

## Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

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\*Sites with two names have co-principal investigators (PIs). Current PIs are noted in cases where the previous PI has left, and previous PIs are also listed.

### Role of Study Sponsor

(a) Trial Design: The Sponsor designed the MOMENTUM 3 trial in collaboration with clinical advisors and the trial oversight committee with feedback from the FDA.

(b) Site Selection: The Sponsor selected experienced centers per established site qualification procedures. Qualification visits were conducted to ensure that investigators were qualified by training, education and experience and had adequate resources, staffing and facilities to conduct the trial.

(c) Patient Assessment, Enrollment, Site Supervision & Data Collection: The Sponsor was responsible for training the clinical sites on patient eligibility assessment, enrollment procedures,

and data collection requirements; once trained, site personnel were responsible for conducting these activities under supervision of the principal investigator.

(d) Data Analysis: The Sponsor was responsible for analyzing the study data per the pre-specified Statistical Analysis Plan (SAP) and an independent statistician was responsible for verifying all the results.

(e) Manuscript Writing, Revision and Publication Decisions: The manuscript writing, revision and decision to submit the paper for publication were driven by the National PI's, the chair of the MOMENTUM 3 Publication and Presentation (P&P) Committee and its members along with the authors in compliance with the P&P Charter; the manuscript was written by the first author, all versions fully controlled by him in collaboration with the other authors; the Sponsor assisted with data requests under the direction of the corresponding author. The decision to submit the paper rested with the P and P committee and principally its chair.

## INCLUSION/EXCLUSION CRITERIA<sup>1</sup>

### Inclusion Criteria

- 1) Patient or legal representative has signed Informed Consent Form (ICF)
- 2) Age  $\geq 18$  years
- 3) Body Surface Area (BSA)  $\geq 1.2$  m<sup>2</sup>
- 4) NYHA Class III with dyspnea upon mild physical activity or NYHA Class IV
- 5) Left Ventricular Ejection Fraction (LVEF)  $\leq 25\%$
- 6) a) Inotrope dependent  
OR  
b) Cardiac Index (CI)  $< 2.2$  L/min/m<sup>2</sup>, while not on inotropes and patient must also meet one of the following:
  - On optimal medical management (OMM), based on current heart failure practice guidelines for at least 45 out of the last 60 days and are failing to respond
  - Advanced heart failure for at least 14 days AND dependent on intra-aortic balloon pump (IABP) for at least 7 days,
- 7) Females of child-bearing age must agree to use adequate contraception



## Exclusion Criteria

- 1) Etiology of heart failure due to or associated with uncorrected thyroid disease, obstructive cardiomyopathy, pericardial disease, amyloidosis, or restrictive cardiomyopathy
- 2) Technical obstacles which pose an inordinately high surgical risk, in the judgment of the investigator
- 3) Existence of ongoing mechanical circulatory support (MCS) other than IABP
- 4) Positive pregnancy test if of childbearing potential
- 5) Presence of mechanical aortic cardiac valve that will not be either converted to a bioprosthesis or oversewn at the time of LVAD implant
- 6) History of any organ transplant
- 7) Platelet count  $< 100,000 \times 10^3/L$  ( $< 100,000/ml$ )
- 8) Psychiatric disease/disorder, irreversible cognitive dysfunction or psychosocial issues that are likely to impair compliance with the study protocol and LVAS management
- 9) History of confirmed, untreated abdominal aortic aneurysm (AAA)  $> 5$  cm in diameter within six (6) months of enrollment
- 10) Presence of an active, uncontrolled infection
- 11) Intolerance to anticoagulant or antiplatelet therapies or any other peri/post-operative therapy that the investigator will require based upon the patient's health status
- 12) Presence of any one of the following risk factors for indications of severe end organ dysfunction or failure:
  - a) An international normalized ratio (INR)  $\geq 2.0$  not due to anticoagulation therapy
  - b) Total bilirubin  $> 43 \mu\text{mol/L}$  (2.5 mg/dl), shock liver, or biopsy proven liver cirrhosis
  - c) History of severe chronic obstructive pulmonary disease (COPD) defined as the ratio of forced expiratory volume in one second to forced vital capacity ( $\text{FEV}_1/\text{FVC}$ )  $< 0.7$ , and  $\text{FEV}_1 < 50\%$  predicted
  - d) Fixed pulmonary hypertension with a most recent pulmonary vascular resistance (PVR)  $\geq 8$  Wood units that is unresponsive to pharmacologic intervention
  - e) History of stroke within 90 days prior to enrollment, or a history of cerebrovascular disease with significant ( $> 80\%$ ) uncorrected carotid artery stenosis
  - f) Serum Creatinine  $\geq 221 \mu\text{mol/L}$  (2.5 mg/dl) or the need for chronic renal replacement therapy
  - g) Significant peripheral vascular disease (PVD) accompanied by rest pain or extremity ulceration
- 13) Patient has moderate to severe aortic insufficiency without plans for correction during pump implant
- 14) Pre albumin  $< 150 \text{ mg/L}$  (15mg/dL) or Albumin  $< 30\text{g/L}$  (3 g/dL) (if only one available); pre albumin  $< 150 \text{ mg/L}$  (15mg/dL) and Albumin  $< 30\text{g/L}$  (3 g/dL) (if both available)
- 15) Planned Bi-VAD support prior to enrollment

- 16) Patient has known hypo- or hyper coagulable state such as disseminated intravascular coagulation and heparin induced thrombocytopenia (HIT)
- 17) Participation in any other clinical investigation that is likely to confound study results or affect the study
- 18) Any condition other than heart failure that could limit survival to less than 24 months

## MAJOR ADVERSE EVENT DEFINITIONS<sup>1</sup>

### Bleeding

An episode of SUSPECTED INTERNAL OR EXTERNAL BLEEDING that results in one or more of the following:

- a. Death,
- b. Reoperation,
- c. Hospitalization,
- d. Transfusion of red blood cells as follows:
  - If transfusion is selected, then apply the following rules:

During first 7 days Post-implant

- ≥ 50 kg: ≥ 4U packed red blood cells (PRBC) within any 24 hour period during first 7 days post- implant.
- <50 kg: ≥20 cc/kg packed red blood cells (PRBC) within any 24 hour period during the first 7 days post-implant

After 7 days Post-implant\*

- Any transfusion of packed red blood cells (PRBC) after 7 days following implant with the investigator recording the number of units given. (Record number of units given per 24 hour period).

Note: Hemorrhagic stroke is considered a neurological event and not as a separate bleeding event.

\*Any transfusion of ≥ 2U packed red blood cells (PRBC) after 7 days following implant will be considered a serious bleed

### Cardiac Arrhythmias

Any documented arrhythmia that results in clinical compromise (e.g., diminished VAD flow, oliguria, pre-syncope or syncope) that requires hospitalization or occurs during a hospital stay. Cardiac arrhythmias are classified as 1 of 2 types:

- 1) Sustained ventricular arrhythmia requiring defibrillation or cardioversion.
- 2) Sustained supraventricular arrhythmia requiring drug treatment or cardioversion.

### Device Thrombosis

Device thrombosis is an event in which the pump or its conduits contain a thrombus that results in or could potentially induce circulatory failure. Suspected device thrombus is an event in which clinical or MCS parameters suggest thrombus on the blood contacting components of the pump, cannulae, or grafts. Signs and symptoms should include at least 2

of the 3 following criteria:

- a. Presence of hemolysis
- b. Worsening heart failure or inability to decompress the left ventricle
- c. Abnormal pump parameters

Suspected pump thrombus should be accompanied by 1 or more of the following events or interventions:

- i. Treatment with intravenous anticoagulation (e.g., heparin), intravenous thrombolytics (e.g., tPA), or intravenous antiplatelet therapy (e.g., eptifibatide, tirofiban)
- ii. Pump replacement
- iii. Pump explantation
- iv. Urgent transplantation (UNOS status 1A)
- v. Stroke
- vi. Arterial non-CNS thromboembolism
- vii. Death

Confirmed device thrombus is an event in which thrombus is confirmed by Sponsor returned product analysis to be found within the blood contacting surfaces of device inflow cannula or outflow conduit or grafts. This can also be reported via direct visual inspection or by incontrovertible contrast radiographic evidence or by the absence of an appropriate Doppler flow signal that results in or could potentially induce circulatory failure or result in thromboembolism.

### **Hemolysis\***

A plasma-free hemoglobin value that is greater than 40 mg/dl, concomitant with a rise in serum LDH above three times the upper limit of normal, in association with clinical signs associated with hemolysis (e.g., anemia, low hematocrit, hyperbilirubinemia) occurring after the first 72 hours post-implant.

\*Hemolysis in the presence of worsening heart failure or inability to decompress the left ventricle or abnormal pump parameters is reported as suspected device thrombosis, not as hemolysis

### **Hepatic Dysfunction**

An increase in any two of the following hepatic laboratory values (total bilirubin, aspartate aminotransferase/AST and alanine aminotransferase/ALT) to a level greater than three times the upper limit of normal for the hospital, beyond 14 days post-implant (or if hepatic dysfunction is the primary cause of death).

### **Major Infection**

A clinical infection accompanied by pain, fever, drainage and/or leukocytosis that is treated by anti-microbial agents (non-prophylactic). A positive culture from the infected site or organ should be present unless strong clinical evidence indicates the need for treatment despite negative cultures. The general categories of infection are listed below:

#### Localized Non-Device Infection

Infection localized to any organ system or region (e.g. mediastinitis) without evidence of systemic involvement (see sepsis definition), ascertained by standard clinical methods and either associated with evidence of bacterial, viral, fungal or protozoal infection, and/or requiring empirical treatment.

#### Percutaneous Site and/or Pocket Infection

A positive culture from the skin and/or tissue surrounding the drive line or from the tissue surrounding the external housing of a pump implanted within the body, coupled with the need to treat with antimicrobial therapy, when there is clinical evidence of infection such as pain, fever, drainage, or leukocytosis.

#### Internal Pump Component, Inflow or Outflow Tract Infection

Infection of blood-contacting surfaces of the LVAD documented by positive site culture.

