FlowTriever Pulmonary Embolectomy Clinical Study – FlowTriever2 (FLARE-FT2)

Statistical Analysis Plan

Version B

Device: FlowTriever2 Catheter

Protocol No.: 21-001

Study Phase: Observational, Non-Interventional

Approval

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Version History

SAP Version	Date	Revision	Reason for Revision
A	09-Sep-2022	Initial release	Not applicable – initial release
B	04-Aug-2023	Section 3 – Study Population	Changed to reflect protocol revision. Consolidated all types of screen failures into one screen failure category.

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LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Term
AC	Anticoagulation
ADE	Adverse Device Effect
AE	Adverse Event
ASADE	Anticipated Serious Adverse Device Effect
BARC	Bleeding Academic Research Consortium
BPM	Beats per minute
CC	Completed Cases
CRFs	Case Report Forms
CTPA/CTA	Computed tomographic pulmonary angiography
EDC	Electronic Data Capture system
ESC	European Society of Cardiology
FAS	Full Analysis Set
FLARE	FlowTriever Clinical Embolectomy Clinical Study
FT2	FlowTriever2 Catheter
HIT	Heparin-induced thrombocytopenia
INR	International normalized ratio
IRB	Institutional Review Board
ISS	Injury Severity Score
ITT	Intent-To-Treat
LV	Left ventricle
MAE	Major adverse event
mITT	Modified Intent-To-Treat
PE	Pulmonary embolism
PESI	Pulmonary Embolism Severity Index
RV	Right ventricle
RV/LV	Right ventricular to left ventricular diameter ratio
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SIR	Society of Interventional Radiology
sPESI	Simplified Pulmonary Embolism Severity Index
TLF	Tables, lists, and figures
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect
VARC-2	Valve Academic Research Consortium-2

1. Description of Study Objectives

The primary study objective is to evaluate the safety and effectiveness of the FlowTriever2 Catheter for the treatment of acute pulmonary embolism (PE).

2. Study Design

The study is a prospective, non-randomized, single-arm, multicenter, observational study to evaluate the safety and effectiveness as the study endpoints of the FlowTriever2 Catheter in patients eligible for endovascular treatment of acute PE. The endpoints will be evaluated in descriptive manner and will not be used to determine study success.

2.1. Primary Safety Endpoints

The study's primary safety endpoint is incidence of Serious Adverse Events (SAE), which is defined as a composite of:

- Mortality through 48 hours after the index procedure related to FlowTriever2 Catheter
- Major bleeding through 48 hours after the index procedure related to FlowTriever2 Catheter
- Intra-procedural device or procedure-related adverse events, including:
    - Clinical deterioration defined by hemodynamic or respiratory worsening
    - Pulmonary vascular injury related to FlowTriever2 Catheter
    - Cardiac injury related to FlowTriever2 Catheter

2.2. Primary Effectiveness Endpoint

The study's primary effectiveness endpoint is the change in mean pulmonary arterial pressure from baseline pre-procedure to post-procedure.

2.3. Secondary Safety Endpoints

The study's secondary safety endpoints will include incidence of adjudicated adverse events, including:

- All-cause mortality through the 30-day visit (visit window = 30 days from procedure -5 / +15 days)
- Device-related SAE through the 30-day visit (visit window = 30 days from procedure -5 / +15 days)
- Symptomatic recurrence of pulmonary embolism through the 30-day visit (visit window = 30 days from procedure -5 / +15 days)

2.4. Secondary Effectiveness Endpoints

- The study's primary effectiveness endpoint is the change in systolic pulmonary arterial pressure from baseline pre-procedure to post-procedure

3. Study Population

The study population consists of subjects that have a PE. Subject eligibility is to be determined based on data available to the Investigator at the time of enrollment. Subjects must meet all inclusion and no exclusion criteria to be eligible for the study. Waivers will not be granted by the Sponsor regarding enrollment criteria. All subjects that complete the procedure and the follow-ups will be included in the analysis.

In this study, subjects will be categorized as follows:

Screen Failure: Any screened patient who does not meet the inclusion and exclusion criteria. No case report forms (CRFs) are required for these patients. All patients screened will be documented on the Screening/Enrollment Log.

