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Protocol title: A Prospective, Multicenter, Non-Randomized, Single-Arm, Open-Label Clinical Study to Demonstrate the Safety and Effectiveness of the ShortCut™ device (The ShortCut™ Study).

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The ShortCut™ Study Protocol Synopsis

1 Full title

A Prospective, Multicenter, Non-Randomized, Single-Arm, Open-Label Clinical Study to Demonstrate the Safety and Effectiveness of the ShortCut™ device (The ShortCut™ Study).

2 Device name

ShortCut™

3 Design

This is a prospective, multicenter study sponsored by Pi-Cardia Ltd.
This clinical study is aimed to demonstrate safety and effectiveness of the ShortCut™ device for splitting bioprosthetic aortic valve leaflets, and to demonstrate coronary artery ostia patency following leaflet split, in patients who are presented for a valve-in-valve (ViV) transcatheter aortic valve replacement (TAVR) procedure, and who are at risk for TAVR-induced coronary artery obstruction.

4 Objective

To assess the safety and effectiveness of the ShortCut™ device for splitting bioprosthetic aortic valve leaflets, and to demonstrate coronary artery ostia patency following leaflet split, in patients who are at risk for TAVR-induced coronary artery obstruction following a ViV procedure.

5 Endpoints

5.1 Primary endpoints

5.1.1 Primary safety endpoint

Each of the following ShortCut™ device and/or ShortCut™ procedure-related serious adverse events will be assessed at discharge or at 7 days post-procedure, whichever occurs first:

- Mortality
- Stroke (fatal, disabling and non-disabling)

5.1.2 Primary effectiveness endpoint

Overall leaflet splitting success using the ShortCut™ device assessed intra-procedurally by echocardiography and or angiography.
Per patient leaflet splitting success will be determined as follows:

- For patients in whom one leaflet was intervened, splitting success per patient will be determined based on the splitting success of the intervened leaflet:
    - Visualization of leaflet split, assessed by intraprocedural TEE immediately post-ShortCut™ procedure and prior to TAVR, OR
    - Increase in aortic regurgitation from pre to post leaflet split, assessed by intraprocedural TEE or angiography.
- For patients in whom two leaflets were intervened, splitting success per patient will be determined based on the splitting success of the first intervened leaflet.

5.2 Secondary endpoints

5.2.1 Secondary safety endpoints

The following events will be assessed through 30 days post index procedure (according to VARC-3):

- All-cause mortality
- All-cause stroke (fatal, disabling and non-disabling)
- Coronary obstruction
- Myocardial infarction with new evidence of coronary artery obstruction requiring intervention
- Major vascular complications
- Cardiac tamponade
- Acute kidney injury[1]
- Access-related type 3-4 bleeding

5.2.2 Secondary effectiveness endpoints

- Per intervened leaflet splitting success will be assessed intra-procedurally and will be determined based on the splitting success of this leaflet:
    - Visualization of leaflet split, assessed by intraprocedural TEE immediately post-ShortCut™ procedure and prior to TAVR, OR

[1] Acute kidney injury (AKI, VARC-3):

- Increase in serum creatinine >300% (>3.0 X increase) within 7 days compared with baseline
- Serum creatinine ≥4.0 mg/dL (≥354 mmol/L) with an acute increase of ≥0.5 mg/dL (≥44 mmol/L)
- AKI requiring new temporary or permanent renal replacement therapy

- Increase in aortic regurgitation from pre to post leaflet split, assessed by intraprocedural TEE or angiography.
- The following endpoints will be assessed through 30 days post index procedure:
    - Freedom from coronary artery ostia obstruction related to the intervened leaflet
    - Freedom from coronary artery intervention related to the intervened leaflet

5.2.3 Technical success endpoint

A composite of the following, which will be assessed at exit from procedure room following the ShortCut™ procedure:

- Successful access, delivery, and retrieval of the ShortCut™ device
- Freedom from ShortCut™ device- and/or ShortCut™ procedure-related mortality
- Freedom from ShortCut™ device- and/or ShortCut™ procedure-related:
    - Surgery or intervention
    - Major vascular or access-related complications
    - Cardiac structural complication

5.3 Tertiary safety endpoints

The following events will be assessed through 90 days post index procedure (according to VARC-3):

- All-cause mortality
- Stroke
- Myocardial infarction with new evidence of coronary artery obstruction requiring intervention.

