements; therefore, the ProtEmbo System can be considered biocompatible for its intended use.

In conclusion, the ProtEmbo System has been fully evaluated through pre-clinical testing per the identified risks and demonstrates compliance with its predetermined performance specifications.

3. Test System (Investigational Device)

3.1. Name of Investigational Device

ProtEmbo Cerebral Protection System (also called 'ProtEmbo System' or 'ProtEmbo Device' or 'System' or 'Device').

3.1.1. Model and version

Product Name: ProtEmbo® Cerebral Protection System
Product Reference (REF): 10100
Product Model Number: PRS_10100_ProtEmbo_System, Final Packaging

3.2. Intended Use

The ProtEmbo System is indicated for use as a temporary intra-aortic filter device to deflect embolic material in patients undergoing cardiovascular procedures.

3.3. Classification

The ProtEmbo System is classified in class III in accordance with Rule 7 of MEDDEV 2. 4/1 Rev. 9 and Rule 6 of Regulation (EU) 2017/745, Annex VIII, Chapter III.

3.4. System Components

The ProtEmbo System is a temporary use, non-active, intra-aortic embolic protection deflection filter device that is positioned across the orifices of the major vessels exiting the aortic arch (Truncus Brachiocephalicus, Left Common Carotid Artery and Left Subclavian Artery), refer to Figure 1. The device is placed in the central arterial system as an adjunctive device at the beginning of an index procedure to deflect embolic particles during the procedure and removed following the completion of the procedure.

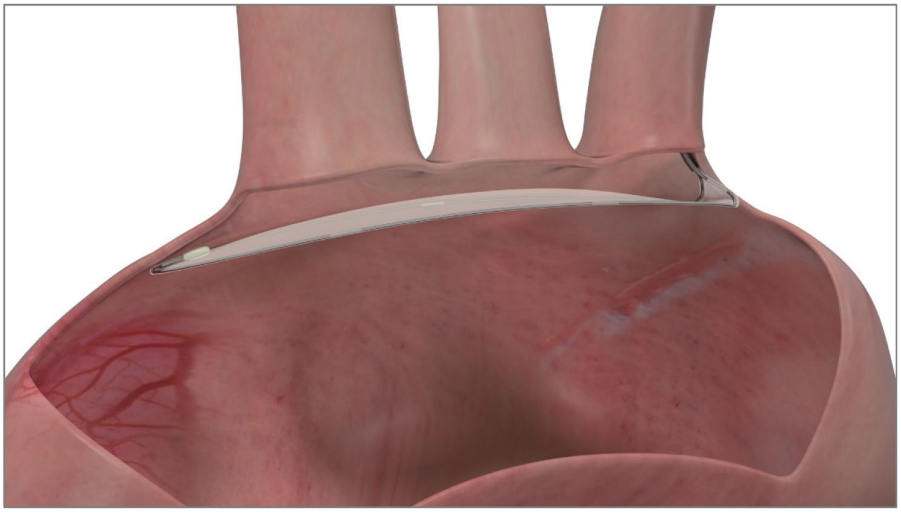

Figure 1. ProtEmbo Cerebral Protection System position in the aortic arch (illustration).

The ProtEmbo System comprises three main components (Device, Shaper and Handle), refer to Figure 2 and Figure 3.

The **ProtEmbo Device** comprises a **Filter** (1), a **Frame** (2) with **Radiopaque Marks** (3 a-e) and a **Shaft** (4). The filter consists of a porous material that allows free passage of the blood cells through it, but blocks embolic particles. The Shaft is connected to the Frame and enables delivery of the unexpanded Device via a Delivery Catheter and placement (expansion) of the Device in the aortic arch of a patient. In its expanded state the Frame spans the Filter to cover all 3 side branch vessels of the aortic arch (Truncus Brachiocephalicus, Left Common Carotid Artery and Left Subclavian Artery). Radiopaque Markers on the Frame enable fluoroscopic visualization to allow for correct placement and positioning of the Device.

The **ProtEmbo Shaper** (5) is used to prepare the Device for placement into the inner lumen of the distal end of a delivery catheter. The Shaper is a sterile placement tool with a dedicated folding mechanism; produced and provided by Protembis GmbH. Markers at the distal end of the Shaper indicate the first point of contact with the proximal end of the device Shaft.

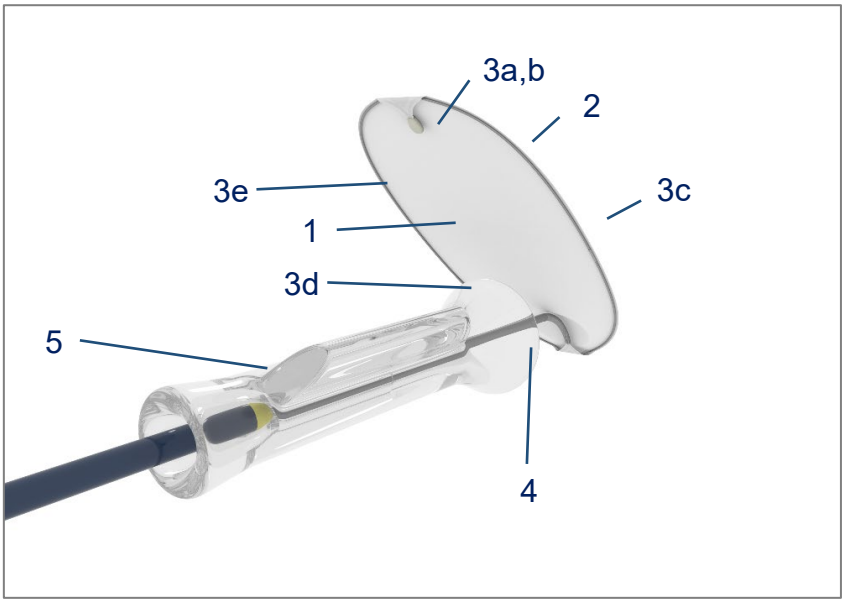

Figure 2. ProtEmbo Cerebral Protection System functional parts (illustration).

The **ProtEmbo Handle** (“Handle”) (6) is used to guide the ProtEmbo Device into the inner lumen of the distal end of a delivery catheter, position the Device tip during deployment and enhance the positioning of the device within the aortic arch. The Handle is connected to the delivery catheter and provides the user interface with a dedicated push, pull and torque functionality as well as flushing and de-aering the system; produced and provided by Protembis GmbH.

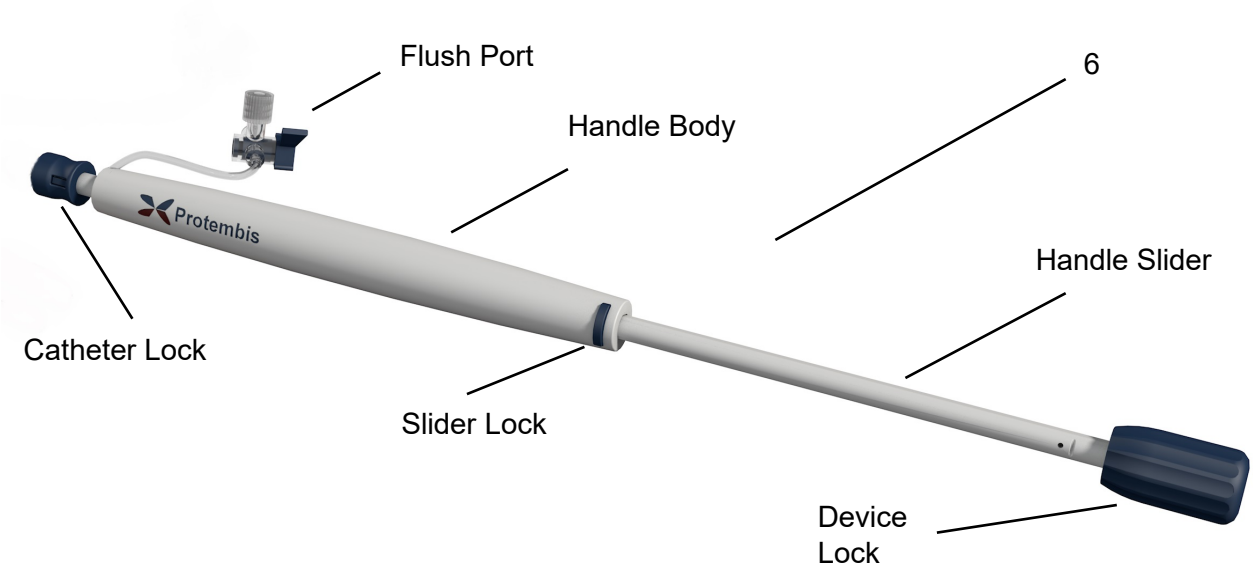

Figure 3. ProtEmbo Cerebral Protection System Handle (illustration).

The ProtEmbo System Components are single-use and sterilized by ethylene oxide sterilization. The materials that have contact with the patient’s blood or tissues are shown below:

Device Component	Material
Shaft	Stainless Steel
Shaft Coating	Polyether block amide (PEBA)
Frame	Nitinol
Filter	Polyamide
Filter Coating	Heparin (porcine source)
Radiopaque Marker	90% platinum/ 10% iridium
Distal Frame Fixation Yarn	Polyethylene Terephthalate (PET) / D&C Green No. 6
Frame/Filter Glue	Polyurethane
Filter Glue	Polyurethane
Filter/Shaft Glue	Polyurethane

Device Component	Material
Frame/Shaft Glue	Polyurethane
Filter/Shaft Fixation Wire	Stainless Steel

Table 1: ProtEmbo System components and materials in contact with the patient's blood or tissues.

3.5. Device Accountability

Access to ProtEmbo System inventory will be controlled and will be housed in a secure location. Records will be maintained to document the physical location of inventory from shipment / removal from Sponsor facility through use and / or return or disposal.

The site will be responsible for keeping a Device Accountability Log provided by the Sponsor or its designated representative in which will be recorded, at a minimum, date of receipt, ProtEmbo System identification number, expiration date, date of use, subject unique identity code and date of disposal of the device.

If there is a product malfunction or other need to return the system or system components to the Sponsor, the Sponsor should be contacted for safe product disposal and / or return details. Such disposal does not include the used ProtEmbo Devices which are to be fixed and submitted to the histopathology lab for analysis.

NOTE: Please contact Sponsor at +49 241 99033622 or CRO at +49 69 2400 3626 immediately for instructions if a device malfunction / failure has occurred.

The Investigator is responsible for ensuring that the investigational devices are used only under the Investigator's supervision and are only used according to this protocol and any approved amendments. The Investigator will not supply an investigational device to any person not authorized to participate in the study. The Investigator shall document in the electronic Case Report Forms (eCRFs) the lot numbers of the devices used during each case.

3.6. Return of Devices

All unused investigational devices will be returned to the study Sponsor upon completion of the clinical study. All used investigational devices will be returned to the study Sponsor for analysis. Any investigational device that fails to perform correctly will be equally returned to the study Sponsor for analysis. The Investigator or his / her designated representative is responsible for device accountability and disposition of all used and unused devices. The study Sponsor or its designated representative will conduct device reconciliation at the completion of subject enrollment or at the conclusion of the study.

4. Study Overview

Sponsor plans to conduct a clinical trial of the ProtEmbo Cerebral Protection System used as an adjunctive device for embolic protection during Transcatheter Aortic Valve Replacement (TAVR). The study plan was developed according to the guidance given by Medical Device Regulation (EU) 2017/745, Annex XV. The rationale for the trial design, endpoints and

variables selected for study are described below. The justification for the study design and the content of the study were fully described in the Protembis Clinical Evaluation Plan.

