Supplementary data

1.1 Supplementary Appendix 1. Clinical investigation protocol.

The sponsor planned 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.

1.1.1 Study Design

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, major vascular complications in the access vessels or aorta and acute kidney injury (stage 2 or 3). Previous studies have used a similar definition of safety and, therefore, results of these previous studies provided useful historical comparison data to evaluate the safety of the ProtEmbo System. Similarly, performance was 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 provided useful historical comparison data against which the performance of the ProtEmbo System can be compared.

1.1.2 Primary Study Endpoints

1.1.2.1 Safety

Major Adverse Cardiac and Cerebrovascular Events (MACCE) at 30 days defined as all-cause mortality, all stroke, life-threatening or disabling bleeding, major vascular complications in the access vessels or aorta and acute kidney injury (stage 2 or 3), all defined by VARC-2.

1.1.2.2 Performance

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

1.1.3 Secondary Study Endpoints

1.1.3.1 Efficacy

The secondary efficacy endpoints for this clinical investigation were 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 was compared to historical data; The total new lesion volume was 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 was compared to historical data.

1.1.4 Number of Patients and Sites

Up to 60 patients were planned to be enrolled at up to 10 clinical study centers.

1.1.5 Study Population

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

1.1.6 Enrollment Criteria

A potential patient 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.

1.1.6.1 Inclusion Criteria

Patients eligible to participate met all of the following at screening and / or baseline visits:

1. The heart team recommends transcatheter valve aortic valve replacement 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 ≥ 90 mm as determined by Multi-Slice Computed Tomography (MSCT) scan or equivalent imaging modality.
3. The patient and the treating physician agree that the patient will undergo the scheduled pre-procedural testing and return for all required post-procedure follow-up visits.
4. The patient 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. Patient is a minimum of 18 years of age.

1.1.6.2 Exclusion Criteria

Potential patients with one or more of the following were excluded from the study even if they met the inclusion criteria:

1.1.6.3 General Exclusion Criteria

1. Left upper limb vasculature in the left extremity precluding 6 Fr 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. Patient 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. Patients in whom anti-platelet and / or anticoagulant therapy is contraindicated, or who will refuse transfusion.
23. Patients who have active bacterial endocarditis or other active infections.
24. Currently participating in an investigational drug or another device study.
25. Patients who have a planned treatment with any other investigational device or procedure during the study follow-up period (30 days).
26. Patients with planned concomitant surgical or transcatheter ablation for Atrial Fibrillation during the study follow-up period (30 days).
27. Any patient with a balloon valvuloplasty (BAV) within 30 days of the procedure.
28. Patient 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. Patients who have a planned concomitant cardiac surgical or interventional procedure (e.g., coronary revascularization) during the TAVI procedure.
35. Patients who have a pre-existing prosthetic heart valve in any position.

1.1.6.4 Neurological Exclusion Criteria

1. Patient had active major psychiatric disease.
2. Patient 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. Patients with neurodegenerative or other progressive neurological disease or history of significant head trauma followed by persistent neurologic defaults or known structural brain abnormalities.

1.1.6.5 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. Patient 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. Patient 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.

1.1.6.6 Magnetic Resonance Imaging Exclusion Criteria

1. Patient Body Mass Index (BMI) precluding imaging in scanner.
2. Contraindications to MRI (patients 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. Patients who have a high risk of complete AV block after TAVR, with the need of permanent pacemaker (e.g. patients 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.

1.1.7 Study Procedures

1.1.7.1 Eligibility Assessments

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

If the patient continued to meet the study's enrollment criteria and continued to be willing and able to participate in the study protocol, the patient was enrolled.

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

1.1.7.2 CT/ Angiographic Eligibility

Computed tomographic images of the aorta were reviewed by the angiographic core lab and the aortic angiogram was reviewed to confirm that the patient was eligible for participation in the PROTEMBO C Trial.

1.1.7.3 Sheath Access Eligibility

Computed tomographic images of the aorta were reviewed by the angiographic core lab and an angiogram of the left radial artery was reviewed to confirm that the patient could have a commercially available vascular sheath inserted into the left radial artery and was, therefore, eligible for participation in the PROTEMBO C Trial.

1.1.8 Procedural Treatment and Timing

1.1.8.1 Medication Regimen

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

For those patients who were not under chronic oral anticoagulation prior TAVR, the use of dual antiplatelet therapy (DAPT) before and after the procedure was recommended. Those patients with chronic DAPT continued 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 were not taking chronic DAPT, it was 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.