6 Patient population

Patients who are planned to undergo a percutaneous valve-in-valve (ViV) procedure for an approved ViV indication, and who are at risk for TAVR-induced coronary artery ostium obstruction, according to the local Heart Team decision.

7 Eligibility Criteria

7.1 Inclusion criteria

1. Male or female ≥ 18 years of age at the time of screening.

2. Patient is planned to undergo a percutaneous valve-in-valve procedure for an approved ViV indication due to a failed bioprosthetic valve.
3. Patient is at risk for TAVR-induced coronary artery ostium obstruction.
4. Written informed consent to participate in the study obtained from the subject or subject's legal representative, according to local regulations, prior to initiation of any study mandated procedure.

7.2 Exclusion criteria

1. An excessive aortic valve leaflet Calcium morphology, such as diffuse massive calcification at the targeted leaflet for splitting or anatomy not suitable for the use of the ShortCut™ device, as determined by the CT core lab.
2. Leaflet planned to be intervened is torn pre-ShortCut device access.
3. Patient has iliofemoral vessel characteristics that preclude safe insertion of the introducer sheath.
4. Anatomy that does not allow safe placement of a cerebral embolic protection device.
5. Planned concurrent intervention in the same setting of the index procedure.
6. Surgery or interventional procedure ≤ 1 month prior to the index procedure.
7. Planned provisional (pre-position coronary artery) stents.
8. Coronary disease that, in the opinion of the local Heart Team, should be treated; or treatment of coronary disease ≤ 1 month prior to index procedure.
9. Carotid or vertebral artery disease that, in the opinion of the local Heart Team, should be treated; or treatment of carotid stenosis ≤ 1 month prior to index procedure.
10. CVA or TIA ≤ 6 months prior to index procedure.
11. Severe neurological disability, as determined by the Investigator.
12. History of a myocardial infarction (MI) ≤ 6 weeks prior to index procedure.
13. Current or suspected endocarditis on the aortic valve.
14. Identified thrombotic material on the valve by either CT or Echocardiography.
15. Cardiac imaging evidence of left ventricular intracardiac mass or thrombus.
16. Hemodynamic or respiratory instability requiring inotropic support, mechanical ventilation or mechanical heart assistance.
17. LVEF < 30%.
18. Ongoing severe infection or sepsis.
19. Known current COVID-19 infection (with or without symptoms), recent positive test for COVID-19, or recent exposure to a person with COVID-19 infection.

20. Patient refuses blood transfusion.
21. Patient has renal insufficiency (GFR < 30 ml/min or serum creatinine > 2.5 mg/dL), or on chronic dialysis.
22. Patient with clinically significant abnormality in cell blood count as defined by WBC < 3000 cell/µL, Hb < 9 g/dL and platelet count < 90,000 cell/µL or history of bleeding diathesis or coagulopathy, or hypercoagulable states.
23. Active peptic ulcer with bleeding.
24. Known allergy to contrast media that cannot be adequately controlled with premedication.
25. Known hypersensitivity or contraindication to all intra-procedural anticoagulation or any product material (Nitinol alloys, stainless steel, Polyamide 12, Polyether block amide, Polytetrafluoroethylene (PTFE, Teflon), Polyphenylsulfone (PPSU), Polyvinyl chloride (PVC, DEHP Free), Polypropylene (PP), SurModics Serene coating (PhotoLink® surface modification), Silicone, Epoxy adhesive, Acrylic glue).
26. Pregnant women or women planning a pregnancy within 1 month of study enrollment.
27. Need for emergency surgery for any reason.
28. Inoperable for emergency open-heart surgery.
29. Patient has a condition that, in the opinion of the Investigator or the Screening Committee, precludes the patient from undergoing the index procedure.
30. Life expectancy is less than one year.
31. Patient is currently participating in another investigational drug or device study. Note: Studies requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational studies. Observational studies are not considered exclusionary.
32. Patient is unwilling to participate or unwilling to return for study follow-up activities.
33. Patient is unable to consent to participate, unless the subject has a legally authorized representative.

