SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Ventricular assist device
Device Trade Name:	HeartWare™ HVAD™ System
Device Procode	DSQ
Applicant's Name and Address:	Medtronic, Inc. 8200 Coral Sea Street, N.E. Mounds View, Minnesota 55112
Date(s) of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P100047/S090
Date of FDA Notice of Approval:	September 27, 2017

The original PMA (PMA P100047) was approved on November 20, 2012 and is indicated for use as a bridge to cardiac transplantation in patients who are at risk of death from refractory end-stage heart failure. The HeartWare VAS is designed for in-hospital and out-of-hospital settings, including transportation via fixed wing aircraft or helicopter. The SSED to support the indication is available on the CDRH website (https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100047B.pdf) and is incorporated by reference here. The current supplement was submitted to expand the indication for the HeartWare Ventricular Assist System to include destination therapy.

II. INDICATION FOR USE

The HeartWare™ HVAD™ System is indicated for hemodynamic support in patients with advanced, refractory left ventricular heart failure; either as a bridge to cardiac transplantation (BTT), myocardial recovery, or as destination therapy (DT) in patients for whom subsequent transplantation is not planned.

III. CONTRAINDICATIONS

The HeartWare™ HVAD™ System is contraindicated in patients who cannot tolerate anticoagulation therapy.

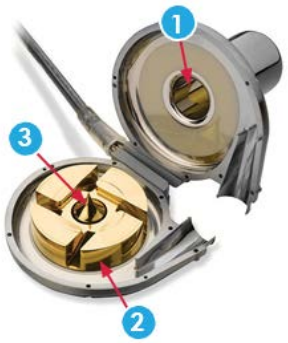
IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the HeartWare™ HVAD™ System labeling.

V. DEVICE DESCRIPTION

Implanted components of the HeartWare™ HVAD™ System include the pump (which includes an integrated inflow cannula), an outflow conduit, a percutaneous driveline, and an apical sewing ring. The HeartWare ventricular assist device (HVAD) pump is a continuous flow blood pump which utilizes magnetic and hydrodynamic forces to elevate and rotate the impeller. Once power is applied to the device, there are no points of mechanical contact between the impeller and the body of the pump. An open view of the pump is shown in Figure 1 below.

Figure 1: Open View of HVAD® Pump



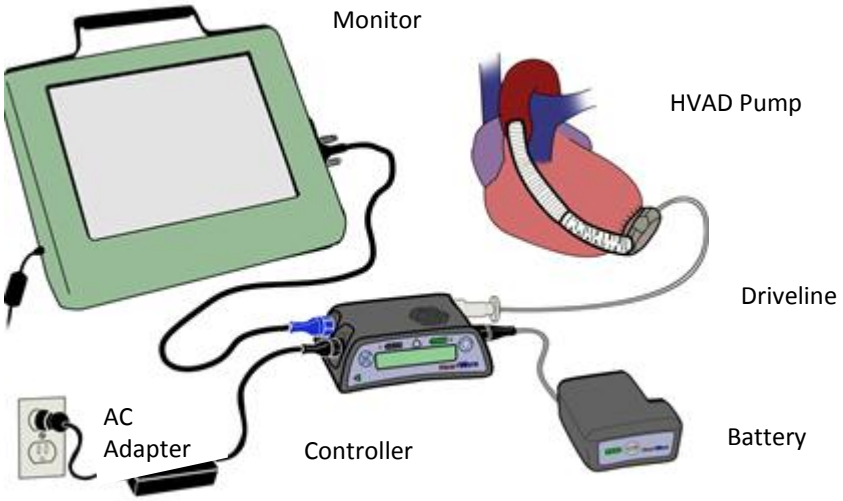
1. Inflow Cannula
2. Impeller
3. Center Post

The pump displaces 50mL of blood, weighs 160g, and is capable of pumping up to 10 liters per minute (L/min) of blood. It is designed to be implanted entirely in the pericardial space, obviating the need for an abdominal pocket.

Surgical tools include an apical coring tool, tunneler, sewing ring wrench, hex driver, inflow cap, and driveline cover.

External components include the controller, clinical monitor, battery charger, battery packs, AC and DC adapters, driveline extension cable, serial communication cable, universal serial bus (USB) flash drive, patient carry pack and shower bag. Some of these components are shown in Figure 2**.**

Figure 2: Key Components of the HeartWare™ HVAD™ System



The controller manages the HVAD pump operation and is depicted in the center of Figure 2**.** A light emitting diode (LED) screen displays real time pump parameters including power, speed, and flow estimation as well as alarm conditions. The percutaneous driveline connects the pump to the controller. The controller is intended to always be connected to two (2) power sources for safety (two (2) batteries or one (1) battery and an AC adapter or DC adapter (car adapter)). Each battery contains lithium ion cells that, when fully charged, can power the HVAD pump for approximately 4 to 7 hours. The batteries are expected to have a useful operating life of greater than 500 charge and discharge cycles.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for patients in end-stage heart failure. These alternatives include pharmacologic therapy, cardiac transplantation, and device therapy such as implantable cardioverter defibrillators (ICDs), biventricular pacemakers (cardiac resynchronization therapy – CRT), and mechanical circulatory support devices. Each treatment alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The HeartWare HVAD System is commercially available in the following countries: Argentina, Australia, Austria, Belarus, Belgium, Bosnia, Brazil, Bulgaria, Canada, Chile, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Europe, Finland, France, Germany, Greece, Herzegovina, Hong Kong, Hungary, India, Ireland, Israel, Italy, Kazakhstan, Republic of Korea, Kuwait, Latvia, Lebanon, Lithuania, Luxembourg, Malaysia, Norway, New Zealand, Poland, Romania, Saudi Arabia, Serbia, Singapore, Slovakia, Slovenia, South Africa, Spain, Sweden, Switzerland, Turkey, Ukraine, United Arab Emirates, United Kingdom, United States, Uruguay, and Vietnam.

The HeartWare HVAD System has not been withdrawn from marketing for any reason related to safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the HeartWare HVAD device.

- Arterial Non-CNS Thromboembolism
  – Air Embolism
- Bleeding
  – Bleeding, perioperative or late
  – GI bleeding / AV malformations
- Burn
- Cardiac Arrhythmias
- Death
- Device Malfunction
  - Device Thrombus
  - Electrostatic Discharge (ESD) damage to device
- Hemolysis
- Hepatic Dysfunction
- Hypertension
- Major Infection
  - Driveline Infection
  - Internal Pump Component, Inflow or Outflow Tract Infection
  - Local Infection
  - Sepsis
- Myocardial Infarction
- Neurological Dysfunction
  - Transient Ischemic Attack (TIA)
  - Stroke
    - Ischemic Cerebral Accident (ICVA)
    - Hemorrhagic Cerebral Accident (HCVA)
- Pericardial Effusion/ Tamponade
- Psychiatric Episodes
  - Suicide
- Pneumothorax
- Renal Dysfunction
- Respiratory Dysfunction
- Right Ventricular Failure
- Venous Thromboembolism
- Wound Dehiscence

- Other
  – Aortic Insufficiency
  – Cardiopulmonary Arrest
  – Multi-organ failure
  – Platelet Dysfunction
  – Pleural Effusion
    - Organ damage during driveline tunneling
    - Pain
  - Syncope
  - Tissue Erosion and other tissue damage
  - Worsening Heart Failure

For the specific adverse events that occurred in the clinical studies, please see Section X below.

IX. SUMMARY OF NON-CLINICAL LABORATORY STUDIES

Pre-clinical laboratory studies that were summarized in the Summary of Safety and Effectiveness for the original PMA (P100047) and subsequent Supplements are equally applicable to the expanded Indications for Use.

Medtronic, Inc. performed the following additional bench testing to support a two (2) year operational life (Table 1).

Table 1: Laboratory Studies

Test	Purpose	Acceptance Criteria	Results
Pump Life Cycle Reliability Test Summary	A pulsatile mock-loop closed system is designed to test the long-term reliability of the VAD pump. This test exercises the pump under physiological blood pressure and flow conditions experienced by a patient.	A minimum of 8 LVAD's must operate reliably through the test period with zero catastrophic or critical failures.	Pass
Sewing Ring–Inflow Tube Junction Integrity Test Summary	This reliability test exposed the Sewing Ring to Inflow Tube junction to 95 million cycles of simulated pulsatile heart movement to test for junction integrity.	Sewing Ring - Axial relative movement ≤ 0.040" Outer inflow tube shall remain attached.	Pass

Test	Purpose	Acceptance Criteria	Results
Strain Relief – Outflow port Junction Integrity Test Summary	This testing involved exposing the junction between the Pump Outflow Port and Graft Strain Relief Clamp to 95 Million cycles of 200/100 mmHg pulsatile internal pressure to test for reliability.	The Strain Relief shall not cause any tearing, abrasion or fraying to the Outflow Graft over 730 days. The outflow graft shall stay attached to the pump for at least 95 M cycles.	Pass

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed two (2) clinical trials in the U.S. to establish a reasonable assurance of safety and effectiveness of the HeartWare HVAD System for destination therapy in patients with advanced refractory left ventricular hear failure under IDE #G090243. The clinical data that demonstrate a reasonable assurance of safety and effectiveness of the HeartWare System for destination therapy came from the following trials:

- ENDURANCE
- ENDURANCE Supplemental

These trials are summarized below.

X.1 ENDURANCE Trial

A. Study Design

Patients in the ENDURANCE trial were enrolled between August 4, 2010 and May 8, 2012. The database for this Panel Track Supplement reflected data collected through June 06, 2016, as well as some additional updated data from March 27, 2017, and included 451 subjects enrolled at 48 investigational sites.

The trial was a prospective, randomized, controlled, multicenter clinical trial. Subjects were randomly assigned using a permuted block, central randomization scheme, in a 2:1 ratio, to receive either the study (HVAD) or control (HeartMate II) device.

The objective of the trial was to compare the safety and effectiveness of HVAD for destination therapy to the HeartMate II, which is legally marketed in the U.S. for destination therapy, in patients with end-stage heart failure who are ineligible for heart transplantation.

The sample size for formal hypothesis testing was to be determined adaptively. Subjects were to be randomized until 450 subjects were randomized and implanted.

It was pre-specified that after the first 300 randomized subjects reached the two-year primary endpoint, the success rate from the control subjects would be assessed. If the observed control success rate was at least 55%, then the data from the first 300 subjects would be analyzed. If the observed control success was less than 55%, then no interim analysis would be performed and the full 450 subjects would be subsequently analyzed. This adaptive sample size for statistical analysis provides at least 90% power to establish non-inferiority.

The ENDURANCE trial was conducted under the oversight of an independent Clinical Events Committee, which adjudicated all the adverse events according to the Interagency Registry of Mechanically Assisted Circulatory Support (INTERMACS) definitions; and an independent Data Safety Monitoring Board reviewed study compliance and monitored adverse events and outcomes.