#### Sepsis

Evidence of systemic involvement by infection, manifested by positive blood cultures and/or hypotension.

#### **Neurologic Dysfunction**

Any new, temporary or permanent, focal or global neurological deficit, ascertained by a standard neurological history and examination administered by a neurologist or other qualified physician and documented with appropriate diagnostic tests and consultation note; or an abnormality identified by surveillance neuroimaging. The examining physician will classify the event as defined below:

- a. Transient ischemic attack\*, defined as an acute transient neurological deficit conforming anatomically to arterial distribution cerebral ischemia, which resolves in < 24 hours and is associated with no infarction on brain imaging (head CT performed >24 hours after symptom onset; or MRI)
- b. Ischemic Stroke\*: a new acute neurologic deficit of any duration associated with acute infarction on imaging corresponding anatomically to the clinical deficit, or a clinically covert ischemic stroke seen by surveillance imaging, without clinical findings of stroke or at the time of event recognition.
- c. Hemorrhagic Stroke\*: a new acute neurologic deficit attributable to intracranial hemorrhage (ICH), or a clinically covert ICH seen by surveillance imaging, without clinical findings of ICH at the time of event recognition.
- d. Encephalopathy: Acute new encephalopathy\*\* due to hypoxic-ischemic injury (HIE), or other causes, manifest as clinically evident signs or symptoms, or subclinical electrographic seizures found by complete neurological diagnostic evaluation to be attributable to acute global or focal hypoxic, or ischemic brain injury not meeting one of ischemic stroke or ICH events as defined above.
- e. Seizure of any kind
- f. Other neurological event (non-CNS event): examples include neuro muscular dysfunction or critical care neuropathy

\*Modified Rankin Score will be used to classify the severity of all strokes

\*\*Acute encephalopathy is a sign or symptom of some underlying cerebral disorder, and is manifest as depressed consciousness with or without any associated new global or multifocal neurologic deficits in cranial nerve, motor, sensory, reflexes and cerebellar function.

### **Renal Dysfunction**

Two categories of renal dysfunction will be identified:

#### Acute Renal Dysfunction

Abnormal kidney function requiring dialysis (including hemofiltration) in Subjects who did not require this procedure prior to implant, or a rise in serum creatinine of greater than 3 times baseline or greater than 5 mg/dL sustained for over 48 hours.

#### Chronic Renal Dysfunction

An increase in serum creatinine of 2 mg/dl or greater above baseline, or requirement for hemodialysis sustained for at least 90 days.

### **Respiratory Failure**

Impairment of respiratory function requiring reintubation, tracheostomy or (the inability to discontinue ventilatory support within six days (144 hours) post-VAD implant. This excludes intubation for reoperation or temporary intubation for diagnostic or therapeutic procedures.

### **Right Heart Failure**

Symptoms and signs of persistent right ventricular dysfunction requiring RVAD implantation, or requiring inhaled nitric oxide or inotropic therapy for a duration of more than 1 week at any time after LVAD implantation.

## SAMPLE SIZE CALCULATION

Enrollment first included 294 patients followed for 6-months which constituted the pre-specified short-term analysis and has been reported<sup>1</sup>. Enrollment continued to 366 patients, to provide sufficient power for the long-term analysis at 2-years<sup>2</sup>. We estimated that to achieve 80% power, 174 patients in each group were required (lower 95% confidence bound for the difference in primary endpoint success between treatment arms (centrifugal-flow pump minus axial-flow pump) greater than -10% would prove non-inferiority with a one-sided  $\alpha = 0.025$  or 2 tailed p of  $<0.05$ ) using the Farrington-Manning risk difference approach. To account for transplant or explant for recovery, 9 additional patients were included per arm. Thus, a total of 366 patients were required for the analysis, which included the 294 patients from the 6-month cohort (therefore 72 additional patients were further randomized and followed for 2-years).

For this report, the full cohort sample size was powered for the principal secondary end point of pump replacement at 2-years<sup>3</sup>. Based on data in the Sponsor's device tracking database, 7% of patients with the axial-flow pump receive a pump replacement by 24 months. The expected proportion of patients with the centrifugal-flow pump to receive a pump replacement by 24 months was assumed to be 3%. We estimated that to demonstrate superiority of the centrifugal-flow pump to the axial-flow pump with a power of 80% and  $\alpha = 0.05$  (2-sided), a total of 1028 patients (514 per arm) were required using the Fisher's exact test.

## CENTRIFUGAL-FLOW PUMP THROMBOSIS NARRATIVES

Seven subjects in the Centrifugal Pump group experienced 7 suspected pump thrombosis events. Individual narratives for these patients appear below.

### **Subject #1**

#### **Outcome/Status: Death due to heart failure**

Subject implanted with Centrifugal Flow Pump developed evidence of hemolysis at day 191 post-VAD implantation with LDH rising to 727 U/L. There were also signs of worsening heart failure and abnormal pump parameters. The subject was hospitalized and managed medically. After discharge, the subject experienced worsening heart failure. The subject was transferred to hospice and eventually expired on day 383. The cause of death was adjudicated as heart failure. No autopsy was performed per the subject's wishes and the device was not recovered for analysis.

### **Subject #2**

#### **Outcome/Status: Death due to right heart failure**

Subject implanted with Centrifugal Flow Pump developed evidence of worsening heart failure at day 241 post-VAD implantation, with LDH rising from 120 to 166 U/L. There was also evidence of abnormal pump parameters. Log files revealed evidence of complete inflow or outflow obstruction. The subject was unable to be anticoagulated due to recent hemorrhagic stroke, and Coumadin had been discontinued for 4 days at time of suspected pump thrombosis. The pump was turned off on day 244. The subject expired on day 270, and the cause of death was adjudicated as right heart failure. No autopsy was performed per the subject's wishes and the device was not recovered for analysis.

### **Subject #3**

#### **Outcome/Status: Outflow graft revision and ongoing at 2 years**

Subject implanted with Centrifugal Flow Pump developed evidence of worsening heart failure at day 484 post-VAD implantation with abnormal pump parameters (low flow alarms). The subject was hospitalized and a chest CT revealed a thrombus in the outflow graft. The subject was admitted and underwent outflow graft thrombectomy and revision on day 488. The device was not recovered for analysis.

### **Subject #4**

#### **Outcome/Status: Pump exchange followed by death due to right heart failure**

Subject implanted with Centrifugal Flow Pump developed evidence of right-sided heart failure at day 52 post-VAD implantation with abnormal pump parameters (low flow alarms). Log file review was suggestive of something dragging on the rotor (pump thrombus) or an electrical issue with the pump. On day 53, the pump was exchanged with another Centrifugal Flow Pump. Thrombosis was confirmed in the returned pump. Examination of the blood-contacting surfaces found depositions in the pump cover, inflow cannula, and around the rotor. The depositions appeared consistent with an interruption in flow. The depositions were identified as clots comprised of variable amounts of hemorrhage and fibrin. The subject expired on day 151, and the cause of death was adjudicated as right heart failure.

**Subject #5****Outcome/Status: Outflow graft revision and ongoing at 2 years**

Subject implanted with Centrifugal Flow Pump developed evidence of worsening heart failure at day 699 post-VAD implantation, with abnormal pump parameters (low flow alarms). There was also evidence of hemolysis with LDH rising to 1053 U/L. The subject was hospitalized and a chest CT revealed a filling defect in the proximal outflow cannula consistent with thrombus. The subject was admitted and underwent mediastinal exploration and untwisting of outflow graft on day 708. The device was not recovered for analysis.

**Subject #6****Outcome/Status: Pump exchange followed by elective transplant**

Subject implanted with Centrifugal Flow Pump developed evidence of worsening heart failure at day 459 post-VAD implantation with abnormal pump parameters (low flow alarms and pump stops). On day 462, pump was exchanged with another Centrifugal Flow Pump. Thrombosis was confirmed in the returned pump. Examination of the of the device found a soft, red deposition in the rotor and rotor well which appeared to obstruct the blood flow path. The analysis determined that the depositions all had histological features consistent with thrombosis. On day 588 subject underwent elective transplant.

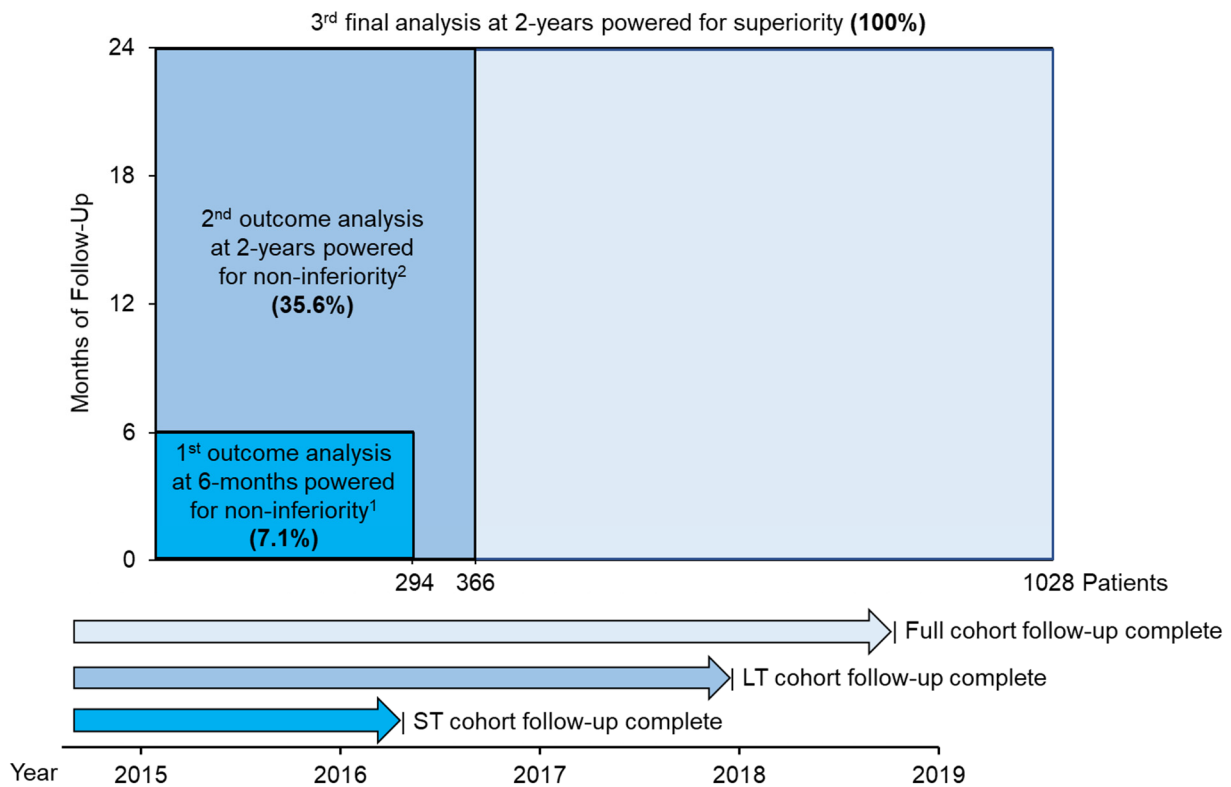
**Subject #7****Outcome/Status: Death due to device thrombosis**

Subject implanted with Centrifugal Flow Pump developed evidence of hemolysis at day 447 post-VAD implantation with LDH baseline 259 rising to 954 U/L and evidence of worsening heart failure. Subject opted for comfort measures and LVAD turned off on day 449. The subject expired the same day and the cause of death was adjudicated as device thrombosis. The device was not recovered for analysis.



