Pi-Cardia
Next-Generation Valve Repair

NCT: 06211296

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™ Continued Access Study (CAS) Protocol Synopsis

1 Full title

A Prospective, Multicenter, Non-Randomized, Single-Arm, Open-Label Continued Access Study of the ShortCut™ device (The ShortCut™ CAS).

2 Intended Use

The ShortCut™ is indicated for use as a splitting device of bioprosthetic aortic valve leaflets to facilitate percutaneous valve-in-valve procedures.

3 Device name

ShortCut™

4 Design

This is a prospective, multicenter study sponsored by Pi-Cardia Ltd.
This Continued Access Protocol has been written to allow ongoing treatment of patients at selected investigational sites while the marketing application for the ShortCut™ device is under review.

5 Objective

The continued access phase will be used to collect additional safety and effectiveness data 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 ostium obstruction following a ViV procedure. The data gathered in this phase will support the objectives and outcomes of the original IDE pivotal study.

6 Endpoints

6.1 Primary Endpoints

6.1.1 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)

6.1.2 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.

6.2 Secondary Endpoints

6.2.1 Secondary safety endpoints

The following 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
- Access-related type 3-4 bleeding

6.2.2 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
    - 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

6.2.3 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

6.3 Tertiary Safety Endpoints

The following 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

7 Patient population

Patient population will include patient 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. Continued Access studies are approved by FDA on a time-limited phased basis, therefore sample size in this study will be based upon FDA-approved limits. The first enrollment phase will include up to 24 patients for whom the ShortCut™ procedure was initiated (up to 30 enrolled). Following this and subject to FDA approval, expansion of the study for the inclusion of up to 20 additional enrolled patients according to time limits agreed with the FDA.

8 Eligibility Criteria

8.1 Main 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.

8.2 Main 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 measurements.
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. Planned concurrent intervention in the same setting of the index procedure.
5. Surgery or interventional procedure ≤ 1 month prior to the index procedure.
6. Planned provisional (pre-position coronary artery) stents.
7. 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.
8. 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.
9. CVA or TIA ≤ 6 months prior to index procedure.
10. Severe neurological disability, as determined by the Investigator.

9 Study schedule and time points

Study requirements from baseline through follow-up

	Screening *60 days prior to procedure*	Baseline *7 days prior to procedure*	Index procedure	Pre-discharge	30 days post-procedure	90 days post-procedure[8]
Informed consent	X					
Medical and surgical history review	X					
NYHA classification	X				X	
Risk assessment, including EuroSCORE II and STS score	X					
Physical examination		X			X	
Blood tests[1]	X[1]	X[1]		X		
12-lead ECG	X	X[9]		X	X	
Modified Rankin Score and NIHSS[8]		X		X[7]	X[7]	
CT of heart, aortic root, and aortic arch	X[2]					
Echocardiographic imaging	X[3]		X[6]			
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[5]	X[5]	X[5]	X[5]
Clinical status remote evaluation						X

[1] The relevant blood assays and exact timepoints, are listed above under each visit 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] Review medications and record only if there is a change from previous visit (e.g. due to change in health condition or as a result of an adverse event)

[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] ECG at baseline will be performed only in case no ECG was performed within 30 days of procedure.

10 Statistical Analysis Plan

10.1 Study Analysis Sets

10.1.1 Safety analysis set

The safety analysis set will include all patients who reached the point of index procedure, i.e., patients in whom the ShortCutdevice 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.

10.1.2 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.

10.1.3 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.

10.1.4 Per Protocol (PP) analysis sets

10.1.4.1 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).

10.1.4.2 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).

10.2 Sample Size Considerations

The data gathered in this continued access phase will support the objectives and outcomes of the original IDE pivotal study. Therefore, the study endpoints will not be statistically powered. The analysis for the efficacy and safety of the Shortcut™device will follow a designated statistical analysis plan. Continued Access studies are approved by FDA on a time-limited phased basis, therefore sample size in this study will be based upon FDA-approved limits. The first enrollment study phase will include up to 30 enrolled patients:

- Up to 24 patients for whom the ShortCut™procedure was initiated and either the following occurred:

- Split was attempted and were determined to have adequate Imaging
- Split was not attempted for any reason, or
- Split was attempted but were determined to have Inadequate Imaging

• Up to 6 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).

Following this phase and subject to FDA's approval, expansion of the study for the inclusion of up to 20 additional enrolled patients according to time-limited phased basis agreed with the FDA.

The population flowchart is provided below:

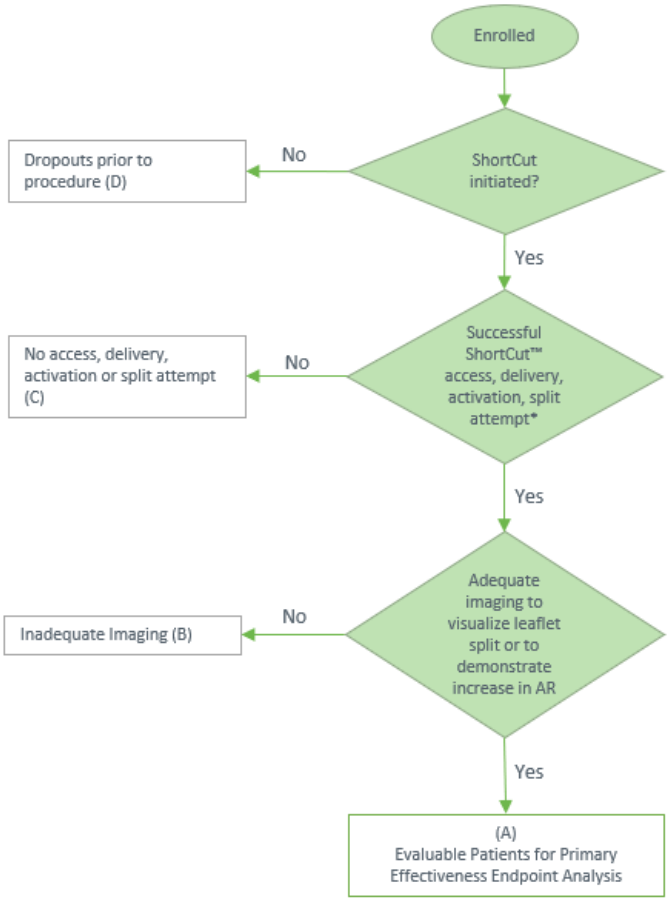

Figure 1: Study population flowchart

10.3 Use of Controls

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

10.4 Statistical Analyses

10.4.1 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.

10.4.2 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.

10.4.3 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.

10.4.4 Secondary safety analysis

The secondary safety analysis will be performed on the safety analysis set.
Frequency distribution of all AEs 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.

10.4.5 Tertiary safety analysis

The tertiary safety analysis will be performed on the safety analysis set.
Frequency distribution of all AEs 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.

10.4.6 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.

10.4.7 Primary effectiveness analysis

The primary effectiveness analysis will be performed on the primary effectiveness analysis set. Frequency distribution of Evaluable Patients with a successful split will be presented along with the Clopper-Pearson 95% confidence interval.

10.4.8 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.

10.4.9 Per Protocol primary effectiveness analysis

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

10.4.10 Per Protocol secondary effectiveness analysis

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

10.4.11 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.

10.4.12 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.