1.1.8.2 MRI Timing

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

MRI was 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 took place within two weeks before the TAVR procedure and no sooner than 5 days after any diagnostic catheterization, and there was no diagnostic catheterization in between baseline MRI and TAVR procedure allowed.

1.1.9 TAVR and ProtEmbo Procedure

Study patients were 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 (see Supplemental Appendix Table 1: Schedule of Events) and are consistent with standard of care for TAVR patients.

The ProtEmbo was used strictly as described in the Instructions for Use (IFU), including the preparation, insertion, dwell time and removal of the device. The ProtEmbo was inserted prior to the insertion of the TAVR device and left in place until after the deployment and removal of the TAVR device.

1.1.9.1 Schedule of Events

Supplemental Appendix Table 1: Schedule of Events

	Screening Period		**Treatment Period**	**Post-procedure Period**			
Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Study Procedure	**Base-line**	**Base-line MRI**	**TAVR Procedure**	**< 24 Hour Follow-up**	**2-7 Days**	**Dis-charge**	**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 Echo-cardiogram within 3 months of TAVR*	✓						
Modified Allen's Test	✓						
NIHSS†	✓				✓		✓
Adverse Event (AE) review			✓	✓	✓	✓	✓

Angiogram			✓		
Multi-Slice or Multi Detector CT‡	✓				
MRI§		✓		✓	
ProtEmbo insertion, dwell and removal times			✓		
ProtEmbo contrast use			✓		
Filter specimen preparation & shipping for histopathology			✓		
Study Exit					✓
Informed consent	✓				

* Conducted as part of the TAVR work up as per institution standard of care and not a dedicated study procedure; †NHISS to be conducted by a neurologist; ‡Conducted as part of the TAVR work up and not a dedicated study procedure**;** §Conducted on a MRI core laboratory certified scanner.
STS = Society of Thoracic Surgeons; ECG = Electrocardiogram; TAVR = Transcatheter aortic valve replacement; NIHSS = National Institutes of Health Stroke Scale; MRI = Magnetic resonance imaging.

1.1.9.2 Study Exit or Premature Withdrawal

Patients were exited from the study by completion of a Study Exit eCRF at the time of study completion provided the patient had not experienced an adverse event that was ongoing and unexplained.

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

- Patient death.
- Voluntary withdrawal – meaning that the patient 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.
- Lost to follow-up – meaning that the patient is more than 14 days late to a study visit and 3 documented attempts to contact the patient are unsuccessful. A patient 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 patient to continue study participation.

All patients enrolled (including those withdrawn or lost to follow-up) were accounted for and documented.

1.2 Supplementary Appendix 2. Derivation of performance goals.

1.2.1 Primary Safety Endpoint

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 patients 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.

1.2.2 Primary Performance Endpoint

The Performance Goal 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.

1.3 **Supplementary Appendix 3. Histological analysis of devices.**

All the devices used in patients were fixed in 10% neutral buffered formalin after the TAVR was completed and shipped in individually labeled plastic containers to the independent histopathology core laboratory. The debris was collected by a Falcon 40-µm Nylon Cell Strainer and photographed before any physical alteration, then the strainer was carefully folded and placed in a biopsy bag. Samples were dehydrated in a graded series of ethanol and xylene and embedded in paraffin by an automated tissue processor. The paraffin blocks were serially sectioned into a total of 12 consecutive sections, with 2 to 3 sections per slide. The slides were stained by hematoxylin and eosin (H&E) and by Movat pentachrome (MP) stains. Some remaining slides were left unstained for future needs, which was determined by the type of material present in the slides examined and the need for identification of the constituent elements of the debris.

The core laboratory randomly selected devices for scanning electron microscope analysis. Specimens were rinsed in 0.1 mmol/L sodium phosphate buffer (pH 7.2 ± 0.1) and then post-fixed in 1% osmium tetroxide for up to 30 minutes. The specimens were then dehydrated in a

graded series of ethanol, critical point dried, and mounted for viewing. After sputter coating with gold, the samples were visualized using scanning electron microscopes. Images were acquired at incremental magnifications of x10 (or x15), x50, x200, and x600. The approximate locations of the higher power images were based on matching [x50, magnification] pictures numerically referenced on the low power [x10 or x15, magnification] montage such that representative regions from the proximal, middle, and distal ends of the device were captured. Thrombus formation was defined as knobby and nodular structures consisting of platelets, fibrin, leukocytes, and red blood cells.

