DE NOVO CLASSIFICATION REQUEST FOR SHORTCUT

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Percutaneous catheter for cutting or splitting heart valve leaflets concomitant to transcatheter valve procedures. This device is a single use percutaneous catheter system that has a cutting element on the distal end. The cutting element makes physical contact with target tissue to cut or split heart valve leaflets in a manner that may reduce obstructive flow complications with transcatheter valve procedures. The device is indicated for use immediately prior to a transcatheter valve procedure.

NEW REGULATION NUMBER: 21 CFR 870.1254

CLASSIFICATION: Class II

PRODUCT CODE: SCZ

BACKGROUND

DEVICE NAME: ShortCut

SUBMISSION NUMBER: DEN240017

DATE DE NOVO RECEIVED: May 1, 2024

SPONSOR INFORMATION: Pi-Cardia Ltd.
5 David Fikes St.
Rehovot 7632805
Israel

INDICATIONS FOR USE

ShortCut is indicated for use as a splitting device of bioprosthetic aortic valve leaflets to facilitate valve-in-valve procedures for patients at risk of coronary obstruction.

LIMITATIONS

The sale, distribution, and use of the ShortCut Device are restricted to prescription use in accordance with 21 CFR 801.109.

The ShortCut should only be used by physicians and/or surgeons trained and qualified in interventional cardiology procedures and that have carefully read and fully understand the IFU and have completed all training required by Pi-Cardia.

At the time of granting of this De Novo, the safety and effectiveness of ShortCut have been demonstrated only for splitting bioprosthetic aortic valve leaflets in patients undergoing a concomitant valve-in-valve procedure, and who are determined to be at high risk of coronary ostia obstruction.

PLEASE REFER TO THE LABELING FOR A COMPLETE LIST OF WARNINGS, PRECAUTIONS AND CONTRAINDICATIONS.

DEVICE DESCRIPTION

The ShortCut is a transfemoral catheter designed to split the bioprosthetic aortic valve leaflets prior to transfemoral aortic valve replacement (TAVR), to reduce the risk of coronary ostium obstruction and coronary access compromise and enable a valve-in-valve procedure for patients at risk of coronary obstruction. Splitting of a leaflet creates a triangular opening in the leaflet that allows blood flow into the adjacent coronary artery.

The ShortCut is a sterile, single use, 16 Fr device which is inserted through the femoral artery over a guidewire into the left ventricle using standard catheter placement techniques. The ShortCut is comprised of the following parts:

a. **Distal Unit (DU)** – Distal end of the catheter which contacts the valve leaflets and splits them (Figure 1). It is comprised of the Splitting Element (SE) and the Positioning Arm (PA). The Splitting Element penetrates the leaflet from the ventricular side at the bottom of the leaflet and performs the cut. The Positioning Arm is positioned on the aortic aspect of the leaflet and acts as a protective stabilizer for the activated SE. The DU is delivered in a sheathed 16 Fr configuration that is opened upon reaching the target site.

b. **Delivery System (DS)** – The catheter shafts connect the Handle to the DU and delivers the required movements from the Handle to the DU. The DS is compatible with a 16 Fr introducer sheath and is delivered over a 0.035" Guide Wire (GW). The outer shaft of the DS (Sheathing Tube) is used to sheathe the DU during introduction and removal from the body. The inner shafts of the DS, together with its pig-tailed tip, enable flexing and positioning of the DU at the valve.

c. **Handle** - The user interface, designed to control the DS and the DU and to enable correct positioning of the DU on the valve (Figure 2).

Figure 1: The ShortCut Device

SUMMARY OF NONCLINICAL/BENCH STUDIES

Nonclinical studies conducted for the ShortCut device are summarized below.

BIOCOMPATIBILITY/MATERIALS

Classification	The ShortCut is considered an externally communicating device that is intended to come in direct contact with circulating blood for a limited duration (< 24 hours). A biocompatibility assessment was performed per the requirements of ISO 10993-1:2018 *Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process* and FDA Guidance for Industry *Use of International Standard ISO 10993-1, "Biological evaluation of medical devices- Part 1: Evaluation and testing within a risk management process"* (September 2023).
Biocompatibility Assessment	The biocompatibility of the ShortCut was evaluated with respect to cytotoxicity, sensitization, intracutaneous reactivity, acute systemic toxicity, material mediated pyrogenicity and haemocompatibility: hemolysis, thromboresistance and complement activation. This testing was partially leveraged from a similar device in the Pi-Cardia product family that shares similar materials and design features as the ShortCut. The ShortCut has been appropriately evaluated to demonstrate biocompatibility for its intended use.

SHELF LIFE/STERILITY

Sterility	The ShortCut is provided as a single-use device, sterilized using ethylene oxide (EtO) gas. The device is intended for one procedure only (single-use, disposable).

	Sterility testing conducted in accordance with ISO 11135:2014/Amd1:2019, demonstrates ShortCut is provided sterile. The ShortCut was adopted into an existing, validated EtO sterilization cycle per AAMI TIR28:2016 *Product Adoption and Process Equivalence for Ethylene Oxide Sterilization*. The sterilization cycle was assured by using the validated overkill half-cycle sterilization method qualified in accordance with ISO 11135:2014. Based on the validation results, a sterility assurance level (SAL) of at least (b)(4) was achieved. The EO and ECH residuals of the ShortCut was shown to meet the limits specified by ISO 10993-7:2008 following double EtO sterilization.
Packaging	The packaging configuration for the Shortcut successfully met the packaging distribution testing qualifications, following 2X sterilization, simulated distribution consistent with ASTM D4169-16, and climatic conditioning cycles per ASTM F4332-14. The results of the testing demonstrate that the packaging design met the predetermined requirements, specifications, and acceptance criteria for packaging validation under typical distribution and climatic conditions, via the following testing: • ASTM 1886 / F1886M-16: *Standard test method for determining integrity of seals for flexible packaging by visual inspection* • ASTM F88/F88M-15: *Standard test method for seal strength of flexible barrier materials* • ASTM F2096-11(2019): *Standard Test Method for Detecting Gross Leaks in Packaging by Internal Pressurization (Bubble Test)* • Visual inspection of packaging components condition, labeling legibility and durability, and product insert legibility.
Shelf Life	The shelf-life of the ShortCut has been established at 1 year based on accelerated aging to simulate up to 1 year shelf-life. Following accelerated aging and 2X sterilization, simulated distribution consistent with ASTM D4169-16, and climatic conditioning cycles per ASTM F4332-14, the device packaging validation testing was repeated and functional tests listed below under "PERFORMANCE TESTING – BENCH" which were deemed to be potentially affected by device aging were repeated with aged test samples. All tests passed.