1. Clinical Inclusion and Exclusion Criteria
   Enrollment in the ENDURANCE trial was limited to patients who met the following inclusion criteria:

   - Patients ≥18 years old with chronic, advanced left ventricular failure with New York Heart Association (NYHA) functional class IIIB or IV limitations despite optimal medical therapy and were transplant ineligible at the time of enrollment in whom informed consent was obtained.

   Patients were not permitted to enroll in the ENDURANCE trial if they met any of the following exclusion criteria:

   - Patients eligible for cardiac transplant or with prior cardiac transplant.
   - Patients with recent (within 14 days) acute myocardial infarction or stroke within 180 days.
   - Patients with a mechanical heart valve.
   - Patients with severe right heart failure in whom right ventricular support is anticipated.
   - Patients who might be unwilling or unable to comply with the study criteria.
   - Additional exclusion criteria available in the Clinical Study Report.

2. Follow-up Schedule
   All patients were scheduled to return for follow-up examinations at 3, 6, 12, 18, and 24 months with a window of ± 7days, and at 30, 36, 42, 48, 54, and 60 months with a window of ± 14 days postoperatively.

   Preoperative baseline assessments included demographics, medical history, physical examination, concurrent medications, laboratory tests, electrocardiogram (ECG), New York Heart Association (NYHA) classification, The National Institutes of Health (NIH) stroke scale, neurocognitive exam, quality of life, and

functional status. Postoperative assessments included LVAD parameters, hemodynamics, concurrent medications, laboratory tests, neurocognitive exam, six-minute walk test, NYHA status, and health status.

3. Clinical Endpoints

The primary endpoint was a composite of two-year survival free of disabling stroke (i.e., modified Rankin score ≥ 4 assessed 24 weeks post-event), while alive on the originally implanted device, electively transplanted or explanted due to left ventricular recovery. Success in meeting the primary endpoint was tested for non-inferiority of the experimental group against the control device. The non-inferiority margin of 15% was based on the observed success rate of the control device at >55%. Estimates of stroke-free survival were performed for each treatment using Kaplan-Meier non-inferiority log-rank methodology, comparing study device to control using a one-sided alpha of 0.05; that is, non-inferiority will be established if the one-sided upper confidence limit on the difference in proportions is less than the non-inferiority margin. Analysis of the primary endpoint was conducted on the Per Protocol (PP) population.

Patients were considered a success if at 730 days post implantation, the subject was alive, did not have a stroke of mRS ≥ 4 assessed 24 weeks post-stroke, and remained on the originally implanted device, unless the device was removed due to heart recovery, or the subject was electively transplanted. Patients were considered a failure if at 730 days post implantation, they expired, had a stroke with a modified Rankin score ≥ 4 assessed 24 weeks post-stroke, or were urgently transplanted or had surgery for LVAD removal or replacement due to failure of the original device.

There were seven (7) secondary endpoints, of which the following three (3) were to be assessed inferentially to test for superiority in a fixed-sequence procedure if non-inferiority was established for the primary endpoint: incidence of bleeding (per INTERMACS definition), incidence of major infections (per INTERMACS definition), and overall survival (time to death). In addition, a number of subgroup analyses were pre-specified, including gender and BSA (<1.5 m^2 vs. ≥1.5 m^2).

B. Accountability of PMA Cohort

Pre-specified Interim Analysis

Per the pre-specified analysis plan, the interim analysis cohort (N=300) was to serve as the principal analysis cohort if the Control group success rate for the primary endpoint was at least 55%; as shown below, the observed success rate for the Control group was 59%. A total of 451 patients (inclusive of the initial 300 patients) were enrolled, of which 445 were implanted with a device. This summary presents the ENDURANCE trial results using both the pre-specified interim analysis and full enrollment cohorts. FDA considered the interim analysis to be the principal analysis of the ENDURANCE trial, but considered all analyses when evaluating the safety and effectiveness of the

HVAD. The analyses from the full enrollment cohort are included in the Other Results section.

At the time of database lock for the interim analysis 100% of the pre-specified interim analysis cohort (300 patients) had been followed through the 2-year primary endpoint time point. The disposition of the patients is shown in Figure 2.

The Randomized population (HVAD N=200 and Control N=100) included all subjects who were consented (Intent-to-Treat (ITT)) and then enrolled in the study.

The Anesthetized Population (AP) included all randomized subjects who receive induction of anesthesia for implantation.

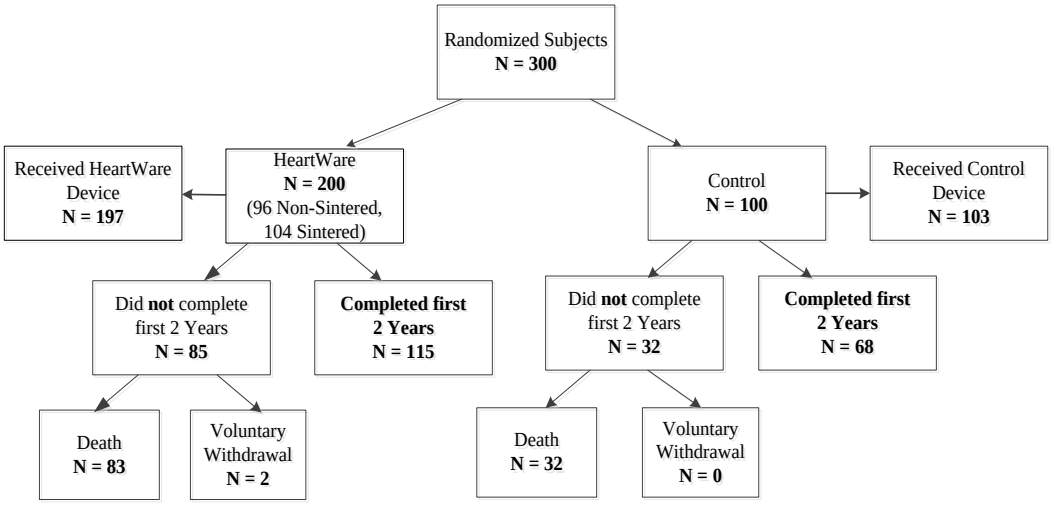
The Anesthetized and Implanted Population (AIP) population, equivalent to an As Treated population, consisted of all randomized subjects who received induction of anesthesia for implantation and received an implant of an LVAD. In the full cohort (N=445), four (4) patients crossed over from HVAD to Control and three (3) patients crossed over from Control to HVAD after randomization but before receiving a device, and one (1) patient in the Control arm did not receive any device. As such, the AT population for the interim analysis consists of 300 patients, 197 in the HVAD arm and 103 in the Control arm.

The Per Protocol (PP) population included all subjects in the AIP population analyzed according to the LVAD to which they were randomized. This definition is more consistent with the ICH definition of what a modified ITT population would be.

The Inclusion Compliant (IC) population included all randomized subjects who received the LVAD to which they were randomized and who did not violate certain inclusion and exclusion criteria that would likely have an effect on outcome.

The primary analysis was performed on the Per Protocol (PP) population. All safety analyses were performed on the AIP population.

Figure 3: Disposition of First 300 Subjects in the ENDURANCE Trial



C. Study Population Demographics and Baseline Parameters

The demographics and baseline characteristics, as summarized in Table 2, are typical for an LVAD study performed in the U.S. The HVAD and Control groups did not differ significantly.

Table 2: Patient Demographics and Baseline Characteristics in the first 300 Subjects in the ENDURANCE Trial

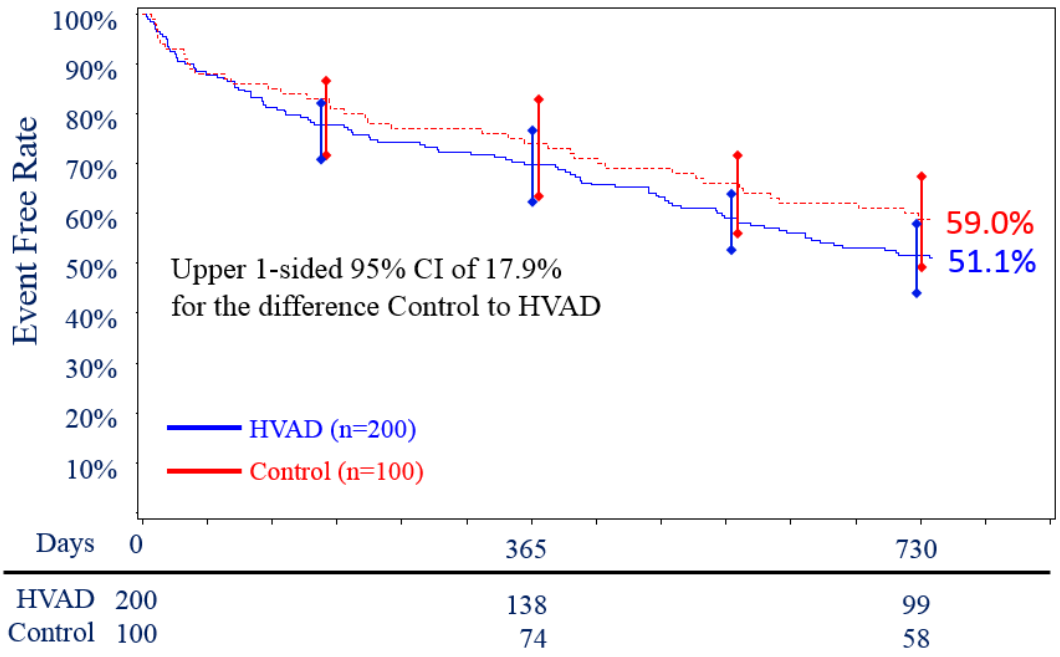
Demographics and Baseline Characteristics	HVAD (N=200)	Control (N=100)	*P*-value
Age (years)	64.4 ± 12.0	66.1 ± 10.4	0.25
Male gender (%)	77.5%	80.8%	0.66
Race (%) White Black or African American Other	 79.5% 19.5% 1.0%	 75.0% 25.0% 0.0%	0.37
Height (cm)	173.5 ± 9.8	175.2 ± 9.3	0.15
Body Surface Area (m^2)	2.0 ± 0.3	2.0 ± 0.3	0.98
INTERMACS Profile (%) 1 2 3 4 5-7	 3.5% 27.5% 39.5% 21.5% 8.0%	 1.0% 38.0% 41.0% 13.0% 7.0%	0.17
Ischemic Etiology of Heart Failure	59.5%	59.0%	>0.99

D. Safety and Effectiveness Results

1. Primary Endpoint

The pre-specified interim analysis was conducted on the first 300 patients to reach two (2) years post implantation. The Kaplan-Meier estimate for stroke-free success at 2 years for the Control arm was 59.0%; as such, the interim analysis represented the primary analysis for the ENDURANCE trial. The Kaplan-Meier estimate for stroke-free success at 2 years for the HVAD arm was 51.1%. The results of the interim analysis are shown in Figure 4. The upper bound of the confidence interval around the difference exceeded the 15% non-inferiority margin (17.9%), resulting in a p-value of 0.1219. The interim analysis showed that the trial failed to demonstrate non-inferiority of the HVAD to the Control.

