CLINICAL EXPERIENCE[1,2]

A prospective, multicenter single-arm, study using a performance goal was conducted to evaluate the safety and effectiveness of the FlowTriever Retrieval/Aspiration System (Models 10-101, 10-102, 10-103, 20-101, and 30-101) for the treatment of patients with acute submassive or massive pulmonary embolism. One hundred and six (106) subjects between the ages of 21 and 75 years, with confirmed PE symptoms for 14 days or less and a right to left ventricular end diastolic diameter ratio (RV/LV ratio) of ≥ 0.9 on CT angiogram, were enrolled in the study.

The primary effectiveness endpoint of this study was the RV/LV ratio change from baseline to 48 hours (± 8 hours, or discharge; whichever occurred first) as assessed by CT angiography. The mean RV/LV ratio change from baseline to 48 hours post-procedure was compared to a performance goal of 0.12 RV/LV ratio improvement derived from a meta-analysis of four (4) historical studies with RV/LV ratio measurements in patients where heparin was a control to an active pharmaceutical drug.

The study's primary safety endpoint was Major Adverse Events ("MAE"), which was a composite of:

- Device-related death within 48 hours (± 8 hours) of the procedure
- Major bleeding within 48 hours (± 8 hours) of the procedure
- Treatment-related adverse events within 48 hours (± 8 hours), including:
  - Clinical deterioration: Clinical deterioration includes treatment-related events, such as endotracheal intubation, mechanical ventilation, arterial hypotension or shock, cardiopulmonary resuscitation, clear worsening in oxygenation, and emergency surgical embolectomy.
  - Pulmonary vascular injury: Pulmonary vascular injury is defined as perforation or injury of a major pulmonary arterial branch requiring intervention, including but not limited to blood transfusion or embolization, to avoid permanent injury.
  - Cardiac injury: Cardiac injury is defined as any damage to the heart requiring intervention, including but not limited to blood transfusion or embolization, to avoid permanent injury.

The percentage of subjects that experience the composite safety endpoint was compared to a Performance goal derived of 25% derived for this endpoint.

The secondary safety endpoints were:

- Device-related death within 48 hours (± 8 hours) of the procedure
- Major bleeding within 48 hours (± 8 hours) of the procedure
- Clinical deterioration within 48 hours (± 8 hours) of the procedure
- Pulmonary vascular injury within 48 hours (± 8 hours) of the procedure
- Cardiac injury within 48 hours (± 8 hours) of the procedure
- Mortality due to any cause within 30 days (± 3 days) of the procedure
- Device-related serious adverse events within 30 days (± 3 days) of the procedure
- Symptomatic recurrence of embolism within 30 days (± 3 days) of the procedure

Inclusion Criteria:

1) Age ≥ 18 and ≤ 75 years;
2) Clinical signs, symptoms and presentation consistent with acute PE;
3) PE symptom duration ≥ 14 days;
4) CTA evidence of proximal PE;
5) RV/LV ratio of ≥ 0.9;
6) Systolic blood pressure ≥ 90 mmHg;
7) Stable heart rate < 130 BPM prior to procedure;
8) Patient is deemed medically eligible for interventional procedure(s), per institutional guidelines and clinical judgment

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%;
6) Platelets < 100,000/μL;
7) Serum creatinine > 1.8 mg/dL;
8) International normalized ratio (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 of 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;
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

Results

A total of 106 subjects that met the eligibility criteria were consecutively enrolled and treated with the FlowTriever System comprising the full Intent-To-Treat ("ITT") population. Of these 106 subjects, two (2) subjects received thrombolytics during their index procedure and were therefore not included in the modified Intent-To-Treat (mITT) population. The mITT population was defined as all subjects in the "ITT Population" with no thrombolytics administered during the operative procedure. The primary effectiveness and safety analyses were done using the mITT population.

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[1] It should be noted that the FlowTriever Retrieval/Aspiration System has been modified from the version used in this clinical study to allow the removal of the FlowTriever Catheter from the patient without the simultaneous removal of the Triever20, also allowing the FlowTriever Catheter to make multiple passes while the Triever20 remains in place. These changes were adequately evaluated with bench data. The clinical data presented here on the previous version of the FlowTriever Retrieval/Aspiration System remains applicable.