8 Study schedule and time points

	Screening	Baseline	Index procedure	Pre-discharge	30 days post-procedure	90 days post-procedure
Informed consent	X					
Medical and surgical history review	X	X				
NYHA classification	X				X	
Risk assessment, including EuroSCORE II and STS score	X					
Physical examination		X			X	
Blood tests[1]		X		X		
12-lead ECG	X	X		X	X	
Modified Rankin Score and NIHSS[8]		X		X[7]	X[7]	
5 Meters-Walk Test		X				
Katz Activities of Daily Living (ADL)		X				
CT of heart, aortic root, and aortic arch	X[2]					
Echocardiographic imaging	X[3]	X[5]	X[6]	X		
Invasive or CT coronary angiography	X[4]					
ShortCut™ assisted TAVR			X			
Angiography for coronary patency			X			
Adverse events recording		X	X	X	X	X
Medications recording		X	X	X	X	X
Clinical status remote evaluation						X

[1] The relevant blood assays are listed above in each timepoint section.

[2] CT scan will be performed only in case no adequate CT scan was performed within 6 months prior to screening.

[3] TTE at screening will be performed only in case no adequate TTE was performed within 90 days prior to screening.

[4] Invasive or CT coronary angiography will be performed only in case no invasive or CT coronary angiography was performed within 1 year prior to screening, or the patient had new ischemic symptoms since last invasive or CT coronary angiography.

[5] TTE at baseline will be done in case no adequate TTE was performed within 30 days prior to index procedure.

[6] Intra-procedure TEE will be performed during the ShortCut™ procedure.

[7] Modified Ranking Score and NIHSS assessments shall be done only for patients who had a suspected neurological event.

[8] In the event a patient experiences a stroke event within 30 days post index procedure, an additional visit at 90 days after the onset of event will be performed and will include Modified Ranking Score and NIHSS assessments.

9 Statistical Analysis Plan

9.1 Study Analysis Sets

9.1.1 Safety analysis set

The safety analysis set will include all patients who reached the point of index procedure, i.e., patients in whom the ShortCut™ device was introduced through the introducer sheath. Patients who were treated with the ShortCut™ without meeting the eligibility criteria will also be included in this analysis set.

9.1.2 Primary effectiveness analysis set

The primary effectiveness analysis set will include the **Evaluable Patients** – patients in whom split with the ShortCut™ device was attempted, and were determined to have Adequate Imaging to visualize split or demonstrate increase in AR according to the echo or angiography core lab. Echocardiography imaging is considered Adequate if either visualization of split or increase in AR can be assessed. Angiography imaging is considered Adequate if increase in AR can be assessed.

9.1.3 Secondary effectiveness analysis set

The secondary effectiveness analysis set will include patients in whom the following ShortCut™ procedure steps have been performed: access, delivery to the aortic valve, activation of the ShortCut™ Splitting Element and split attempt.
All intervened leaflets of these patients will be included in the secondary effectiveness analysis set.

9.1.4 Per Protocol (PP) analysis sets

9.1.4.1 Per Protocol Primary Effectiveness (PPPE) analysis set

The PPPE analysis set will include patients who are included in the primary effectiveness analysis set and who do not have major protocol violations that are likely to affect the study primary endpoints (effectiveness or safety).

9.1.4.2 Per Protocol Secondary Effectiveness (PPSE) analysis set

The PPSE analysis set will include patients who are included in the secondary effectiveness analysis set and who do not have major protocol violations that are likely to affect the study primary endpoints (effectiveness or safety).

9.2 Sample Size Considerations

The primary objective of this study is to provide accurate description of the device safety profile, and to assess its effectiveness.
The study will include up to 80 enrolled patients:

- A minimum of 60 patients for whom the ShortCut™ procedure was initiated, split was attempted and were determined to have Adequate Imaging (Figure 1-A)
- Up to 10 additional patients for whom the ShortCut™ procedure was initiated but:
    - split was not attempted for any reason (Figure 1-C), or
    - split was attempted but were determined to have Inadequate Imaging (as defined in section 8.2.1.2) (Figure 1-B)
- Up to 10 additional enrolled patients who dropped out from the study prior to the index procedure (before the ShortCut™ procedure was initiated, due to: death, consent withdrawal by patient or by physician, patient lost to follow up, or other reasons) (Figure 1-D).