## SUPPLEMENTARY FIGURES

**Figure S1. Net Trial Experience for MOMENTUM 3 Pre-specified Analyses**



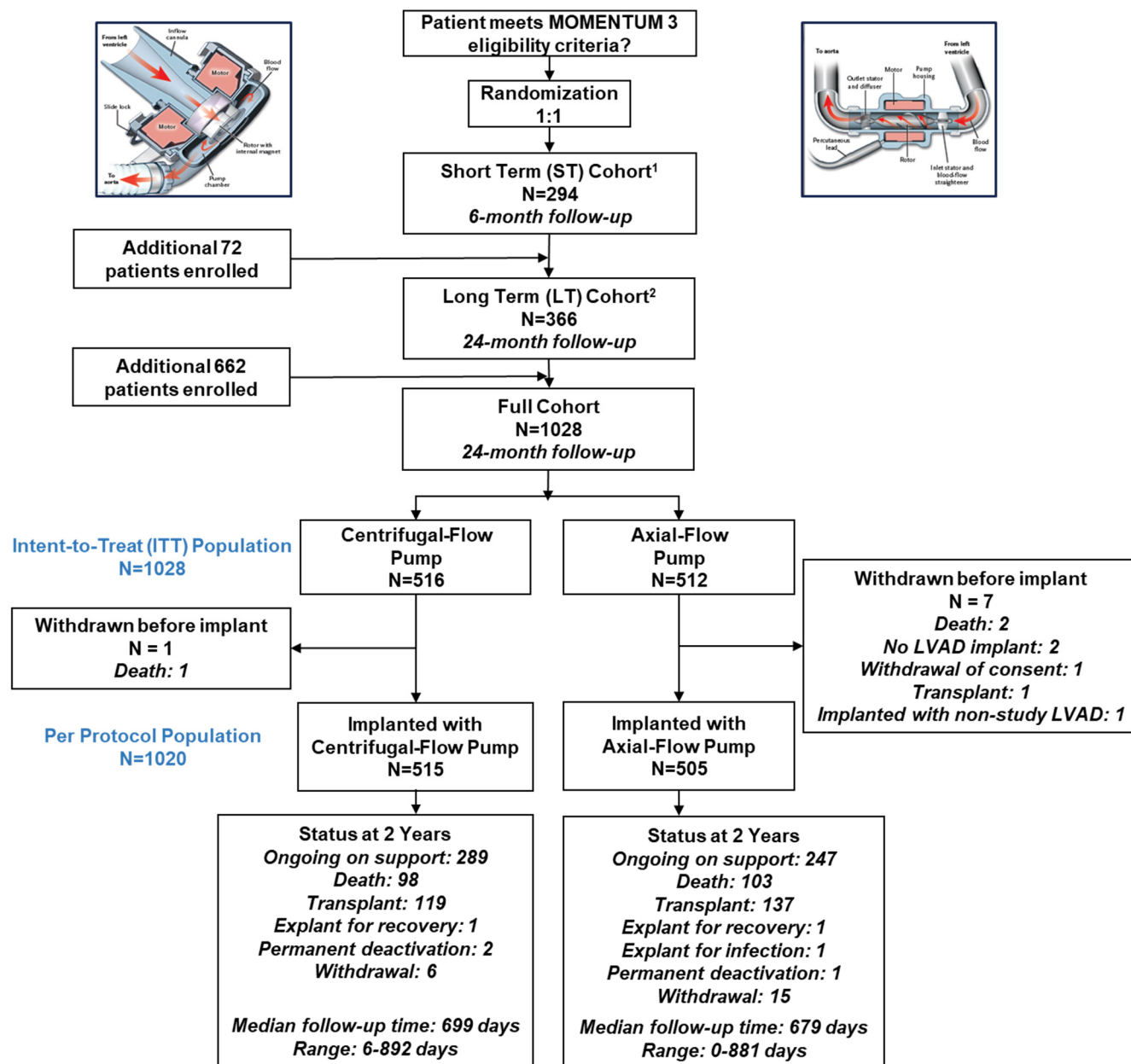
MOMENTUM 3 was designed to have 3 pre-specified analyses:

1. Short-term (ST) cohort analysis (294 patients at 6-months): demonstrate non-inferiority with regards to the primary end point of 6-month survival free of disabling stroke or reoperation to replace or remove a malfunctioning device<sup>1</sup>.
2. Long-term (LT) cohort analysis (366 patients at 2-years): demonstrate non-inferiority at 2-years with regards to the primary end point of 2-year survival free of disabling stroke or reoperation to replace or remove a malfunctioning device<sup>2</sup>.
3. Final analysis of full cohort (1028 patients at 2-years): demonstrate superiority at 2-years for the principal secondary end point of pump replacement.

The percentages depict how much of the total trial experience was previously reported in the ST and LT cohort analyses. The ST cohort was composed of 294 patients with 6-month follow-up, which accounts for 7.1% of the entire trial experience ( $[(294 \text{ patients} \times 6 \text{ months}) \div (1028 \text{ patients} \times 24 \text{ months})]$ ). The LT cohort was composed of 366 patients with 24-month follow-up, which accounts for 35.6% of the entire trial experience ( $[(366 \text{ patients} \times 24 \text{ months}) \div (1028 \text{ patients} \times 24 \text{ months})]$ ). The timeline depicts when follow-up was completed for each cohort. Enrollment for the entire study was completed in August 2016 prior to presentation of any study results.

<sup>1</sup>Mehra MR, Naka Y, Uriel N, et al. A Fully Magnetically Levitated Circulatory Pump for Advanced Heart Failure. *N Engl J Med* 2017;376(5):440-450. <sup>2</sup>Mehra MR, Goldstein DJ, Uriel N, et al. Two-Year Outcomes with a Magnetically Levitated Cardiac Pump in Heart Failure. *N Engl J Med* 2018;378(15):1386-1395.

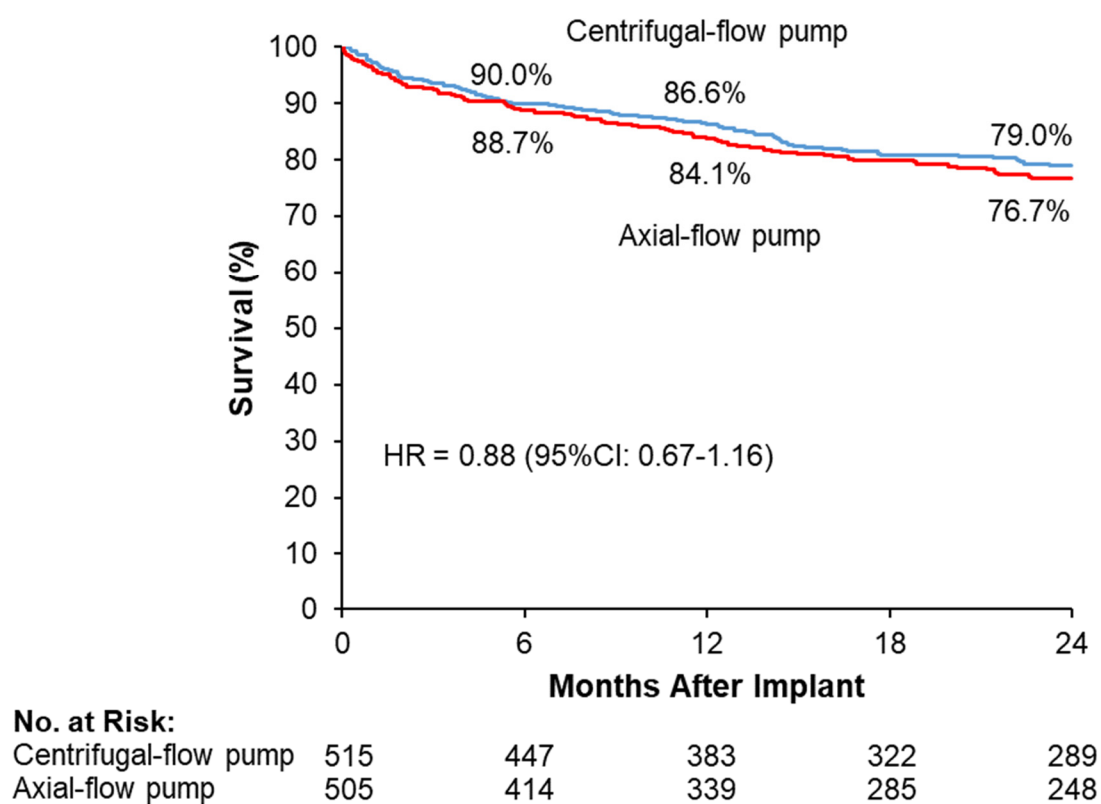
**Figure S2. CONSORT Diagram for the MOMENTUM 3 Full Cohort**



Reasons for withdrawal post-implant in the centrifugal-pump group include withdrawn consent (n=1), implant with non-study device (n=2), subject non-compliance (n=1), subject depression (n=1), and subject incarceration (n=1). Reasons for withdrawal post-implant in the axial-flow pump group include withdrawn consent (n=1), implant with non-study device (n=5), implant with centrifugal-flow pump (n=6), cancer diagnosis (n=1), suicide attempt (n=1), and subject relocation to non-study site (n=1).