Moreover, a device thrombus formation score was assessed by scanning electron microscope using a semi-quantification scoring system (see Supplemental Appendix Table 2: Semi-quantification of device thrombus formation score as assessed by SEM).

Supplemental Appendix Table 2: Semi-quantification of device thrombus formation score as assessed by SEM

Score	Device Thrombus Formation Score assessed by SEM
0	No to little adherent material covering the device surface
1	Minimal adherent material covering ≤ 10% of the device surface
2	Mild adherent material covering > 10% and ≤ 25% of the device surface
3	Moderate adherent material covering > 25% and ≤ 50% of the device surface
4	Extensive adherent material covering > 50% and ≤ 75% of the device surface
5	Severe adherent material covering > 75% of the device surface

SEM = Scanning electron microscope.

1.4 **Supplementary Appendix 4. MRI and stroke analysis methodology.**

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 (31); 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) (32).

All of the MRI scans in the study were evaluated at a central MRI Reading Center based at The Buffalo Neuroimaging Analysis Center (BNAC), Buffalo, NY, USA. The BNAC evaluated a test scan of a volunteer from each site as part of the dummy run process to ensure that its scanning techniques are compliant with the requirements of the study. This review took place before the site is permitted to enroll any patients into the study. Subsequently, MRI scans were conducted at baseline and 2-7 days post-TAVR and MRI data was transferred to BNAC directly from the site via a secure web-based transfer system. Alternatively, appropriate media (e.g., DICOM format on CD via courier) was sent to the CRO, and they transferred to BNAC using the web-based transfer system. BNAC provided specific MRI online transfer instructions, and CRO provided shipping instructions prior to the start of enrollment to all sites that opt to transfer the scans on physical media (e.g., DICOM format on CD via courier). MRI exam images were evaluated by physicians/technicians at BNAC according to a pre-specified imaging review protocol. These physicians/technicians were blinded to each patient's treatment. A study-specific case report form (CRF) was used to collect all final data for each patient, and served as the official reading record. This CRF included site identifier, patient identifier, exam timepoint data, BNAC-assigned unique examination identifiers, BNAC-assigned source analysis identifiers linked to locked BNAC database records.

For the analysis of stroke all cerebrovascular events were considered by the medical monitor and independent DSMB as defined by the VARC-2 criteria. 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 (33). 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).