Enrolled Subject: All patients who met the inclusion/exclusion criteria and in whom the FlowTriever2 Catheter is inserted into the vasculature. These subjects will comprise the "Enrollment Population." Patients who are found to fail any inclusion/exclusion criteria at any point in the study will be considered ineligible and removed from the Enrollment Population.

Intent-To-Treat (ITT): All "Enrolled Subjects" in whom the procedure was attempted and the FlowTriever System was deployed, whether successful or not.

Modified Intent-To-Treat (mITT): All subjects in the "ITT Population" who have no thrombolytics administered during the procedure.

Full Analysis Set (FAS): All subjects in the "mITT Population" that have successfully received the procedure and have completed the 48-hour post- procedure follow-up (+36 hours or discharge, whichever comes first) per study protocol.

Completed Cases (CC): All subjects in the "mITT Population" that have successfully received the procedure and have completed all follow-up visits.

3.1. Study Enrollment Criteria

Only patients who meet all inclusion criteria and none of the exclusion criteria are considered eligible for enrollment. The decision to use the FlowTriever2 Catheter will occur prior to the procedure and written informed consent will be obtained prior to all study-specific procedures. The enrollment period is expected to last over a period of approximately 12 months. Each study subject will actively participate for up to 30 days (-5 / +15 days) following treatment. Study participation includes screening, baseline, treatment, 48-hour visit, and 30-day follow-up.

If the FlowTriever2 Catheter is not inserted into the vasculature, the subject is considered a screen failure (not meeting inclusion criteria for use of FT2) and is not enrolled into nor entered the EDC.

3.1.1. Inclusion Criteria

Subjects must meet all the following inclusion criteria to be considered eligible for enrollment.

1. Age ≥ 18 and ≤ 75 years
2. Clinical signs and symptoms consistent with acute PE
3. PE symptom duration ≤ 14 days
4. CTA evidence of proximal PE (filling defect in at least one main or lobar pulmonary artery)

5. RV/LV ratio of ≥ 0.9 (**NOTE**: Enrollment qualification assessment based on Investigator's interpretation of RV/LV ratio)
6. Systolic blood pressure ≥ 90 mmHg (initial SBP may be ≥ 80 mmHg if the pressure recovers to ≥ 90mmHg with fluids)
7. Stable heart rate < 130 BPM prior to procedure
8. Patient is deemed medically eligible for interventional procedure(s), per institutional guidelines and/or clinical judgment.
9. FlowTriever2 Catheter enters the vasculature

3.1.2. Exclusion Criteria

Subjects must not meet any of the following general exclusion criteria.

1. Thrombolytic use within 30 days of baseline CTA
2. Pulmonary hypertension with peak pulmonary artery pressure > 70 mmHg by right heart catheterization
3. Vasopressor requirement after fluids to keep pressure ≥ 90 mmHg
4. FiO2 requirement > 40% or > 6 LPM to keep oxygen saturation > 90%
5. Hematocrit < 28% (**NOTE**: hematocrit required within 6 hours of index procedure)
6. Platelets < 100,000/µL
7. Serum creatinine > 1.8 mg/dL
8. INR > 3
9. Major trauma Injury Severity Score (ISS) > 15
10. Presence of intracardiac lead in the right ventricle or right atrium placed within 6 months
11. Cardiovascular or pulmonary surgery within last 7 days
12. Actively progressing cancer
13. Known bleeding diathesis or coagulation disorder
14. Left bundle branch block
15. History of severe or chronic pulmonary arterial hypertension
16. History of chronic left heart disease with left ventricular ejection fraction ≤ 30%
17. History of uncompensated heart failure
18. History of underlying lung disease that is oxygen dependent
19. History of chest irradiation
20. History of heparin-induced thrombocytopenia (HIT)
21. Any contraindication to systemic or therapeutic doses heparin or anticoagulants
22. Known anaphylactic reaction to radiographic contrast agents that cannot be pretreated
23. Imaging evidence or other evidence that suggests, in the opinion of the Investigator, the Subject is not appropriate for mechanical thrombectomy intervention (e.g., inability to navigate to target location, predominately chronic clot, or non-clot embolus)
24. Life expectancy of < 90 days, as determined by Investigator
25. Female who is pregnant or nursing
26. Current participation in another investigational drug or device treatment study

4. Incomplete Date Handling and Missing Data

Incomplete dates will follow the following imputation assignment rules:

1. If day is missing but month and year are present, the day will be set to the first date of the month.
2. If both day and month are missing but year is present, then January 1st will be used as imputed value.
3. If year is missing, then the date is considered missing. In general, missing data points are not imputed.