ELECTROMAGNETIC COMPATIBILITY AND ELECTRICAL SAFETY

The ShortCut does not have active or powered electrical components.

MAGNETIC RESONANCE (MR) COMPATIBILITY

The ShortCut is intended as a temporary use device and has not been tested for MR compatibility.

PERFORMANCE TESTING - BENCH

The ShortCut was evaluated through a series of bench tests to verify that the design met the functional specifications. Certain verification tests were leveraged from testing performed on a similar device from the Pi-Cardia product family that shares similar design with ShortCut for the Delivery System and Handle components. The bench tests were performed on final sterilized product, as well as subjected to simulated distribution consistent with ASTM D4169-16, climatic conditioning cycles per ASTM F4332-14, and simulated use in a benchtop anatomical model per the clinical use instructions.

The engineering bench testing summarized in Table 1 below demonstrate acceptable performance of the device for its intended use.

Table 1: Benchtop Performance Testing Summary

Test	Description / Acceptance Criteria
Tubing Strength	Longitudinal (tensile and/or compression) strength of the Catheter tubes: • Internal tube, • Frame tube – tensile and compressive, • Deflection tube – tensile, and • External tube – tensile and compressive
Positioning Stability - Compression Bond Test	Measure the axial forces the Positioning Arm mechanism can withstand under worst-case conditions
Splitting Stability Bond Test	Evaluate the maximum axial forces the distal unit can withstand under worst-case conditions
Handle Bond Strength	Evaluate the bond strength of the joints and/or fixed connections of the handle mechanism: • Internal tube to Internal tube washer • Frame tube to Frame tube washer • External tube to External Tube Slider • Deflection tube to Deflection Tube washer
Tip Bond Strength	Evaluate the bond strength of the joints and/or fixed connections of the tip: • Soft Tip to insert

	• Tip connected to internal tube
DU to Frame Tube bond	Evaluate the bond strength of the joint
Torsional Strength	Torsional strength of Catheter components under worst case torsional conditions
Corrosion*	Evaluation of the corrosion resistance of the Catheter metal parts
Pushability Force	Measure the force required to track the Catheter over a guide-wire through a simulated tortuous path across the aortic arch and valve (Pushing and Withdrawal forces)
Sheathing / Unsheathing forces	Measure the sheathing / unsheathing forces in worst-case anatomical model (Sheathing and Unsheathing)
Axial Splitting Force Repeatability	Measure the splitting axial force repeatability using the tensile machine and a worst-case polymeric material (no statistical difference in splitting force after 4 cuts)
Flushing Test	Verify the ability to flush the air existing between the shafts and in the internal tube lumen
Hydrophilic Coating integrity	Visual assessment of unintended delamination or degradation of the coating after simulated use ((b)(4) coverage of the hydrophilic coating, before and after simulated use is required)
Particulate Evaluation	Evaluation of particulate generation from the ShortCut device where the External tube and Deflection tube are coated with a hydrophilic coating, during simulated use: • Pre-specified maximum allowed particles in each particle bin size quantified per device • Coating integrity evaluation post particulate evaluation test: ○ (b)(4) coverage of the hydrophilic coating, before and after simulated use is required
Simulated Use	Verify the ability of the catheter to successfully perform the splitting procedure including all procedural steps according to the IFU while maintaining the integrity of the catheter in a worst-case anatomical model and an engineered valve; including compatibility with introducer sheath, guidewire and connectors: 1) Correct penetration point and successful leaflet split. 2) Interface compatibility with off-the-shelf accessories (guidewire, sheath, embolic protection device, pigtail catheter) 3) Successful performance of all procedural steps according to the clinical Instructions for Use 4) Intact catheter markings after test 5) Catheter integrity after test
Dimensional Verification	Evaluation of the critical dimension of the system: 1) Catheter weight 2) Catheter working length 3) Catheter Handle's length 4) Distal Unit travel distance

	5) External Tube travel distance from DU unsheathed state to DU sheathed state 6) External shaft OD (Crossing profile)
Deflection Verification Test	Measure the angle and radius when the device is fully deflected (Deflection curve angle (b)(4))
Leak Test	Measure the liquid leak rate through the ShortCut catheter and between the catheter and the introducer sheath in a simulated use scenario ((b)(4)
Sheathing with Blockage Verification*	Evaluate the ability of the catheter to collapse the Splitting Element (SE) and sheath the device when blockage (tissue) is placed under the SE mechanism
Abort Splitting Verification*	Evaluate the ability to terminate the splitting procedure (collapse the SE) prior to completing the split
Usability Data	Summative usability evaluation and design validation of the ShortCut device were conducted during animal and clinical studies. Animal studies: Usability assessment scores for all categories were passing with scores of either 3 ('good and acceptable') or 4 ('very good and acceptable') for all procedures. Clinical studies: 24 physician users at 13 sites evaluated the ShortCut device for usability in 60 subjects. The results demonstrated acceptable performance in terms of its user interface and clear instructions. Users reported high levels of satisfaction with its functionality and ease of operation.

**These characterization tests were performed on unaged devices only.*

PERFORMANCE TESTING – ANIMAL

One *in vivo* animal study was performed according to Good Laboratory Practices (GLP) to support the acute safety and functionality of the ShortCut.