1.5 **Supplementary Appendix 5. Disposition of patients.**

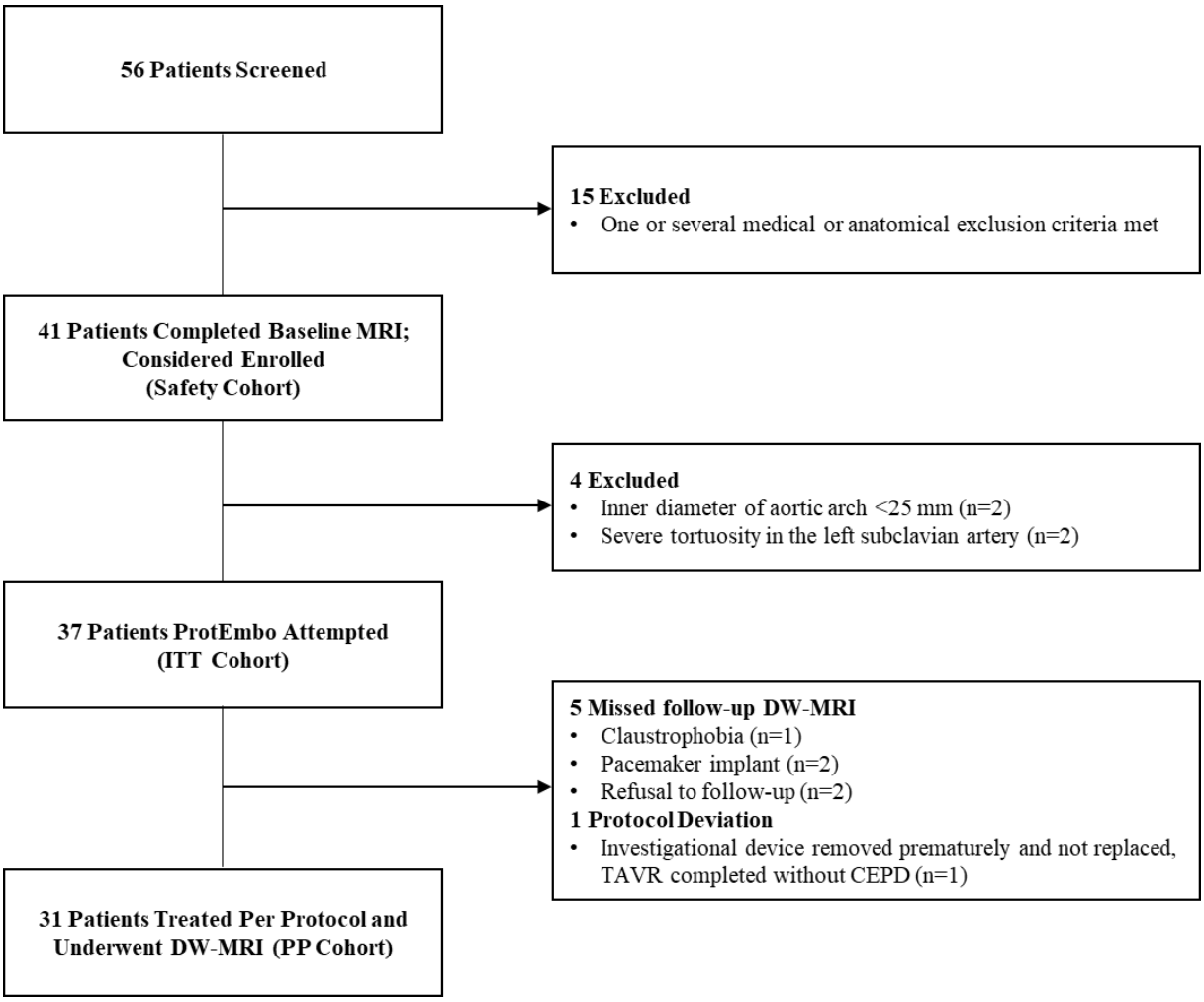
Supplemental Appendix Table 3: Overview Clinical Sites and Enrollment Status

Clinical Site	Site ID	Treating Investigators	Safety Cohort	ITT Cohort	PP Cohort
Gdansk, Poland	003	2	15	15	14
Lübeck, Germany	006	2	7	6	5
Leipzig, Germany	008	1	6	6	5
Trier, Germany	005	1	4	3	2
Poznan, Poland	004	1	4	3	1
Riga, Latvia	001	2	3	3	3
Warsaw, Poland	002	1	1	1	1
Kiel, Germany	010	1	1	0	0
Total number of patients			**41**	**37**	**31**

ITT = intention to treat; PP = per protocol.

1.6 Supplementary Appendix 6. Flow chart patient cohorts.

Supplemental Appendix Figure 1: Flow Chart Patient cohorts



1.7 Supplementary Appendix 7. Patients excluded from ITT cohort.

Supplemental Appendix Table 4: Overview Patients Excluded from ITT cohort

Site ID	Patient ID	Reason for Screen Failure
006	005-HLB	The diameter of the patient's aorta was below the allowed size of 25 mm as stipulated in the protocol (general exclusion criteria no. 30).
005	006-AAB	Patient was found to have severe tortuosity of the left subclavian artery which is an exclusion criterion as stipulated by the protocol (angiographic exclusion criteria no.1).
004	006-ATF	Patient was found to have severe tortuosity of the left subclavian artery which is an exclusion criterion as stipulated by the protocol (angiographic exclusion criteria no.1).
010	002-LKI	The diameter of the patient's aorta was below the allowed size of 25 mm as stipulated in the protocol (general exclusion criteria no. 30).

1.8 Supplementary Appendix 8. Overview of all adverse events in study and adjudication by DSMB.

Supplemental Appendix Table 5: Overview of Adverse Events (Safety Cohort) as adjudicated by DSMB

	Events	Safety Cohort (N = 41)
Overall	36	48.8% (20/41)
Serious Adverse Events	**16**	**26.8% (11/41)**
Device-related	0	0% (0/41)
Procedure-related	2	4.9% (2/41)
Definitely related	*1*	*2.4% (1/41)*
Possibly related	*1*	*2.4% (1/41)*
Unrelated	14	22.0% (9/41)
Adverse Events	**20**	**34.1% (14/41)**
Device-related	0	0% (0/41)
Procedure-related	4	9.8% (4/41)
Definitely related	*4*	*9.8% (4/41)*
Possibly related	*0*	*0% (0/41)*
Unrelated	16	29.3% (12/41)

Values are N, % (n/N), or n (%).