The population flowchart is provided below:

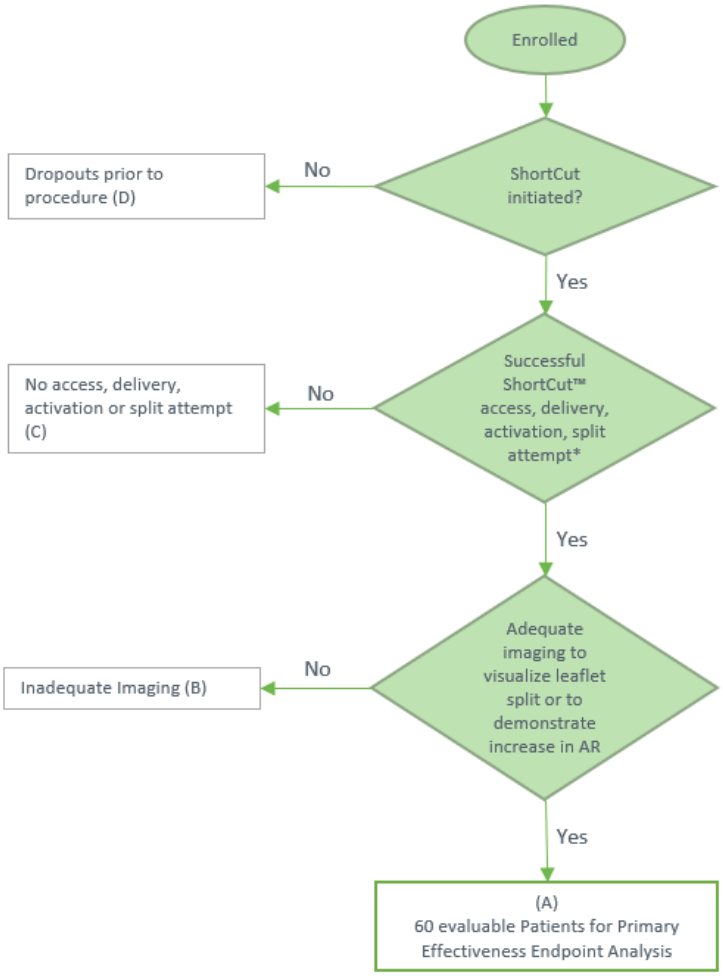

Figure 1: Study population flowchart

The study is statistically powered to achieve significance for the primary effectiveness hypothesis that aims to demonstrate that the rate of Evaluable Patients with successful split is at least 75% (performance goal).
Assuming the rate of Evaluable Patients with successful split with the ShortCut™ device is 90%, a sample size of N=60 Evaluable Patients will provide 80% power to reject the primary effectiveness null hypothesis (see section 9.4.7). The power estimation is based on an exact Binomial distribution and uses two-sided Alpha = 0.05.
To meet the performance goal of 75%, at least 52 of the 60 Evaluable Patients should have a successful split.

The study is not statistically powered to achieve significance for the primary safety endpoint. At the same time, based on pre-established event rates calculated from ViV

TAVR clinical studies, a sample size of a minimum of 60 patients for whom the ShortCut™ procedure was initiated will allow capturing relatively rare Adverse Events (AEs), such as stroke and all-cause mortality, with high probability.
The expected rates of stroke and all-cause mortality in ViV TAVR studies are estimated at 1.4% and 3.5%, respectively. The rates of stroke and all-cause mortality reported for ViV TAVR small studies (N ≤ 70) tend to be somewhat larger, and with much wider confidence intervals. Due to this difference in rate variability, a minimum of 60 patients for whom the ShortCut™ procedure was initiated will allow demonstrating that the stroke rate (lowest of the two) does not increase more than 2-fold (i.e., more than 2.8%) compared to reported rates in ViV TAVR studies.

A sample size of a minimum of 60 patients with an initiated ShortCut™ procedure will allow detecting at least 1 event whose incidence in the intended use patient population is 2.8% with high probability (>80%), and thus to estimate the incidence of stroke and all-cause mortality in the intended use patient population.

9.3 Use of Controls

In this clinical study, there is no control group, no use of blinding techniques and no randomization distribution system.

9.4 Statistical Analyses

9.4.1 Overview

The data will be summarized in tables listing the mean, standard deviation, median, minimum, maximum and number of patients for continuous data, or in tables listing count (frequency) and percentage for categorical data.
All statistical analyses will be performed, and data appendices will be created, using the SAS® or Stata system. The effects of noncompliance, dropouts and possible covariates will be assessed to determine the impact on the general applicability of results from this study; however, no imputation for missing data will be performed. The results will be presented descriptively or in listings.