Figure 4: ENDURANCE Trial Primary Endpoint. Survival at 2 years free from disabling stroke (mRS≥4) and alive on the originally implanted device, or transplanted or explanted for recovery.



A binary analysis from the pre-specified interim analysis is presented in Table 3.

Table 3: Binary Analysis of the Primary ENDURANCE Endpoint and its Components for Subjects Receiving Study or Control Device

Event Free Survival at 2 years	HVAD (N=200)	Control (N=100)
Success	51.5% (103)	59 (59.0%)
Failure	48.5% (97)	41.0% (41)
If Failure, reason:		
Patient dies	35.5% (71)	25.0% (25)
Device malfunction or failure requiring exchange, explant or urgent transplant Exchange Explant Urgent Transplant	11.0% (22) 9.5% (19) 0.0% (0) 1.5% (3)	16.0% (16) 14.0% (14) 0.0% (0) 2.0% (2)
Disabling stroke (MRS $\geq$4 at 24 weeks)	1.5% (3)	0.0% (0)
Imputed failure*	0.5% (1)	0.0% (0)

A subject may have multiple reasons for not completing the first two (2) years, only the first failure type for each subject is specified.
*Patient experienced a stroke prior to their 2-year endpoint, and died beyond the 2 year endpoint, but before the 24 week MRS assessment.

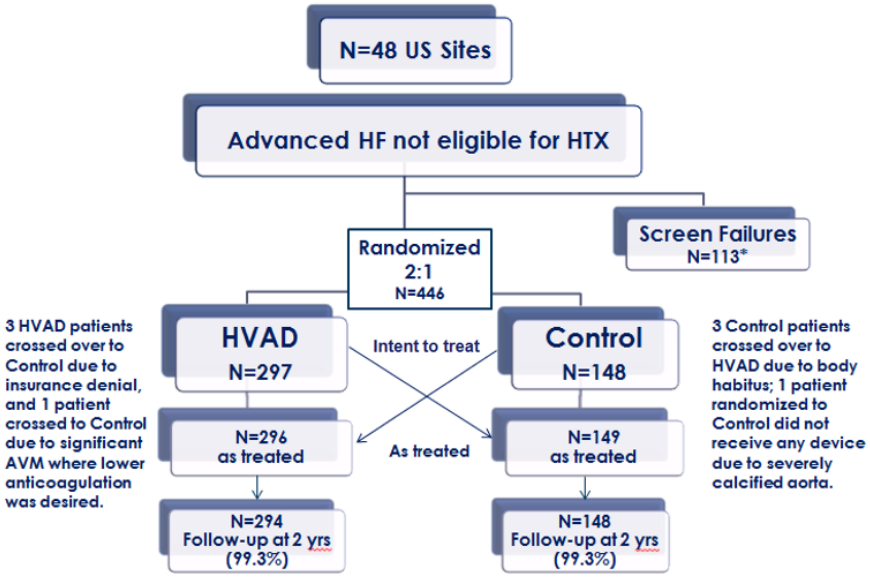
2. Secondary Endpoints

Because the primary endpoint was not met per the pre-specified interim analysis, the hypotheses associated with the secondary endpoints of incidence of bleeding (per INTERMACS definition), incidence of major infections (per INTERMACS definition), and overall survival (time to death) could not be tested. As such, the secondary endpoints were not reported.

3. Other Results - Adjunctive analysis: Primary Endpoint Using Expanded Dataset

Following the interim analysis at 300 patients, the trial was expanded to enroll additional patients to further investigate various device, procedural, and clinical changes introduced during the trial. A total of 451 patients (inclusive of the initial 300 patients) were enrolled, of which 445 were implanted with a device. The patient disposition is summarized in Figure 5. The results of the expanded dataset are summarized below.

Figure 5: Disposition of Subjects in the ENDURANCE Expanded Dataset



The demographics and baseline characteristics of the ENDURANCE expanded dataset is summarized in Table 4. The demographics and baseline characteristics are typical for an LVAD study performed in the U.S. The HVAD and Control groups did not differ significantly with respect to severity of illness, baseline hemodynamic characteristics, or treatment with evidence-based therapy for heart failure at the time of enrollment. However, subjects in the control group were slightly older (66.2 versus 63.9, control versus HVAD, P=0.04).

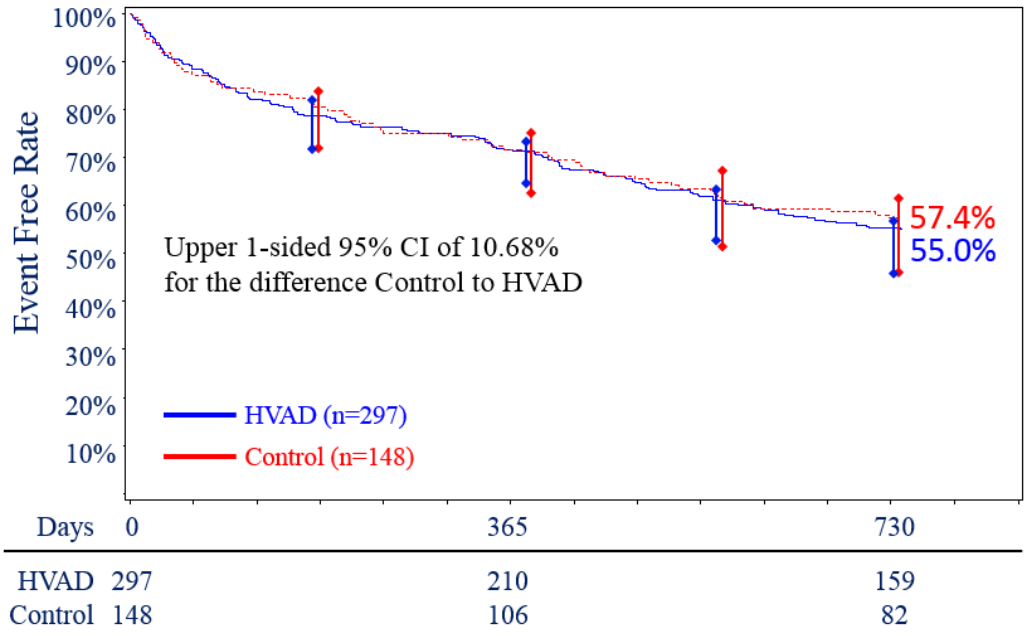
Table 4: Patient Demographics and Baseline Characteristics of the ENDURANCE Expanded Dataset

Demographics and Baseline Characteristics	HVAD (N=297)	Control (N=148)	*P*- value
Age (years)	63.9 ± 11.6	66.2 ± 10.2	0.044
Male gender (%)	76.4%	82.4%	0.178
Race (%) White Black or African American Other	 76.8% 22.2% 1.0%	 77.7% 21.6% 0.7%	0.962
Height (cm)	173.8 ± 9.4	175.5 ± 9.1	0.068
Body Surface Area (m^2)	2.0 ± 0.3	2.0 ± 0.3	0.615
INTERMACS Profile (%) 1 2 3	 3.4% 29.0% 40.4%	 3.4% 31.1% 40.5%	0.989

Demographics and Baseline Characteristics	HVAD (N=297)	Control (N=148)	*P*- value
4 5-7	19.9% 7.4%	18.2% 6.8%	
Ischemic Etiology of Heart Failure	57.9%	60.1%	0.684
Smoker	68.0%	62.2%	0.243
Diabetic	44.4%	43.9%	>0.999
Previous Stroke/TIA	19.2%	16.2%	0.515
Hypertension requiring medication	65.3%	70.9%	0.241
Serum creatinine (mg/dL)	1.5 $\pm$ 0.5	1.4 $\pm$ 0.5	0.760
Severe tricuspid valve insufficiency	12.0% (N=292)	5.5% (N=146)	0.040
Left ventricular ejection fraction (LVEF, %)	17.1 ± 4.6	16.2 ± 4.8	0.055

Survival free from disabling stroke (mRS>4) and alive on the originally implanted device, or transplanted or explanted for recovery for the complete ENDURANCE population is shown below in Figure 6. The expanded dataset includes a higher proportion of HVAD devices having titanium-sintered inflow cannulae, a device modification that was introduced during ENDURANCE and designed to decrease thromboembolic adverse event rates. *Post hoc* one-year comparisons of all sintered HVADS (pooled from both ENDURANCE and ENDURANCE-Supplemental) to pooled Control subjects were also performed, as shown in Figure 7.

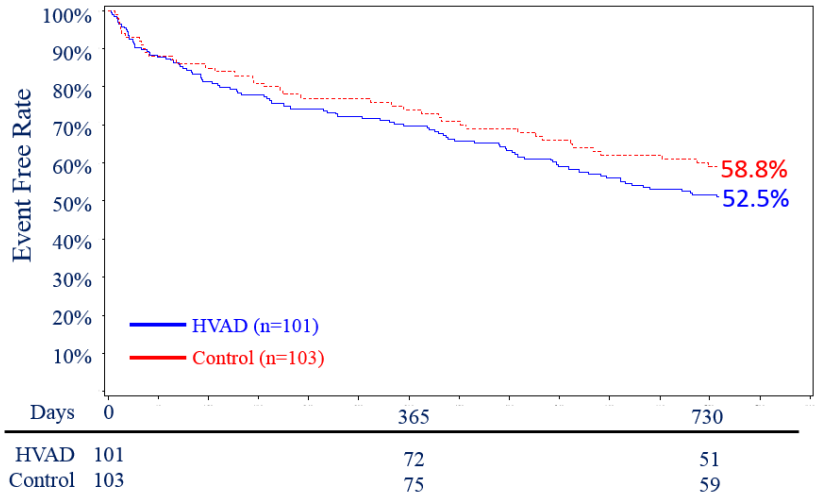
Figure 6: ENDURANCE Trial Expanded Dataset: Survival free from disabling stroke (mRS≥4) and alive on the originally implanted device, or transplanted or explanted for recovery in the overall study dataset.



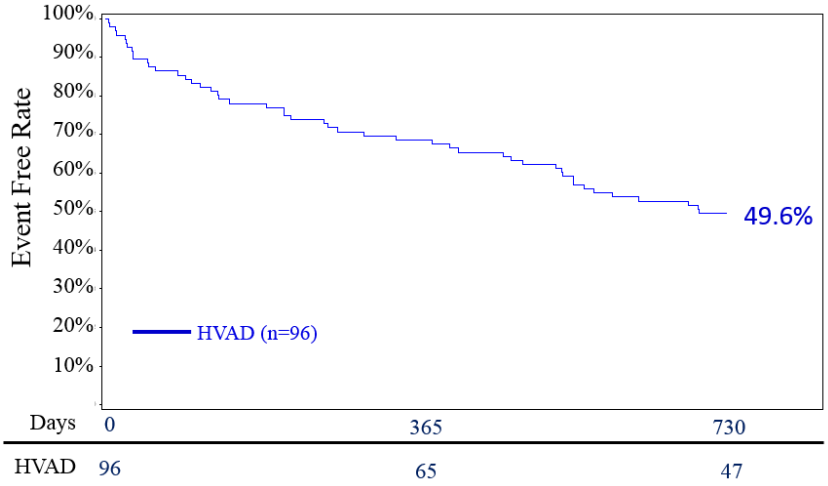
The *post hoc* comparison of sintered and non-sintered HVAD pumps in the interim analysis cohort did not demonstrate markedly different results (See Figure 7A, 7B).