4.1. Study Design

The PROTEMBO C Trial is an exploratory, international, multi-center, single-arm study of the safety and performance of using the ProtEmbo System in subjects with severe symptomatic native aortic valve stenosis indicated for TAVR. As described in the Protembis Clinical Evaluation Plan, an adequate body of historical data pertaining to embolic protection devices exists against which Protembis can test the safety and performance of the ProtEmbo System in a single-arm trial.

As described in the Clinical Evaluation Plan and the Background for the current study, the appropriate safety endpoint for embolic protection devices used during TAVR is defined as Major Adverse Cardiac and Cerebrovascular Events (MACCE) at 30 days defined by VARC-2 including all-cause mortality, all stroke, life-threatening or disabling bleeding, vascular injury and acute kidney injury (stage 2 or 3). Previous studies have used a similar definition of safety and, therefore, results of these previous studies provide useful historical comparison data to evaluate the safety of the ProtEmbo System. Similarly, performance is defined as the ability to deliver, deploy, and remove the device successfully, the ability to secure positioning and stability of the position throughout the procedure, and the ability to deflect embolic material, as assessed by adequate coverage, while not impeding blood flow. Results from previous studies of embolic protection devices used during TAVR provide useful historical comparison data against which the performance of the ProtEmbo System can be compared.

4.2. Primary Study Endpoints

4.2.1. Safety

Major Adverse Cardiac and Cerebrovascular Events (MACCE) at 30 days defined by VARC-2 including all-cause mortality, all stroke, life-threatening or disabling bleeding, vascular injury and acute kidney injury (stage 2 or 3).

Stroke severity will be quantified according to the National Institutes of Health Stroke Scale (NIHSS) score and the occurrence of other Serious Adverse Events up to 30 days.

4.2.2. Performance

Technical success, defined as ability to safely deliver, deploy, and remove the device, ability to secure positioning and stability of the position throughout the procedure and ability to deflect embolic material, as assessed by adequate coverage, while not impeding blood flow.

4.3. Secondary Study Endpoints

4.3.1. Efficacy:

The secondary efficacy endpoints for this clinical investigation will be based on magnetic resonance (MR) imaging and a composite of death or strokes, each compared to historical data:

For the MR imaging endpoint, the median new lesion volume in the brain assessed by diffusion weighted magnetic resonance images (DW-MRI) at 2 to 7 days will be compared historical data; The total new lesion volume is defined as the sum of all diffusion-positive new cerebral lesions in post-procedural DW-MRI relative to the pre-TAVR DW-MRI.

For the composite death or stroke endpoint, the rate of death or all strokes according to VARC-2 criteria (to define occurrence and type stroke) within 3 days (72 hours) of the TAVR procedure will be compared to historical data; Stroke severity will be quantified according to the National Institutes of Health Stroke Scale (NIHSS) score.

4.4. Number of Subjects and Sites

Up to 60 treated patients in whom the ProtEmbo device is used during a TAVR procedure may be enrolled at up to 10 clinical study centers.

4.5. Study Population

The study population comprises of subjects with severe symptomatic calcified native aortic valve stenosis who meet the approved indications for TAVR with commercially available transcatheter aortic valves by transfemoral route.

4.6. Enrollment Criteria

A potential subject must meet all of the inclusion criteria and none of the exclusion criteria as outlined below in order to be considered eligible to participate in this study.

4.6.1. Inclusion Criteria

Subjects eligible to participate must meet all of the following at screening and / or baseline visits:

1. The heart team recommends transcatheter valve aortic valve replace consistent with the 2017 ESC/EACTS Guidelines for the management of valvular heart.
2. Compatible left subclavian artery (≥ 4 mm diameter) without significant stenosis (> 70%) and distance between the origin of left subclavian artery and valve plain of ≥ 90mm as determined by Multi-Slice Computed Tomography (MSCT) scan or equivalent imaging modality.
3. The subject and the treating physician agree that the subject will undergo the scheduled pre-procedural testing and return for all required post-procedure follow-up visits.

4. The subject is able to provide informed consent, has been informed of the nature of the trial, agrees to its provisions and has provided written informed consent as approved by the relevant regulatory authority of the respective clinical site.
5. Subject is a minimum of 18 years of age.

4.6.2. Exclusion Criteria

Potential subjects with one or more of the following shall be excluded from the study even if they meet the inclusion criteria:

4.6.2.1. General Exclusion Criteria

1. Left upper limb vasculature in the left extremity precluding 6Fr sheath radial / brachial / subclavian access.
2. Inadequate circulation to the left extremity as evidenced by signs of artery occlusion (modified Allen's test) or absence of radial / brachial pulse.
3. Hemodialysis shunt, graft, or arterio-venous fistula involving the upper extremity vasculature.
4. TAVR conducted via other than transfemoral access (subclavian, axillar, transapical, transaortic, carotid or transcaval).
5. Evidence of an acute myocardial infarction ≤ 1 month before the intended treatment.
6. Aortic valve is a congenital unicuspid or bicuspid valve.
7. Mixed aortic valve disease (aortic stenosis and aortic regurgitation with predominant aortic regurgitation >3+).
8. Any therapeutic invasive cardiac procedure resulting in a permanent implant that is performed within 30 days of the index procedure (unless part of planned strategy for treatment of concomitant coronary artery disease).
9. Blood dyscrasias as defined: Leukopenia, acute anemia, thrombocytopenia, history of bleeding diathesis or coagulopathy.
10. Hemodynamic instability requiring inotropic support or mechanical heart assistance.
11. Need for emergency surgery for any reason.
12. Severe hypertrophic cardiomyopathy with or without obstruction.
13. Severe ventricular dysfunction with LVEF ≤30%.
14. Echocardiographic evidence of intracardiac or aortic mass, thrombus, or vegetation.
15. Symptomatic or asymptomatic severe (≥ 70%) occlusive carotid disease requiring concomitant CEA / stenting.
16. Subject has undergone carotid stenting or carotid endarterectomy within the previous 6 weeks.
17. Active peptic ulcer or upper GI bleeding within the prior 6 months.
18. A known hypersensitivity or contraindication to aspirin, heparin, ticlopidine, or clopidogrel, device component material, or sensitivity to contrast media, which cannot be adequately pre-medicated.
19. Recent (within 6 months) CVA or a TIA.
20. Renal insufficiency (creatinine > 3.0 mg / dL or GFR < 30) and / or renal replacement therapy at the time of screening.
21. Life expectancy < 12 months due to non-cardiac co-morbid conditions.

22. Subjects in whom anti-platelet and / or anticoagulant therapy is contraindicated, or who will refuse transfusion.
23. Subjects who have active bacterial endocarditis or other active infections.
24. Currently participating in an investigational drug or another device study.
25. Subjects who have a planned treatment with any other investigational device or procedure during the study follow-up period (30 days).
26. Subjects with planned concomitant surgical or transcatheter ablation for Atrial Fibrillation during the study follow-up period (30 days).
27. Any subject with a balloon valvuloplasty (BAV) within 30 days of the procedure.
28. Subject is a woman of child-bearing potential.
29. Patient with Heparin-Induced Thrombocytopenia Syndrome.
30. Inner diameter of aortic arch is less than 25mm.
31. Brachiocephalic trunk originating from the aortic arch that splits into the bilateral subclavian arteries and a bicarotid trunk (Origin D).
32. Hepatic failure (defined as liver enzyme elevations two times the upper limit of normal) or active infectious hepatitis
33. Cardiogenic shock or severe hypotension (systolic blood pressure < 90 mm Hg) at the time of the index procedure
34. Subjects who have a planned concomitant cardiac surgical or interventional procedure (e.g., coronary revascularization) during the TAVI procedure
35. Subjects who have a pre-existing prosthetic heart valve in any position

4.6.2.2. Neurological Exclusion Criteria

1. Subject had active major psychiatric disease.
2. Subject has severe visual, auditory, or learning impairment and is unable to comprehend English or local language and therefore unable to be consented for the study.
3. Subjects with neurodegenerative or other progressive neurological disease or history of significant head trauma followed by persistent neurologic defaults or known structural brain abnormalities.

4.6.2.3. Angiographic Exclusion Criteria

1. Excessive tortuosity or severe peripheral arterial disease in the left radial / brachial / subclavian artery preventing ProtEmbo System access and insertion.
2. Subject whose left radial / brachial / subclavian artery reveals significant stenosis, calcification, ectasia, dissection, occlusion or aneurysm, in particular at or within 3 cm of the aortic ostium.
3. Subject with significant stenosis, ectasia, dissection, or aneurysm in the ascending aorta or in the aortic arch, or with abnormal aortic arch angulation or abnormal anatomical conditions of the aorta.

4.6.2.4. Magnetic Resonance Imaging Exclusion Criteria

1. Subject Body Mass Index (BMI) precluding imaging in scanner.

2. Contraindications to MRI (subjects with any implantable temporary or permanent pacemaker or defibrillator, metal implants in field of view, metallic fragments, clips, or devices in the brain or eye before TAVR procedure).
3. Subjects who have a high risk of complete AV block after TAVR, with the need of permanent pacemaker (e.g. subjects with pre-existing bifascicular block or complete right bundle branch block plus any degree of AV block).
4. Planned implantation of a pacemaker or defibrillator implantation within the first 4 days after TAVR.
5. Claustrophobia precluding MRI scanning.
6. No scanner hardware, software, coil or protocol changes should occur during the course of the study.

4.7. Written Informed Consent

Subjects cannot be asked to sign the Informed Consent document until the trial has been fully approved by the respective institution's EC. Subjects who meet all of the inclusion criteria and none of the exclusion criteria will be asked to sign a Patient Informed Consent form as approved by the relevant regulatory authorities before any study-specific tests or procedures are performed. The Investigator or a designated member of his / her staff should approach the subject to obtain written informed consent. As far as possible, non-technical language shall be used that is understandable to the subject. The background of the proposed study and the benefits and risks of the procedures and study should be explained. The subject should be provided with ample time to read the consent form and discuss it with their family and physician. The subject shall be informed that his / her participation in the clinical investigation is confidential. The Informed Consent Form must be read and understood by the subject and the subject's questions answered and must include information and a separate explicit consent regarding the patient's rights under the GDPR and/or national data protection laws or regulations. The form must be signed and dated by both the subject and investigator conducting informed consent before the subject undergoes any study related procedures. All subjects are to receive copies of their signed and dated Informed Consent Form. A copy of the approved informed consent form along with a copy of each patient's signed consent form will be maintained by each Investigator in a designated clinical study administrative file. The subject and the investigator must sign the consent form prior to enrollment. Subjects may not be consented after receiving any medication that might alter their ability to comprehend the consent form (e.g. sedatives, narcotics, etc.). Study personnel should explain that even if a subject agrees to participate in the study and signs the Patient Informed Consent form, the subject may not be eligible to participate if he / she fails to meet the screening criteria.

Written informed consent must be obtained prior to performing any protocol driven tests or any procedures that are not standard of care for a TAVR procedure.

Once written consent has been obtained, the subject will be entered on a Screening Log, which will be maintained at each site. All subjects who provide written informed consent will be entered on the screening log regardless of whether or not they are enrolled in the study.

As appropriate, important and new information will be provided to new and existing subjects throughout the duration of the study.

4.8. Unique Study Identification Code

Each subject will be assigned a unique study identification code in an effort to protect subject confidential information. The unique study identity code will be pseudonymized and will not include date of birth or subject's first and last initials and will be used to link study data and other study information to the subject in lieu of the subject name. The Subject Name Log will be used to link the unique study identity code to the subject and will be maintained at each site. This log will remain confidential and will not be provided to the Sponsor, but only used for reference when monitoring at the study site.