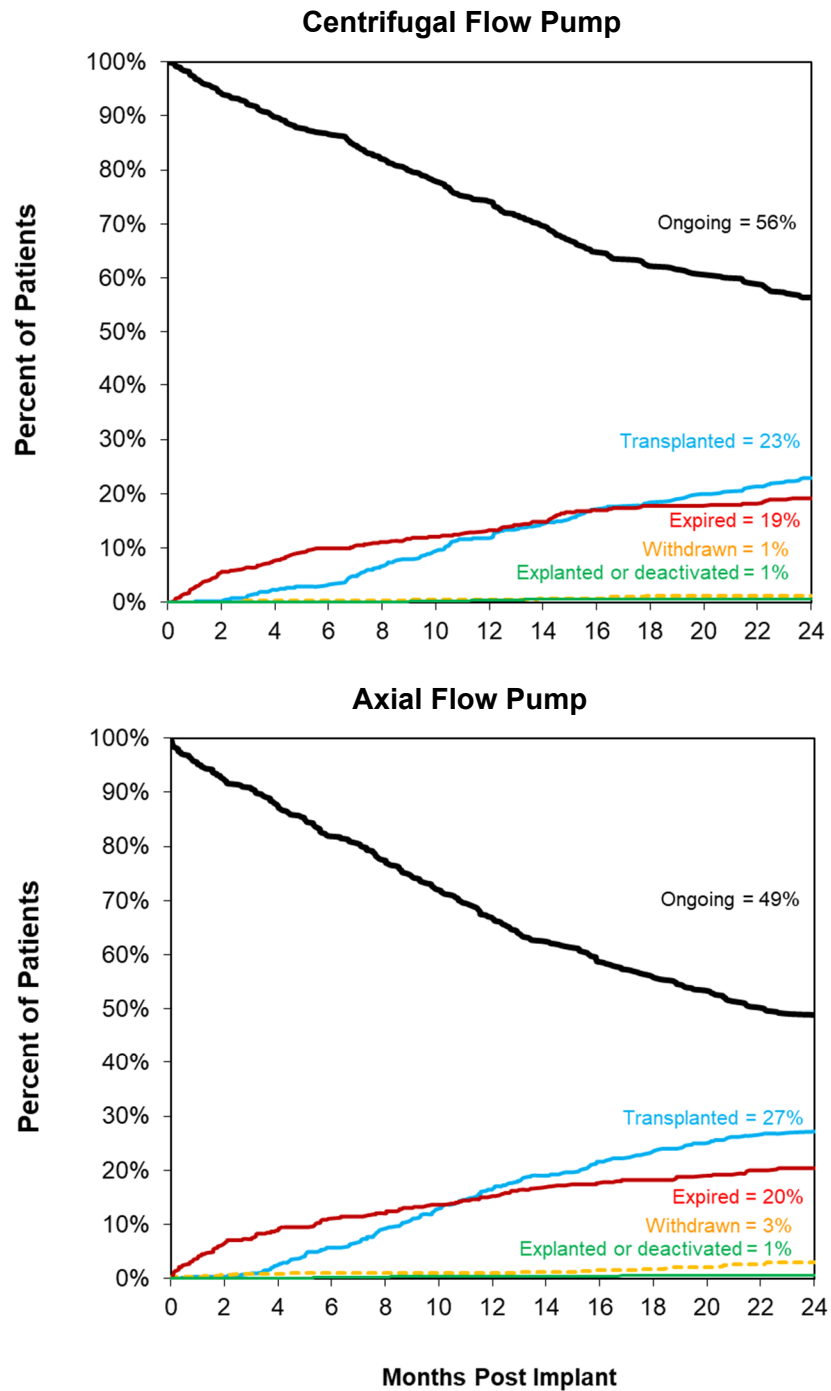
<sup>1</sup>Mehra MR, Naka Y, Uriel N, et al. A Fully Magnetically Levitated Circulatory Pump for Advanced Heart Failure. *N Engl J Med* 2017;376(5):440-450. <sup>2</sup>Mehra MR, Goldstein DJ, Uriel N, et al. Two-Year Outcomes with a Magnetically Levitated Cardiac Pump in Heart Failure. *N Engl J Med* 2018;378(15):1386-1395.

**Figure S3. Actuarial Overall Survival (Per Protocol Population)**



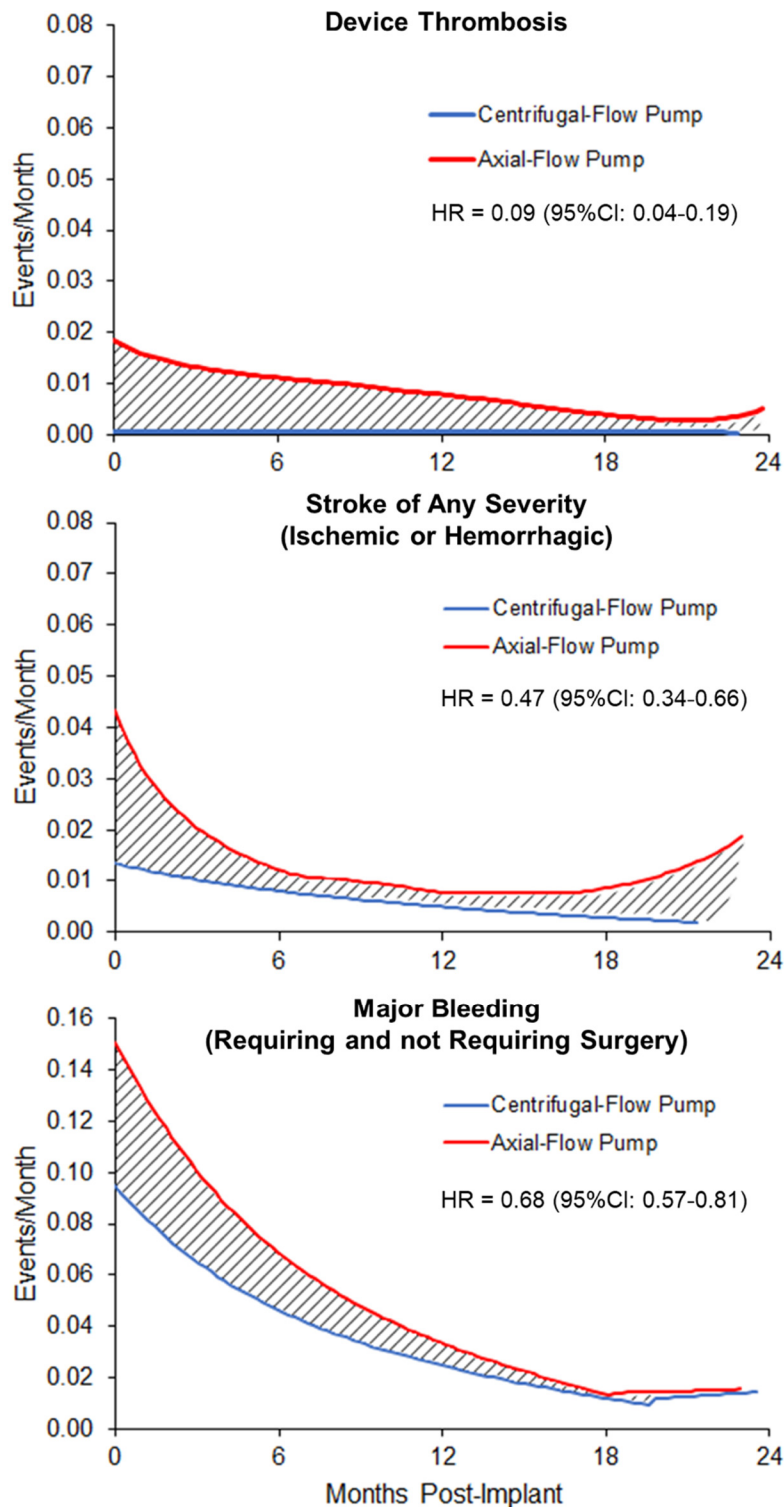
95% confidence intervals have not been adjusted for multiplicity and therefore inferences drawn from these intervals may not be reproducible.