Figure 7: Comparison of Outcomes from the Interim analysis of Subjects with Sintered Pumps Compared to Control: Survival free from disabling stroke (mRS≥4) and alive on the originally implanted device, or transplanted or explanted for recovery in **A)** the subset of subjects receiving a sintered HVAD Pump, compared to Control, and in **B)** the subset of subjects receiving the non-sintered HVAD Pump. This analysis is based on the as-treated population.

A) Sintered:



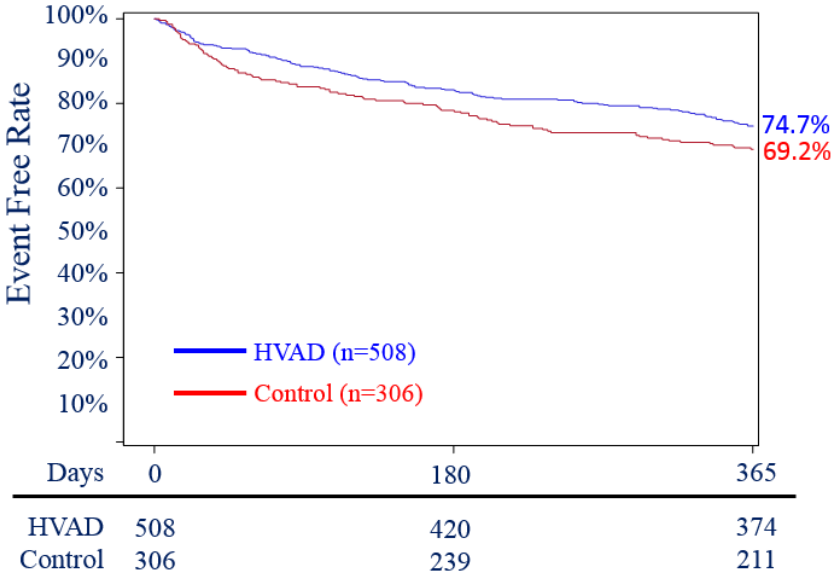
B) Non-Sintered:



Additional post *hoc* one-year comparisons of all sintered HVADS (pooled from both ENDURANCE and ENDURANCE-Supplemental) to pooled Control subjects were also performed, and analyzed against the primary endpoint definition of the ENDURANCE Trial (at one year, Figure 8A) and against the primary endpoint of the ENDURANCE Supplemental Trial (Figure 8B).

Figure 8: An Analysis of Patients Receiving Sintered HVAD Pumps (Pooled ENDURANCE and ENDURANCE Supplemental) Compared to Control.
A) the Primary Endpoint of the ENDURANCE Trial at 1 year, and **B)** the Primary Endpoint of the ENDURANCE Supplemental Trial

A) Survival on Original Device Free from Disabling Stroke (MRS≥4)



B) Survival on Original Device Free from Neurologic Events (Strokes with MRS>0, TIA or SCI)

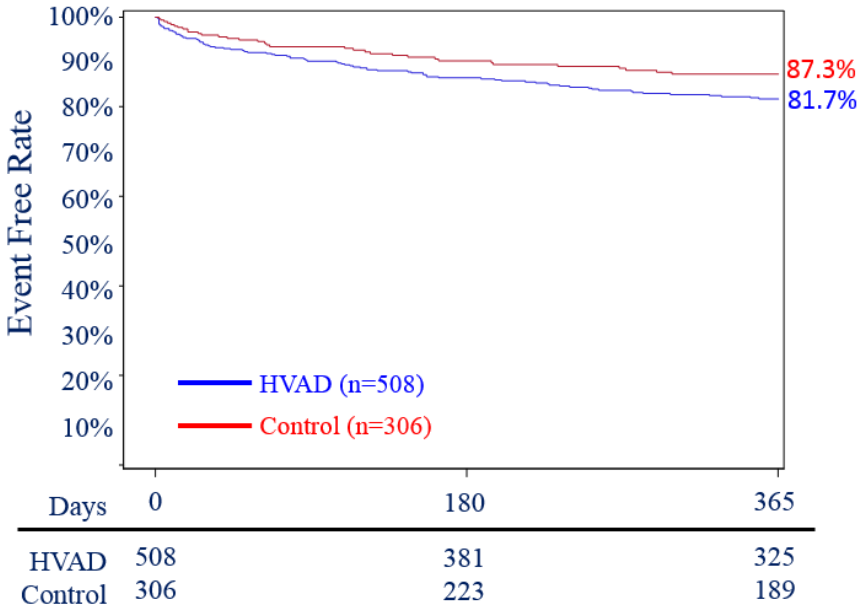


Table 5: Binary Analysis of ENDURANCE Expanded Dataset: Survival at 2 years free from disabling stroke (mRS>4) and alive on the originally implanted device, or transplanted or explanted for recovery.

Event Free Survival at 2 years	HVAD (N=297)	Control (N=148)
Success	55.2% (164)	57.4% (85)
Failure	44.8% (133)	42.6% (63)
If Failure, reason:		
Patient dies	34.7% (103)	26.4% (39)
Device malfunction or failure requiring exchange, explant or urgent transplant Exchange Explant Urgent Transplant	8.8% (26) 7.7% (23) 0.0% (0) 1.0% (3)	16.2% (24) 13.5% (20) 0.7% (1) 2.0% (3)
Disabling stroke (MRS ≥4 at 24 weeks)	1.0% (3)	0
Imputed failure*	0.3% (1)	0

A subject may have multiple reasons for not completing the first two (2) years, only the first failure type for each subject is specified.

*Patient experienced a stroke prior to their 2-year endpoint, and died beyond the 2 year endpoint, but before the 24 week MRS assessment.

In the analyses presented on the entire ENDURANCE trial cohort, the secondary endpoints were analyzed and descriptive data include the following:

- The incidence of bleeding was 60.1% for the HVAD compared to 60.4% for the Control.
- The incidence of major infections was 69.3% for the HVAD and 62.4% for the Control.
- Overall survival was 60.2% for the HVAD and 67.6% for the Control.

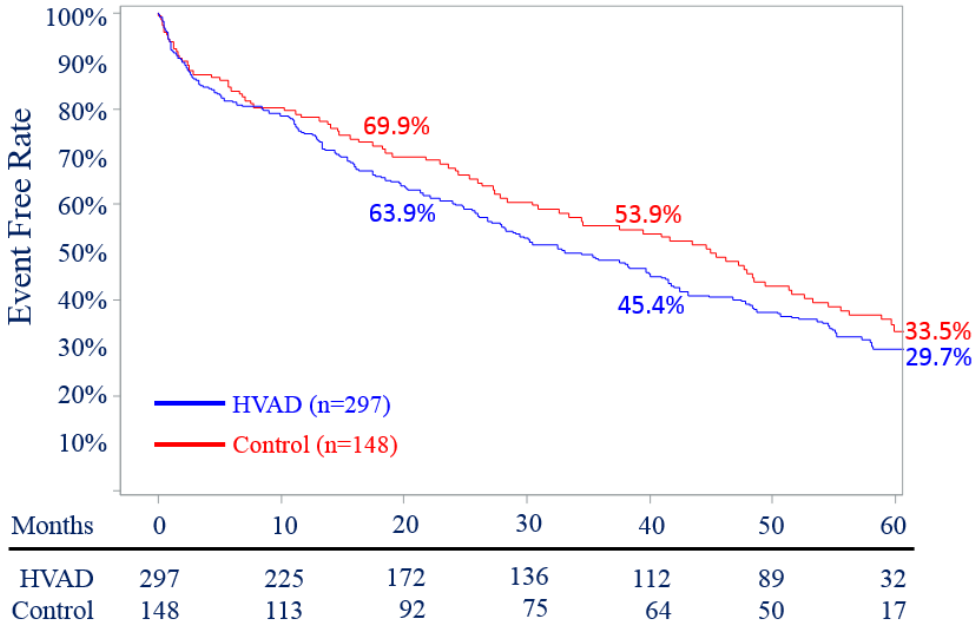
The CEC adjudicated causes of death for the entire ENDURANCE trial cohort are shown in Table 6.

Table 6: ENDURANCE Expanded Dataset Cause of CEC Adjudicated on Device Death within 730 days (AIP as Received)

Cause of Death	HVAD (N=296)	Control (N=149)
Total	38.5% (114)	30.9% (46)
Bleeding	0.3% (1)	0.7% (1)
Cardiovascular procedure	1.4% (4)	1.3% (2)
Heart failure	16.2% (48)	14.8% (22)
Infection	3.0% (9)	2.7% (4)
Malignancy	1.4% (4)	0.7% (1)
Multisystem organ failure	0.0% (0)	0.7% (1)
Respiratory failure	0.0% (0)	0.7% (1)
Stroke	8.4% (25)	6.0% (9)
Sudden death	3.7% (11)	2.0% (3)
Trauma	0.7% (2)	0.0% (0)
Other cardiovascular	2.7% (8)	1.3% (2)
Other non-cardiovascular	0.7% (2)	0.0% (0)

Overall survival for the ENDURANCE trial expanded dataset beyond the two (2) year timepoint is included below in Figure 9. Aggregate 5-year mortality results for all ENDURANCE subjects were similar.

Figure 9: Kaplan Meier Survival (Time to Death) in ENDURANCE through 5 years (PP, Per Protocol).



Adverse events

The key safety/adverse event outcomes for the ENDURANCE trial expanded dataset are presented in Table 7 below. Patients in the HVAD arm had a higher rate of ischemic and hemorrhagic stroke, sepsis, and right heart failure compared to control. An analysis of the patient-level data indicated that elevated blood pressure appeared to be a risk factor for stroke, particularly hemorrhagic stroke.