Purpose	A GLP study was conducted to evaluate the acute safety (per thrombogenicity and hemodynamic stability evaluations) and functionality (per leaflet split verification and usability evaluation) of the ShortCut device.
Design	• A total of five (5) pigs were used in the acute study. • In each animal, a ShortCut procedure was performed to split both the left and right coronary leaflets of the aortic valve. • The study included assessment of device usability, visual inspection for thrombus formation, and gross pathology and histopathology examination. • The study was performed at a GLP accredited laboratory.

Results	• For usability assessment, all categories were scored at either 3 (*'good and acceptable'*, 1 animal) or 4 (*'very good and acceptable'*, 4 animals) for all procedures.
	• Visual examination of the intervened leaflets showed that all target leaflets were successfully split.
	• In general, no hemodynamic abnormalities were observed during the procedures.
	  o Increased heart rate was observed in one animal.
	• The following organs were evaluated: heart, aorta, lungs, kidneys, liver, brain and spleen:
	  o There were no visible emboli or signs of ischemia.
	  o Slight abrasions of the inner aortic walls were observed.
	• Thrombus was not observed on the devices after removal from the animals.

SUMMARY OF CLINICAL INFORMATION

The clinical data that supported the ShortCut De Novo request included a primary pivotal study titled, "A Prospective, Multi-center, Non-Randomized, Single-Arm, Open-Label Pivotal Study to Demonstrate the Safety and Effectiveness of the ShortCut Device (The ShortCut Study)" and outside of the United States (OUS), first-in-human compassionate use cases. Details of the clinical experiences and selected results are provided below.

Pivotal Study – The ShortCut Study

Objective

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

Study Design

Prospective, international, multi-center study sponsored by Pi-Cardia Ltd. The single-arm study analyzed sixty (60) subjects who were planned to undergo a percutaneous ViV procedure for an approved ViV indication, and who were determined at risk for TAVR-induced coronary artery ostium obstruction. The study included 23 sites worldwide: 13 in the US, 8 in EU and 2 in Israel.

Eligibility Criteria Summary

The study population consisted of male and female patients, at least 18 years of age.

Key inclusion criteria included the following:

- Plan for a percutaneous ViV procedure for an approved ViV indication due to a failed bioprosthetic valve.
- Subject is at risk for TAVR-induced coronary artery ostium obstruction.

Key exclusion criteria included the following:

- Excessive aortic valve leaflet calcium morphology.
- Leaflet planned to be intervened is torn pre-ShortCut access.
- Iliofemoral vessel characteristics that preclude safe insertion of the introducer sheath.
- Anatomy that does not allow safe placement of a cerebral embolic protection device.
- Intervention ≤ 1 month prior to index procedure.
- Planned provisional stents.
- Coronary disease that should be treated, or treatment of coronary disease ≤ 1 month prior to index procedure.
- Carotid or vertebral artery disease that should be treated, or treatment of carotid stenosis ≤ 1 month prior to index procedure.
- CVA or TIA ≤ 6 months prior to index procedure.
- Inoperable for emergency open-heart surgery.
- Identified thrombotic material on the valve by either CT or Echocardiography.

Primary Effectiveness Endpoints

Overall leaflet splitting success using the ShortCut for each subject, assessed intra-procedurally by echocardiography or angiography.

Per-subject leaflet splitting success was determined based on the splitting success of the first intervened leaflet, as follows:

- 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.

Primary Safety Endpoints

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

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

Additional Endpoints

The Secondary Effectiveness endpoints are:

- Per intervened leaflet splitting success assessed intra-procedurally for each intervened leaflet according to the criteria described above for per-subject leaflet splitting success
- The following endpoints 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.

The following Secondary Safety endpoints were 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

The following Technical Success endpoints were composites of the following 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

Statistical Methods

The data is summarized listing the mean, standard deviation, median, minimum, maximum and number of subjects for continuous data, or listing count (frequency) and percentage for categorical data.

The study was designed to provide 80% power to achieve significance for the primary effectiveness endpoint with a performance goal of 75% of subjects with evidence of a successful split.

The study was not statistically powered to achieve significance for the primary safety endpoint; however, a sample size of at least 60 subjects allows capturing at least 1 rare event, such as stroke or all-cause mortality, with an event rate of 2.8% or greater at high probability (>80%). Stroke or mortality rates in small ViV TAVR studies are reported at rates of 1.4% and 3.5%, respectively. Therefore, the study size is sufficient to observe stroke or mortality events for subjects receiving the ShortCut procedure within a 2-fold margin (i.e., 2.8%) of rates expected in ViV TAVR studies.

Accountability

A total of 137 subjects were screened for the study worldwide (US, Europe, and Israel). 66 of the 137 subjects were screening failures, 6 subjects dropped out of the study before treatment, and 5 subjects enrolled from OUS sites were considered not poolable by the conditions of the US protocol. Therefore, sixty (60) enrolled subjects were eligible for inclusion in the IDE Shortcut Pivotal study.

- There were multiple reasons for the 66 screening failures, including but not limited to: subject not as risk for TAVR-induced coronary artery obstruction, subject not planning to undergo percutaneous ViV procedure for an approved indication, excessive aortic valve leaflet calcium morphology, and/or unsuitable anatomy or condition for the device or procedure.

- The 5 OUS subjects that did not meet the US eligibility criteria per the approved IDE clinical protocol were considered non-poolable for the following reasons:
    - Planned provisional stent (2);
    - Coronary disease that should be treated or treatment of coronary disease =< 1 month prior to index procedure (1);
    - Subject is not planned to undergo a percutaneous ViV procedure for an approved ViV indication (1);
    - Surgery or interventional procedure ≤ 1 month prior to the index procedure (1).

Reasons for the 6 subjects that dropped out of the study and did not undergo the procedure include are listed in Table 2 below.

Of the 60 subjects that initiated the overall transcatheter aortic valve procedure, 100% (60/60) underwent the index procedure with ShortCut. The 30-day visit compliance for the subjects was 95.0% (57/60), with 2 of the 3 missed visits due to death.

The disposition of study subjects up to 90-day follow-up is presented in Table 2.