**Figure S4. Competing Risk Analyses (Per Protocol Population)**



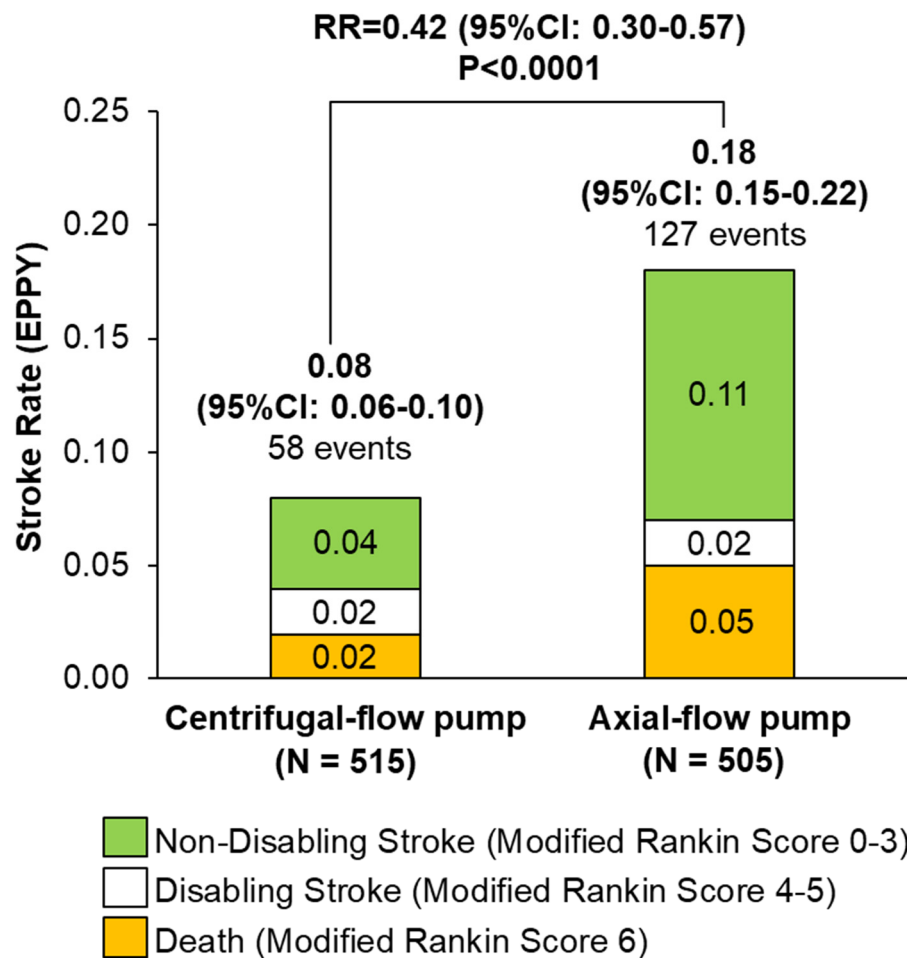
The competing outcome curves show the cumulative percentage of patients reaching an outcome of interest over the course of the study follow-up. At the end of the study, 56% of patients in the centrifugal-flow pump group compared to 49% of patients in the axial-flow pump group remained ongoing on LVAD support. Similar percentages of patients expired or were transplanted in both arms. To analyze survival in the presence of competing outcomes, the Fine-Grey model was used to calculate the hazard ratio for death while accounting for the competing risk of heart transplantation: 0.91 (95% CI: 0.69-1.20). 95% confidence intervals have not been adjusted for multiplicity and therefore inferences drawn from these intervals may not be reproducible.

**Figure S5. Hazard Function of Key Adverse Events (Per Protocol Population)**



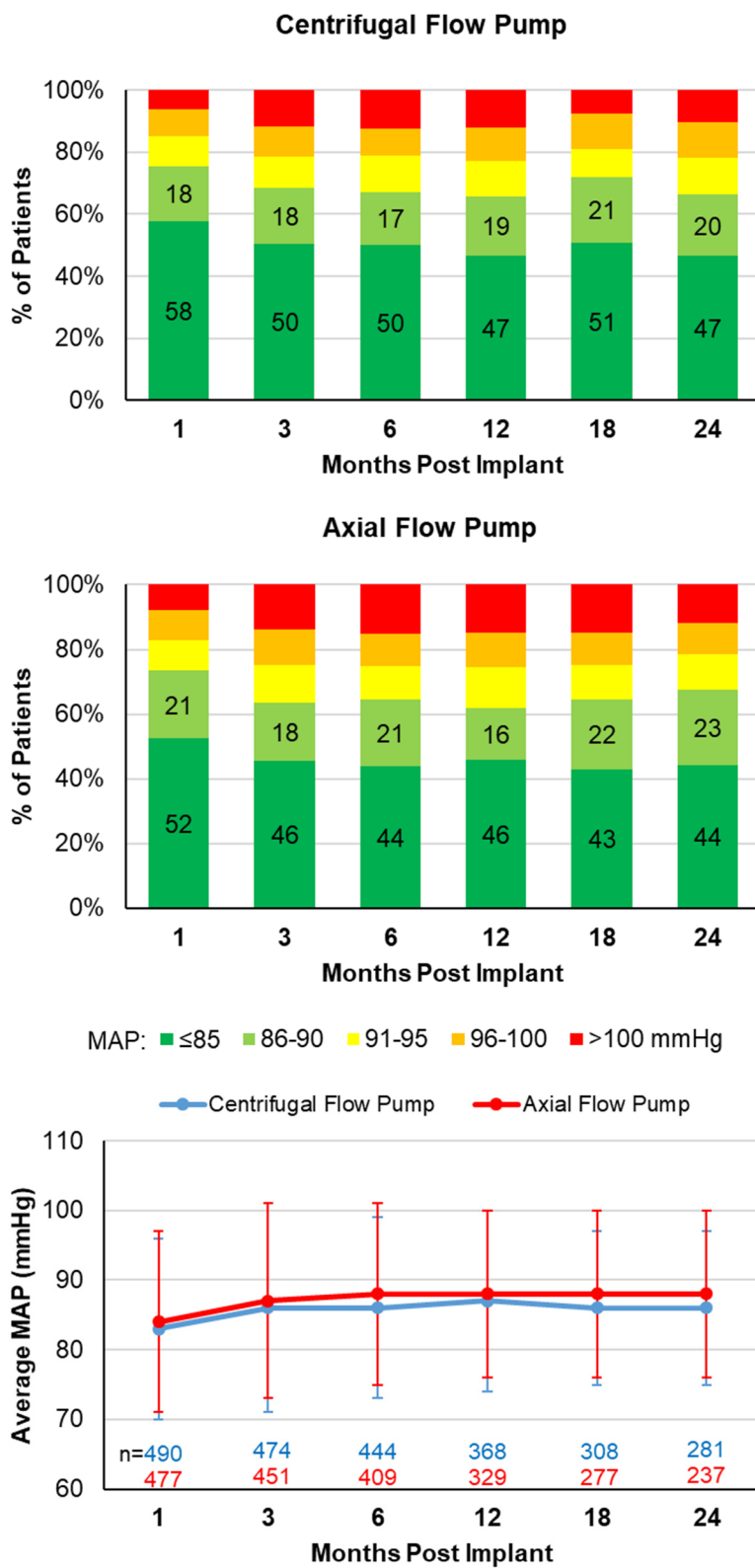
Hazard functions are derived from the Kaplan Meier analysis of freedom from the adverse event of interest. Hash marks indicate the difference between the pumps. The hazard rates change over time for both pumps, and rates are higher for the axial-flow pump for the majority of the 2-year follow-up. 95% confidence intervals have not been adjusted for multiplicity and therefore inferences drawn from these intervals may not be reproducible.

**Figure S6. Stroke Events and Severity (Per Protocol Population)**



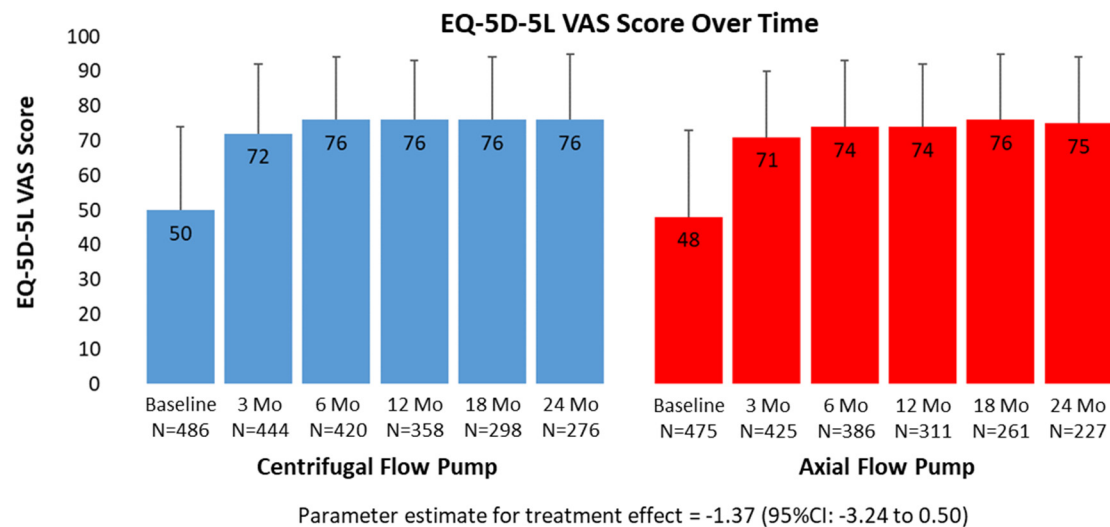
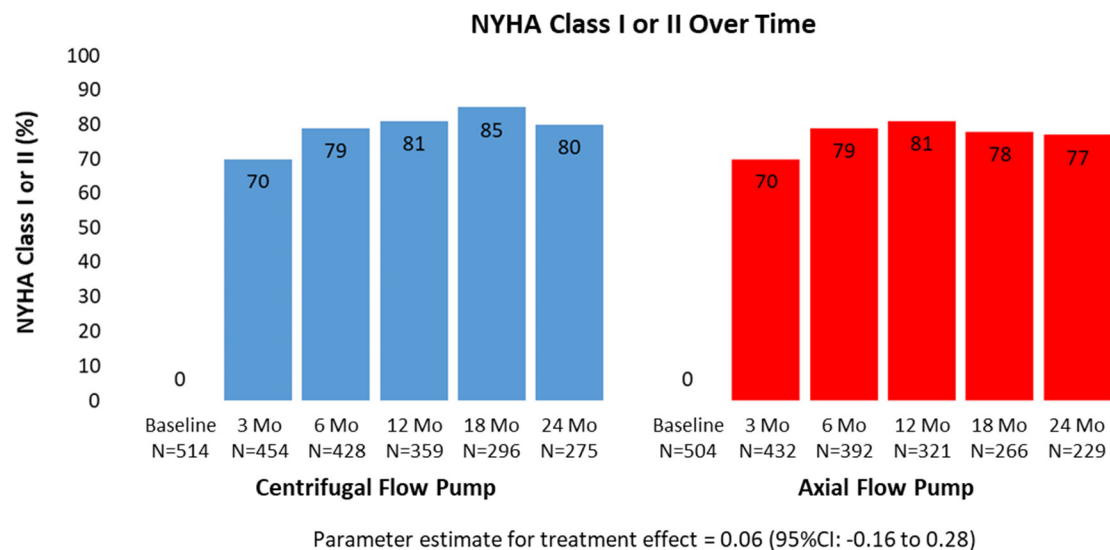
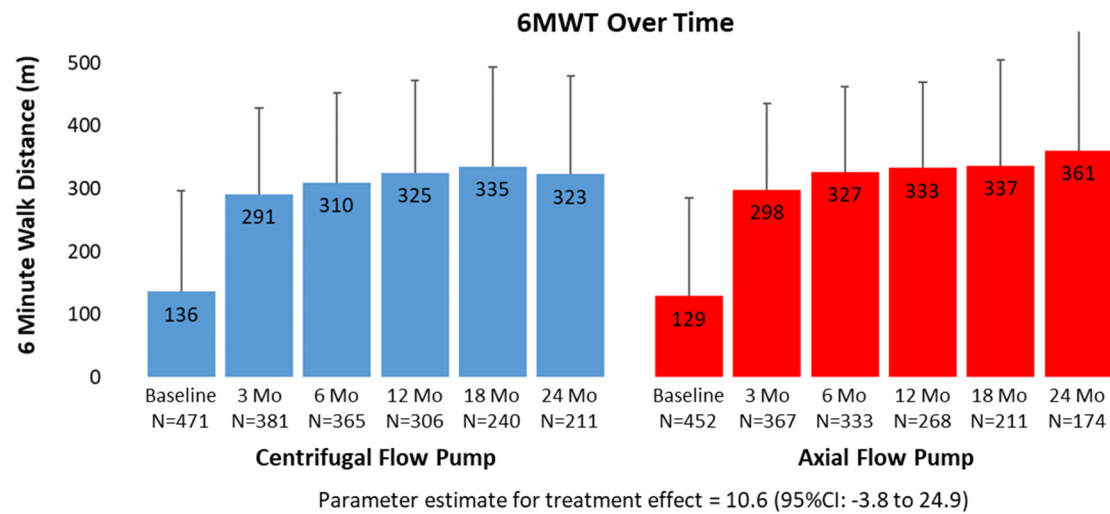
There were 29 disabling strokes in the centrifugal-flow pump group and 49 disabling strokes in the axial-flow pump group. 10 strokes in the centrifugal-flow pump group and 30 strokes in the axial-flow pump group resulted in a modified Rankin score of 0 at 60 days post-stroke. 1.0% of centrifugal-flow pump patients (n=5) and 5.1% of axial-flow pump patients (n=26) had >1 stroke. CI denotes confidence interval, EPPY events per patient year, and RR relative risk. 95% confidence intervals have not been adjusted for multiplicity and therefore inferences drawn from these intervals may not be reproducible.

