Statistical Analysis Plan

Vortex Temporary Percutaneous Transvalvular Circulatory Support System Feasibility Study

Vortex Feasibility Study
S2465

APPROVALS (Check/Complete one below):

☒ Approvals are captured electronically

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TABLE OF CONTENTS

1 PROTOCOL SUMMARY 3
2 INTRODUCTION 8
3 ENDPOINT ANALYSIS 8
3.1 Primary Endpoint 8
3.1.1 Hypotheses 8
3.1.2 Sample Size 8
3.1.3 Statistical Methods 8
3.2 Additional Measurements 8
3.2.1 Statistical Methods 9
4 GENERAL STATISTICAL METHODS 9
4.1 Analysis Sets 9
4.2 Control of Systematic Error/Bias 9
4.3 Number of Subjects per Investigative Site 10
5 ADDITIONAL DATA ANALYSES 10
5.1 Other Endpoints/Measurements 10
5.2 Interim Analyses 10
5.3 Subgroup Analyses 10
5.4 Justification of Pooling 10
5.5 Multivariable Analyses 10
5.6 Other Analyses 10
5.7 Changes to Planned Analyses 10
6 Validation 10
7 Programming Considerations 11
7.1 Statistical Software 11
7.2 Format of Output 11
7.3 Methods for Handling Missing Data 11
7.4 Rules and Definition 11
7.4.1 General 11
7.4.2 Body Mass Index (BMI) 12
7.4.3 Denominator using Sufficient Follow-up for Endpoints and Additional Measurements 12

1 PROTOCOL SUMMARY

<table>
<tr><th colspan="2">Vortex Temporary Percutaneous Transvalvular Circulatory Support System Feasibility Study: Vortex Feasibility Study</th></tr>
<tr><td>Study Objective(s)</td><td>To evaluate the feasibility and safety of the Vortex Temporary Percutaneous Transvalvular Circulatory Support System (Vortex System) in subjects undergoing elective high-risk percutaneous coronary intervention (HR-PCI)</td></tr>
<tr><td>Planned Indication(s) for Use</td><td>The Vortex System is indicated to provide temporary (≤ 4 hours) circulatory support in subjects undergoing elective high-risk percutaneous coronary intervention (HR-PCI).</td></tr>
<tr><td>Test Device</td><td>The Vortex System is a minimally invasive device that is in direct contact with the heart while in use. Components are summarized below.
<table>
<tr><th>Component</th><th>Description</th></tr>
<tr><td>[redacted]</td><td>[redacted]</td></tr>
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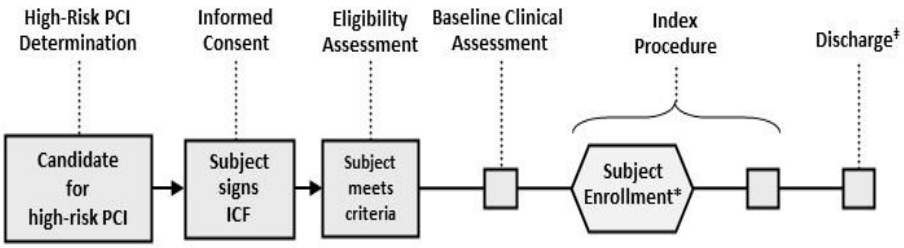
Vortex Temporary Percutaneous Transvalvular Circulatory Support System Feasibility Study: Vortex Feasibility Study	
Study Design	The Vortex Feasibility Study is a prospective, open-label, single-arm study designed to assess the safety and feasibility of the Vortex System to provide temporary (≤ 4 hours) circulatory support in subjects undergoing HR-PCI. The study design is summarized in the figure below.  * Subjects who provide informed consent are considered enrolled as soon as an attempt is made to insert any part of the Vortex System into the subject's femoral artery. ‡ ≤72 hours or discharge, whichever comes first **Vortex Feasibility Study Design Overview** The Vortex study will be conducted in accordance with the International Standard ISO 14155:2020 Clinical Investigation of Medical Devices for Human Subjects – Good Clinical Practice; European Medical Device Regulations; ethical principles that have their origins in the Declaration of Helsinki; and pertinent individual country/state/local laws and regulations. The study shall not begin until the required approval/favorable opinion from the Independent Ethics Committee (IEC)/Human Research Ethics Committee (HREC) and/or regulatory authority has been obtained, if appropriate.
Planned Number of Subjects / Investigational Centers / Countries	There will be up to 10 subjects enrolled in up to 3 centers in Australia and Europe.
Primary Endpoint	The primary endpoint consists of Technical Success and Clinical Success, defined as follows. <u>Technical Success</u> • Successful delivery of the device to the correct anatomical position; and