Table 2: Study Cohort Disposition & Compliance

Disposition / Compliance Variable	US Subjects N (%)	OUS Subjects N (%)	All Subjects, N (%)
Consented Subjects	68	69	137
Passed Screening	35	36	71
IDE Study Eligible / Enrolled	35	31	66
Enrolled and Not Treated (Dropouts) [1]	4 (11.4)	2 (6.5)	6 (9.1)
Subject Withdrew Consent [2]	2 (50.0)	0	2 (33.3)
Investigator excluded/ withdrew subject [2]	0	1 (50.0)	1 (16.7)
Death [2]	1 (25.0)	1 (50.0)	2 (33.3)
Other [2]	1 (25.0)	0	1 (16.7)
Started Overall Procedure	31	29	60
Started Index Procedure [3]	31 (100.0)	29 (100.0)	60 (100.0)
At Least One Leaflet Split was Attempted [3]	31 (100.0)	29 (100.0)	60 (100.0)
Completed the Study According to Protocol [3]	28 (90.3)	27 (93.1)	55 (91.7)
30-Day Visit Completed [3, †]	29 (93.5)	28 (96.6)	57 (95.0)
90-Day Visit Completed [3, ‡]	28 (90.3)	27 (93.1)	55 (91.7)

[1] Percentages are based on the 'IDE Study Eligible / Enrolled' total per column.

[2] Percentages are based on the 'Enrolled and Not Treated' totals per column.

[3] Percentages are based on the 'Started Overall Procedure' totals per column.

† Two (2) subjects died 19 and 24 days post-procedure; One (1) subject did not perform the 30-days follow-up visit (but did return for 90-day visit).

‡ One (1) additional subject died 57 days post-procedure; One (1) subject is lost to follow-up; One (1) subject did not perform the 90-day follow-up visit.

Demographics

The mean subject age was 77.0±9.6 years and 70.0% of participants were female. The most common comorbidities included hypertension (85.0%), significant renal impairment (73.3%), and coronary artery disease (43.3%). Subjects presented with isolated bioprosthetic valve stenosis (58.3%), isolated aortic regurgitation (11.7%), or mixed bioprosthetic valve failure (30.0%). The majority of subjects (96.7%) had a failed surgically implanted bioprosthetic valve (SAVR), while two subjects (3.3%) had a failed transcatheter bioprosthetic valve replacement (TAVR). Information on the subject demographics and baseline characteristics is provided in Table 3 below.

Table 3: Study Cohort Demographics & Baseline Characteristics

Demographic Parameter / Baseline Characteristic	**n = 60 n (%) or mean ± SD**
Age, yr	77.0 ± 9.6
Male	18 (30.0)
Female	42 (70.0)
Race / Ethnicity	
Asian	1 (1.7)
Black of African American	1 (1.7)
Hispanic/Latino	1 (1.7)
White	42 (70.0)
Unknown*	15 (25.0)
STS score, %	4.5 ± 2.4
EuroSCORE II	8.5 ±5.7
Surgical risk (assessed by the heart team)	
Intermediate / low	0 (0.0)
High	54 (90.0)
Extreme	6 (10.0)
NYHA Class	
I-II	20 (33.3)
III-IV	40 (66.7)
Left ventricular ejection fraction, %	54.2 ± 10.4
AV peak gradient, mmHg	65.3 ± 21.3
AV mean gradient, mmHg	38.1 ± 13.2
AVA, cm^2	1.0 ± 0.5
Failed Valve Type	
SAVR	58 (96.7)
TAVR	2 (3.3)
Failed Valve Disease	
Isolated aortic stenosis (AS)	35 (58.3)
Isolated aortic regurgitation (AR)	7 (11.7)
Mixed (AS and AR)	18 (30.0)
Failed bioprosthetic valve label size	
19 mm	8 (13.3)

21 mm	26 (43.3)
≥ 23 mm	26 (43.3)

* Unknown = Not applicable, Not asked, Asked but unknown, Not done, or Missing
BMI, body mass index; AVA, aortic valve area; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; STS, Society of Thoracic Surgeons; AV, aortic valve; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement.

All subjects (100%) were determined to be at risk for coronary obstruction. Key anatomical risk factors included mean VTC distance of 3.3±1.2 mm, mean VTS distance of 2.2±1.4 mm, and coronary height<10mm for 91.7% of the subjects. Additional factors indicating risk for coronary obstruction in the study cohort are depicted in Table 4.

Table 4: Study Cohort Risk Factors of Coronary Artery Ostia Obstruction

Risk Factors of Coronary Artery Ostia Obstruction	**n = 60 n (%) or mean ± SD**
Anatomical Risk Factors (per CT core lab analysis)	
Coronary height, mm	6.9 ± 2.7
Coronary ostia eccentricity, deg	10.6 ± 8.0
Coronary height < 10 mm	55 (91.7)
Sinus of Valsalva width, mm	27.9 ± 3.3
Sinus of Valsalva height, mm	16.2 ± 3.2
VTC distance, mm	3.3 ± 1.2
VTS distance, mm	2.2 ± 1.4
Bioprosthetic Valve Factors (per site evaluation)	
Supra-annular position	16 (26.7)
Internal stent frame	23 (38.3)
No stent frame	4 (6.7)
Long, thick, or bulky bioprosthetic leaflets	11 (18.3)
Stents posts that extend beyond Sinotubular Junction	17 (28.3)
Intended over-expansion / fracture of bioprosthetic valve frame during TAVR	17 (28.3)
None of the above	11 (18.3)
Transcatheter Valve factor (per site evaluation)	
Extended sealing cuff	19 (31.7)
High implantation	20 (33.3)
None of the above	32 (53.3)

VTC, virtual transcatheter heart valve-to-coronary-artery; VTS, virtual transcatheter heart valve to sinotubular junction.

Results

Procedural Outcomes

All procedures were performed under general anesthesia utilizing TEE and all used an embolic protection device. A single leaflet split was performed in 63.3% of subjects and two leaflets split in 36.7% of subjects. ShortCut procedure time was 31±18 min (single split 26.9

± 19.7 min, dual split 37.0±14.7 min). In all subjects, valves were implanted successfully following the ShortCut procedure. One subject required emergency open-heart surgery for replacement valve implant due to index procedure-related adverse event (guidewire perforation of left ventricle). Selected procedural outcomes are provided in Table 5 below.