**Figure S7. Mean Arterial Pressure (MAP) over Time (Per Protocol Population)**

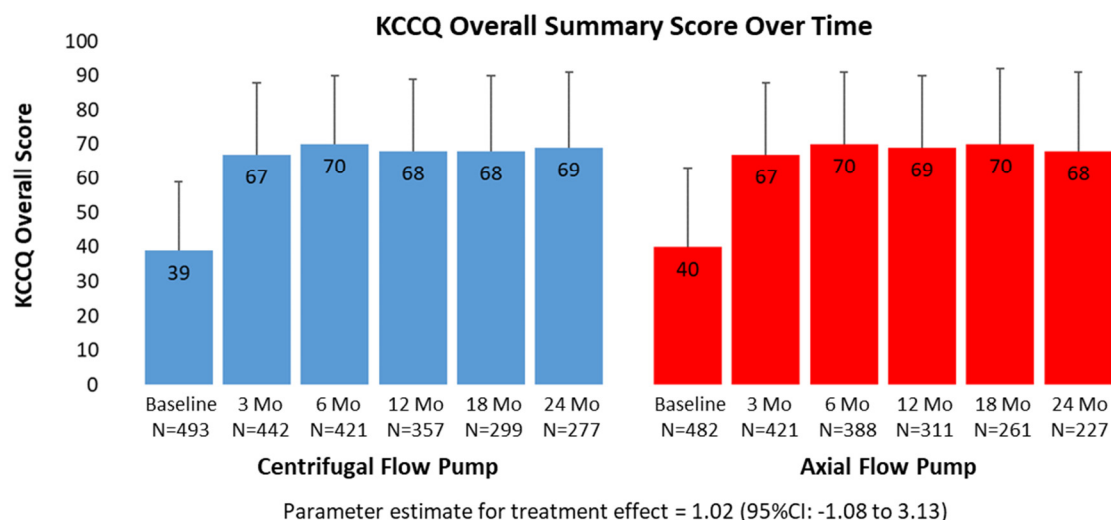
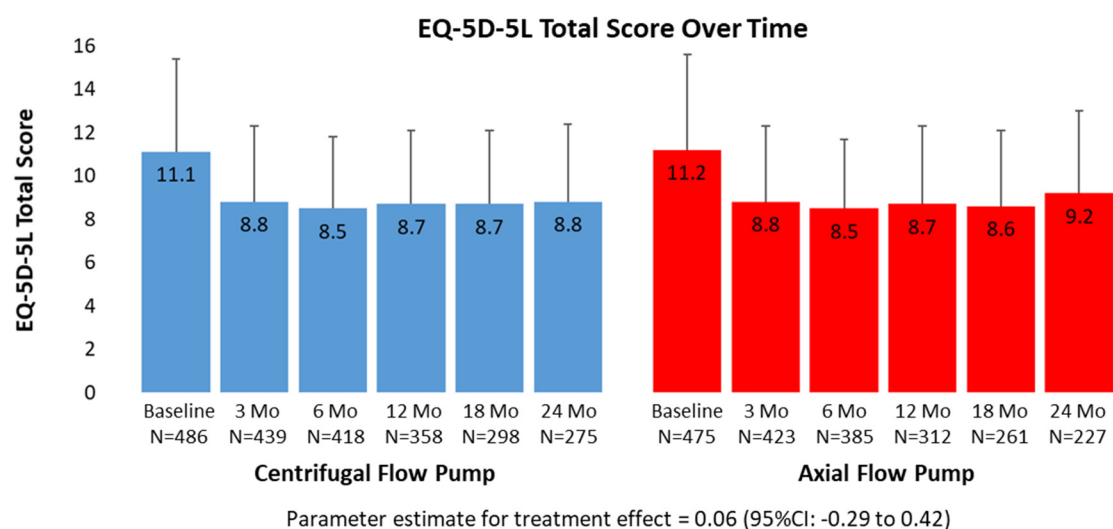


There were no significant differences in the proportion of patients with MAP ≤ 90 mmHg between treatment groups at each follow-up visit by Fisher's exact test.

**Figure S8. Functional Status and Quality of Life (Per Protocol Population)**

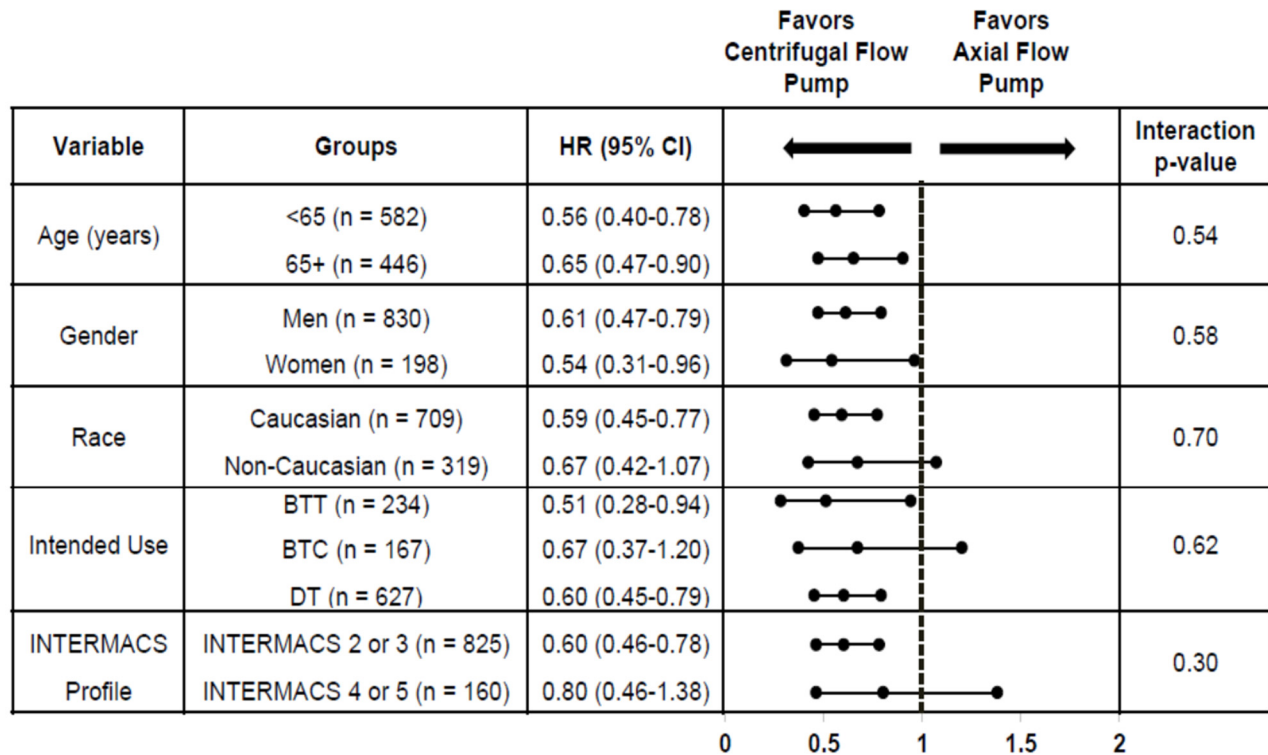






On the European Quality of Life–5 Dimensions questionnaire (EQ-5D-5L), scores range from 1 to 5, with higher scores indicating more problems across five categories of quality of life. On the EQ-5D visual-analogue scale (EQ-5D VAS), scores range from 0 to 100, with higher scores indicating better health status. On the Kansas City Cardiomyopathy Questionnaire (KCCQ), scores range from 0 to 100, with higher scores indicating better quality of life and fewer symptoms. Patients who did not complete a six-minute walk test (6MWT) due to heart failure were assigned zero meters. There were patients who did not complete the 6MWT due to reasons other than heart failure (e.g., other illnesses, refusal to perform the test, site scheduling issues). Some patients who did not complete the 6MWT at a particular visit were able to complete quality of life questionnaires. Thus, the total number of patients at each time interval may not be the same across these tests. The data was analyzed using linear mixed models (fixed term for treatment arm and a term for the visit to model repeated measures), and parameter estimates for the treatment effects are shown above. There were no significant differences between treatment arms. A sensitivity analysis was performed in which all missing data for both treatment arms were assigned the worst possible score for the test. The data continue to show that functional status and quality of life improve over baseline in both treatment arms. There were no differences between arms in the 6MWT and KCCQ measures. However, patients assigned to the centrifugal-flow pump arm had more favorable NYHA class and EQ-5D-5L VAS scores than the axial-flow pump group. 95% confidence intervals have not been adjusted for multiplicity and therefore inferences drawn from these intervals may not be reproducible.