Table 7: Summary of INTERMACS Adverse Events Occurring Through 2 Years in Subjects in the ENDURANCE Trial Expanded Dataset

Adverse Event	HVAD (N=296)	Control (N=149)
Overall Bleeding events GI Bleed	60.1% (178) 35.1% (104)	60.4% (90) 34.2% (51)
Cardiac Arrhythmia	37.8% (112)	40.9% (61)
Hepatic Dysfunction	4.7% (14)	8.1% (12)
Hypertension	15.9% (47)	16.8% (25)
Sepsis	23.6% (70)	15.4% (23)
Driveline Exit Site Infection	19.6% (58)	15.4% (23)
Stroke Ischemic Cerebrovascular Event Hemorrhagic Cerebrovascular Event	29.7% (88) 17.6% (52) 14.9% (44)	12.1% (18) 8.1% (12) 4.0% (6)

Adverse Event	HVAD (N=296)	Control (N=149)
TIA	8.4% (25)	4.7% (7)
Renal Dysfunction	14.9% (44)	12.1% (18)
Respiratory Dysfunction	29.1% (86)	25.5% (38)
Right Heart Failure Need for RVAD*	38.5% (114) 2.7% (8)	26.8% (40) 3.4% (5)
Pump Replacement Exchange for Pump Thrombosis	7.8% (23) 6.4% (19)	13.4% (20) 10.7% (16)
Device Malfunction or Failure	31.4% (93)	25.5% (38)

*Site-reported event.

Abbreviations: GI - gastrointestinal; RVAD=right ventricular assist device; TIA= transient ischemic attack (<24 hours).

Note: The event of device thrombosis reported is not an INTERMACS-defined event.

Stroke-related Deaths

Per CEC adjudication, among the full AIP population 12.5% (37/296) of HVAD patients and 6.7% (10/149) of Control patients had stroke-related deaths (data lock date of May 30, 2017, all patients with follow-up > 4 years or censored). HVAD subjects in the ENDURANCE trial had a risk of death from stroke that was 87% greater than the risk of Control patients. The rate of stroke-related death within 2 years of implantation was 8.4% (25/296) for HVAD patients and 6.0% (9/149) for Control patients. The rate of later-onset stroke-related death (i.e., stroke occurring after 2 years of LVAD support) was 3.7% (11/296) for HVAD patients and 0.7% (1/149) for Control patients. The majority of HVADs which were involved with stroke-related deaths had sintered inlet cannulae.

Device Failures and Malfunctions

The incidence of device failures and device malfunctions within 730 days was 31.4% in the HVAD arm vs. 25.5% in the Control arm. The rates of pump thrombosis were similar in both arms, though sintering of the HVAD did appear to decrease this event. Device malfunctions related to controller faults were substantially more frequent in the HVAD arm.

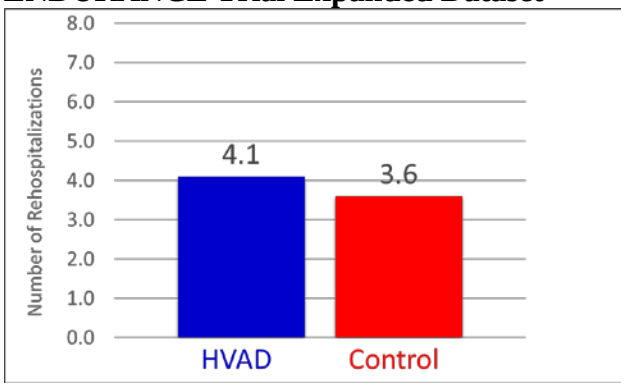
Table 8: Device Failure or Malfunctions in the ENDURANCE Trial Expanded Dataset

Parameter	HVAD Sintered (N=200)	HVAD Non-Sintered (N=96)	Control (N=149)
Based on CEC Adjudication Data			
Device Failure	30.5% (6)	33.3% (32)	25.5% (38)
Type of Device Malfunction			
Controller fault	10.0% (20)	7.3% (7)	2.7% (4)
Critical low battery	0.0% (0)	1.0% (1)	0.7% (1)
Damaged battery	1.0% (2)	0.0% (0)	0.0% (0)
Damaged cable	2.5% (5)	3.1% (3)	4.0% (6)
Damaged controller	2.0% (4)	3.1% (3)	0.0% (0)
Electrical fault	2.0% (4)	0.0% (0)	0.0% (0)
Iatrogenic/Recipient-Induced Failure	0.5% (1)	0.0% (0)	0.7% (1)
Insufficient battery charging	1.5% (3)	1.0% (1)	0.0% (0)
Power disconnect	2.5% (5)	0.0% (0)	1.3% (2)
Pump	0.0% (0)	0.0% (0)	2.7% (4)
Pump Thrombosis	10.0% (20)	22.9% (22)	11.4% (17)
Other	4.5% (9)	1.0% (1)	3.4% (5)

Rehospitalizations

The average number of re-hospitalizations within 730 days after the initial hospitalization was similar between the HVAD arm and the Control arm, as shown in Figure 10. For the AIP population, the HVAD subjects were re-hospitalized on average, 4.1 times, compared to 3.6 times in the Control group.

Figure 10: Average Number of Rehospitalizations over Two Years in the ENDURANCE Trial Expanded Dataset



Functional Status

Functional status was assessed by the NYHA class and the 6-minute walk test (6MWT), as shown in Figures 11 and 12. Following LVAD implant, approximately 70-80% of subjects in both arms improved to NYHA class I or II by Month 12. The median baseline 6-minute walk distance (6MWD) was 0 meters for both study and control subjects. At 3 months following LVAD implant, 6MWD increased to a median of 210 meters and 201 meters for study and control subjects, respectively. These improvements were sustained through two (2) years.

Figure 11: ENDURANCE Trial Expanded Dataset Six-Minute Walk Test

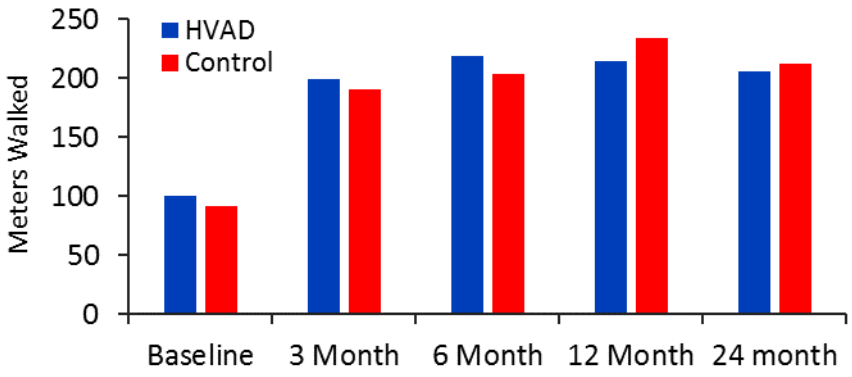
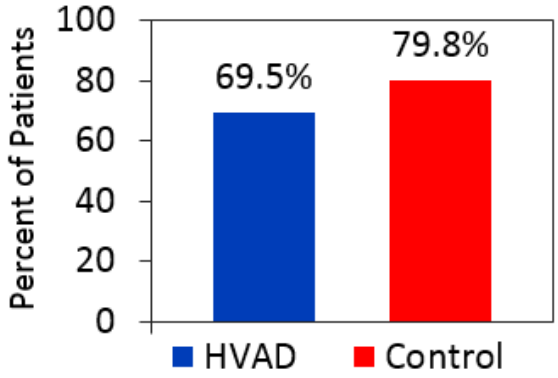


Figure 12: ENDURANCE Trial Expanded Dataset NYHA Classification Improvement

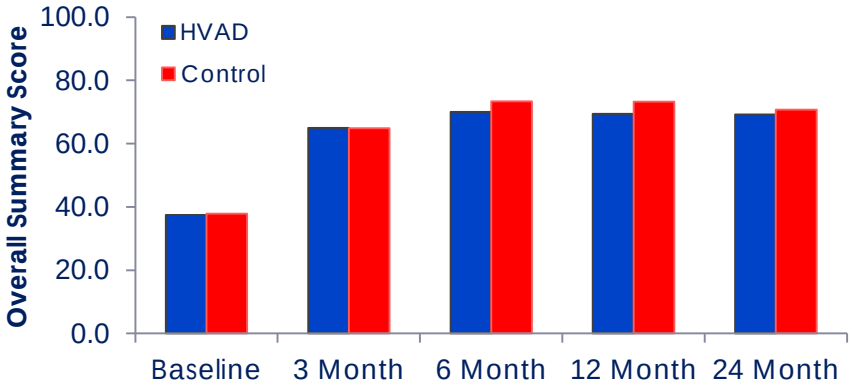


Quality of Life

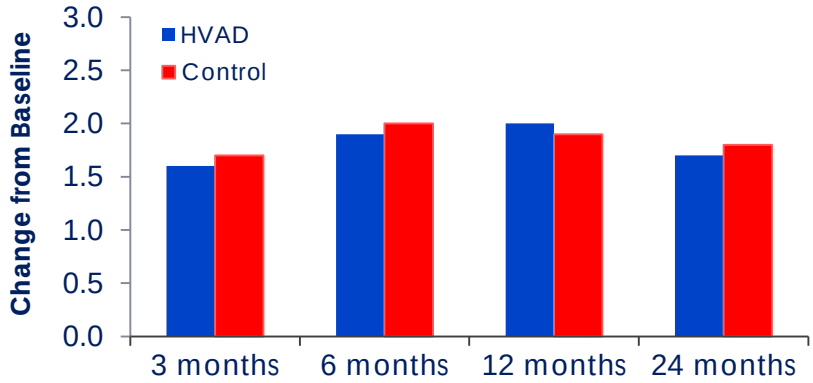
The quality of life was assessed by the EQ-5D-5L and the KCCQ questionnaires, as summarized in Figure 13. At baseline, subjects in both cohorts had poor quality of life and health status assessed by KCCQ and EuroQOL EQ-5D. At 3 months, median KCCQ score had improved by 27.3 points and 24.2 points for study and control subjects, respectively. EuroQOL EQ-5D VAS improved an average of 1.6 points at 3 months for subjects in the study arm and 1.7 points at 3 months for subjects in the control arm. Improvements in KCCQ and EuroQOL EQ-5D were sustained during the follow-up period.

Figure 13: Improvements in Quality of Life and Functional Capacity in the ENDURANCE Trial Expanded Dataset. A) Change over time of the KCCQ Overall Summary Score. **B)** Change over baseline in the EQ-5D Visual Analog Scale.

A. KCCQ



A. EQ-5D



4. Subgroup Analyses

The following preoperative characteristics were evaluated for potential association with outcomes: gender, and BSA ($< 1.5\ m^2$, $\geq 1.5\ m^2$). The pre-specified sub-group analyses showed no major clinical differences in outcomes based on gender or BSA.