Table 5: Summary of Procedural Outcomes

Procedure Detail	**n = 60** **n (%) or mean ± SD**
Transfemoral access for TAVR	60 (100.0)
Embolic protection device placed	60 (100.0)
Intervened Leaflet	
Left	30 (50.0)
Right	8 (13.3)
Left and Right	22 (36.7)
Overall procedure time (skin-to-skin), min*	119.7 ± 51.3
ShortCut procedure time, min**	30.6 ± 17.9
One leaflet split, min	26.9 ± 19.7
Two leaflet split, min	37.0 ± 14.7
ShortCut procedure contrast media volume, ml	23.3 ± 43.9
ShortCut procedure fluoroscopy time, min	16.8 ± 10.1
ViV TAVR procedure time, min***	7.9 ± 7.1

*Total procedure time - time from access site incision to access site closure.

**ShortCut procedure time: time between ShortCut catheter insertion to its full retrieval including imaging time for split documentation.

***n=59; Data does not exist for 1 subject who had surgical implant procedure rather than TAVR.

Fifty-three subjects (53/60) were treated using only the first ShortCut device attempted. In six cases (6), the first device was removed prior to cutting a leaflet and a second device was used to make either a single split (3) or dual split (3). For one subject (1), the first device successful performed the first leaflet split and a second device was used to make the second leaflet cut. Overall, fifty-nine subjects (59/60) had all leaflet intervention(s) performed by a single (either first or second introduced) ShortCut device, as shown in Table 6 below.

Table 6: Procedural Outcomes Per Device and Intervened Leaflet

ShortCut Procedure Outcome	**First ShortCut Device (n=60), n (%)**	**Second ShortCut Device (n=7), n (%)**	**Overall**
ShortCut Successfully Reached the Left Ventricle [1]	59 (98.3)	7 (100.0)	
ShortCut Successfully Positioned on Leaflet(s) [1]	56 (93.3)	7 (100.0)	
Number of subjects for whom splitting performed [1]	54 (90.0)	7 (100.0)	60 (100.0)
LCC Split Only [2]	27 (50.0)	3 (42.9)	30 (50.0)

RCC Split Only [2]	8 (14.8)	0 (0.0)	8 (13.3)
RCC and LCC [2]	19 (35.2)	4 (57.1)	22 (36.7)
Withdrawn Successfully [1]	58 (96.7)	7 (100.0)	

[1] Percentages are based on the number of devices per column.
[2] Percentages are based on the 'Number of subjects for whom splitting performed' totals per column.

Primary Effectiveness Endpoints

The primary effectiveness endpoint of per-subject leaflet splitting success was achieved in all subjects (100%) by one of the two pre-defined methods using intra-procedural echocardiography or angiography, and was statistically significantly higher ($p<.001$) then the study performance goal of 75%, as shown in Table 7 below.

Table 7: Per-Subject Splitting Success

Primary Effectiveness Endpoint	Subjects with Successful First Split (n=60), n (%)	95% Confidence Interval	P-Value
Evidence of a split	60 (100.0)	(94.0, 100.0)	<0.001
Split visualization	54 (90.0)	(79.5, 96.2)	
Increase in transvalvular AR	55 (91.7)	(81.6, 97.2)	

Confidence intervals were calculated using Clopper-Pearson method.
P-value was calculated using Exact Binomial test versus the performance goal of 0.75.

Primary Safety Endpoints

The study primary safety endpoint of stroke or death by discharge or 7 days post-index procedure was analyzed per CEC adjudication and is provided in Table 8. There were no deaths (0.0%) within 7 days post-procedure or by discharge. There was one stroke (1.7%) occurring at 4 days post-procedure that was determined not related to the ShortCut device and possibly related to ShortCut procedure.

Table 8: Mortality & Stroke Through Discharge or 7-Day Follow-up

Primary Safety Endpoint	Subjects with Successful First Split (n=60), n (%)
Mortality	0 (0.0)
Stroke	1 (1.7)
Fatal Stroke	0 (0.0)
Disabling*	1 (1.7)
Non-disabling**	0 (0.0)

* Disabling Stroke (mRS ≥2 and increase of at least 1 from baseline).
**Non disabling Stroke (mRS <2 or without increase from baseline).

Additional Endpoints:
The Secondary Effectiveness endpoints of per-intervened leaflet splitting success and freedom from coronary artery ostia obstruction or interventions are summarized in Tables 9 and 10 below:

When considering all splitting attempts, successful leaflet split was demonstrated in 80 out of the 82 (97.6%) intervened leaflets. For the two cases in which successful leaflet split was not determined, one case indicated unsuccessful split per the pre-established conditions and the other case was inconclusive due to inadequate imaging.

Table 9: Per-Leaflet Splitting Success

Per-Leaflet Splitting Effectiveness Endpoint	Intervened Leaflet with Successful Split (n=82), n (%)
Evidence of a split	80 (97.6)
Split visualization	73 (91.3)
Increase in transvalvular AR	68 (85.0)

There were 3 cases of coronary artery ostia obstruction (5%) within 30 days of the procedure, as well as 1 additional case of coronary artery intervention without evidence of coronary ostia obstruction.

Table 10: Coronary Artery Ostia Obstruction or Intervention within 30 Days Post-procedure

Secondary Effectiveness Endpoints	Total Subjects (n=60), n (%)
Freedom from Coronary Artery Ostia Obstruction related to the intervened leaflet	57 (95.0)
Freedom from Coronary Artery Intervention related to the intervened leaflet	56 (93.3)

The Secondary Safety endpoints were assessed through 30 days post-index procedure according to VARC-3 and per CEC adjudication, as presented in Table 11 below:

Table 11: Safety Endpoints Through 30 Days Post-procedure

Secondary Safety Endpoints	Total Subjects (n=60), n (%)
All-cause mortality	2 (3.3)
Cardiovascular mortality	0 (0.0)
Non-cardiovascular mortality	2 (3.3)
All-cause stroke	1 (1.7)
Coronary obstruction	3 (5.0)
Myocardial infarction with new evidence of coronary artery obstruction requiring intervention	2 (3.3)
Major vascular complications	0 (0.0)

Secondary Safety Endpoints	Total Subjects (n=60), n (%)
Cardiac tamponade	1 (1.7)
Acute kidney injury (AKI)	2 (3.3)
Access-related type 3-4 bleeding	0 (0.0)

The Technical Success endpoints evaluated at exit from procedure room following the ShortCut procedure on a per-subject basis are summarized in Table 12 below. One subject had cardiac tamponade caused by the guidewire position who underwent open-heart valve replacement, accounting for both reported technical failure reasons.