Vortex Temporary Percutaneous Transvalvular Circulatory Support System Feasibility Study: Vortex Feasibility Study	
	• Successful operation and removal of the Vortex circulatory support system <u>Clinical Success</u> • No conversion to open heart surgery; and • No in-hospital mortality
Additional Measurements	Safety events will be collected through 72 hours post-procedure or hospital discharge, whichever comes first, as listed below. • Stroke/transient ischemic attack (TIA; see **Note 1** below) • Cardiac tamponade • Cardiac death (see **Note 1** below) • Myocardial infarction (MI) • Bleeding complications: Type 3–5 based on the Mechanical Circulatory Support Academic Research Consortium (MCS-ARC) definitions[a] (see **Note 1** below) • Acute kidney injury (AKI; based on the AKIN System Stage 3 [including renal replacement therapy] or Stage 2) • Major vascular complications (see **Note 1** below) • Any device-related adverse event (adverse device effect [ADE]/serious adverse device effect [SADE]) • Any procedure-related adverse event • Any adverse event related to management practices • Any adverse event related to patient specific adherence • Any unanticipated serious adverse device effect (USADE) **Note 1:** Death, stroke, bleeding complications, and major vascular complications are adjudicated by an Independent Medical Reviewer (IMR). a: Kormos RL, et al. *J Heart Lung Transplant* 2020;39:735-50
Method of Assigning Patients to Treatment	Subjects who provide written informed consent and are confirmed eligible for the study are considered enrolled in the study as soon as an attempt is made to insert any part of the Vortex System into the subject's femoral artery (e.g., Vortex sheath).

Vortex Temporary Percutaneous Transvalvular Circulatory Support System Feasibility Study: Vortex Feasibility Study	
Follow-up Schedule	Follow up will occur through 72 hours after enrollment or hospital discharge, whichever comes first.
Study Duration	Enrollment/total study duration may be completed in approximately 12 months.
Participant Duration	The study duration for each subject is expected to be through 72 hours or hospital discharge, whichever comes first.
Index Procedure	The Vortex sheath will be inserted percutaneously into the femoral artery. The Vortex wire and Vortex pump will pass though this sheath during the procedure and will be advanced through the aorta, across the aortic valve, and into the left ventricle. The wire will be withdrawn before the pump is turned on, but the sheath and pump will stay in place throughout the HR-PCI procedure and will be withdrawn as soon as the mechanical circulatory support is deemed to be unnecessary.
Statistical Methods	
Primary Statistical Hypothesis	There is no formal statistical hypothesis in this observational feasibility study.
Statistical Test Method	Descriptive statistics will be used for baseline, procedure, and follow-up data collected during the study. The primary endpoint and additional measurements will be analyzed on an intention-to-treat (ITT) basis and a per-protocol basis. Analysis sets are listed below. Subjects are considered enrolled in the study as soon as an attempt is made to insert any part of the Vortex System into the subject's femoral artery. • ITT: This population includes all subjects who sign an Informed Consent Form (ICF) and are enrolled in the study, whether or not a study device is successfully inserted and used. • Per-protocol: This population includes all ITT subjects in whom the device is successfully advanced across the aortic valve into the left ventricular outflow tract and turned on.

Vortex Temporary Percutaneous Transvalvular Circulatory Support System Feasibility Study: Vortex Feasibility Study	
Sample Size Parameters	This is a prospective, multicenter, non-randomized feasibility study with no formal pre-specified hypothesis and therefore sample size estimates are not applicable. In order to support the stated objectives of this feasibility study, the study sample size has been limited to a maximum of up to 10 subjects enrolled.

2 INTRODUCTION

The Vortex System is intended to support stable subjects undergoing HR-PCI by temporarily decreasing the load on the heart and ensuring adequate organ perfusion. The statistical analysis for this first-human-use study will provide data to assess device safety and technical feasibility of device use in subjects undergoing elective HR-PCI.

3 ENDPOINT ANALYSIS

There is no formal statistical hypothesis for the endpoints. Descriptive statistics will be provided.

3.1 Primary Endpoint

The primary endpoint consists of Technical Success and Clinical Success.

Technical Success

- Successful delivery of the device to the correct anatomical position; and
- Successful operation and removal of the Vortex circulatory support system

Clinical Success

- No conversion to open heart surgery; and
- No in-hospital mortality

3.1.1 Hypotheses

There is no formal statistical hypothesis for the primary endpoint.

3.1.2 Sample Size

To support the stated objective of this feasibility study, while also limiting the potential exposure to risk of study subjects, the study sample size has been arbitrarily set at a maximum of 10 subjects enrolled.

3.1.3 Statistical Methods

Descriptive statistics for the primary endpoint will be provided including numerator, denominator, and proportion.

3.2 Additional Measurements

Safety events will be collected through 72 hours post-procedure or hospital discharge, whichever comes first, as listed below. Death, stroke, bleeding complications, and major vascular complications are adjudicated by an Independent Medical Reviewer (IMR).