9.4.2 Patient disposition

Patient disposition will be tabulated; the number of enrolled, treated, prematurely terminated and completed patients will be summarized. Baseline demographics and characteristics will be summarized at the level of patient.
A list of dropouts will be prepared including reason for discontinuation and time of discontinuation.

9.4.3 Primary safety analysis

The primary safety analysis will be performed on the safety analysis set.
Frequency distribution of patients with ShortCut device and/or ShortCut procedure related mortality and/or stroke events, as determined by the CEC, and assessed at discharge or at 7 days post-procedure, whichever occurs first, will be presented, along with the 95% confidence intervals.

9.4.4 Secondary safety analysis

The secondary safety analysis will be performed on the safety analysis set.
Frequency distribution of all AEs listed in section **Error! Reference source not found.** will be presented by body system and preferred term, severity and relation to ShortCut device and/or ShortCut procedure, as determined by the CEC. For each AE of interest, the tabulation will include the number of AEs and the number and percentage of patients experiencing it.

9.4.5 Tertiary safety analysis

The tertiary safety analysis will be performed on the safety analysis set.
Frequency distribution of all AEs listed in section 5.3 will be presented by body system and preferred term, severity and relation to ShortCut device and/or ShortCut procedure, as determined by the CEC. For each AE of interest, the tabulation will include the number of AEs, the number and percentage of patients experiencing it.

9.4.6 Additional safety analyses

Survival analysis of time to all-cause mortality and time to first stroke will be done using Kaplan-Meier curve. Estimates of all-cause mortality and stroke rates at day 30 and day 90 will be estimated based on the Kaplan-Meier curve.
All AEs and SAEs obtained throughout the 90 days of follow up will be coded and presented by body system, preferred term, severity and relation to the device and/ or procedure. AEs will be presented separately for the first month post-procedure, and the subsequent two months.

9.4.7 Primary effectiveness analysis

The primary effectiveness analysis will be performed on the primary effectiveness analysis set.
The primary effectiveness hypothesis will test whether the rate of patients with a successful split, exceeds the Performance Goal, set to 75%. The following primary effectiveness hypothesis will be tested:

$$H_0: P(split) \leq 0.75$$
$$H_1: P(split) > 0.75$$

where *P(split)* is the rate of Evaluable Patients with a successful split.
Frequency distribution of Evaluable Patients with a successful split will be presented along with the Clopper-Pearson 95% confidence interval. The primary effectiveness null hypothesis will be rejected (i.e., the primary effectiveness hypothesis is met) if the lower limit of the confidence interval is above 0.75.

9.4.8 Secondary effectiveness analysis

The secondary effectiveness analysis will be performed on the secondary effectiveness analysis set.

Per Intervened Leaflet Splitting Success

The secondary effectiveness analysis will present the rate of successful splits along with the Clopper-Pearson 95% confidence interval.
The overall rate of successful splits will also be estimated via generalized estimating equations (GEE, SAS PROC GENMOD) that account for potential dependency between the two leaflets outcomes of the same patient.

Coronary Artery Ostia Obstruction and Intervention

The secondary effectiveness analysis will present the following:

- Frequency distribution and the corresponding 95% confidence interval of patients with:
    - Coronary artery ostia obstruction related to the intervened leaflet within 30 days post-procedure, as determined by the CEC
    - Coronary artery intervention related to the intervened leaflet within 30 days post-procedure, as determined by the CEC

  For patients who experienced any of the above events, a by-patient listing will be provided with extended event description, time from the procedure and relation to ShortCut device and/or ShortCut procedure.

9.4.9 Per Protocol primary effectiveness analysis

For the Per Protocol primary effectiveness analysis, the primary effectiveness analysis will be repeated using the PPPE analysis set.

9.4.10 Per Protocol secondary effectiveness analysis

For the Per Protocol secondary effectiveness analysis, the secondary effectiveness analysis will be repeated using the PPSE analysis set.

9.4.11 Technical success analysis

The technical success analysis will be performed on the safety analysis set.
Frequency distribution of patients with technical success will be presented along with a 95% confidence interval, including the rate of each individual component.
For patients that did not have technical success, a by-patient listing will be provided with detailed description of the reason.

9.4.12 Covariate analysis

Covariate analysis will examine descriptively whether the study results are affected by different patient characteristics. Due to the relatively small sample size, the number of covariates will be limited to age, sex, race and ethnicity.