Table 12: Technical Success Endpoints following ShortCut Procedure

Technical Success Endpoints	Total Subjects (n=60), n (%)
Overall Technical Success	59 (98.3)
Successful access, delivery, or retrieval of the ShortCut™ device	60 (100.0)
Freedom from ShortCut device and/or procedure related mortality	60 (100.0)
Freedom from ShortCut device and/or procedure related:	59 (98.3)
- surgery or intervention	59 (98.3)
- major vascular or access-related complications	60 (100.0)
- cardiac structural complication	59 (98.3)

Adverse Events

The total number of events adjudicated by the CEC for treated subjects from the point of index procedure through the study was 91 events. Following CEC adjudication, the reviewed events were classified as 40 serious adverse events (SAE) and 51 adverse events (AE), as shown in Table 13 below.

Table 13: Summary of Adverse Events and Serious Adverse Events Through 90-Day Study Duration

Type of Event	Adjudicated events n (%)	Events with relatedness to the ShortCut device or procedure, n (%)
Total # as adjudicated *	91	25
SAE [1]	40 (44.0)	9 (36.0)
AE [1]	51 (56.0)**	16 (64.0)

[1] Percentages are based on the total number of events per column.

* Additional 23 AEs, determined by site as non-serious and not related to the ShortCut device or procedure or the overall ViV, were not adjudicated by the CEC, per protocol.

** 3 out of the 51 AEs were adjudicated as 'no event'.

Three total deaths occurred in the study cohort: two deaths prior to 30 days (see Table 11) and one additional death within 90 days. The deaths were determined to be non-cardiovascular causes and were not related to ShortCut device or procedure, as shown in Table 14 below.

Table 14: Critical Adverse Events Through 90-Day Study Duration by Relation to ShortCut Device or Procedure

Adverse Event	Not Related to ShortCut*	Related to ShortCut*	Total Subjects (n=60), n (%)
All-cause mortality	3 (5.0)	0 (0.0)	3 (5.0)
Cardiovascular mortality	0 (0.0)	0 (0.0)	0 (0.0)
Non-cardiovascular mortality	3 (5.0)	0 (0.0)	3 (5.0)
All-cause stroke	0 (0.0)	1 (1.7)	1 (1.7)
Myocardial infarction with new evidence of coronary artery obstruction requiring intervention	2 (3.3)	0 (0.0)	2 (3.3)

* Assesses "Not Related" or "Related" that includes Possibly / Probably / Definitely Related AEs to either ShortCut Device or Procedure, per CEC adjudication.

Conclusions

Key findings of the ShortCut Study include:

- The primary effectiveness endpoint of per-subject leaflet splitting success using the ShortCut device was achieved for the first intervened leaflet in 100% subjects, which was significantly higher ($p < 0.001$) than the study performance goal of 75%.
- There was no mortality (0.0%) and one stroke (1.7%) within 7 days post-procedure or at discharge, which are comparable to death and stroke rates expected for patients undergoing ViV TAVR. The stroke event occurred 4 days post-procedure and determined to be possibly related to the ShortCut procedure.
- Coronary obstruction was reported in three subjects (5%); however, these events were adjudicated as not related to the ShortCut device or procedure, and all were successfully managed via coronary intervention post-TAVR. An observed occurrence of 5% coronary obstruction is not unreasonable in the study patient population of high risk for coronary obstruction receiving ViV.
- Technical success was achieved in 98.3% of the subjects.

The ShortCut Pivotal Study demonstrated that splitting failed bioprosthetic aortic valve leaflets using ShortCut is safe and effective in subjects at high risk for coronary artery obstruction undergoing ViV TAVR.

OUS Compassionate Use Cases

Scope

The eight (8) initial clinical cases performed with the ShortCut device during December 2020 – December 2021 and with follow-up data up to 18 months.

Study Design

All patients consented to the treatment under Compassionate Use provision. The institutional ethics committees and relevant regulatory agencies reviewed and approved each patient per the local regulations.

Eight patients (n=8) were treated with the ShortCut by two physicians at 2 sites in Israel and in Germany. Patients were followed according to the hospitals' standard-of-care protocols.

Eligibility Criteria Summary

All patients were at risk of left coronary obstruction, and three patients were at additional risk for right coronary obstruction. Patients were required to be >18 years old and recommended for an approved ViV TAVR indication. Patients were not suitable in cases of severe or moderate thickened and calcified aortic valve leaflets at the intended laceration site, or anatomy that would not allow safe placement of an embolic protection device. In addition, patients who had a cerebral vascular accident or transient ischemic attack in the 12 months prior to procedure were not approved.

Demographics

Subject demographics, baseline characteristics, and risk factors for coronary artery obstruction are presented in the Table 15, below:

Table 15: Compassionate Use Patient Demographics, Baseline Characteristics, and Risk Factors for Coronary Obstruction

	n = 8 **n or mean ± SD**
Age, yr	77.0 ± 9.6
Male	2
Female	6
STS score, %	6.6 ± 4.5
NYHA Class	
I-II	0
III-IV	8
Left ventricular ejection fraction, %	56 ± 9
Failed Valve Type	
SAVR	6
TAVR	2
Failed Valve Disease	
Isolated aortic stenosis (AS)	4
Isolated aortic regurgitation (AR)	1
Mixed (AS and AR)	3
Risk factors for coronary obstruction (8 patients, 11 leaflets)	
Coronary height, mm	7.7 ± 3.8
Sinus of Valsalva width, mm	27.2 ± 5.6
Sinus of Valsalva height, mm	15.6 ± 7.0
VTC distance, mm	2.9 ± 0.7
VTS distance, mm	2.9 ± 0.8

Clinical Results

Procedural Outcomes

The procedural outcomes of the compassion use cases are shown below.