4.9. Subject Recruitment

Subjects who present with severe symptomatic calcified native aortic valve stenosis who the heart team recommends transcatheter valve aortic valve replace (TAVR) consistent with the 2017 ESC/EACTS Guidelines for the management of valvular heart disease and who have no concomitant cardiac valvular intervention or pre-existing prosthetic heart valve in any position will be considered potential study candidates. Due to the nature of this procedure, the Sponsor does not intend to advertise or otherwise actively recruit subjects.

4.10. Subject Reimbursement

Subjects will not be reimbursed or compensated for participating in the trial. Reasonable travel costs associated with follow-up visits will be reimbursed upon request.

4.11. Enrollment

Initial screening at each site will determine whether a patient is suitable for inclusion in the PROTEMBO C Trial. No PROTEMBO C Trial required assessments (baseline DW-MRI) will be performed until the patient has signed an informed consent form. After the patient has signed the informed consent, the patients will be considered enrolled in the study at the time just preceding the baseline DW-MRI assessment.

Subjects who sign consent but are excluded before enrollment will not be included in the primary analysis of the study endpoints. The reason for exclusion will be documented in the Screening Log and the consent document maintained in the site's study records.

Subjects who sign a consent form and are enrolled in the study will be considered part of the safety cohort of the study. Patients who withdraw or are lost from the study for any reason before use of the ProtEmbo device during the TAVR procedure will be replaced so that the target enrollment of 60 treated patients in whom the ProtEmbo device is used during the TAVR procedure may be achieved. Patients who are enrolled and in whom the skin is broken to insert the ProtEmbo Device, i.e. as soon as the device is inserted in the preplaced 6 Fr. equivalent guiding sheath of the radial / brachial / subclavian artery access, will form the intention to treat cohort, and patients who complete both the baseline and follow-up DW-MRI after completion of the TAVR procedure will constitute a per protocol cohort.

4.12. Duration of Subject Participation

Subjects enrolled in the trial will participate for approximately 30 days.

4.13. Study Duration

This study is expected to enroll up to 60 subjects in the intention to treat cohort within approx. 12 months. The closeout phase of the study is expected to be completed within 2 months following the last subject follow-up visit. The total duration of the study is estimated to be 14 months.

4.14. Withdrawal of Subjects

Each subject may voluntarily withdraw his / her participation from the study at any time. Investigators may discontinue a subject's participation in the study as deemed appropriate for safety considerations and / or if the subject's medical condition contraindicates further study participation. All enrolled subjects will undergo the complete study follow-up for safety evaluation.

4.15. Loss to Follow-up Considerations

A subject will be considered lost to follow-up and terminated from the study when all of the following criteria have been met:

- Documentation of three unsuccessful attempts on three different days over a period of three (3) months by the Investigator or his / her designee to contact the subject or next of kin, one of which should be by certified mail with signature confirmation.
- Prior agreement of the Sponsor to remove the subject from the clinical investigation.

If permitted by the subject in the informed consent, contact with the family doctor may be made only after three unsuccessful attempts have been made to contact the study subject.

4.16. Subject Confidentiality

All information concerning subjects or their participation in this trial will be considered confidential. Only authorized representatives, designated personnel of CRO, designated consultants, or regulatory agencies will have access to these confidential files. Subject names or other non-pseudonymous data that could directly identify a patient will not be captured on the case report forms. In addition, all patient identifiers except the unique study identification code will be redacted from any x-ray, CT and MRI images submitted from the participating site to the Sponsor or the Sponsor's designated reviewers for analysis.

4.17. Study Procedures

4.17.1. Screening and Enrollment

The overall screening and enrollment scheme for the study is shown in schematic form in Figure 4 and identifies the various phases for screening, consenting, continued eligibility assessment and assignment into the subject cohorts for the study.

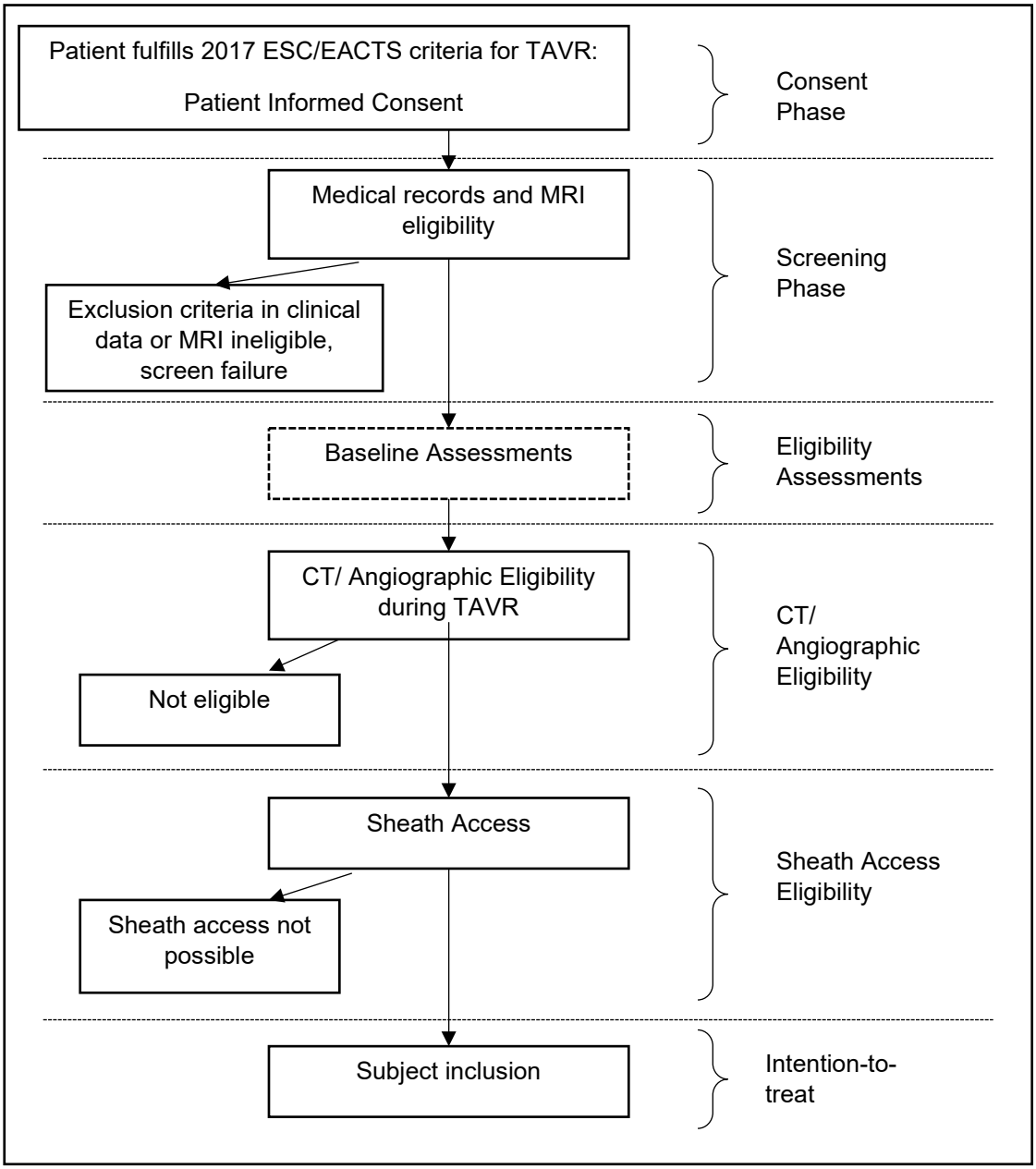

Figure 4: Screening and Enrollment Scheme.

4.17.2. Consent Phase

Prior to obtaining written informed consent, the subject's existing medical records may be reviewed by the site to determine whether or not the subject might be an acceptable candidate for this study.

If initial review of the medical records indicate that the subject may be eligible (i.e., the heart team recommends transcatheter valve aortic valve replace consistent with the 2017 ESC/EACTS Guidelines for the management of valvular heart disease and no concomitant cardiac valvular intervention or pre-existing prosthetic heart valve in any position), the informed consent process may commence.

4.17.3. Screening Phase

Each patient's medical records will be reviewed to assess compliance with the eligibility of the PROTEMBO C Trial, and the patient's ability to undergo MRI will be assessed. Patients who are eligible based on the study enrollment criteria and are capable of undergoing MRI will proceed to the next phase of the study.

4.17.4. Eligibility Assessments

Baseline evaluation will be performed after the subject has provided written informed consent in order to ensure that the subject is an appropriate candidate for this study and to obtain baseline values for study endpoint evaluation.

If the subject continues to meet the study's enrollment criteria and continues to be willing and able to participate in the study protocol, the subject will be enrolled.

All subjects will undergo a series of baseline evaluations (if not already available as part of the existing medical records). Baseline visit and data collection can occur anytime within 14 days before the TAVR procedure (unless otherwise indicated).

4.17.5. CT/ Angiographic Eligibility

Computed tomographic images of the aorta will be reviewed by the angiographic core lab and the aortic angiogram will be reviewed to confirm that the subject is eligible for participation in the PROTEMBO C Trial.

4.17.6. Sheath Access Eligibility

Computed tomographic images of the aorta will be reviewed by the angiographic core lab and an angiogram of the left radial artery will be reviewed to confirm that the subject can have a commercially available vascular sheath inserted into the left radial, brachial or subclavian artery and is, therefore, eligible for participation in the PROTEMBO C Trial.

4.18. Procedural Treatment and Timing

4.18.1. Medication Regimen

Administration of anticoagulation medication and monitoring of activated clotting time (ACT) per institution guidelines is to be performed throughout the procedure. Anticoagulant therapy should be administered pre-, peri- and post-procedure to maintain an Activated Clotting Time of at least 250 seconds for the duration of the procedure. Refer to the Instructions for Use for additional procedure specific information.

For those patients who are not under chronic oral anticoagulation prior TAVR, the use of dual antiplatelet therapy (DAPT) before and after the procedure is recommended. Those patients with chronic DAPT should continue with acetylsalicylic acid and clopidogrel therapy for at least 1 month after TAVR, as per the standard practice of the institution.

For those patients who are not taking chronic DAPT, it is recommended to administer 300 mg of each acetylsalicylic acid and clopidogrel within 24 hours (and at least 2 hours) before the procedure or the equivalent as per the standard of care at the institution.

Refer to hospital protocol for dual antiplatelet therapy.

4.18.2. MRI Timing

Standardization of the timing of scans across study sites is required to maintain integrity of the MRI analysis. The primary evaluation of the MRI scan will be performed by the MRI core lab (independent expert).

MRI will be performed at baseline and at 2-7 days following TAVR procedure. To avoid imaging any new lesions on the baseline MRI caused by the diagnostic catheterization, the baseline MRI exam should take place within two weeks before the TAVR procedure and no sooner than 5 days after any diagnostic catheterization, and there should be no diagnostic catheterization in between baseline MRI and TAVR procedure.

4.19. TAVR and ProtEmbo Procedure

Study subjects will be asked to undergo evaluation prior to and during the course of the clinical study. Such tests and procedures are outlined in the Schedule of Events and are consistent with standard of care for TAVR subjects.

The ProtEmbo device should be used strictly as described in the Instructions for Use (IFU), including the preparation, insertion, dwell time and removal of the device, specifically as detailed on pages 10-17 of the IFU. The ProtEmbo device should be inserted prior to the insertion of the TAVR device and left in place until after the deployment and removal if the TAVR device.