5 Pediatric Extrapolation

In this premarket application, clinical data from the ENDURANCE trial were not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal study included 388 investigators of which none were full-time or part-time employees of the sponsor and five (5) had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c), and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 1
- Significant payment of other sorts: 3
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 1

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

X.2 ENDURANCE Supplemental Trial

A. Study Design

The objective of the ENDURANCE Supplemental trial was to evaluate the safety and effectiveness of a prospective blood pressure management strategy in HVAD DT patients. The purpose of implementing the prospective blood pressure management strategy was to investigate its effect on the stroke rates in HVAD subjects. The trial was a prospective, randomized, controlled, un-blinded, multicenter clinical study. Subjects were randomly assigned using a permuted block, central randomization scheme, in a 2:1 ratio, to receive either the study (HVAD) or control (HeartMate II) device. All HVAD subjects, in addition to receiving standard of care management, were required to adhere to a blood pressure management protocol that aimed to maintain mean arterial pressure (MAP) $\leq$ 85 mmHg (automated pneumatic cuff method) or < 90 mmHg (Doppler cuff method). Control patients were not managed with a blood pressure management protocol.

Patients in the ENDURANCE Supplemental trial were enrolled between October 25, 2013 and August 7, 2015. 475 subjects were randomized, with 465 patients implanted at 47 investigational sites.

Similar to the ENDURANCE trial, the ENDURANCE Supplemental trial was conducted under the oversight of an independent Clinical Events Committee and monitored by an independent Data Safety Monitoring Board.

1. Clinical Inclusion and Exclusion Criteria
   Enrollment in the ENDURANCE Supplemental trial was limited to patients who met the same inclusion and exclusion criteria as in the ENDURANCE trial.

2. Follow-up Schedule
   All patients were scheduled to return for follow-up examinations at 3 and 6 months with a window of ± 7 days, at 12 months with a window of + 7 days, and at 18, 24, 30, 36, 42, 48, 54, and 60 months with a window of ± 14 days postoperatively.

   The pre- and post-operative assessments were the same the in the ENDURANCE trial.

3. Clinical Endpoints
   The primary endpoint was the incidence of neurologic injury at 12 months. Neurologic injury was defined as an ICVA or HCVA with mRS > 0 at 24 weeks post-stroke, or a TIA, or as a spinal cord infarct (SCI).

   The HVAD was to be considered non-inferior to the HeartMate II if the upper bound of the two-sided 90% exact binomial confidence interval of the difference in the primary endpoint between the HVAD arm and the control arm was less than 6%.

   There were two (2) secondary endpoints. The first secondary endpoint was incidence of HVAD stroke and TIA by 12 months on the originally implanted HVAD. Unlike the primary endpoint, this secondary endpoint included those strokes that were classified as mRS=0 at 24 weeks post-stroke. This endpoint was to be tested by comparison to a performance goal of 17.7%; the performance goal was equivalent to the lower 95% confidence interval of the one-year stroke/TIA rate among sintered HVAD patients in the ENDURANCE trial.

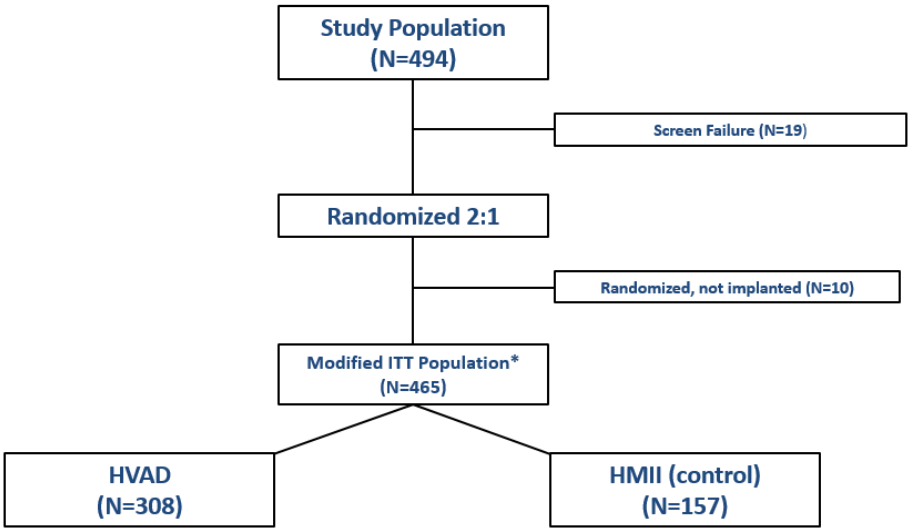
   The second secondary effectiveness endpoint was analogous to the ENDURANCE trial's primary endpoint, in that it compared the composite of stroke-free (mRS < 4 at 24 weeks post-stroke) survival while on the original device between HVAD and Control arms; however, the time point for this endpoint was one year, unlike the ENDURANCE trial's 2-year endpoint. This endpoint was to test for non-inferiority of the HVAD to the control device, with a non-inferiority margin of 15%.

   Additional endpoints included adverse events, device malfunctions and failures, as well as health status and functional improvements.

B. Accountability of PMA Cohort

At the time of database lock, of the 494 patients enrolled in the ENDURANCE Supplemental trial, 93.7% (463) patients were available for analysis of the primary objective at the completion of the study, the 12-month post-operative visit. The disposition of the patients is shown in Figure 14.

Figure 14: Disposition of Subjects in the ENDURANCE Supplemental Trial



* Modified Intent-to-Treat subjects in which the pump was surgically inserted and turned on. Modified ITT and As-Treated (AT) populations were identical.

The Modified Intent-to-Treat Population (mITT; Total N=465; HVAD, N=308 and Control, N=157) included all subjects who received a device. It was analyzed according to the device to which the subjects were randomized.

All safety analyses were performed on the safety population (SAF), which assigned subjects to the device they actually received. The SAF was equivalent to the mITT population.

The Complete Case Population includes all subjects in the mITT population except those who withdraw, are lost to follow-up, or have missing outcomes (any subject with missing post-event mRS) on original device. It differs for each objective. For the primary endpoint, the Complete Case Population was defined as the mITT population excluding any subjects who withdrew or were lost to follow-up, and any subjects who were missing CEC adjudicated mRS scores (both day of event and 24 weeks post-event) for the latest stroke event on original device. For the secondary endpoint of stroke/TIA incidence at 12 months on the originally implanted HVAD, the Complete Case Population was defined as the mITT population excluding the subjects who withdrew or were lost to follow-up. For the secondary endpoint of stroke-free success (mRS < 4 at 24 weeks post-stroke) at 12 months, the Complete Case Population was defined as the mITT population excluding subjects who withdrew or were lost to follow-up, and those subjects who were missing a 24 week mRS score for their last stroke on original device (within 1 year post original implant).

C. Study Population Demographics and Baseline Parameters

The demographics and baseline characteristics of the study population, as summarized in Table 9, are typical for an LVAD study performed in the U.S. The baseline characteristics of the two (2) arms were similar; there was no clinically significant difference in the severity of illness or treatments at the time of enrollment.

Table 9. Patient Demographics and Baseline Characteristics in the ENDURANCE Supplemental Trial.

Demographics and Baseline Characteristics	HVAD (N=308)	Control (N=157)	P-value
Age (years)	63.3 ± 11.4	64.2 ± 11.1	0.39
Female gender (%)	18.2%	20.4%	0.62
Race (% White)	71.8%	75.2%	0.51
Height (cm)	175.0 ± 9.4	175.1 ± 9.8	0.91
Body Mass Index (kg/m^2)	28.2 ± 5.5	27.4 ± 5.2	0.13
INTERMACS Profile (%) 1 2 3 4-7	 3.9% 32.8% 43.3% 20.0%	 2.5% 32.5% 43.3% 21.7%	0.90
Ischemic Etiology of Heart Failure	55.2%	58.0%	0.62
History of smoking	68.2%	65.6%	0.60
Diabetic	49.4%	48.4%	0.92
Previous Stroke	10.4%	8.3%	0.51
Hypertension requiring medication	75.0%	72.0%	0.50
Atrial Fibrillation	50.6%	51.0%	>0.99
Mean arterial blood pressure (mmHg)	78.9 ± 11.5 (N=296)	77.6 ± 11.1 (N=153)	0.23
Tricuspid regurgitation (≥ moderate)	40.4% (N=302)	44.2% (N=154)	0.48
Left ventricular ejection fraction (LVEF, %)	17.3 ± 5.1	18.2 ± 4.5	0.07
Previous intervention (%) ICD CRT IABP	 80.8% 28.9% 19.2%	 82.2% 28.7% 15.9%	 0.80 >0.99 0.45

Abbreviations: CRT=cardiac resynchronization therapy; ICD=implantable cardioverter defibrillator; LVEF=left ventricular ejection fraction.

Note: P-values are post-hoc and are included for information purposes only. P-values comparing categorical values are from the Fisher's Exact Test. P-values comparing continuous values are from a two-sample t-test.

D. Safety and Effectiveness Results

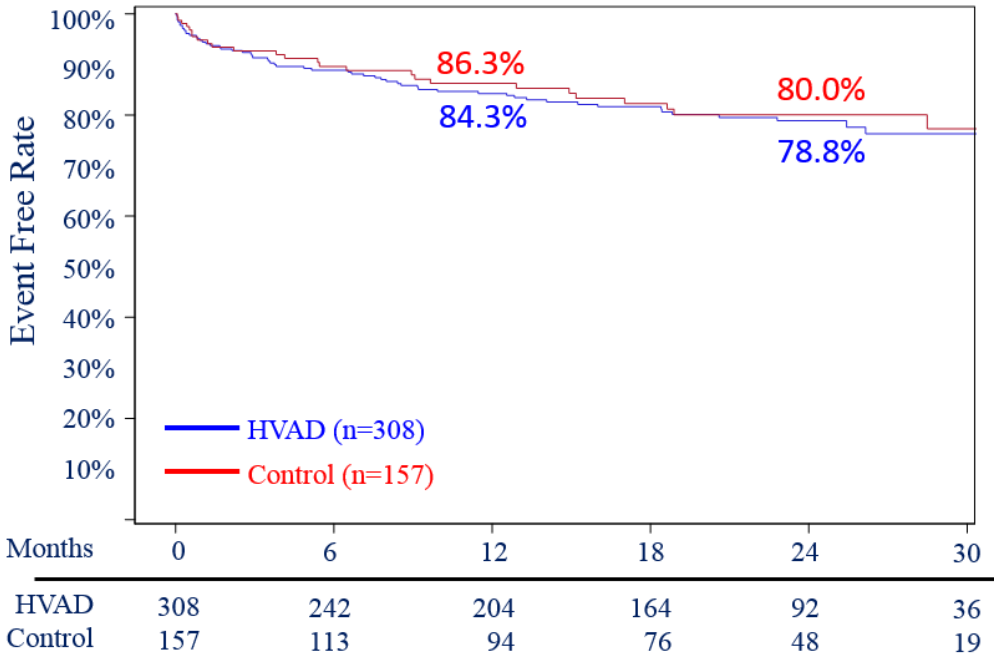
1. Primary Endpoint

The outcome and analysis of the primary endpoint are shown in Table 10 and Figure 15. The results show that 14.7% of the HVAD subjects experienced endpoint-defined neurologic injury as compared to 12.1% of the control subjects, with a difference of 2.6% between the two arms. The upper bound of the two-sided 90% exact binomial confidence interval of the difference in the neurologic injury incidence was 10.7%, which was above the pre-specified non-inferiority margin of 6%. Thus, the primary endpoint of the ENDURANCE Supplemental trial was not met.