1.9 Supplementary Appendix 9. Serious adverse events.

Supplemental Appendix Table 6: Serious Adverse Event Listings and Descriptions

SAE Description and Resolution	Days to SAE	Device/ Procedure related	Outcome
Radial artery dissection Radial artery dissection due to spasm. Difficulties in sheath removal. Bleeding was stopped by applying a peripheral balloon twice for 5 minutes. A pressure dressing was applied.	0	Definitely Procedure-related	Resolved
Cerebral infarct When the TAVR catheter was withdrawn, the ProtEmbo was pulled out of position (i.e. interaction between TAVR catheter and ProtEmbo) and withdrawn as a consequence. After the ProtEmbo was removed, the patient, who had heavy calcification of the aortic annulus (including the left ventricular outflow track - LVOT), had twice further balloon dilation of the transcatheter heart valve prosthesis without embolic protection in place. In the evening following the TAVR (12 hours after procedure), the patient developed a neurological deficit with left hemiparesis as well as dysarthria due to infarction of the right thalamus.	0	Possibly Procedure-related	Resolved with sequelae
Bradycardia	1	Unrelated	Resolved

One day after TAVR, the patient developed bradycardia for 25 minutes. A temporary pacemaker was inserted. The cardiac rhythm stabilised and the pacemaker could be removed on the same day.			
Cardiac Tamponade, Sternotomy The procedure was complicated by postoperative bleeding. Cardiac tamponade was confirmed clinically and via echocardiogram. An incision was made under the xiphoid process and the pericardium was opened. Blood exited when pressure was being applied. A pericardial drain was placed and the pericardium was closed in layers, and a sterile dressing was applied. However, hemodynamic instability continued to be observed and bleeding increased (a total of 500 ml). The decision was made to perform a full sternotomy to find the source of the bleeding. After opening the pericardium, approximately 200 ml of clots and blood were removed. The pericardium was rinsed with warm saline. Repeated inspection of all potential bleeding sites revealed no significant source. The heart rhythm was a sinus rhythm, and temporary epicardial electrodes were sewn onto the ventricle. The pericardium was partially closed, and drains were placed in the pericardial sac and the mediastinum. Over the subsequent hospitalization, atrial fibrillation was observed, and evidence of inflammation was detected. Therefore, empirical antibiotic therapy was started. No further accumulation of fluid was observed in the x-rays or echocardiogram of the heart.	0	Unrelated	Resolved
Femoral artery dissection After the right femoral artery had been closed with the Proglide and Angioseal systems, artery dissection with decreased peripheral inflow was noticed in the control angiograms. Treatment was performed with a peripheral balloon (8 mm x 4 cm) which was inflated for 5 minutes. Afterwards inflow was sufficient again with only a slight dissection.	0	Unrelated	Resolved
3rd degree AV block requiring pacemaker implantation Third degree atrioventricular block developed 2 days after the procedure. A DDD cardiac device was implanted the next day. The procedure was successful; there were no complications.	2	Unrelated	Resolved
Femoral access site hematoma	1	Unrelated	Resolved

A hematoma (82x33 x130 mm on CT) developed at the femoral access site (including groin and scrotum). There was no active bleeding seen on CT, but as there was a drop in hemoglobin, two units of PRBC were administered the day after.			
Left Bundle Branch Block After the procedure, the ECG showed a left bundle branch block (140 ms). As the left bundle branch block persisted for some days, the decision was made to keep the patient in the hospital for additional observation and to perform a long-term ECG. The average heart rate was 76/min, with a range between 71/min and 106/min. There was no relevant bradycardia, and no sinus pauses during the night of recording. There were also no signs of atrial fibrillation. No further actions were deemed necessary.	0	Unrelated	Stabilized, not expected to resolve (SAE closed)
Fever/ Urinary tract infection Patient developed a less than 24 hour episode of otherwise asymptomatic fever, likely related to a mild urinary tract infection. Patient received 5 days of intravenous Piperacillin/Tazobactam antibiotic therapy which required prolonged hospitalization.	2	Unrelated	Resolved
Sedative circulatory complications Patient experienced drop in blood pressure due to accumulation of sedative during the procedure. Remifentanil was paused and the patient was given norepinephrine and atropine which led to recovery of the patient after the half-life of remifentanil was reached.	0	Unrelated	Resolved
1st degree AV Block and LBB Block After the TAVR procedure, the patient developed a new first-degree AV block and a left bundle branch block and a permanent pacemaker had to be implanted.	0		
Left Bundle Branch Block The patient developed a new left bundle branch block after the TAVR/ProtEmbo procedure. The patient had a history of atrial fibrillation with multiple failed attempts at electrical and medical cardioversion. The patient developed symptomatic atrial fibrillation and required cardioversion again, on May 17, 2021. The cardioversion was initially successful, but two days later recurrent atrial fibrillation was noted with primary arterio-ventricular block with 280 ms PR	0	Unrelated	Resolved