4.19.1. Schedule of Events

	Screening Period		Treatment Period	Post-procedure Period			
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Study Procedure	**Baseline**	**Baseline MRI**	**TAVR Procedure**	**< 24 Hour Follow- up**	**2-7 Days**	**Discharge**	**30 Day (± 7 Days)**
Informed consent							
Inclusion and exclusion criteria							
Medical history/ baseline characteristics							
Medication profile							
Physical exam							
STS score							
Blood work (Chemistry Panel)							
ECG							
Diagnostic Transthoracic Echocardiogram within 3 months of TAVR[1]							
Modified Allen's Test							
NIHSS[2]							
Adverse Event (AE) review							
Angiogram							
Multi-Slice or Multi Detector CT[3]							
MRI[4]							
ProtEmbo insertion, dwell and removal times							
ProtEmbo contrast use							
Filter specimen preparation & shipping for histopathology							
Study Exit							

Table 2: Schedule of Events.

4.19.2. Study Exit or Premature Withdrawal

Subjects will be exited from the study by completion of a Study Exit eCRF at the time of study completion provided the subject has not experienced an adverse event that is ongoing and unexplained.

Subjects may be prematurely terminated or withdrawn from the study for, including but not limited to, the following reasons:

- Subject death.
- Voluntary withdrawal – meaning that the subject voluntarily chooses not to further participate in the study.
- Preplacement of a 6 Fr. equivalent guiding sheath for radial / brachial / subclavian artery access is attempted but is not possible to complete.

[1] Conducted as part of the TAVR work up as per institution standard of care and not a dedicated study procedure.
[2] NHISS must be conducted by a neurologist. For the secondary efficacy endpoint NHISS score must be taken both on day 3 after TAVR and on the same day as the follow up MRI assessment, i.e. at 2-7 days. If MRI happens on day 3 post TAVR one singe NHISS score will suffice.
[3] Conducted as part of the TAVR work up and not a dedicated study procedure. CT should include imaging from chin to diaphragm and be done prior as per institutional standard of care ≤ 1 year of the procedure.
[4] Must be conducted on a MRI core laboratory certified scanner.

- Lost to follow-up – meaning that the subject is more than 14 days late to a study visit and 3 documented attempts to contact the subject are unsuccessful. A subject who misses a study visit but attends a subsequent visit will no longer be considered lost to follow-up. A missed visit will be considered a protocol deviation and the deviation will be documented and reported.
- In the physician's opinion, it is not in the best interest of the subject to continue study participation.

All subjects enrolled (including those withdrawn or lost to follow-up) shall be accounted for and documented.

5. Risk Benefit Assessment

Sponsor has conducted an analysis of the benefits and risks of the ProtEmbo Cerebral Protection System and procedure. A detailed Risk Assessment has been completed and reviewed with physicians and interventional cardiologists with significant TAVR experience, and potential study investigators. The conclusion of this review is that this research study is justified because the overall potential benefit to the population outweighs its attendant risks.

5.1. Potential Adverse Events

The ProtEmbo System is introduced to the vascular system via radial / brachial / subclavian vascular access which is standard medical practice for contemporary coronary-related interventions (e.g. PCI). The risks of this access route are well known and tolerated (Bavishi *et al.*, 2016). In addition, the ProtEmbo System does not have any associated unique clinical risks associated with this access route. Procedural risks are reduced by non-femoral access, the main thoroughfare during TAVR procedures where valve delivery systems and catheter-based accessory devices have the potential for interaction and entanglement. Additionally, the closure of a 6 French radial / brachial access is generally accepted as lower risk than closure of a femoral access.

There are Adverse Events associated with any endovascular / cardiovascular intervention and complications may develop. The following anticipated events have been identified as possible complications of transcatheter procedures in general and these and others may be associated with the ProtEmbo System:

- Acute cardiovascular surgery (need for)
- Acute neurological events such as: Stroke or transient ischemic attack (TIA)
- Allergic reactions to contrast, antiplatelet therapy or device component materials
- Aneurysm or pseudo-aneurysm
- Aortic dissection
- Arteriovenous fistula
- Ascending or descending aorta trauma
- Atrial or ventricular arrhythmias or fibrillation, hearth palpitations (sustained requiring therapy)
- Bleeding complications such as hematoma and hemorrhage

- Blood loss requiring transfusion
- Blue toe syndrome or blue discoloration of a toe
- Bowel ischemia
- Death
- Device failure and subsequent need to use a snare or other medical interventional techniques to retrieve the pieces
- Dissection of the left radial, left brachial, or left subclavian artery
- Embolism (air, tissue, device, or thrombus)
- Hemodynamic changes
- Infection, including endocarditis and septicemia
- Local trauma to the aortic wall due to device migration
- Peripheral ischemia, peripheral nerve damage
- Pyrogenic reactions, fever
- Renal complications, injury, or failure
- Systemic embolization
- Vascular complications which may require vessel repair
- Vessel spasm (sustained, not responding to therapy)

The following anticipated events have been identified as possible complications of transcatheter procedures in general and these and others may be associated with the TAVR procedure:

- Access site complication or injury including infection or thrombus
- Acute cardiovascular surgery (need for)
- Acute coronary or other artery occlusion
- Acute myocardial infarction
- Acute neurological events such as: Stroke, transient ischemic attack (TIA), encephalopathy
- Allergic reactions to contrast, antiplatelet therapy or device component materials
- Anesthesia reactions
- Aneurysm or pseudo-aneurysm
- Angina pectoris
- Aortic dissection
- Arteriovenous fistula
- Ascending or descending aorta trauma
- Atrial or ventricular arrhythmias or fibrillation, hearth palpitations (sustained requiring therapy)
- Bleeding complications such as hematoma and hemorrhage
- Blood loss requiring transfusion
- Blue toe syndrome or blue discoloration of a toe
- Bowel ischemia
- Cardiac tamponade
- Cardiac conduction abnormalities requiring temporary or permanent pacemaker

- Cardiogenic Shock
- Conduction system injury
- Congestive Heart Failure
- Coronary artery or other vascular injury, dissection, or perforation which may need repair
- Death
- Device failure and subsequent need to use a snare or other medical interventional techniques to retrieve the pieces
- Embolism (air, tissue, device, or thrombus)
- Encephalopathy
- Femoral nerve damage
- Hemodynamic changes
- Hypertension or hypotension (sustained requiring therapy)
- Infection, including endocarditis and septicemia
- Pain (at puncture site, adnominal, back or other)
- Percutaneous coronary intervention (need for)
- Pericardial effusion
- Peripheral ischemia, peripheral nerve damage
- Pneumonia
- Pulmonary edema or embolism
- Pyrogenic reactions, fever
- Radiation injury
- Renal complications, injury, or failure
- Renal insufficiency / failure due to excessive contrast load
- Respiratory insufficiency or failure
- Systemic embolization
- Unstable angina
- Vascular complications which may require vessel repair
- Vessel spasm (sustained, not responding to therapy)

There are standard risks associated with any interventional procedures and TAVR as well as risks specific to the ProtEmbo System and procedure. Risks associated with any interventional procedure include access site hemorrhage or hematoma, access site pain, acute vessel closure, infection, renal insufficiency / failure due to excessive contrast load, and death. The risks stated below concern each system manufactured by Sponsor and their use in the ProtEmbo procedure.

Possible risks related to the delivery system used to deliver the ProtEmbo Device include, but are not limited to, the following: Vessel dissection, perforation or wall trauma, embolism, infection, bruising or hemorrhage at the procedural access site, vessel thrombosis, bleeding or infection.

Possible risks related to the ProtEmbo Device include, but are not limited to, the following: Vessel thrombosis, stenosis or occlusion, vessel dissection, perforation or wall trauma, embolism, bleeding infection or arterial side branch occlusion.

Additionally, subjects will be exposed to risks associated with conscious sedation, use of radiographic contrast and procedural medications. An Investigator will discuss with each subject the standard risks associated with these procedures and medications.

Non-contrast MRI may cause feelings of anxiety or claustrophobia during the MRI.

5.2. Potential Risks to Subject Confidentiality and Privacy

In all clinical studies, confidentiality of protected health information may be breached due to study-related activities beyond those of routine clinical care. This also includes risks of privacy and release of protected health information (PHI). This risk will be minimized through the use of a unique and anonymous study identification code. No identifying information will be reported on electronic Case Report Forms (eCRFs) or other study related documentation that is provided to the Sponsor.

5.3. Minimization of Anticipated Risks

Efforts to minimize risk include the following:

- Clearly defining the subject inclusion / exclusion criteria.
- Selecting a sufficient number of at least 3 intended users and only qualified, experienced Investigators who have participated in an extensive training program to assure thorough knowledge of the Investigational Plan and proper technique for implantation of the ProtEmbo System.
- Monitoring angiographic, electrocardiographic and hemodynamic parameters during placement of the device to evaluate for any compromise of the subject's condition.
- Attending to arterial access techniques to minimize the trauma to vascular structures.
- Ensuring that treatment and follow-up of subjects is consistent with standard and current medical practice.
- Providing clinical support for device related guidance during the implant procedure.
- Safety oversight by Medical Monitor, for individual subjects as well as across the entire study population.
- If the Investigator and / or the Medical Monitor determine that an AE is sufficiently severe to remove the subject from the study, a termination assessment will be performed. The subject will then be given appropriate treatment under medical supervision.
- If the Medical Monitor determines a negatively high rate for a particular safety issue across the subject population, a termination assessment will be performed, and the Medical Monitor may recommend enrollment in the study to be stopped. PHI protection measures such as use of a unique study identification code and a commitment from all participants to protect subject confidentiality at every step during the investigation.
- PHI protection measures such as use of a unique study identification code and a commitment from all participants to protect subject confidentiality at every step during the investigation.

5.4. Potential Benefits

Based upon literature review and pre-clinical evaluations performed to date, it is expected that the ProtEmbo System may provide benefit to the subject by deflecting potentially harmful embolic debris liberated during the TAVR procedure. Without the ProtEmbo System, embolic debris would otherwise travel unimpeded via the cerebral circulation to the brain and could lead to cerebral vascular events such as stroke and / or TIA. There is currently no FDA cleared treatment option for embolic protection during TAVR. The potential benefits include a reduction in median total new cerebral lesion volume as assessed by DW-MRI, which may lead to a decrease in cerebral vascular events, such as stroke or TIA and neurocognitive deficits after the TAVR procedure.

However, the actual benefits are not known and are the subject of this investigational study. There may be no direct benefits of study participation. However, subject participants will undergo an enhanced level of clinical scrutiny of health compared to routine clinical care, which may provide some indirect health benefits.

6. Statistical Analysis Plan

6.1. Overview

The primary objective of this study is to assess the safety and performance of the ProtEmbo Cerebral Protection System used for embolic protection during Transcatheter Aortic Valve Replacement (TAVR) compared to TAVR standard of care (without embolic protection). The secondary objective of the study is to assess the efficacy of the ProtEmbo system by comparing the median new lesion volume in the brain and the rate of death or all strokes compared to historical data.

All enrolled subjects will form the safety cohort. All subjects in whom the skin is broken to insert the ProtEmbo Device, i.e. as soon as the device is inserted in the preplaced 6 Fr. equivalent guiding sheath of the radial / brachial / subclavian artery access will be followed on an intent-to-treat basis. Those subjects who complete the baseline and follow-up DW-MRI studies after completion of the TAVR procedure constitute the per protocol cohort. The device safety will be assessed based on an analysis of the primary safety endpoint within the safety cohort. The primary performance endpoint will be assessed in the intention to treat cohort, and secondary efficacy endpoints will be assessed based on a per protocol analysis.

Standard summary statistics will be calculated for all study variables. For continuous variables, statistics will include means, standard deviations, medians and ranges. Categorical variables will be summarized using frequency distributions.