[2] DISCLAIMER: A single component of the FlowTriever Retrieval/Aspiration System has not been demonstrated to be safe and effective for the treatment of PE.

All except three (3) subjects completed the study follow-up at 30 days; one (1) subject died from metastatic breast cancer that was undiagnosed at enrollment, and two (2) subjects were lost to follow-up.

Two (2) technical complications were observed in the study. After removal of the device from the subject, the Triever20 was observed to be kinked. For one (1), the cause of the kink was attributed to the Gore DrySeal Sheath. For one (1), the subject experienced a mild hematoma at the access site which was treated with pressure and Fem Stop without consequence.

- **Subject Demographics and Medical History:**

  Of the 104 subjects enrolled as per mITT population, 56 were male (53.8%), 86 subjects were Caucasian (82.7%), the median age was 57 years (range 21-75) and the mean BMI was 35.8 (± 9). Hypertension was the most common medical comorbidity (56.7%) and common risk factors for PE include obesity (mean BMI was 35.8), deep vein thrombosis (13.5%) and history of prior PE in 9.6%.

- **PE Characteristics and PE Location by CT Scan:**

  The majority of subjects (71.2%) came from the emergency department (ED) and 26.0% came from the Intensive Care Unit (ICU). Elevated biomarkers, including cardiac troponin, D-dimer, and natriuretic peptides, were present in the majority of the subjects that were tested (59.6%, 75.9% and 72.4% respectively). Concurrent DVT was present in 73 subjects (70.2%). The PE was unilateral in 5 subjects; for the remaining 99 subjects, the PE was central/saddle in 5 subjects, bilateral in 53 subjects and both central/saddle and bilaterally located in 41 subjects.

- **Procedure Characteristics:**

  Local sedation and right femoral access was most frequently used for device insertion (96.2% and 95.2%, respectively). There were no subjects with failed access. Qualitative angiographic analysis provided by the centralized Core Laboratory revealed a mean baseline RV/LV ratio was 1.5 ± 0.4 (N=104). The mean treatment time from the time of access sheath placement through sheath removal was 94 minutes with a range from 39 minutes to 191 minutes. A total of 178 FlowTriever devices were used amongst the 104 subjects. Between 1 and 3 FlowTriever devices were introduced per procedure; 41.3% of procedures were completed with 1 device, 46.2% with 2 devices and 12.5% with 3 devices. The mean number of passes with a FlowTriever device per procedure was 3.9 (± 1.7) with a range from 1 to 10 passes. The majority of the procedures were completed without technical complications (98.1%, 102/104).

- **Additional Metrics or Variables**

  The median length of stay in the ICU following the index procedure was 1 day (mean 1.5 ± 2.1 days) with a range from 0 to 11 days. The median number of days from the index procedure to hospital discharge was 3 days (mean 4.1 ± 3.5 days) with a range from 2 to 25 days.

Effectiveness

Of the 104 subjects in the mITT population, three (3) did not receive their 48-hour CT exam. There was one (1) subject missing the 48-hour RV/LV measurement due to complications related to the procedure. Two (2) subjects had 48-hour RV/LV values missing due to reasons not related to the procedure.

The resulting mean change in RV/LV ratio was 0.37 and the p-value < 0.0001, indicating that the null hypothesis is rejected. Additionally, the lower one-sided 97.5% confidence limit is 0.32 (which was greater than 0.12), so we can conclude that the mean change in RV/LV ratio was significantly greater than the performance goal and the FlowTriever device met the performance goal at the 0.025 one-sided significance level.

Primary Endpoint Analysis – mITT

Visit Statistics	mITT Population
Baseline	
n	104
Mean (SD)	1.53 (0.36)
SE	0.04
Median	1.51
Min, Max	0.88, 2.52
Change from Baseline to 48-hour[1]	
n	104
Mean (SE)	0.37 (0.03)
97.5% one-sided lower CL	0.32
p-value[2]	< 0.0001

[1] Change is defined as the baseline RV/LV ratio minus the 48-hour ratio taken as a positive number

[2] P-value is from a one-sided t-test (Wald statistic) in a multiple imputation analysis, testing the null that the mean change is not greater than the performance goal of 0.12.