Table 10: Analyses of the Primary Endpoint

	HVAD (N=306)	**Control (N=157)**
Number of subjects who had a stroke/TIA at 12 Months	58	24
Number of subjects who had a stroke at 12 months	51	23
Number of subjects who had a TIA at 12 months	13	1
Number of subjects who had mRS > 0 at 24 weeks post-stroke	38	18
Number of subjects who had spinal cord infarction at 12 months	0	0
Number of subjects with endpoint-defined neurologic injury events at 12 months	45 (14.7%)	19 (12.1%)
Difference of neurologic injury incidence	2.6%	
Two-sided 90% confidence interval	[-5.5%, 10.7%]	
Non-inferiority criteria	Fail	
p-value	0.1444	

Figure 15: ENDURANCE Supplemental Trial Primary Endpoint Survival

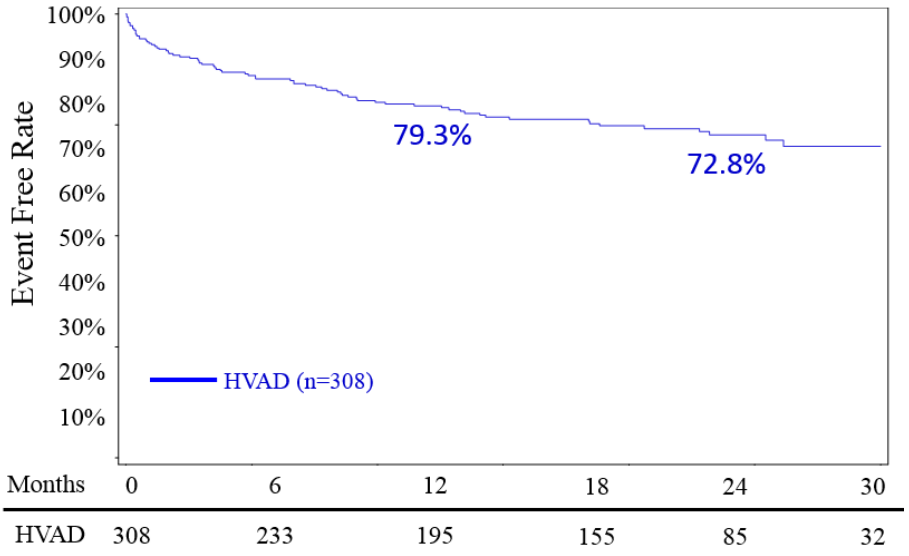


2. Secondary Endpoints

Because the primary endpoint was not met, the hypotheses associated with the secondary endpoints of stroke/TIA incidence and stroke-free success rate could not be tested. Thus, only descriptive data are presented for the two secondary endpoints.

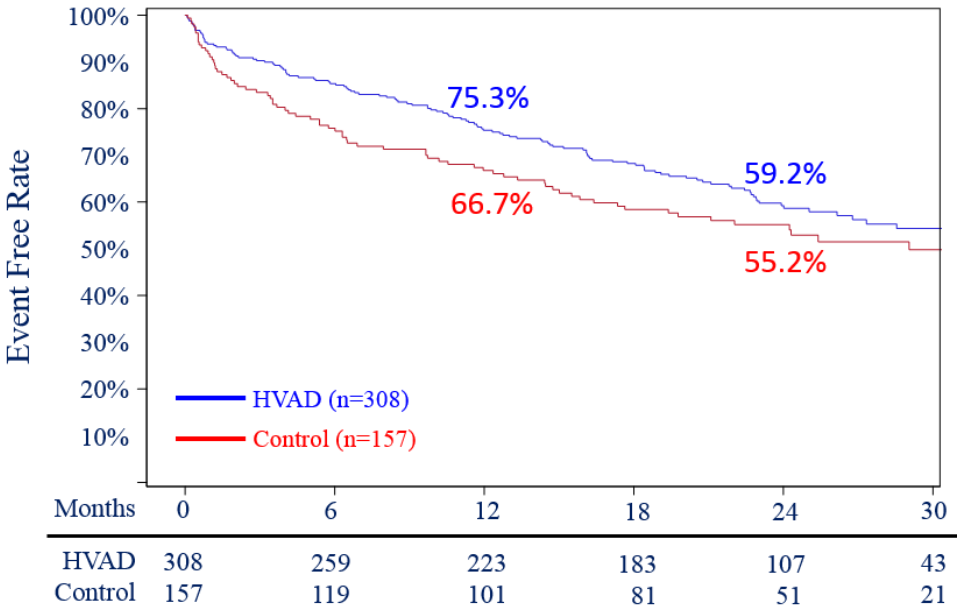
The incidence of stroke/TIA (inclusive of strokes with mRS=0 at the 24 week time point) in HVAD patients was 19.2% at 12 months. The Time to event curve is shown in Figure 16.

Figure 16: ENDURANCE Supplemental Trial Survival Free from Stroke or TIA



The proportion of subjects who survived to one year on the original device in the absence of "disabling" stroke (mRS ≥ 4), death, device exchange or urgent transplantation was 75.3% in the HVAD arm and 66.7% in the Control arm. A freedom from event analysis is shown in Figure 17, using data from March 27, 2017. The magnitude of the rate differential for this composite decreased with follow-up more analogous to the ENDURANCE trial's 2-year endpoint time frame.

Figure 17: ENDURANCE Supplemental Trial Survival Free from Death, Disabling Stroke or Device Malfunction/Failure Requiring Exchange



In the ENDURANCE Supplemental trial, freedom from ischemic stroke was numerically greater in the Control arm, as shown in Figure 18; freedom from hemorrhagic stroke was similar in HVAD and Control, as shown in Figure 19.

Figure 18: ENDURANCE Supplemental Trial Survival Free from Ischemic Stroke

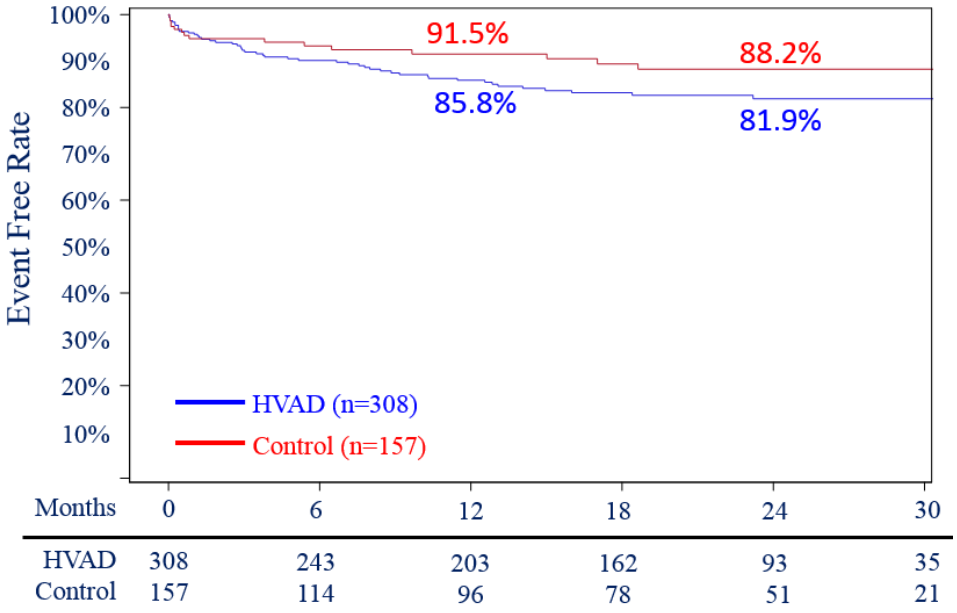
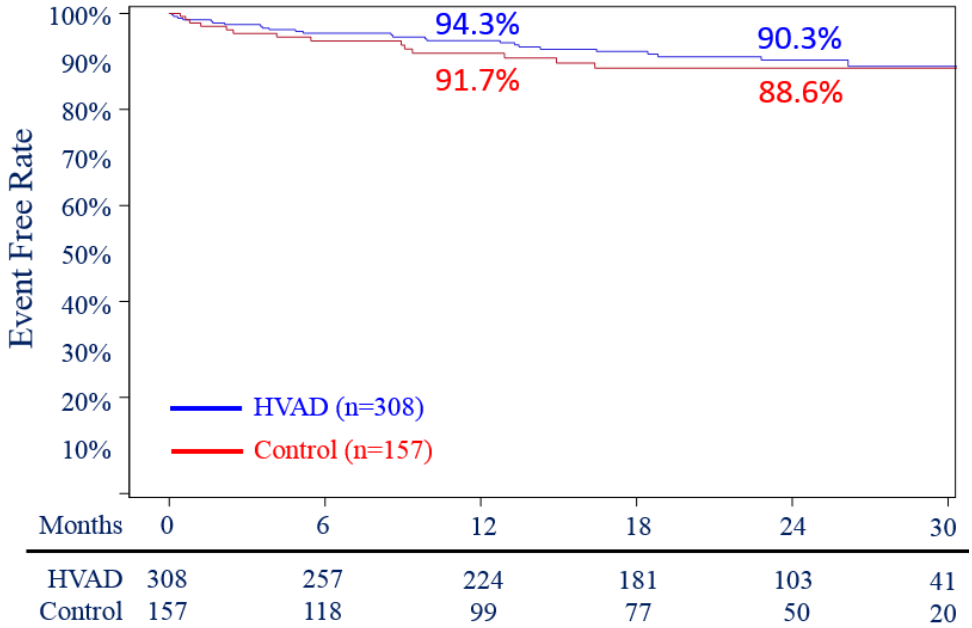


Figure 19: ENDURANCE Supplemental Trial Survival Free from Hemorrhagic Stroke



3. Adverse Events

Table 11 lists all the adverse events that occurred in the safety cohort.

Table 11: Summary of Adverse Events at 1 Year in the ENDURANCE Supplemental Trial.

Adverse Event	HVAD (N=308)	Control (N=157)
Major Bleeding	51.6% (159)	56.7% (89)
Cardiac Arrhythmia	34.1% (105)	31.2% (49)
Hepatic Dysfunction	3.9% (12)	3.8% (6)
Hypertension	13.0% (40)	12.7% (20)
Major Infection	53.9% (166)	59.2% (93)
Driveline Exit Site Infection	16.2% (50)	12.1% (19)
Device Malfunction/Failure	24.0% (74)	24.2% (38)
Hemolysis	1.3% (4)	5.7% (9)
Stroke Ischemic Cerebrovascular Event Hemorrhagic Cerebrovascular Event TIA	16.9% (52) 13.0% (40) 5.2% (16) 4.2% (13)	14.6% (23) 7.6% (12) 7.0% (11) 0.6% (1)
Renal Dysfunction	10.4% (32)	14.6% (23)
Respiratory Failure	19.8% (61)	19.7% (31)
Right Heart Failure	35.4% (109)	38.2% (60)
Pump replacement Exchange for pump thrombosis	5.2% (16) 4.5% (14)	11.5% (18) 10.2% (16)

Stroke-related deaths

Within the mITT population, the CEC-adjudicated rate of stroke-related death within 1 year of implantation was 3.2% (10/308) for HVAD patients and 2.5% (4/157) for Control patients.