6.2. Primary Safety Endpoint

The primary safety endpoint is Major Adverse Cardiac and Cerebrovascular Events (MACCEs) at 30 days as defined by VARC-2, including all-cause mortality, all stroke and acute kidney injury (stage 3). The objective is to assess whether MACCE rate at 30 days for the ProtEmbo System meets the Performance Goal (PG). The null and alternative hypotheses are given by:

$$H0: \pi \geq PG$$

HA: π < PG,

Where π is the ProtEmbo System MACCE rate at 30 days and the performance goal (PG) is 25%.

The safety hypothesis will be tested in the safety cohort (all enrolled subjects) by calculating the one-sided upper 95% confidence limit using the Wilson Method. The null hypothesis will be rejected if the upper limit of the 95% confidence interval is less than the PG.

Derivation of the Performance Goal (PG):

The PG for the primary endpoint was established based upon data available in the literature for patients undergoing embolic protection for TAVR using the Sentinel and the TriGuard embolic protection devices.

In the randomized controlled SENTINEL trial (Sentinel device) of 363 patients, the rate of MACCE (defined as death from any cause, any type of stroke, or stage-3 acute kidney injury [AKI]) in the cerebral protection group (7% [17/234]) was not statistically significantly different from that of the control group (10% [11/111]) at 30 days (p=0.40).

In the randomized controlled DEFLECT III trial (TriGuard device) of 85 patients, the rate of in-hospital MACCE (defined as all-cause mortality, all stroke, life-threatening or disabling bleeding, stage-2 or stage-3 AKI, or major vascular complications) was similar in both groups (control TAVR group without TriGuard device versus TAVR plus TriGuard device): 22% compared with 31% (RR 0.71, 95% CI 0.34 to 1.46; p=0.34). The rates of 30-day MACCE were also similar: 26% compared with 31% (RR 0.83, 95% CI 0.37 to 1.84; p=0.62).

The MACCE rate of individuals undergoing TAVR without embolic protection is the appropriate MACCE rate to set the PG for the ProtEmbo System. Based on the number of subjects treated in the control groups of both trials, we estimate a weighted MACCE rate of 15% (23/150), 95% CI: 10%, 22%.

To establish the PG for ProtEmbo System, a statistical margin of 10% is added to 15% to obtain a PG of 25% for the primary safety endpoint.

Sample Size:

Under a desired power of 85% and a one-sided test of the hypothesized MACCE rate for the ProtEmbo System of 10% at alpha = 0.025, a sample size of 60 treated patients is required (Chow et al., 2008).

6.3. Primary Performance Endpoint

The primary performance endpoint is technical success, defined as ability to safely deliver, deploy, and remove the device, ability to secure positioning and stability of the position throughout the transcatheter intracardiac procedure and ability to deflect embolic material as assessed by adequate coverage while not impeding blood flow. The objective is to assess whether rate of technical success for the ProtEmbo System meets the Performance Goal (PG).

The null and alternative hypotheses are given by:

H0: $\pi \leq$ PG

HA: $\pi > PG$,

where π is the ProtEmbo System success rate and the performance goal (PG) is 75%.

The performance hypothesis will be tested in the intention to treat cohort by calculating the one-sided lower 95% confidence limit using the Wilson Method. The null hypothesis will be rejected if the lower limit of the 95% confidence interval is greater than the PG.

Derivation of the Performance Goal (PG):

The PG for the primary performance endpoint was established based upon data available in the literature for patients undergoing embolic protection for TAVR using the TriGuard embolic protection device.

In the randomized controlled DEFLECT III trial of 85 patients, 45 TriGuard devices were used in 44 patients; 2 randomized patients withdrew consent before device introduction, and 1 patient received 2 TriGuard devices over the course of a valve-in-valve procedure. The device was successfully positioned and maintained in position throughout prosthetic-valve deployment, implantation, and retrieval in 89% (40/45, 95% CI [75% to 96%]) of patients. There were no device failures.

The performance success rate of the test arm is the appropriate rate to set the PG for the ProtEmbo System. The comparator rate is therefore set at 90%.

To establish the PG for the ProtEmbo System, a statistical margin of 15% is subtracted from 90% to obtain a PG of 75% for the primary performance endpoint, which is the lower limit of the 95% confidence interval for the DEFLECT III trial.

Under a desired power of 85% and a one-sided test of the hypothesized success rate for the ProtEmbo System of 89% at alpha = 0.025, the required sample size is 42 (Chow et al., 2008). The sample size necessary to test the Primary Safety Endpoint requires a larger number of subjects, and the PROTEMBO C Trial will, therefore, be adequately powered to test the null and alternate hypotheses for the Primary Performance Endpoint.

6.4. Secondary Efficacy Endpoint

The use of magnetic resonance imaging (MRI) is a well-established tool for quantifying ischemic lesions in the brain. Diffusion weighted MRI (DW-MRI) is used to characterize ischemic lesions that have occurred within the first several days of an embolic event (Lansky *et al.*, 2017). Total lesion volume and likelihood of neurological deficit are strongly associated. The occurrence of a single or few small lesions may result in large total lesion volumes. Therefore, the number of lesions may not correlate well to the total volume or clinical outcome and will not be of primary interest. The use of DW-MRI as a surrogate endpoint for risk of sub-clinical stroke has been proposed (Lansky, 2017), and the DW-MRI analysis of new lesion volume will use the standard assessments as outlined by Lansky et al. Therefore, a secondary efficacy endpoint for this clinical investigation will be based on magnetic resonance (MR) imaging comparing the median new lesion volume in the brain assessed by diffusion weighted magnetic resonance images (DW-MRI) at 2 to 7 days with historical data. The total new lesion volume will be defined as the sum of all diffusion-positive new cerebral lesions in post-procedural DW-MRI relative to the pre-TAVR DW-MRI. The analyses of secondary endpoints will be conducted in the per protocol cohort.

The median value of lesions among patients has been selected because the distribution of new lesions is not normally distributed and the median value appears to represent the distribution of lesion volumes among patients (Kapadia *et al.*, 2017). Nevertheless, the number of new lesions, the mean of new lesion volumes, and the variances of these measures will also be analyzed.

The severity of pre-existing central nervous system lesions on baseline T2-weighted MRI (FLAIR) is an independent predictor of the number of lesions on DW-MRI obtained 3 days after TAVR (Dwyer *et al.*, 2017); patients with a large number of vascular / embolic lesions at baseline tend to have a large number of new lesions after TAVR. FLAIR-MRI can be used to account for baseline lesions and has been proposed as a mechanism of differentiating silent cerebral events (regions of increased intensity on the DW-MRI) from silent cerebral lesions (more permanent white matter changes identifiable on FLAIR-MRI) (Deneke *et al.*, 2015). To account for the presence and predictive power of pre-TAVR lesions, multilevel mixed effects models in which time will be a repeated within subject factor and subject will be treated as a random effect (a random intercept model) will be used to evaluate median, and mean lesion volumes and number of new lesions. Separate analyses will be performed for the main secondary MRI endpoint (median new lesion volume) and subsidiary analyses (mean new lesion volume, number of new lesions and variances of these measures). We will make no assumption about the structure of the covariance matrix. This regression model permits us to determine the rate of new lesion occurrence after TAVR (the slope of the regression) and the effect of baseline lesion values on the number of lesions after TAVR (the random subject effect / random intercept). We will include demographic data (e.g. age and pre-existing cerebral lesions determined from the FLAIR-MRI) and other relevant variables as covariates in these models, and we will stratify outcomes *a priori* based on the type of valve used during the TAVR.

An additional secondary efficacy endpoint for this clinical investigation is defined as the composite rate of death or all strokes according to VARC-2 criteria, to define occurrence and type stroke, within 3 days (72 hours) of the TAVR procedure compared to historical data. Stroke severity will be quantified according to the National Institutes of Health Stroke Scale (NIHSS) score.

In previous studies, such as the SENTINEL US IDE trial, stroke rates of 9.1% have been reported for patients receiving no embolic protection at 30 days (111 patients in control arm and 234 in device arm). All assessments were assessed by neurologists. A patient-level pooled analysis for the SENTINEL US IDE, the CLEAN-TAVI and the SENTINEL-Ulm studies was also conducted (Seeger et al.). A total of 1,066 patients were analyzed in this study (533 with Sentinel versus 533 control). The rate for all-strokes for patients without embolic protection within 3 days was 5.44% (29/533). The rate of all-cause mortality or stroke within 3 days was 6.0% for patients with no embolic protection (32/533).

6.5. Demographic, Safety, Feasibility and Efficacy Data

Demographic and baseline clinical and disease characteristics will be summarized in tables. For continuous variables, the summary will include number, mean, and standard deviation and 95% confidence intervals. Summaries for categorical variables will include the number and percent of subjects in each category.

6.6. Imputation of Missing Data

Missing data will be replaced using the “worst” value in each subject.

7. Adverse Event and Incident Reporting

The occurrence of Adverse Events will be monitored during this study. All Adverse Events will be recorded on the Complication / Adverse Event Form at onset and at each follow-up visit until resolved. To meet the objectives of this study, the following definitions will apply (DIN EN ISO 14155:2012-01 Clinical investigation of medical devices for human subjects - Good Clinical Practice, including DIN EN ISO 14155:2018-08 – draft 18-06-29).

7.1. Adverse Event (AE)

An **Adverse Event (AE)** is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the medical device. This includes events related to the device or events related to the procedures involved.

An **Adverse Device Effect** is an adverse event related to the use of a medical device, including adverse events resulting from insufficient or inadequate Instructions for Use, deployment, implantation, installation or operation, or any malfunction of the medical device or any event resulting from user error or intentional misuse of the medical device.

The Investigator is responsible for assessing the severity of the AE, the causal relationship between any events and the clinical study procedure, activities or device. Additionally, the Investigator is responsible for providing appropriate treatment for the event and for adequately following the event until resolution. The following categories of adverse event severity are to be used:

1. **Mild:** Awareness of a sign or symptom that does not interfere with the subject’s usual activity or is transient, resolved without treatment and with no clinical sequelae.
2. **Moderate:** Interferes with the subject’s usual activity.
3. **Serious:** Any fatal or immediately life-threatening clinical experience that requires a subject to be hospitalized, or hospitalization is unduly prolonged because of potential disability or danger to life or because an intervention has been necessitated. This includes any permanently disabling event.

7.2. Serious Adverse Events (SAE)

A **Serious Adverse Event (SAE)** is any problem or unwanted event encountered in a clinical trial or a performance evaluation that has led, or could have led, directly or indirectly to death or to a serious deterioration in the health of a subject or user or any other person, without regard to whether the event was caused by a medical product. The following events (including laboratory results and outcome events) will be considered to be SAEs and must immediately (within 24 hours) be reported to the study Sponsor and / or designated representative by telephone, fax and / or email. These events must be reported whether or not the Investigator believes they are related to study procedures, activities or device:

- Death
- Serious deterioration in the health of the subject, that either resulted in
  - a life-threatening illness or injury, or
  - a permanent impairment of a body structure or a body function, or
  - in-patient or prolonged hospitalization, or
  - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

7.3. Serious Adverse Device Effect (SADE)

A **Serious Adverse Device Effect** is an adverse device effect that has resulted in any of the consequences of a Serious Adverse Event.

NOTE: Planned hospitalization for a pre-existing condition, a condition unrelated to the treatment or a procedure required by this study, that is without serious deterioration in health, is not considered a serious adverse event.

7.4. Unanticipated Serious Adverse Device Effect (USADE)

Unanticipated Serious Adverse Device Effect (USADE): Serious adverse device effect which, by its nature, incidence, severity or outcome has not been identified in the risk analysis.

7.5. Anticipated Serious Adverse Device Effect (ASADE)

Anticipated Serious Adverse Device Effect (ASADE): An effect, which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

7.6. Unanticipated Adverse Device Effect (UADE)

Unanticipated Adverse Device Effect (UADE): An adverse device effect which by its nature, incidence, severity or outcome has not been identified in the risk analysis report.