For the primary safety endpoints, missing data are imputed with a range of possible-worse case scenarios and reported the corresponding incidence rates using a tipping point analysis assuming missing at random. For the primary effectiveness endpoints, missing data at pre- or post-procedures are imputed with values resampled from the non-missing data with replacements assuming missing at random. A number (e.g., 10,000) of replicates of data with imputed values can be generated and the mean and 95% confidence interval based on the averaged change in each replicate are reported. No imputations are performed in the secondary endpoints.

5. Statistical Methods and Analysis

5.1. Sample Size

The sample size of 50 subjects was adopted to confirm the FlowTriever2 Catheter performance. Given the sample size, at least 80% power can be achieved under one-sample fixed design with one-sided alpha = 0.05 for assuming observed FT2 safety event proportions of 11% compared to the hypothesized performance goal of 25% from FLARE. Descriptive statistics on safety and effectiveness endpoints will be provided based on all subjects to conclude the study objectives, no hypothesis testing was relied. Sensitivity analysis will be performed on a sub-population of the 50 subjects that did not receive adjunctive thrombolytics.

5.2. Primary Safety Endpoint Analysis

The primary safety endpoint analysis is performed by assessing the incidence rate of the composite endpoint of SAE, including device-related mortality through 48 hours, device-related major bleeding through 48 hours, intra-procedural device or procedure-related adverse events.

5.3. Primary Effectiveness Endpoint Analysis

The primary effectiveness endpoint analysis is performed by assessing the means, standard deviations, medians, and inter-quartile ranges of the mean pulmonary arterial pressure changes and/or percentage change between pre- and post-procedure.

5.4. Secondary Safety Endpoint Analysis

The secondary safety endpoint analysis is performed by assessing the incidence rates of adjudicated adverse events, including all-cause mortality through the 30-day visit, device-related SAE through the 30-day visit, and symptomatic recurrence of pulmonary embolism through the 30-day visit.

5.5. Secondary Effectiveness Endpoint Analysis

The secondary effectiveness endpoint analysis is performed by assessing the means, standard deviations, medians, and inter-quartile ranges of the systolic pulmonary arterial pressure changes and/or percentage change between pre- and post-procedure. Adjunctive thrombolytic use is reported as numbers and percentages.

6. Terms and Definitions

Term	Definition
Primary Safety Definitions	
Clinical Deterioration	Clinical deterioration will include treatment-related events, such as unplanned endotracheal intubation, unexpected requirement for mechanical ventilation, arterial hypotension (>1 hour or requiring vasopressors) or shock, cardiopulmonary resuscitation, persistent worsening in oxygenation, and emergency surgical embolectomy.
Device Related Death	Device-related death is defined as any death directly related to thedevice not performing as expected. Device-related death would include death from: • Vascular or cardiovascular injury • Device malfunction • Device-induced cardiac arrhythmia
Life Threatening or Disabling Bleeding (VARC-2)	• Fatal bleeding, OR • Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome, OR • Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery, OR • Overt source of bleeding with drop in hemoglobin ≥5 g/dL or whole blood or packed red blood cells (RBCs) transfusion ≥ 4 units*
Major Bleeding (VARC- 2)	Overt bleeding that is: • Associated with a drop in the hemoglobin level of at least 3 g/dL, OR • Requires transfusion of 3 units of whole blood/RBC, OR • Causes hospitalization, permanent injury, or requiring surgery, AND • Does not meet criteria of life-threatening or disabling
Minor Bleeding (VARC- 2)	Any bleeding worthy of clinical mention (e.g., access site hematoma) that does not qualify as life-threatening or disabling bleeding or major bleeding.
Pulmonary Vascular Injury	Pulmonary vascular injury is defined as perforation or injury of a major pulmonary arterial branch during the index procedure requiring intervention, including but not limited to blood transfusion, open or endovascular intervention, to avoid permanent injury.
Cardiac Injury	Cardiac injury is defined as any damage to the heart during the index procedure requiring intervention, including but not limited to blood transfusion, open or endovascular intervention, to avoid permanent injury.
Additional Definitions	
Adverse Event (AE)	An Adverse Event (AE) is an untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated (ISO 14155:2020, 3.2). **NOTE 1**: This definition includes events related to the investigational medical device. **NOTE 2**: This definition includes events related to the procedures involved.
Serious Adverse Event (SAE)	An AE that led to any of the following: • death, • serious deterioration in the health of the subject, users or other persons as defined by one or more of the following: ○ a life-threatening illness or injury, or