The effectiveness data confirm that the use of the FlowTriever System was associated with a significantly better mean reduction in the RV/LV ratio between baseline and 48 hours compared to the performance goal of 0.12.

Safety

A total of 106 subjects were treated with the FlowTriever System and comprise the full ITT population. Of these 106 subjects, two (2) subjects received thrombolytics during their index procedure and were not included in the mITT population.

All but three (3) subjects completed the study follow-up; one (1) subject died from metastatic breast cancer that was undiagnosed at enrollment, and two (2) subjects were lost to follow-up. Four (4) subjects experienced endpoint-related MAE, all of which were CEC adjudicated to be procedure-related.

Primary Safety Analysis

Four subjects (3.8%) in the mITT population experienced one or more MAEs defined as a composite of the following events: device-related death (no subjects), major bleeding (one subject), treatment-related clinical deterioration (three subjects), treatment-related pulmonary vascular injury (no subjects), and treatment-related cardiac injury (no subjects) within 48 hours of the procedure. One subject had their MAE classified as major bleeding (primary), as well as pulmonary vascular injury and clinical deterioration.

This composite MAE rate in the mITT population was 3.8% and the p–value < 0.0001, indicating that the null hypothesis is rejected. Additionally, the upper one-sided 95% confidence limit is 8.6% (which was less than 25%), so we can conclude that the composite MAE rate was significantly less than the performance goal and the FlowTriever device met the performance goal at the 0.05 one-sided significance level.

Primary Safety Analysis – mITT

Statistics	mITT Population
Composite Safety Endpoint	
N	104
n (%)[1]	4 (3.8%)
95% one-sided upper confidence limit	8.6%
p-value[2]	< 0.0001

[1] Percentages reflect the number of subjects that experienced the composite AE at least once.

[2] P-value is from a one-sided Binomial test, testing the null that the true proportion of subjects experiencing a composite AE is greater than the performance goal of 25%.

Secondary Safety Analysis

In addition to the components of the primary composite endpoint, all-cause mortality, device-related serious AE, serious AE, symptomatic recurrence of embolism, non-serious device related AEs and non-serious procedure-related AEs within 30 days of the procedure were

investigated; rates are presented in Table 1, below.

When the four (4) subjects in the composite MAE were broken down into the individual components, there were six (6) MAE endpoint categories amongst these subjects that comprised the secondary safety endpoint. The major bleeding primary event experienced by one subject was also classified as both pulmonary vascular injury and clinical deterioration. Upon further assessment of the clinical data provided and the CEC adjudication, from surgical pathology the left lower lobectomy clearly demonstrated "diffuse hemorrhage and areas of necrosis consistent with hemorrhagic infarction." It is important to reiterate that there was no mention of pulmonary artery injury and the pulmonary hemorrhage was consistent with hemorrhagic infarction and was not device related event. The additional secondary safety event belonged to the subject who died from metastatic breast cancer 23 days following the procedure.

Table 1: Secondary Safety Analyses – mITT (N=104)

Analysis Outcome	N (%)[1]
Composite Primary Safety Endpoint	4 (3.8%)
Secondary Safety Endpoints	
Device-Related Death Within 48 Hours of Procedure	0 (0.0%)
Major Bleeding Within 48 Hours of Procedure	1 (1.0%)
Clinical Deterioration Within 48 Hours of Procedure	4 (3.8%)
Pulmonary Vascular Injury Within 48 Hours of Procedure	1 (1.0%)
Cardiac Injury Within 48 Hours of Procedure	0 (0.0%)
Death Due to Any Cause Within 30 Days of Procedure	1 (1.0%)
Device-Related Serious Adverse Events Within 30 Days of Procedure	0 (0.0%)
Symptomatic Recurrence of Embolism Within 30 Days of Procedure	0 (0.0%)
Additional Safety Endpoints	
Serious Adverse Events Within 30 Days of Procedure	14 (13.5%)
Non-Serious Device-Related Adverse Events Within 30 Days of Procedure	0 (0.0%)
Non-Serious Procedure-Related Adverse Events Within 30 Days of Procedure	7 (6.7%)

[1] Percentages reflect the number of subjects that experienced each specified outcome at least once.