7.7. Anticipated Adverse Device Effect (AADE)

Anticipated Adverse Device Effect (AADE): An effect, which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

7.8. Reporting of Adverse Events (AEs) and Serious Adverse Events (SAEs)

Documentation of all AEs / SAEs: All incidents will be captured as a part of this clinical study. At each contact with the subject, the Investigator will seek information on adverse device effects by specific questioning and, as appropriate, by examination. Information on all adverse device effects will be recorded immediately in the source document, and also in the appropriate adverse effect electronic Case Report Form (eCRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document.

Reporting of SAEs: All SAEs, UADEs and possible device and / or procedure- related adverse events must be recorded on the Adverse Event eCRF by the Investigator (or his / her designee) and reported to the Sponsor and its designated representative (MAXIS Medical GmbH) within

24 hours via fax or email. The report should include: Description of incident, severity, duration, action taken, treatment outcome and relationship of the adverse event to the study device, procedure, concomitant medications, pre-existing condition, etc. (i.e., unrelated, relation or relationship unknown).

In the case of serious adverse events (SAE), procedure and / or device failures and malfunctions, medical record documentation (e.g., procedure notes, operative notes, discharge summary, relevant progress notes, imaging or lab studies) must be provided to the Sponsor and its designated representative, if requested .This information shall be faxed or send by email as requested as soon as possible but latest within 24 hours to the Study Monitor / Sponsor. If appropriate, Sponsor shall inform the Competent Authority and the relevant Ethics Committee about the event within the appropriate timelines. In accordance with MEDDEV 2.7/3 rev.3 (May 2015), the Sponsor must report:

- all reportable events as described in section 5.1 which indicate an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients / subjects, users or other persons or a new finding to it,
- to the National Competent Authorities where the clinical investigation has commenced,
- Immediately, but not later than 2 calendar days after awareness by Sponsor of a new reportable event or of new information in relation with an already reported event.

7.9. Reporting of Device Failures and Malfunctions

All reported device malfunctions or failures of the ProtEmbo System are required to be documented in the eCRF and must be immediately reported to the study sponsor and its designated representative (MAXIS Medical GmbH) by telephone, fax and / or email within 24 hours. Device failures and malfunctions should also be documented in the subject's medical record. Instructions for returning the investigational device will be provided.

NOTE: Device failures or malfunctions are NOT to be reported as adverse events. However, if there is an adverse event that results from a device failure or malfunction, that specific event would be recorded in the usual way as per the previous chapter.

7.10. Documentation, Evaluation and Notification of Serious Adverse Events

The Investigator shall report all serious adverse events (anticipated or unanticipated) to Sponsor and Sponsor's designated representative within 24 hours upon becoming aware of events.

Authorized Representative / CRO Contact Information:

MAXIS Medical GmbH
Stichlingstrasse 1
60327 Frankfurt am Main
Germany
Tel: +49 69 2400 3626
Fax: +49 69 2400 3627
Email: maxisoperations@maxismedical.com

Sponsor:

Protembis GmbH
Pauwelsstraße 17
D-52074 Aachen
Germany
Tel: +49 241 99033622
Fax: +49 241 99033623
Email: info@protembis.com

The Sponsor and / or its designated representative will ensure compliance with all country-specific reporting requirements to the appropriate Ethical Committees and Competent Authorities.

8. Monitoring

The Sponsor or its designated representative, qualified by training and experience, will be responsible for monitoring and overseeing the conduct of the trial. The accuracy of all collected data will be verified for:

- Eligibility criteria
- Baseline characteristics
- Primary safety and feasibility endpoints
- Adverse events
- Secondary endpoints

with source documents including, but not limited to, medical records, office / clinic notes, procedure reports, laboratory results, physician and nursing progress notes. Verification and quality of data, monitoring of clinical study progress and Investigator compliance with the approved protocol will be conducted by the Sponsor or its designated representative.

The Sponsor or its designated representative must be allowed to visit the clinical site and have direct access to all study records throughout the duration of the study. The monitor will review all source data and compare them to the data documented in the case report forms, in addition to performing a review of the Regulatory Binder and conducting device accountability. The Investigator and / or institution will provide direct access to source data / documents for trial-related monitoring, audits, and regulatory review and inspection.

It is important that the Investigator and relevant study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

Additionally, telephone, email contact, and onsite visits will be conducted on a regular basis with the Investigator and the site staff to ensure that the protocol is being followed and to address any issues that may occur during the trial.

If a deficiency is noted during the course of the trial the clinical monitor is required to discuss the situation with the site and the Sponsor (if required) to secure compliance.

9. Study Management

The Sponsor has overall responsibility for the conduct of the study according to Good Clinical Practice Guidelines (ICH E6 Consolidated Guidance to Good Clinical Practice) as well as any conditions imposed by local and national regulatory authorities.

For this study, Sponsor will have direct responsibilities and will delegate other responsibilities to appropriate and qualified consultants, contractors and / or Contract Research Organizations (CROs). Together, the Sponsor, consultants and CROs will ensure that the study is conducted according to the Clinical Investigational Plan and all applicable and governing regulations. All personnel to participate in the conduct of this clinical trial will be qualified by education and / or experience to perform their tasks.

9.1. Key Contributors

9.1.1. Study Sponsor

Protembis GmbH, Pauwelsstraße 17, 52074 Aachen

Phone: +49 241 99033622; Email: info@protembis.com

9.1.2. Authorized CRO / Representative

MAXIS Medical GmbH, Karpfenweg 12, D-60327 Frankfurt am Main

Office Phone: +49 69 2400 3626; Fax: +49 69 2400 3627

Email: MaxisOperations@maxismedical.com

9.1.3. Clinical Sites

A complete listing of all clinical sites will be maintained by the Sponsor and will be available upon request.

9.1.4. MRI Core Laboratory

Robert Zivadinov, M.D., Buffalo Neuroimaging Analysis Center, University at Buffalo, State University of New York, 100 High Street, Buffalo, NY 14203; Office Phone: +1-716-859-3579

An MRI Core Laboratory will be utilized in this clinical study for the independent confirmation of MRI findings at the site level. The independently confirmed findings will be utilized in the reporting of the clinical data. A standard measurement process will be designed by the independent reviewer and each investigative site will receive training on the acquisition and transmission of images.

9.1.5. Histopathology Core Laboratory

Renu Virmani, M.D., CVPath Institute, Inc., 19 Firstfield Road, Gaithersburg, MD 20878; Office Phone: +1-301-208-3570

A Histopathology Core Laboratory will be used in this clinical study for the independent review of the ProtEmbo System. The independently confirmed findings will be utilized in the reporting of the clinical data.

9.1.6. CT Core Laboratory

AngioConsult GmbH, Heydenreichstr. 5, 67346 Speyer, Germany; Office Phone: +49-6232-6042890

A CT Core Laboratory will be used in this clinical study to assess the including and exclusion criteria based on CT data. The independently confirmed assessment will be utilized in the enrollment process.

9.2. Ethical Considerations

The rights, safety and well-being of clinical investigation subjects shall be protected consistent with the ethical principles as defined in the Declaration of Helsinki 2013. These principles shall prevail over interests of science and society and shall be understood, observed and applied at every step in this clinical investigation.

It is expected that all parties will share in the responsibility for ethical conduct in accordance with their respective roles in the investigation. The Sponsor and the Investigator(s) shall avoid improper influence or inducement of the subject, monitor, the clinical investigator(s) or other parties participating in or contributing to the clinical investigation.

9.3. Insurance

The Sponsor will maintain the appropriate and necessary insurance coverage for the duration of the study.

9.4. Study Conduct

This study will be performed in accordance with the relevant parts of the ICH E6 Guidelines for Good Clinical Practices (GCP), DIN EN ISO 14155:2012-01 Clinical investigation of medical devices for human subjects - Good Clinical Practice (including DIN EN ISO 14155:2018-08 – draft 18-06-29), the Declaration of Helsinki 2013, and any regional and / or national regulations. The clinical investigation shall not begin until the required approval has been obtained from the relevant national regulatory authority and the local Ethical Committee. Any additional requirements imposed by the regulatory authority or EC shall be followed.

9.5. Audits and Inspections

The principal Investigator will also allow and support representatives of the governing EC, the Competent Authority, and other applicable regulatory agencies to inspect all study records, eCRFs, and corresponding portions of the subject's office and / or hospital medical records at regular intervals throughout the trial. The principal investigator will provide direct access to source data / documents. These inspections are for the purpose of verifying adherence to the protocol, completeness and exactness of the data being entered onto the eCRFs and compliance with European Union or other regulatory agency regulations.

The principal investigator will inform the Sponsor or the Sponsor's designee should they be 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 inspection by a regulatory agency.

Audits may also be conducted by the Sponsor or the Sponsor's designee to evaluate compliance with the protocol, written procedures, ICH Guidelines for Good Clinical Practices, the European Standard ISO 14155:2012, and other applicable regulatory requirements. These audits are independent of and separate from routine monitoring visits. The audit results will be documented and communicated to relevant parties, if applicable.

9.6. Sponsor Responsibilities

Sponsor has the overall responsibility of the study and will:

- Select qualified Principal Investigators, clinical investigators and study sites
- Select qualified monitors
- Provide the Investigational Plan and any subsequent amendments
- Provide appropriate information and System training to Investigators and study site staff, including on-site clinical/technical support by qualified staff of Sponsor or Sponsor's representative for each clinical case in the study
- Ensure that all deviations from the Investigational Plan are reviewed with the appropriate Investigator(s) and reported in the eCRF and the final report and that any necessary preventative or corrective action is taken
- Ensure that all adverse events and all adverse device effects (ADEs) are reported and reviewed with the Investigator(s), and where appropriate, that all serious adverse events (SAEs) and all serious adverse device effects (SADEs) are appropriately reported
- During the course of the investigation, inform in writing all Investigators about adverse events and adverse device effects that have been reported to Sponsor (this information shall be sent to each Investigator based on perceived risk)
- Promptly inform the Investigators and where applicable, any regulatory authorities, if the study is prematurely terminated or suspended and the reason for the termination or suspension
- Ensure proper device usage, uniform data collection and protocol compliance
- Provide protocol initiation training to include review of the ProtEmbo System instructions for use, the Investigational Plan, eCRF completion guidelines, and guidelines for obtaining informed consent
- Provide the ProtEmbo System to participating study sites, in quantities to support study activities
- Coordinate ongoing communication with CRO(s), consultants and study sites to resolve any problems concerning the protocol or data collection
- Every effort will be made to ensure compliance with the protocol
- Retain ownership of all clinical data generated in this study, and control the use of the data for purposes of regulatory submissions to CAs
- Protect subject confidentiality

9.7. Monitor Responsibilities

The Sponsor has contracted MAXIS Medical as the Clinical Monitor to support the Sponsor in implementing and monitoring the clinical investigation until its termination. Clinical monitors,

qualified by training and experience, will be responsible for monitoring and overseeing the conduct of the trial.

Clinical monitors will conduct site initiation visits at each investigational site to ensure that the principal investigator and other investigational site personnel involved in the conduct of this investigation have received and understood the requirements and contents of this clinical investigational protocol, the Investigator's Brochure, the patient informed consent form, the eCRFs, the Instructions for Use and the institution and / or investigator agreement.

Clinical monitors will ensure that the site facilities are adequate for the conduct of this investigation and that resources, laboratories, equipment and personnel remain adequate throughout the investigation.