Table 16: Summary of Procedural Outcomes & Results

Procedure Detail	n = 8 n or mean ± SD
Intervened Leaflet	
Left	5
Right	0
Left and right	3
Total procedure time* (min)	141.1 ± 46.9
ShortCut™ procedure time* (min)	18.0 ± 5.9
ViV TAVR procedure time* (min)	11.0 ± 10.5
Procedure Outcome – post TAVR	
Coronary obstruction	0
AR ≥ moderate AR	0
Mean gradient (mmHg)	9.5 ± 3.7

Safety Outcomes

No serious adverse events (SAE) related to the ShortCut device or ShortCut procedure were reported for the 8 compassionate cases. All patients were discharged from the hospital in good condition and without coronary obstruction, stroke, or major complications. With follow-up between 15 to 18 months post-procedure, there were no reports of stroke or coronary obstruction.

Conclusions

The results from the first human experience in 8 reported compassionate use cases demonstrated that the ShortCut device and procedure is feasible to safely split one or two aortic bioprosthetic valve leaflets.

Pediatric Extrapolation

In this De Novo request, existing clinical data were not leveraged to support the use of the device in a pediatric patient population.

LABELING

The ShortCut labeling consists of Instructions for Use and packaging labels. The labeling satisfies the requirements of 21 CFR 801.109.

The Instructions for Use includes:

- Indications for Use;
- Description of the device;
- Patient population the device has been demonstrated to be effective;
- Contraindications, warnings, & precautions;
- Recommended training for safe use of the device;

- Instructions for the safe use of the device, including the maximum number of cutting actions and deployments for each device and target site;
- Detailed summary of the clinical data collected in support of the device;
- Prescription statement;
- Shelf life.

Please see the Limitations section above for important warnings and precautions presented in the device labeling.

RISKS TO HEALTH

The table below identifies the risks to health that may be associated with heart valve leaflet splitting devices and the measures necessary to mitigate these risks.

Table 17: Identified Risks to Health and Mitigation Measures

Risks to Health	Mitigation Measures
Infection	Sterilization validation Shelf life testing Labeling
Adverse tissue reaction	Biocompatibility evaluation
Incomplete valve tissue splitting	Clinical performance testing *In vivo* performance testing Non-clinical performance testing Electrical safety testing Electromagnetic compatibility testing Shelf life testing Labeling
Tissue injury: non-targeted tissue, vascular injury, dissection	Clinical performance testing *In vivo* performance testing Non-clinical performance testing Electrical safety testing Electromagnetic compatibility testing Labeling
Embolic events: thromboembolic, e.g.; stroke; bioprosthetic embolism; device embolism	Clinical performance testing *In vivo* performance testing Biocompatibility evaluation Non-clinical performance testing Shelf life testing Labeling
Blood flow obstruction	Clinical performance testing *In vivo* performance testing
Interaction with cardiac conduction system leading to postoperative arrythmias, including atrial fibrillation and heart block	Clinical performance testing *In vivo* performance testing Labeling

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the percutaneous catheter for cutting or splitting heart valve leaflets concomitant to transcatheter valve procedures is subject to the following special controls:

(1) Clinical performance testing of the device must demonstrate that the device performs as intended under anticipated conditions of use. Testing must evaluate:
   (i) The ability to safely deliver and remove the device;
   (ii) Performance in cutting or splitting of the target valve leaflets;
   (iii) Compatibility with concomitant transcatheter valve procedures; and
   (iv) All adverse events observed, including device malfunctions, tissue or vascular injury, hemodynamic abnormalities, embolic events, cerebrovascular adverse events, and unanticipated surgical interventions.

(2) *In vivo* performance testing must demonstrate that the device performs as intended under anticipated conditions of use. The following performance characteristics must be assessed:
   (i) Delivery, use, and retrieval of the device;
   (ii) Cutting or splitting of target leaflet(s); and
   (iii) Gross pathology and histopathology assessing leaflet splitting, soft tissue damage, and downstream embolization.

(3) Non-clinical performance testing data must demonstrate that the device performs as intended under anticipated conditions of use. The following performance characteristics must be tested:
   (i) Simulated use testing in a clinically relevant bench anatomic model to assess feasibility of device operation under worst-case clinical conditions, including device delivery, use, retrieval, and compatibility with accessory devices via transcatheter approach;
   (ii) Consistency and reliability of cutting action;
   (iii) Ability to advance and position the device to reach the target site;
   (iv) Mechanical integrity testing (e.g., bond/joint strength, torsional strength) of the device under anticipated loading conditions;
   (v) Assessment of material-specific risks, such as corrosion if the device contains metal components, or coating integrity and particulates if the device contains lubricious coatings; and
   (vi) Characterization and verification of critical dimensions.

(4) Compatibility testing for devices that contain electrical components must include:
   (i) Electrical safety and electromagnetic compatibility (EMC) testing; and
   (ii) Software verification, validation, and hazard analysis for all devices that contain software.

(5) All patient-contacting components of the device must be demonstrated to be biocompatible.

(6) Performance data must demonstrate the sterility of the device components intended to be provided sterile.

(7) Performance data must support the shelf-life of the device by demonstrating continued sterility, package integrity, and device functionality over the labeled shelf life.

(8) Labeling must include the following:
   (i) The recommended training for safe use of the device;
   (ii) Information on the patient population for which the device has been demonstrated to be effective;
   (iii) Identification of the maximum number of cutting actions and deployments for each device and for each target site; and
   (iv) A detailed summary of the clinical testing conducted; and
   (v) A shelf life.