**Figure S9. Subgroup Analyses of the Primary End Point for Age, Gender, Race, Implant Strategy and INTERMACS Profile between Treatment Groups (Intent to Treat Population)**



BTT denotes Bridge to Transplant, BTC Bridge to Candidacy, DT Destination Therapy, INTERMACS Interagency Registry for Mechanically Assisted Circulatory Support. 95% confidence intervals have not been adjusted for multiplicity and therefore inferences drawn from these intervals may not be reproducible.

## SUPPLEMENTARY TABLES

**Table S1. Other Baseline Characteristics (Intention to Treat Population)**

Characteristic	Centrifugal-Flow Pump Group (N=516)	Axial-Flow Pump Group (N=512)
Valvular insufficiency – no. (%)		
Aortic	152 (29.5)	147 (28.7)
Moderate or severe	11 (2.1)	7 (1.4)
Mitral	465 (90.1)	443 (86.5)
Moderate or severe	217 (42.1)	231 (45.1)
Tricuspid	432 (83.7)	422 (82.4)
Moderate or severe	159 (30.8)	128 (25.0)
Concomitant medication or intervention – no. (%)		
Intravenous inotropic agents	445 (86.2)	423 (82.6)
Diuretic	436 (84.5)	465 (90.8)
Angiotensin-converting-enzyme inhibitor or Angiotensin II-receptor antagonist	158 (30.6)	173 (33.8)
Beta-blocker	284 (55.0)	273 (53.3)
Cardiac resynchronization therapy with or without defibrillator	188 (36.4)	157 (30.7)
Implantable cardioverter-defibrillator with or without cardiac resynchronization therapy	352 (68.2)	382 (74.6)
Intraaortic balloon pump	64 (12.4)	79 (15.4)
INTERMACS profile – no. (%) <sup>*</sup>		
1	11 (2.1)	18 (3.5)
2	156 (30.2)	146 (28.5)
3	272 (52.7)	251 (49.0)
4	67 (13.0)	82 (16.0)
5-7 or not provided <sup>+</sup>	10 (1.9)	15 (2.9)

\*Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profiles range from 1 to 7; a profile of 1 represents the most severe illness and a profile of 7 the least severe illness. <sup>+</sup>Assessments were not performed in 2 centrifugal-flow pump patients and 5 axial-flow pump patients.

**Table S2. Total Disabling Strokes and Deaths and their Contribution to the Primary Endpoint Component Analysis (Per Protocol Population)**

	<b>Centrifugal-Flow Pump Group (N = 515)</b>				<b>Axial-Flow Pump Group (N =505)</b>			
	Contributing 1st to primary endpoint failure	Total occurring during study			Contributing 1st to primary endpoint failure	Total occurring during study		
<b>Event Type</b>	# patients	# patients	# events	EPPY	# patients	# patients	# events	EPPY
Disabling stroke	20	26	29	0.04	30	38	49	0.07
Death	80	98	98	-	67	103	103	-

The primary endpoint is a composite and records as failure the first component event of the composite that is reached. However, it is possible for patients to have more than one subsequent event of the same type or also events of a different component type. This table shows this issue in the context of the total number of disabling strokes and deaths occurring post-implant by separating out a) how many first events led to primary endpoint failure, b) total number of patients with such events (which includes recurrent events) and c) rates of events per patient year (EPPY). The number of those contributing first to primary endpoint failure match the number shown in the component analysis of the primary end point (Table 2).

**Table S3. Sensitivity Analysis of Primary End Point (Intention to Treat Population)**

	<b>Percent Success</b>	<b>95% Confidence Interval</b>	
Centrifugal-Flow Pump (n=516)	76.9%	73.1%	80.5%
Axial-Flow Pump (n=512)	69.7%	65.5%	73.7%
RR = 0.91 (95% CI: 0.84-0.98)			

Subjects that were randomized to the axial-flow pump but not implanted (n = 7) are considered Success and those randomized to centrifugal-flow pump are considered a Failure (n = 1). Axial-flow pump subjects receiving urgent transplants for device malfunction (n=15) are also considered Success and those in the centrifugal-flow pump group are considered a Failure (n=2). Axial-flow pump subjects withdrawn after implant (n=3) are also considered Success and those in the centrifugal-flow pump group are considered a Failure (n=4). 95% confidence intervals have not been adjusted for multiplicity and therefore inferences drawn from these intervals may not be reproducible. CI denotes confidence interval and RR relative risk.

**Table S4. Reasons for Pump Replacement for Principal Secondary End Point (Per Protocol Population)**

<b>Centrifugal-flow pump</b>	
<b>Reasons for Pump Replacement</b>	<b>N</b>
Driveline damage or communication faults causing electrical failure	4
Suspected pump thrombosis or elevated LDH	3
Outflow graft twist occlusion	2
Right heart failure	1
Infection	1
Bioprosthetic mitral valve dysfunction	1
<i>Total</i>	<i>12</i>
<b>Axial-flow pump</b>	
<b>Reasons for Pump Replacement</b>	<b>N</b>
Suspected pump thrombosis	44
Driveline damage or communication faults causing electrical failure	7
Infection	4
Inflow cannula malposition resulting in arrhythmia	1
Patient disconnected device in suicide attempt	1
<i>Total</i>	<i>57</i>

**Table S5. Adjudicated Causes of Death (Per Protocol Population)**

<b>Adjudicated Cause of Death</b>	<b>Centrifugal-flow pump (n=515)</b>	<b>Axial-flow pump (n=505)</b>	<b>Total</b>
<b>Cardiopulmonary related</b>			
Cardiac arrest	0	1	1
Heart failure	4	1	5
Pericardial tamponade	0	2	2
Respiratory failure	3	2	5
Right heart failure	31	26	57
Ventricular arrhythmia	2	1	3
<b>Brain related</b>			
Anoxic brain injury	3	0	3
Head trauma	2	0	2
Intracranial Bleed Due to Trauma	2	2	4
Stroke	13	29	42
<b>Bleeding related</b>			
Aortic dissection	0	1	1
Abdominal or gastrointestinal bleeding	1	3	4
<b>Infection related</b>			
Infection or sepsis	14	14	28
Pneumonia	4	2	6
<b>Device related</b>			
Driveline or power cable disconnect*	5	1	6
MPU disconnected from power	1	0	1
Pump stop	0	1	1
Pump thrombosis	1	8	9
Unintentional battery depletion	0	1	1
<b>Other</b>			
Bowel Perforation	0	1	1

Cancer	2	0	2
Failure to thrive	1	1	2
Hepatic failure	0	2	2
Intravenous drug use	1	0	1
Ischemic bowel	2	0	2
Multi-organ failure	1	0	1
Renal failure	1	1	2
Suicide	1	0	1
Trauma	1	0	1
Unknown	2	3	5
<b>Total</b>	<b>98</b>	<b>103</b>	<b>201</b>

\*Two of the deaths in the centrifugal-flow pump group were associated with 180-degree misalignment between the modular driveline cable connector and the system controller.



**Table S6. Adverse Event Rates (Per Protocol Population)**

	<b>Centrifugal-Flow Pump (N=515)</b>		<b>Axial-Flow Pump (N=505)</b>			
<b>Event</b>	<b>No. of patients (%)</b>	<b>EPPY (95% CI)</b>	<b>No. of patients (%)</b>	<b>HMII EPPY (95% CI)</b>	<b>RR (95%CI)</b>	<b>P*</b>
Suspected or confirmed pump thrombosis	7 (1.4)	0.01 (0.00 - 0.02)	70 (13.9)	0.12 (0.10 - 0.15)	0.08 (0.04-0.16)	<0.0001
Pump thrombosis resulting in reoperation	5 (1.0)	0.01 (0.00 - 0.02)	56 (11.1)	0.09 (0.07 - 0.12)	0.07 (0.03-0.18)	<0.0001
Stroke						
Any stroke	51 (9.9)	0.08 (0.06 - 0.10)	98 (19.4)	0.18 (0.15 - 0.22)	0.42 (0.30-0.57)	<0.0001
Hemorrhagic stroke	25 (4.9)	0.03 (0.02 - 0.05)	43 (8.5)	0.07 (0.05 - 0.09)	0.49 (0.31-0.79)	0.004
Ischemic stroke	29 (5.6)	0.04 (0.03 - 0.06)	65 (12.9)	0.11 (0.09 - 0.14)	0.37 (0.24-0.56)	<0.0001
Disabling stroke	26 (5.0)	0.04 (0.03 - 0.05)	38 (7.5)	0.07 (0.05 - 0.09)	0.54 (0.34-0.85)	0.008
Other neurologic event <sup>†</sup>	59 (11.5)	0.09 (0.08 - 0.12)	47 (9.3)	0.08 (0.06 - 0.10)	1.25 (0.88-1.79)	0.21
Transient ischemic attack	16 (3.1)	0.03 (0.02 - 0.04)	19 (3.8)	0.03 (0.02 - 0.04)	1.10 (0.60-2.02)	0.75
Bleeding						
Any bleeding	225 (43.7)	0.61 (0.56 - 0.67)	278 (55.0)	0.95 (0.88 - 1.03)	0.64 (0.57-0.72)	<0.0001
Bleeding requiring surgery	50 (9.7)	0.08 (0.06 - 0.10)	89 (17.6)	0.14 (0.12 - 0.17)	0.54 (0.39-0.74)	<0.001
Bleeding not requiring surgery	197 (38.3)	0.53 (0.48 - 0.58)	251 (49.7)	0.81 (0.74 - 0.88)	0.66 (0.58-0.75)	<0.0001
Gastrointestinal bleeding	126 (24.5)	0.31 (0.28 - 0.35)	156 (30.9)	0.49 (0.44 - 0.54)	0.64 (0.54-0.75)	<0.0001
Major infection						
Any infection	300 (58.3)	0.82 (0.76 - 0.89)	285 (56.4)	0.82 (0.76 - 0.89)	1.00 (0.89-1.12)	0.96
Sepsis	78 (15.1)	0.13 (0.11 - 0.16)	75 (14.9)	0.13 (0.11 - 0.16)	0.99 (0.75-1.31)	0.94
LVAS driveline infection	120 (23.3)	0.23 (0.20 - 0.27)	98 (19.4)	0.22 (0.18 - 0.25)	1.06 (0.85-1.32)	0.60
Local infection not associated with LVAS	210 (40.8)	0.46 (0.41 - 0.51)	186 (36.8)	0.47 (0.42 - 0.52)	0.97 (0.84-1.13)	0.73