The clinical monitors will conduct routine on-site monitoring visits and phone calls to evaluate compliance with the protocol, any specific recommendations made by the site's Ethics Committee (EC) and the signed Institution and/or Investigator Agreement and to ensure that the protocol is being followed and that any protocol deviations are properly documented on respective form. Clinical monitoring will include a verification that Informed Consent Form was properly obtained for all enrolled trial participants, a review of clinical records for accuracy and completeness, resolution of missing or inconsistent results and a review of source documents.

Clinical monitoring will include a review of all adverse events and device malfunctions to ensure that all information has been reported to the sponsor, EC and regulatory authorities as required by this investigational plan and applicable standards and laws.

The clinical monitor will verify that the electronic Case Report Forms (eCRFs) are complete and in agreement with the source documentation and other records. The clinical monitor will ensure that all eCRFs have been electronically signed and dated by the investigator.

The investigator will make available to the clinical monitor for review all Informed Consent documents, all completed eCRFs, source documentation and other relevant records for all enrolled subjects at the site. It is important that the investigator and other relevant site personnel are available for consultation with the clinical monitors during the monitoring visits and that sufficient time is devoted at the site for the monitoring process.

If a deficiency is noted during an on-site visit or at any other time during the course of the trial, the clinical monitor is required to discuss the situation with the investigator and the Sponsor, and to subsequently monitor the implementation of corrective actions that are required to address the situation.

All monitoring activities will be documented by the clinical monitor and will include, at a minimum, the date, investigational site visited, names of all personnel involved in the visit, a listing of all documents reviewed and a summary of all findings, facts, deviations conclusions and recommended actions to be taken. Key findings will be reviewed with the clinical investigator.

Upon completion of the study, a study close out visit will be conducted to ensure that all data collection and study requirements are complete.

9.8. Investigator Responsibilities

At a minimum, the following documents will be provided by the investigational site to the Sponsor prior to study start (consent of the first subject):

- Signed Clinical Trial Agreements
- Signed Financial Disclosure Form
- Signed Clinical Investigational Plan Signature Page
- Relevant regulatory approvals
- Investigator and Co-Investigator's current Curriculum Vitae
- Any other additional documents as required by the Sponsor

The Investigator is responsible for ensuring that the investigation is conducted according to all signed agreements, the study protocol, governing regulations, data protection regulations, the medical device laws, the Declaration of Helsinki and any other conditions imposed by the relevant regulatory authorities. The Investigator is responsible for maintaining medical and study records for every subject participating in the clinical study (including information maintained electronically such as digital imaging). The Investigator will also maintain original source documents from which study-related data are derived.

The Investigator(s) shall be responsible for the day to day conduct of the investigation as well as for the safety and well-being of the human subjects involved in the clinical investigation.

The Investigator(s) shall:

- Have the resources to conduct the investigation properly
- Ensure that conducting the investigation will not give rise to a conflict of interest
- Obtain from the Sponsor the information which the Investigator(s) judges essential about the device and be familiar with this information
- Be well acquainted with the Clinical Investigation Protocol (CIP) before signing the signature page
- Support the monitor, auditor, if applicable, in their activities to verify compliance with the CIP, to perform source data verification and to correct the eCRF where inconsistencies or missing values are identified
- Discuss with the Sponsor management any question of modification of the CIP
- Make sure that the CIP is followed by all responsible for the conduct of the study at his / her institution. Any deviation shall be documented and reported to the study Sponsor
- Make the necessary arrangements to ensure the proper conduct and completion of the investigation
- Make the necessary arrangements for emergency treatment, as needed, to protect the health and welfare of the subject
- Ensure that appropriate regulatory approval is obtained prior to the start of the investigation
- Provide regulatory approvals to the Sponsor
- Inform Sponsor about adverse events in a timely manner
- Endeavor to ensure an adequate recruitment of subjects
- Ensure that the subject has adequate information to give informed consent
- Ensure that informed consent is obtained and documented
- Ensure that clinical records are clearly marked to indicate that the subject is enrolled in this study
- Provide subjects with well-defined procedures for any emergency situation and safeguard the subject's interest. Under these circumstances, deviations from the CIP

shall not require the prior approval of the Sponsor or the national and local regulatory authorities. Such deviations shall not be considered as a breach of agreement but shall be documented and reported to Sponsor

- Ensure that information which becomes available as a result of the clinical investigation which may be of importance to the health of a subject and the continuation of the investigation shall be made known to the Sponsor and, if pertinent to the safety or well-being of the subject, and the private clinician
- Inform the subject and / or the subject's physician about any premature termination or suspension of the investigation with a rationale for study termination
- Have primary responsibility for the accuracy, legibility and security of all investigation data, documents and subject records both during and after the investigation
- Sign each subject's eCRF, as applicable
- Be responsible for the supervision and assignment of duties at his / her clinical center
- Ensure that all investigational devices are kept in a secure location and that all Systems are accounted for (number of devices used, discarded and returned to Sponsor)

9.9. Study Funding

This clinical investigation is fully funded by the Sponsor. The Sponsor or its designated representative will enter into clinical research / clinical trial agreements with all clinical sites participating in the study. Comparable research agreements will be executed with core laboratories or other contributors in this clinical investigation.

9.10. Investigator Training

The ProtEmbo System is intended for use by experienced physicians. A limited number of Investigators at each site will be authorized to use the study device. These investigators will be provided with comprehensive training by Sponsor personnel (or designated representative) in the use of the device with a bench top model or equivalent prior to their participation in the clinical study.

9.11. Medical Monitor

A Medical Monitor will be responsible for overseeing the overall progress of the protocol. The Medical monitor will review patient recruitment, any Serious Adverse Events, any Unanticipated Adverse Events, and non-compliance with the protocol at individual centers. All Serious Adverse Events will be reviewed and adjudicated by the Medical Monitor.

9.12. Data Management

Electronic Data Capture (EDC) will be used for collection of primary data at all participating sites. Data Management procedures for computerized system are in compliance according to DIN EN ISO 14155:2012-01, including DIN EN ISO 14155:2018-08 – draft 18-06-29, GDPR (EU) 2016/679 and MDR (EU) 2017/745 (CRO Maxis Medical).

Investigators are responsible for the accurate completion and timely submission of the data collected during the trial. All data from the trial will be entered via electronic CRFs (eCRFs) into a central database. Incoming data will be frequently reviewed to identify inconsistent or

missing data and any adverse events. Any data issues are to be promptly addressed with the investigator by the CRO (MAXIS Medical). By Quality assurance procedures it is ensured that complete, accurate and timely data are submitted; that protocol requirements are followed; and that complications, adverse events and adverse device effects are correctly reported and investigated, as appropriate.

9.13. Study Suspension or Early Termination

The study can be discontinued at the discretion of the Investigator or study Sponsor for reasons including, but not limited to, the following:

- Occurrence of adverse events unknown to date in respect to their nature, severity, or duration, or the unexpected incidence of known adverse events
- Obtaining new scientific knowledge that shows that the study is no longer valid or necessary
- Data demonstrates a benefit to subjects who undergo TAVR with the ProtEmbo System making treatment without the ProtEmbo unethical
- Insufficient recruitment of subjects
- Unanticipated adverse device effect (UADE) presenting an unreasonable risk to subjects (Sponsor may terminate the study immediately)
- Persistent non-compliance with the protocol
- Persistent non-compliance with regulatory requirements

If the study is discontinued or suspended prematurely, the Sponsor shall promptly inform all clinical investigator(s) / investigational center(s) of the termination or suspension and the reason(s) for this. The national and local regulatory authorities shall also be informed promptly and provided with the reason(s) for the termination or suspension by the Sponsor or by the clinical investigator / investigation center(s).

9.14. Criteria for Suspending / Terminating a Study Center

Sponsor reserves the right to stop the screening of subjects at a study center at any time after the study initiation visit if no subjects have been enrolled or if the center has multiple or severe protocol violations without justification or fails to follow remedial actions.

Possible reasons for suspending / terminating a study center include, but are not limited to:

- Repeated failure to complete case report forms prior to scheduled monitoring visits;
- Failure to obtain written Informed Consent;
- Failure to report SAEs / UADEs to Sponsor within 24 hours of knowledge;
- Loss of (or unaccounted for) investigational product inventory.

9.15. Final Report

A Final Report will be prepared even if the study is prematurely terminated. The Final Report will be submitted to each participating Investigator, and regulatory agencies, as required.

9.16. Protocol Deviations

A protocol deviation is defined as an event where the Investigator or site personnel did not conduct the study according to the protocol.

Investigators shall be required to obtain prior approval from Sponsor or its designated representative before knowingly deviating 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 clinical study management and Investigator files. Prior approval is generally not expected in situations where unforeseen circumstances are beyond the Investigator's control, (e.g., subject was not available for scheduled follow-up office visit, blood sample lost by laboratory, etc.); however, the event is still considered a deviation and will be reported via the appropriate eCRF.

Deviations must be reported to Sponsor or designated representative regardless of whether medically justifiable, pre- approved by Sponsor or designated representative, or taken to protect the subject in an emergency. Subject specific deviations will be reported on the Protocol Deviation case report form. Non-subject specific deviations, (e.g., unauthorized use of an investigational device outside the study, unauthorized use of an investigational device by a physician who has not signed an Investigator agreement or not been trained in the use of the device, etc.), will be reported to Sponsor or designated representative. Investigators will also adhere to procedures for reporting study deviations to their Ethics Committee or Competent Authority, where required, in accordance with their specific reporting policies and procedures.

Regulations require that Investigators maintain accurate, complete and current records, including documents showing the dates of and reasons for each deviation from the protocol.

10. Regulatory Considerations

10.1. Maintaining Records

The Sponsor will maintain copies of critical correspondence, clinical data, shipment of devices, serious adverse device effects and other records related to the clinical trial.

10.2. Site Record Retention Policy

The Sponsor and clinical sites will maintain all records pertaining to this study in accordance with local and national regulations. The Sponsor will ensure that the CRFs will be kept available for review by the authorities for 10 years after completion or early termination of the study, in accordance with §10(7) MPKPV, and that the information regarding the investigational devices listed in Section 3.2 of Appendix VIII of Directive 93/42/EEC will be kept available for a minimum of 5 years in accordance with Section 4 of Appendix VIII and with §12(2) MPG. Prior to the destruction of study records the investigator or his representative should contact the Sponsor to ensure that they no longer need to be retained. In addition, Sponsor should be contacted if the Investigator plans to leave the investigational site so that arrangements can be made for the handling or transfer of study records.

10.3. Ethics Committee (EC) and Competent Authority (CA) Approval

Regulatory approvals must be obtained prior to enrolment of the first patient. The Sponsor is responsible for obtaining regulatory and local approvals for the study. The Sponsor or its designated representative will require a copy of any Ethics Committee and Competent Authority correspondence, as well as the final approval letter from the Ethics Committee and Competent Authority, where applicable. The Sponsor confirms and is aware that the Competent Authority may contact the Ethics Committee that is assessing or has assessed the application.

An Investigator may not make protocol changes without prior approval by Sponsor. All significant protocol changes that may affect the following must be submitted and approved by the Ethics Committee and Competent Authority before initiating the change:

- Validity of the data or information resulting from the completion of the approved protocol;
- Relationship of the likely subject risk to benefit relied upon to approve the protocol;
- Scientific soundness of the investigational plan;
- Rights, safety, or welfare of the human subjects involved in the investigation.

The Sponsor may make certain administrative changes to the protocol without prior approval of the relevant Ethics Committee and Competent Authority. The Sponsor will notify all investigative sites of such changes to ensure the study continues to be conducted consistently across all sites.