interval and left bundle block as well. Therefore, a permanent pacemaker was implanted on May 19, 2021.			
Drop of HB treated with Blood Infusions The patient experienced a drop in hemoglobin and was administered two units of erythrocyte concentrates, which brought the hemoglobin level close to normal. Pericardial effusion was excluded via echocardiogram post-procedurally at which point a minimal paravalvular insufficiency was noticed. The site provided additional information about the drop in hemoglobin noting that the patient received a large volume of fluid as part of the preparation and execution of the TAVR in the setting of left ventricular hypertrophy to provide adequate preload immediately after the new valve is placed. As there was no source of blood loss identified, the drop in hemoglobin was likely dilutional.	3	Unrelated	Resolved
AV Block III without replacement rhythm Immediately after the procedure the patient developed a complete AV Block III without replacement rhythm. As the placement of the temporary pacer was unstable and the patient had permanent AFIB, a pacemaker was implanted immediately without complications.	0	Unrelated	Resolved
Acute kidney injury Patient, who suffered from chronical renal insufficiency, developed acute kidney injury. On APR/2021 the creatinine level was 4,89 mg/dl and the GFR was 10ml/dl. Patient was put on dialysis from April 18-20.	2	Unrelated	Resolved
Pulmonary Edema Patient had a history of aortic and mitral valve disease, atrial fibrillation, diabetes and ongoing renal insufficiency. Developed pulmonary edema during hospitalization. Pulmonary edema resolved following treatment with non-invasive ventilation and standard treatment.	2	Unrelated	Resolved

SAE = Serious adverse event; TAVR = Transcatheter aortic valve replacement; LVOT = Left ventricular outflow track; AV = Atrioventricular; CT = Computed tomography; PRBC = Packed red blood cells; HB = Hemoglobin; ECG = Electrocardiogram; GFR = Glomerular filtration rate; NIV = Non-invasive ventilatory support; AFIB = Atrial fibrillation.

1.10 **Supplementary Appendix 10. Adverse events.**

Supplemental Appendix Table 7: Procedure-related Adverse Event Listings and Descriptions

AE Description and Resolution	Days to AE	Outcome

Hematoma left brachial access site Forearm hematoma after left brachial access for ProtEmbo. Sense, mobility, and brachial pulse were normal. Vascular surgeon was consulted; no urgent intervention was required. Hematoma to be re-evaluated in 3-4 weeks.	5	Resolved
Hematoma/Pseudoaneurysm left radial access site A small hematoma developed at the left arteria radialis. Sonography was performed, and no further action was required.	2	Resolved
Occlusion of the left Arteria Radialis During the 30 day follow-up closure of the left A. radialis was noticed. As the patient had no symptoms, conservative therapy was chosen.	27	Event stabilized, not expected to resolve
Occlusion of the left Arteria Radialis During the 30 day follow-up closure of the left A. radialis was noticed. As the patient had no symptoms, conservative therapy was chosen.	32	Event stabilized, not expected to resolve

AE = Adverse event; A. radialis = Arteria radialis.

1.11 **Supplementary Appendix 11. Supra-threshold DW-MRI lesion volume analysis.**

Supplemental Appendix Table 8: Supra-Threshold DW-MRI Lesion Volume Analysis

	ProtEmbo* (mm^3)	**No Device† (mm^3)**
Mean total	376	508
Mean >100 mm^3	72	341
Mean >200 mm^3	34	262
Mean >500 mm^3	0	162
Mean >1000 mm^3	0	141

*Patients in per-protocol cohort (N=31) who completed follow-up DW-MRI were considered for secondary efficacy analysis, individual lesions with volume smaller than threshold were excluded from supra-threshold analysis; †Analysis according to REFLECT II trial control arm (N=57) (2).