BENEFIT-RISK DETERMINATION

The ShortCut device is indicated for use as a splitting device of bioprosthetic aortic valve leaflets to facilitate valve-in-valve procedures for patients at risk of coronary obstruction. In general, the risks of ShortCut are expected to be similar to those observed with transcatheter cardiac devices and procedures.

The probable risks of the device are based on nonclinical laboratory and/or animal studies, as well as data collected in a clinical study described above. There are known difficulties and risks associated with ShortCut that are inherent to transcatheter heart valve procedures, and which are outlined below:

- Aortic regurgitation
- Cardiovascular injury including perforation or dissection of vessels, aorta, ventricles, myocardium or valvular structures that may require intervention
- Conduction system disturbance or injury which may require a permanent pacemaker
- Cardiogenic shock
- Coronary ostium obstruction
- Embolization including air, calcific valve material or thrombus
- Hematoma or hemorrhage requiring transfusion or intervention
- Infection including septicemia and endocarditis, pneumonia
- Myocardial infarction
- Pain or bleeding at the access site
- Pericardial tamponade
- Acute kidney injury
- Stroke or transient ischemic attack
- Death

Clinical investigation of ShortCut for splitting bioprosthetic aortic valve leaflets to facilitate valve-in-valve procedures for patients at risk of coronary obstruction demonstrated 0% mortality

through discharge or 7-day follow-up period. Three (3) deaths were reported occurring through the 90-day follow-up period which were determined non-cardiovascular related and not related to the ShortCut device or procedure. There was one (1) disabling stroke reported, which was adjudicated as not related to the ShortCut device, possibly related to ShortCut procedure, and definitely related to the overall ViV procedure. Through the 90-day follow-up, there were 114 adverse events reported in the study cohort (91 events adjudicated per protocol as 40 serious adverse events (SAE) and 51 adverse events (AE)). Overall, the adverse events reported in the clinical study are anticipated events for transcatheter cardiac procedures. As the ShortCut procedure is performed concomitant with TAVR, isolating events and risks specific to ShortCut is confounded; however, the frequency of adverse events reported in the clinical study, including death and stroke, are at rates that are expected and reasonable for a patient population undergoing ViV TAVR. Therefore, ShortCut does not add new or different clinical risks, nor does it exacerbate the risks inherent with transcatheter cardiac procedures.

The probable benefits of the device are also based on nonclinical laboratory and/or animal studies, as well as data collected in a clinical study described above. Probable benefits of the device are based on demonstration that ShortCut performs reliably and effectively in splitting the targeted aortic leaflet(s) on a failed bioprosthetic valve in preparation for ViV TAVR. Nonclinical and animal studies demonstrated the device met all design specifications and achieved repeatable leaflet cutting. In the clinical study, the primary effectiveness endpoint of per-subject leaflet splitting success was achieved in all subjects (100%) with only one technical failure (98.3% technical success). The clinical study was not statistically powered to demonstrate subsequent clinical benefit of leaflet splitting; however, it can be reasonably expected that successful leaflet splitting will provide the following benefits:

- Provide ViV TAVR as a treatment option for patients at high risk of coronary obstruction who may otherwise be denied treatment or undergo risky surgical procedures;
- Reduce occurrence of coronary obstruction compared to the expected rates in the high-risk target population.

All subjects enrolled and treated in the clinical study were determined to be at high risk of coronary artery ostia obstruction in the context of ViV TAVR and the clinical outcomes were favorable with use of ShortCut to facilitate ViV TAVR. Partial or complete coronary artery obstruction was noted in 3 subjects (5%) despite use of ShortCut. Of these subjects, no mortality or significant change in LV function occurred throughout study duration. Further, all three patients were successfully managed using standard percutaneous coronary intervention technique without surgical bailout. Overall, the reported 5% coronary obstruction and subject outcomes in the ShortCut Study compare favorably to reported rates of coronary artery ostia obstruction and related-mortality in patients at high-risk of coronary obstruction undergoing ViV TAVR without ShortCut assistance.

Additional factors to be considered in determining probable risks and benefits for the ShortCut include: limitations of the ShortCut Pivotal Study; that the ShortCut is intended to be used concomitant with TAVR procedure; and that the treatment principle of splitting aortic valve leaflets to facilitate a TAVR procedure has been validated in clinical practice. Limitations of the submitted clinical study are that the study was designed to analyze sixty (60) subjects with

primary endpoints assessed no later than 7 days post-index procedure. The study cohort had low racial and ethnic diversity. The study was powered for an effectiveness endpoint of functional performance; yet, the study was not designed to statistically determine clinical effectiveness or powered to assess the primary safety endpoint. While identifying adverse events or risks specific to ShortCut is confounded by concomitant TAVR, it is not expected that use of ShortCut will increase the risks of the TAVR procedure. Moreover, the treatment principle of ShortCut is similar to that validated in the BASILICA (Bioprosthetic or native Aortic Scallop Intentional Laceration to prevent Iatrogenic Coronary Artery obstruction during TAVR) procedure and study, which also splits aortic valve leaflets but using a different cutting modality. Therefore, clinical outcomes with BASILICA may be leveraged to address certain limitations of the ShortCut Study, as listed above.

Overall, the known or probable risks are considered not to be meaningfully different than risks associated with other transcatheter cardiac procedures. When considering the totality of evidence, there is a reasonable expectation that ShortCut will provide an effective treatment option for patients at risk of coronary obstruction when undergoing a valve-in-valve procedure.

Patient Perspectives

This submission did not include specific information on patient perspectives for this device.

Benefit/Risk Conclusion

In conclusion, given the available information, the probable benefits outweigh the probable risks of ShortCut for the following indication statement:

> The ShortCut is indicated for use as a splitting device of bioprosthetic aortic valve leaflets to facilitate valve-in-valve procedures for patients at risk of coronary obstruction.

The device provides benefits and the risks can be mitigated by the use of general controls and the identified special controls.

CONCLUSION

The De Novo request for ShortCut is granted and the device is classified as follows:

Product Code:	SCZ
Device Type:	Percutaneous catheter for cutting or splitting heart valve leaflets concomitant to transcatheter valve procedures
Regulation:	21 CFR 870.1254
Class:	II