Term	Definition
	○ a permanent impairment of a body structure or a body function, including chronic disease, or ○ in-patient or prolonged hospitalization, or ○ medical or surgical intervention to prevent life- threatening illness or injury or permanent impairment to a body structure or a body function, • fetal distress, fetal death or a congenital abnormality or birth defect including physical or mental impairment **NOTE 1**: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered an SAE. (ISO 14155:2020, 3.45)
Minor Complications (SIR Classification)	Minor complications: • No therapy, no consequence • Nominal therapy, no consequence (includes overnight admission for observation only)
Major Complications (SIR Classification)	Major complications: • Require therapy, minor hospitalization (≤ 48 hours) • Require major therapy, unplanned increase in level of care, prolonged hospitalization (>48 hours) • Permanent adverse sequelae • Death
Adverse Device Effect (ADE)	AE related to the use of an investigational medical device **NOTE 1**: This definition includes AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. **NOTE 2**: This definition includes any event resulting from an error use or from intentional misuse of the investigational medical device. **NOTE 3**: this includes 'comparator' if the comparator is a medical device. (ISO 14155:2020, 3.1)
Serious Adverse Device Effect (SADE)	Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. (ISO 14155:2020, 3.44)
Unanticipated Serious Adverse Device Effect (USADE) (pre-market term only)	USADE is a serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current risk assessment. (ISO 14155:2020, 3.51)
Anticipated Serious Adverse Device Effect (ASADE) (pre-market term only)	ASADE is a serious adverse device effect which by its nature, incidence, severity or outcome has been identified in the risk assessment. (ISO 14155:2020, 3.51)
Unanticipated Adverse Device Effect (UADE) (pre-market term only)	Any serious adverse effect on health or safety or any life- threatening problem or death caused by, or associated with, a device, if that effect, problem, or death, was not previously identified in a nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. (21 CFR 812.3(s))
Device Deficiency	Inadequacy of a medical device with respect to its identity, quality, durability, reliability,

Term	Definition
	usability, safety or performance. **NOTE 1**: Device Deficiencies include malfunctions, use errors and inadequacy in the information supplied by the manufacturer including labeling. **NOTE 2**: This definition includes device deficiencies related to the investigational medical device or the comparator. (ISO 14155:2020, 3.19)
High-Risk PE	Per ESC guidelines 2019: High-Risk PE determined by hemodynamic instability, PESI III-V or sPESI ≥ 1, RV Dysfunction, and Elevated cardiac troponins. Note Definition of hemodynamic instability, which delineates acute high-risk pulmonary embolism (one of the following clinical manifestations at presentation). 1. Cardiac Arrest: Need for cardiopulmonary resuscitation, 2. Obstructive Shock: Systolic BP < 90 mmHg or vasopressors required to achieve a BP ≥ 90 mmHg despite adequate filling status AND End-organ hypoperfusion (altered mental status; cold, clammy skin; oliguria/anuria; increased serum lactate), OR 3. Persistent Hypotension: Systolic BP < 90 mmHg or systolic BP drop ≥ 40 mmHg, lasting longer than 15 min and not caused by new-onset arrhythmia, hypovolemia, or sepsis.
Intermediate High-Risk PE	Per ESC guidelines 2019: Intermediate High-Risk PE determined by no hemodynamic instability, PESI III- V or sPESI ≥ 1, RV Dysfunction, and Elevated cardiac troponins.
Intermediate Low-Risk PE	Per ESC guidelines 2019: Intermediate Low-Risk PE determined by no hemodynamic instability, PESI III- V or sPESI ≥ 1, and 1 or none of the following: RV Dysfunction; Elevated cardiac troponins.
Patient/ Subject	Participants in the study.
Recurrent PE	Symptomatic worsening from baseline of the embolism that was successfully treated with the index procedure with documentation of a change on CTPA or other suitable imaging modality, as determined by the independent Medical Monitor.

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