Right heart failure						
Any right heart failure	176 (34.2)	0.27 (0.23 - 0.30)	143 (28.3)	0.23 (0.20 - 0.27)	1.15 (0.94-1.42)	0.18
Right heart failure managed with RVAS	21 (4.1)	0.03 (0.02 - 0.04)	21 (4.2)	0.03 (0.02 - 0.05)	0.91 (0.50-1.67)	0.76
Cardiac arrhythmia						
Any cardiac arrhythmia	185 (35.9)	0.37 (0.33 - 0.41)	207 (41.0)	0.45 (0.40 - 0.50)	0.82 (0.70-0.97)	0.02
Ventricular arrhythmia	107 (20.8)	0.20 (0.17 - 0.24)	128 (25.3)	0.27 (0.23 - 0.31)	0.76 (0.62-0.94)	0.01
Supraventricular arrhythmia	97 (18.8)	0.15 (0.12 - 0.18)	98 (19.4)	0.15 (0.13 - 0.18)	0.98 (0.75-1.27)	0.87
Atrial fibrillation	84 (16.3)	0.13 (0.11 - 0.16)	86 (17.0)	0.14 (0.11 - 0.17)	0.95 (0.72-1.26)	0.72
Respiratory failure	111 (21.6)	0.19 (0.16 - 0.22)	98 (19.4)	0.17 (0.14 - 0.20)	1.10 (0.86-1.40)	0.44
Renal dysfunction	73 (14.2)	0.11 (0.09 - 0.14)	56 (11.1)	0.08 (0.07 - 0.11)	1.36 (0.98-1.89)	0.07
Hepatic dysfunction	25 (4.9)	0.03 (0.02 - 0.05)	27 (5.3)	0.04 (0.03 - 0.06)	0.78 (0.46-1.34)	0.38

\*P values and relative risk are from Poisson regression. \*Other neurologic events included transient ischemic attack, seizure, encephalopathy and neurologic events other than stroke. 95% confidence intervals have not been adjusted for multiplicity and therefore inferences drawn from these intervals may not be reproducible. EEPY denotes events per patient year, RR relative risk, LVAS left ventricular assist system, RVAS right ventricular assist system.

**Table S7. Summary of Pump Thrombosis Events (Per Protocol Population)**

	<b>Centrifugal-Flow Pump</b>	<b>Axial-Flow Pump</b>
Total Patients	7/515 (1%)	70/505 (14%)
Total Events	7	84
Mean time to first event (days)	368	220
<b>Signs and Symptoms</b>		
Hemolysis	2/7 (28.6%)	71/84 (84.5%)
Worsening heart failure	7/7 (100.0%)	48/84 (57.1%)
Abnormal pump parameters	6/7 (85.7%)	45/84 (53.6%)
<b>Action Taken/Outcome</b>		
Device exchange	2/7 (28.6%)	52/84 (61.9%)
Urgent transplant	0/7 (0%)	10/84 (11.9%)
Death due to pump thrombosis	1/7 (14.3%)	8/84 (9.5%)
<b>Returned Product Analysis Result</b>		
Confirmed	2/7 (28.6%)	47/84 (56.0%)
Not confirmed	0/7 (0%)	1/84 (1.2%)
Inconclusive/ongoing investigation	0/7 (0%)	13/84 (15.5%)
Not determined/device not returned	5/7 (71.4%)	23/84 (27.4%)

**Table S8. Subjects with Aspirin and Other Antiplatelet Therapy (Per Protocol Population)**

	<b>Centrifugal Flow Pump (N=515)</b>	<b>Axial Flow Pump (N=505)</b>
<b>Baseline</b>		
Any Aspirin	55.0% (283/515)	53.5% (270/505)
325 mg Aspirin	2.7% (14/515)	4.0% (20/505)
> 1 Anti-Platelet*	4.9% (25/515)	3.8% (19/505)
<b>Month 6</b>		
Any Aspirin	83.9% (374/446)	82.8% (341/412)
325 mg Aspirin	36.1% (161/446)	30.3% (125/412)
> 1 Anti-Platelet	9.6% (43/446)	11.9% (49/412)
<b>Month 12</b>		
Any Aspirin	79.0% (293/371)	76.3% (254/333)
325 mg Aspirin	32.6% (121/371)	30.6% (102/333)
> 1 Anti-Platelet	8.6% (32/371)	15.6% (52/333)
<b>Month 18</b>		
Any Aspirin	76.8% (241/314)	75.1% (211/281)
325 mg Aspirin	30.3% (95/314)	30.2% (85/281)
> 1 Anti-Platelet	6.7% (21/314)	15.7% (44/281)
<b>Month 24</b>		
Any Aspirin	77.6% (222/286)	68.3% (164/240)
325 mg Aspirin	27.3% (78/286)	29.2% (70/240)
> 1 Anti-Platelet	6.6% (19/286)	12.9% (31/240)

\*Defined as aspirin, clopidogrel, dipyridamole, IIb/IIIa platelet inhibitor and/or cangrelor/ticagrelor. In a repeated measures logistic regression of any aspirin use, no significant difference over time was found between the centrifugal-flow pump and axial-flow pump groups.

**Table S9. Subjects with Normal, Sub, and Supratherapeutic INR Values over Time (Per Protocol Population)**

	<b>Centrifugal Flow Pump (N=515)</b>	<b>Axial Flow Pump (N=505)</b>
<b>Baseline</b>	n=515	n=504
INR < 2	95.0% (489/515)	95.2% (480/504)
INR 2-3	4.5% (23/515)	4.2% (21/504)
INR > 3	0.6% (3/515)	0.6% (3/504)
<b>Month 6</b>	n=444	n=410
INR < 2	29.1% (129/444)	28.5% (117/410)
INR 2-3	57.2% (254/444)	61.7% (253/410)
INR > 3	13.7% (61/444)	9.8% (40/410)
<b>Month 12</b>	n=371	n=332
INR < 2	29.4% (109/371)	26.8% (89/332)
INR 2-3	60.9% (226/371)	61.1% (203/332)
INR > 3	9.7% (36/371)	12.0% (40/332)
<b>Month 18</b>	n=310	n=281
INR < 2	30.6% (95/310)	29.2% (82/281)
INR 2-3	58.7% (182/310)	60.1% (169/281)
INR > 3	10.6% (33/310)	10.7% (30/281)
<b>Month 24</b>	n=283	n=239
INR < 2	27.9% (79/283)	36.4% (87/239)
INR 2-3	61.1% (173/283)	54.4% (130/239)
INR > 3	11.0% (31/283)	9.2% (22/239)

The proportion of patients with normal, sub, and supratherapeutic INR values were not significantly different between the centrifugal-flow pump and axial-flow pump groups at each follow-up visit using Fisher's Exact Test.

**Table S10. Laboratory Values over Time (Per Protocol Population)**

		Centrifugal Flow Pump (N=515)		Axial Flow Pump (N=505)	
Variable	Visit	n	Mean±SD	n	Mean±SD
Creatinine (mg/dl)	Baseline	515	1.4±0.4	505	1.4±0.4
	Month 6	445	1.3±0.5	409	1.3±0.5
	Month 12	370	1.4±0.5	331	1.4±0.5
	Month 24	284	1.4±0.5	240	1.4±0.6
Total Bilirubin (mg/dl)	Baseline	514	1.0±0.6	505	1.1±0.6
	Month 6	444	0.8±1.1	406	0.7±0.4
	Month 12	368	0.7±0.5	326	0.7±0.4
	Month 24	281	0.7±0.5	237	0.8±0.6
BUN (mg/dl)	Baseline	515	28.3±14.0	504	27.6±12.6
	Month 6	445	24.9±15.1	409	23.2±12.3
	Month 12	370	24.4±12.0	331	22.6±9.6
	Month 24	284	24.4±13.4	240	23.5±11.2
AST (U/L)	Baseline	512	33.7±44.0	504	34.4±60.2
	Month 6	444	27.1±13.0	406	29.8±24.7
	Month 12	369	34.5±142.4	325	29.2±12.3
	Month 24	282	28.4±15.8	237	29.1±14.3
ALT (U/L)	Baseline	513	52.0±172.2	505	47.7±166.3
	Month 6	445	26.2±19.4	406	27.0±25.9
	Month 12	369	28.6±60.5	326	25.3±13.2
	Month 24	282	26.7±27.9	237	24.7±16.3
LDH (U/L)	Baseline	481	290±263	479	282±152
	Month 6	438	253±102	406	345±178
	Month 12	365	276±419	328	356±192
	Month 24	280	252±95	237	344±190

Most lab values were similar between the two groups. However, after implant, LDH levels diverged with average values of >300 U/L in the axial-flow pump group and <300 U/L in the centrifugal-flow pump group. BUN denotes blood urea nitrogen, AST aspartate aminotransferase, ALT alanine aminotransferase, and LDH lactate dehydrogenase.

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