11. Publications

The Sponsor's publications policy for this study is as follows: Following the earliest of a) receipt of a notice from Sponsor stating that the study has been terminated or, b) twenty-four (24) months after completion or termination of the study at all Investigative sites, Investigators shall have the right to publish, in appropriate scientific journals or other professional publications, information and data collected or produced at their site as a result of their participation in the study, provided that drafts of the publications have been delivered to Sponsor for purposes of review and comment at least sixty (60) days prior to the first submission for publication or public release, to which investigating parties shall give due consideration. Sponsor shall return comments to the Investigator within forty-five (45) days upon receipt of the draft. In addition, the Investigator shall delay any proposed publication / presentation in the event Sponsor so requests to enable Sponsor to secure patent or other proprietary protection. In all such publications, credit shall be given to Sponsor for its sponsorship of the study. Similarly, in publications by Sponsor regarding the study, appropriate recognition will be given of the contribution made by the institutions and principal Investigators, as applicable. Sponsor may use, refer to, and disseminate reprints of scientific, medical, and other published articles relating to the study, including such reprints that disclose the name of Investigators and / or the relevant institution.

A description of this clinical study is available on http://clinicaltrials.gov.

12. Definitions

Acute Cardiovascular Surgery

An immediate transfer from the catheterization lab to the operative room during the initial treatment phase due to the need for emergency coronary artery bypass graft surgery, cardiac valve surgery, or other vascular surgical intervention.

Access Related

Any adverse clinical consequence possibly associated with any of the access sites used during the procedure.

Access Site

Any location (arterial or venous) traversed by a guide wire, a catheter or a sheath, including the left ventricular (LV) apex and the aorta.

Allergic Reaction

An overreaction of the body's immune system to a component of an investigational device (e.g., nitinol metal, polyester, plastics), contrast agents and / or anesthesia medication given to the subject for completion of a study related procedure (e.g., MSCT, angiogram, investigational device), which requires medical intervention to treat the allergic reaction.

Acute Kidney Injury (AKI)

- Stage 1: Increase in serum creatinine to 150–199% (1.5– 1.99 × increase compared with baseline) OR increase of ≥0.3 mg / dL (≥26.4 µmol / L) OR Urine output <0.5 ml / kg per hour for >6 but <12 hours
- Stage 2: Increase in serum creatinine to 200–299% (2.0– 2.99 × increase compared with baseline) OR Urine output <0.5 ml / kg per hour for >12 but <24 hours
- Stage 3: Increase in serum creatinine to ≥300% (>3 × increase compared with baseline) OR serum creatinine of ≥4.0 mg / dL (≥354 mmol / L) with an acute increase of at least 0.5 mg / dL (44 mmol / L) OR Urine output <0.3 ml / kg per hour for ≥24 hours OR Anuria for ≥12 hours [Subjects receiving renal replacement therapy are considered to meet Stage 3 criteria irrespective of other criteria]

AV Block

Atrioventricular block is a type of heart block in which the conduction between the atria and ventricles of the heart is impaired.

Blood Loss

- Major Blood Loss – Defined as transfusion of >2 units packed red blood cells (PRBC)).
- Estimated Procedural Blood Loss – Defined as the total estimated blood loss (mL) during the index procedure. Includes blood loss resulting from adjunctive procedures performed during the index-procedure.

Bleeding

- Life-threatening or disabling bleeding:
  - Fatal bleeding (BARC type 5) OR

  - Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome (BARC type 3b and 3c) OR
  - Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery (BARC type 3b) OR
  - Overt source of bleeding with drop in haemoglobin of ≥5 g / dL or whole blood or packed red blood cells (RBCs) transfusion ≥4 units* (BARC type 3b)
  - Given one unit of packed RBC typically will raise blood hemoglobin concentration by 1 g / dL, an estimated decrease in hemoglobin will be calculated; BARC: Bleeding Academic Research Consortium.
- Major bleeding:
  - Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0 g / dL or requiring transfusion of 2 or 3 units of whole blood / RBC, of causing hospitalization or permanent injury, or requiring surgery AND
  - Does not meet criteria of life-threatening or disabling bleeding.
- Minor bleeding:
  - Any bleeding worthy of clinical mention (e.g. access site hematoma) that does not qualify as life-threatening, disabling or major.

Cerebral Infarction

Evidence of brain cell death from imaging studies or pathological examination. If there are clinical symptoms, then it is a stroke; otherwise, it is an asymptomatic cerebral infarction.

Contrast Volume

Total volume of contrast (mL) administered during the index procedure. Includes contrast administered for adjunctive procedures performed during the index procedure.

Death

Death is divided into two categories and will be reported anytime in a subject's study participation:

- Device or procedure related death - Death related to the Study Device or to any procedure (index or subsequent) intended to treat the target vessel.
- Non-device or procedure related death – Death NOT related to any procedure (index or subsequent) intended to treat the target vessel or death not related to the Study Device.

Device Deficiency

Inadequacy of the Study Device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling.

Device Time

Number of minutes from initial study device insertion to final study device removal. It does not include time needed to perform adjunctive procedures.

Explant

Removal of the study device implant for any reason.

Fluoroscopy Time

Total fluoroscopy time (minutes) used during the index procedure and includes time utilized for adjunctive procedures performed during the index procedure.

Major Adverse Cardiovascular and Cerebrovascular Event (MACCE)

MACCE is defined as:

- All-cause mortality
- All strokes (major, minor and TIA)
- Acute kidney injury – Stage 3 (including renal replacement therapy)

Myocardial Infarction (MI)

Peri-procedural MI (≤72 h after the index procedure):

- New ischemic symptoms (e.g. chest pain or shortness of breath), or new ischemic signs (e.g. ventricular arrhythmias, new or worsening heart failure, new ST-segment changes, hemodynamic instability, new pathological Q waves in at least two contiguous leads, imaging evidence of new loss of viable myocardium or new wall motion abnormality),
- Elevated cardiac biomarkers (preferably CK-MB) within 72 h after the index procedure, consisting of at least one sample post-procedure with a peak value exceeding 15x upper reference limit (troponin) or 5x for CK-MB. If cardiac biomarkers are increased at baseline (> 99th percentile), a further increase of at least 50% post-procedure is required AND the peak value must exceed the previously stated limit.

Spontaneous MI (>72 h after the index procedure):

Any one of the following criteria:

- Detection of rise and / or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile URL, together with evidence of myocardial ischemia with at least one of the following:
  - Symptoms of ischemia
  - ECG changes indicative of new ischemia [new ST-T changes or new left bundle branch block [LBBB]
  - New pathological Q waves in at least two contiguous leads
  - Imaging evidence of new loss of viable myocardium or new wall motion abnormality
- Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, or new LBBB, and / or evidence of fresh thrombus by coronary angiography and / or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
- Pathological findings of an acute myocardial infarction.

Post-Procedure Intensive Care Unit Time

Number of hours a patient is in an intensive care unit prior to discharge or moving to a step down or standard care unit.

Post-Procedure Length of Hospital Stay

Number of days from the end of the procedure until the patient is discharged from the hospital. This does not include time spent in a skilled care facility.

Procedural Success

Successful delivery of the investigational devices to the identified area and removal of delivery system in the absence of in-hospital SAEs.

Procedure Time

Number of minutes needed to perform the index procedure from time of initial vessel cut down time to time of final guidewire removal. Also referred to as skin-to-skin time.

Renal Failure

Need for dialysis or a laboratory finding of serum creatinine > 3.5 mg / dL.

Respiratory Failure

The need for mechanical ventilation beyond the first 24 hours post-index procedure (and / or reintervention) or the need for re-intubation or ventilator support after the first 24 hours (unless the subject was ventilator dependent pre-procedure).

Stroke Diagnostic Criteria:

- Acute episode of a focal or global neurological deficit with at least one of the following: Change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke
- Stroke - Duration of a focal or global neurological deficit ≥24 h; OR, <24 h, if available neuroimaging documents a new hemorrhage or infarct; OR the neurological deficit results in death
- TIA – Duration of a focal or global neurological deficit < 24 h, any variable neuroimaging does not demonstrate a new hemorrhage or infarct
- No other readily identifiable non-stroke cause for the clinical presentation (e.g. brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences), to be determined by or in conjunction with designated neurologist
- Confirmation of the diagnosis by at least one of the following:
    - Neurologist or neurosurgical specialist
    - Neuroimaging procedure (CT scan or brain MRI), but stroke may be diagnosed on clinical grounds alone

- Ischemic Stroke:
    - An acute symptomatic episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of central nervous system tissue.
- Hemorrhagic Stroke:
    - An acute symptomatic episode of focal or global cerebral or spinal dysfunction caused by an intraparenchymal, intraventricular, or subarachnoid hemorrhage.

(A stroke may be classified as undetermined if there is insufficient information to allow categorization as ischemic or hemorrhagic)

Transient Ischemic Attack (TIA)

A transient (<24 hours) episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction. No evidence of infarction if imaging performed.

Vascular Access Site and Access-related Complications

- Major Vascular Complications:
  - Any thoracic aortic dissection
  - Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arteriovenous fistula, pseudoaneurysm, hematoma, irreversible nerve injury, or compartment syndrome) leading to either death, need for significant blood transfusions (≥4 U), unplanned percutaneous or surgical intervention, or irreversible end-organ damage (e.g., hypogastric artery occlusion causing visceral ischemia or spinal artery injury causing neurological impairment)
  - Distal embolization (noncerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage
- Minor Vascular Complications:
  - Access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arteriovenous fistula or pseudoaneurysms requiring compression or thrombin injection therapy, or hematomas requiring transfusion of ≥2 but not 4 U) not requiring unplanned percutaneous or surgical intervention and not resulting in irreversible end-organ damage
  - Distal embolization treated with embolectomy and / or thrombectomy and not resulting in amputation or irreversible end-organ damage
  - Failure of percutaneous access site closure resulting in interventional (e.g., stent-graft) or surgical correction and not associated with death, need for significant blood transfusions (≥4 U), or irreversible end-organ damage

13. Acronyms

ACT	Activated clotting time
AE	Adverse Event
AKI	Acute kidney injury
AMI	Acute myocardial infarction
ASA	Acetylsalicylic acid
AV	Atrioventricular
BAV	Balloon aortic valvuloplasty
BMI	Body mass index
CA	Competent Authority
CEA	Carotid endarterectomy
CIP	Clinical Investigation Protocol
CK	Creatine kinase
CK-MB	Creatine kinase-MB fraction
CRF	Case Report Form
CRO	Contract Research Organization
CT	Computed tomography
CVA	Cerebrovascular accident
DAPT	Dual antiplatelet therapy
DW-MRI	Diffusion-weighted magnetic resonance imaging
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	electronic Clinical Report Form
EDC	Electronic Data Capture
EPD	Embolic protection device

GFR	Glomerular Filtration Rate
EU	European Union
FLAIR-MRI	Fluid attenuated inversion recovery magnetic resonance imaging
Fr	French
GI	Gastro-intestinal
IFU	Instructions for Use
IV	Intravenous
LBBB	Left bundle branch block
LVEF	Left ventricular ejection fraction
MACCE	Major Adverse Cardiac and Cerebrovascular Events
MI	Myocardial Infarction
MoCA	Montreal Cognitive Assessment
MSCT	Multi-Slice Computed Tomography
MRI	Magnetic Resonance Imaging
NIHSS	National Institutes of Health Stroke Scale
PCI	Percutaneous coronary intervention
PHI	Protected health information
PRBC	Packed red blood cells
RBBB	Right bundle branch block
RBC	Red blood cells
SAE	Serious Adverse Event
TAVR / TAVI	Transcatheter aortic valve replacement (TAVR) or transcatheter aortic valve implantation (TAVI)
TIA	Transient ischemic attack
VARC	Valve Academic Research Consortium
VCI	Vascular cognitive impairment

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