- Stroke/transient ischemic attack (TIA)
- Cardiac tamponade
- Cardiac death

- Myocardial infarction (MI)
- Bleeding complications: Type 3–5 based on the Mechanical Circulatory Support Academic Research Consortium (MCS-ARC) definitions
- Acute kidney injury (AKI; based on the AKIN System Stage 3 [including renal replacement therapy] or Stage 2)
- Major vascular complications
- Any device-related adverse event (adverse device effect [ADE]/serious adverse device effect [SADE])
- Any procedure-related adverse event
- Any adverse event related to management practices
- Any adverse event related to patient specific adherence
- Any unanticipated serious adverse device effect (USADE)

3.2.1 Statistical Methods

Descriptive statistics will be provided including numerator, denominator, and proportion.

4 GENERAL STATISTICAL METHODS

4.1 Analysis Sets

The primary endpoint and additional measurements will be analyzed on an intention-to-treat (ITT) basis and a per-protocol basis. Analysis sets are listed below. Subjects are considered enrolled in the study as soon as an attempt is made to insert any part of the Vortex System into the subject's femoral artery.

- ITT: This population includes all subjects who sign an ICF and are enrolled in the study, whether or not a study device is successfully inserted and used.
- Per-protocol: This population includes all ITT subjects in whom the device is successfully advanced across the aortic valve into the left ventricular outflow tract and turned on.

4.2 Control of Systematic Error/Bias

The selection of subjects will be made from the Investigator’s usual case load. Subjects who are candidates for HR-PCI, provide written informed consent, and are eligible to be treated with the Vortex System will be evaluated for enrollment in this study. The study center’s heart team assessments and imaging measurements before device placement will contribute to the determination of subject eligibility for the study.

To control for inter-observer variability, an independent IMR will adjudicate mortality, stroke, major vascular complications, and bleeding endpoints.

4.3 Number of Subjects per Investigative Site

There will be up to 10 subjects enrolled in up to 3 centers in Australia and Europe. There is not limit on number of subjects per investigative site.

5 ADDITIONAL DATA ANALYSES

Additional study data collected will be summarized using descriptive statistics (e.g., mean, standard deviation, n, minimum, maximum) for continuous variables and discrete variables (e.g., numerator, denominator, proportion). The main analysis dataset is ITT.

5.1 Other Endpoints/Measurements

Additional analysis may include analyses for the following data:

- Subjects disposition
- Baseline
- Procedure and device performance
- Medication
- Adverse event
- Protocol deviation

5.2 Interim Analyses

No interim analysis is planned.

5.3 Subgroup Analyses

No subgroup analysis is planned.

5.4 Justification of Pooling

No poolability analysis is planned for the small study with 10 subjects.

5.5 Multivariable Analyses

No multivariate analysis is planned.

5.6 Other Analyses

Subject listings with selected variables may be provided (e.g., patient characteristics, procedure and device related data, and events or outcomes)

5.7 Changes to Planned Analyses

Any changes to the planned statistical analyses made will be documented in a Statistical Analysis Plan approved prior to database lock.

6 VALIDATION

All clinical data reports generated per this plan will be validated per 90702587, Global WI: Clinical Data Reporting Validation.

7 PROGRAMMING CONSIDERATIONS

7.1 Statistical Software

All statistical analyses will be performed using the SAS System software, version 9.2 or later (Copyright© 2000 SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA. All rights reserved).

All statistical analyses will be conducted according to applicable Standard Operating Procedures, Work Instructions, and the study-specific statistical analysis plan.

7.2 Format of Output

Results of analysis will be output programmatically to Microsoft Office® Word documents from SAS with no manual intervention. All output for the final statistical report will be in the form of a Word document containing tables, figures, graphs, and listings, as appropriate, or in Excel format.

7.3 Methods for Handling Missing Data

All subjects who are enrolled will be eligible for evaluation. Handling of dropouts and missing data will depend on their frequency and the nature of the outcome measure. All data will be included in the analysis unless judged to be invalid.

When calculating rates of adverse events, missing and partial dates will be handled as shown in the table below.

Partial Date	Action Taken
Entire adverse event onset date is missing	The procedure date will be used for the onset date.
The month and the day of the month are missing but the year is available	January 1st will be used for the month and day of the onset date. However, if the imputed date falls before the procedure date, then the procedure date will be used for the onset date.
Day is missing, but the month and year are available	The 1st will be used as the day of the onset date. However, if the imputed date falls before the procedure date, then the procedure date will be used for the onset date.

7.4 Rules and Definition

7.4.1 General

For baseline categorical variables, “unknown” responses and missing values will not be counted in rate denominators

7.4.2 Body Mass Index (BMI)

In case the weight is calculated in “lbs” and/or height in “in” then the following formula will be used to convert into kg and cm, respectively.

Weight (Kg) = Weight (lbs) / 2.20462262.
Height (cm) = Height (in) / 0.393700787

$$BMI = \frac{Weight\,(Kg) \times 10000}{\left(Height\,(cm)\right)^2}$$

7.4.3 Denominator using Sufficient Follow-up for Endpoints and Additional Measurements

All subjects in the specific analysis sets (ITT or PP) will be included in the denominator for the analysis for the primary endpoint and additional measurements. All subjects are considered as having sufficient follow-up through 72 hours or hospital discharge, whichever comes first.