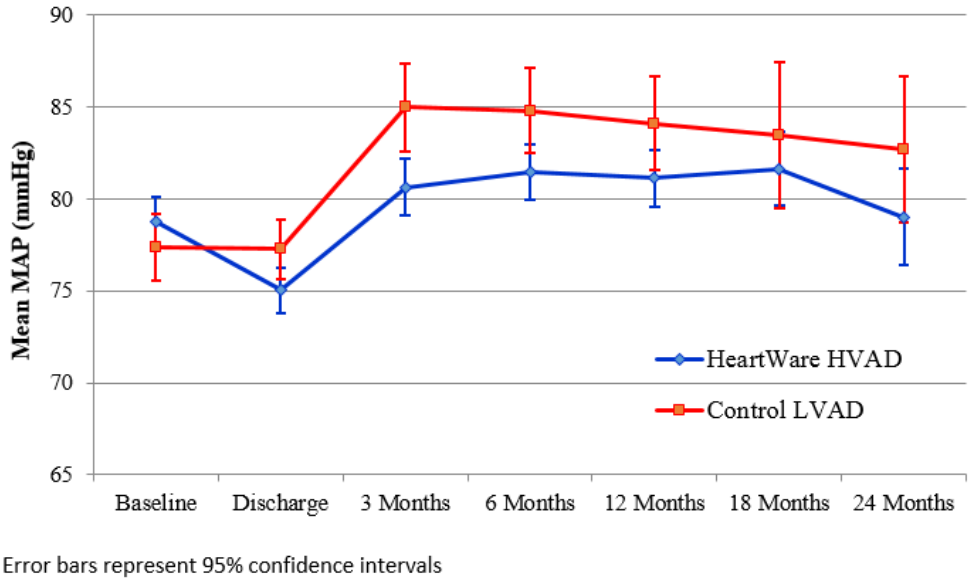
Comparing the results of ENDURANCE and ENDURANCE Supplemental, the rates of stroke-related death decreased by the same proportions (approximately 58%) for both HVAD and Control arms; only the HVAD arm was exposed to the trial's investigational intervention of a blood pressure management protocol. The stroke-related deaths are compared in Table 12. The MAP over time from the ENDURANCE Supplemental trial for the HVAD compared to the Control is

shown in Figure 20.

Table 12: Stroke-related Deaths in ENDURANCE and ENDURANCE Supplemental Trials

	ENDURANCE Within 2 years of implant (AIP)	ENDURANCE Supplemental Within 1 year of implant (mITT)
HVAD	25/296 (8.4%)	10/308 (3.2%)
HMII (control)	9/149 (6.0%)	4/157 (2.5%)

Figure 20: ENDURANCE Supplemental Trial MAP over Time



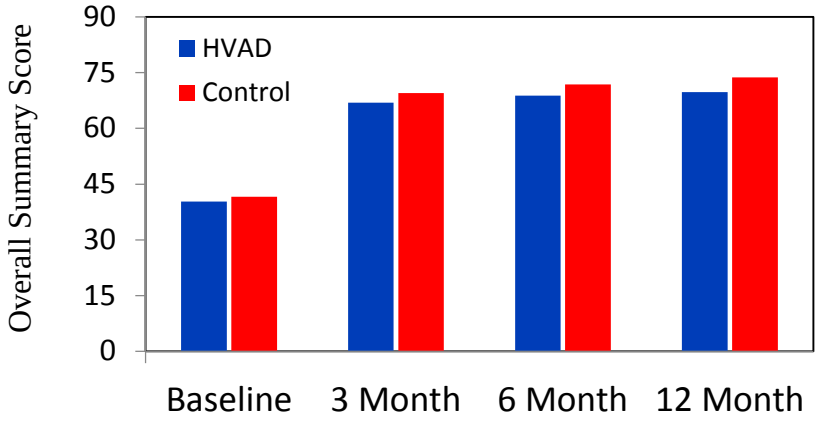
Error bars represent 95% confidence intervals

Health Status and Functional Improvements

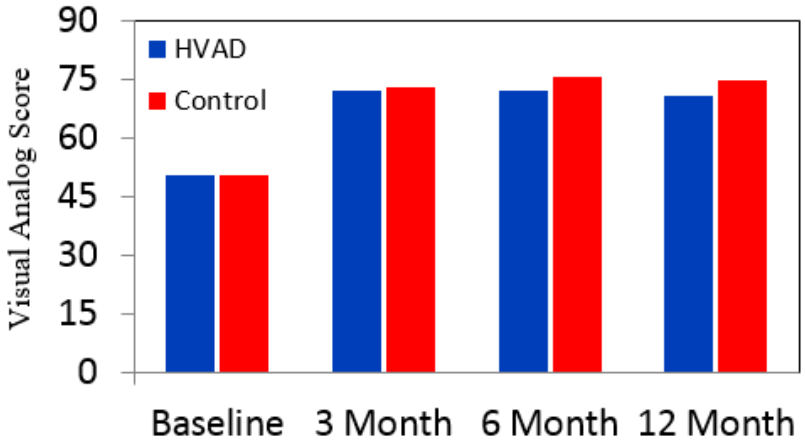
The improvements in quality of life, as measured by the KCCQ and EQ-5D-5L, and functional capacity, as measured by the 6 minute walk test and NYHA Class improvement, in the ENDURANCE Supplement trial patients are presented in Figure 21.

Figure 21: Improvements in Quality of Life and Functional Capacity in ENDURANCE Supplemental Subjects. A) Change over time of the KCCQ Overall Summary Score. **B)** Change over time in the EQ-5D Visual Analog Scale. **C)** Change over time of total distance walked in the Six Minute Walk Test. **D)** Percent of patients with 2 or more class increase in NYHA Classification at 12 months compared to baseline.

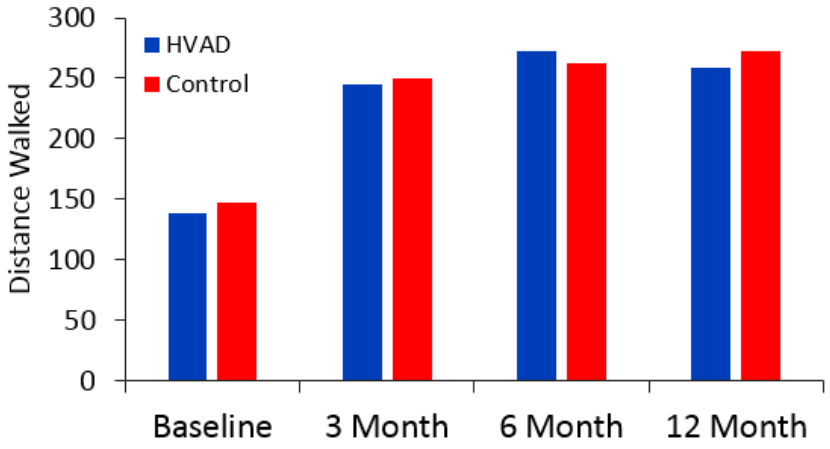
A. KCCQ



B. EQ-5D



C. Six-Minute Walk



D. NYHA Classification Improvement

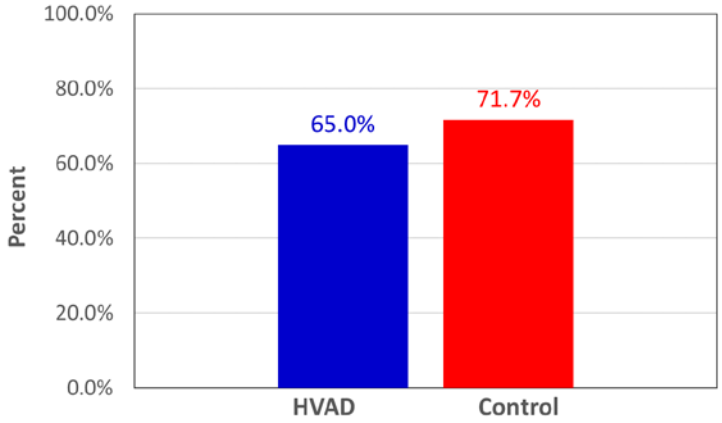
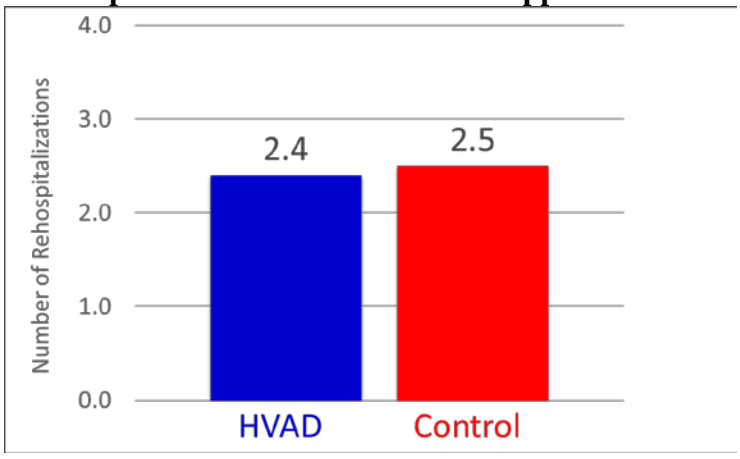


Figure 22: Average Number of Rehospitalizations in the First Year Post Implant in the ENDURANCE Supplemental Trial



3. Subgroup Analyses

The following preoperative characteristics were evaluated for potential association with outcomes: gender, BSA ($< 1.5\ m^2$, $\geq 1.5\ m^2$). No associations to outcomes of the primary and secondary endpoints were found for these two preoperative characteristics.

4. Pediatric Extrapolation

In this premarket application, clinical data from the ENDURANCE Supplemental trial were not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 337 investigators of which none were full-time or part-time employees of the sponsor and six (6) had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0
- Significant payment of other sorts: 3
- Proprietary interest in the product tested held by the investigator: 1
- Significant equity interest held by investigator in sponsor of covered study: 2

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The ENDURANCE trial did not meet its pre-specified primary endpoint, a demonstration of non-inferiority of the HVAD to the control device for patients alive on original device at two (2) years free from disabling stroke (mRS >4). However, an adjunctive analysis using the full-enrollment dataset demonstrated similar endpoint results, with 57.4% success for control and 55% success for HVAD. Following LVAD implant, approximately 80% of subjects in both arms improved to NYHA class I or II symptomatology. At 3 months following LVAD implant, median 6 minute walk distance increased in both arms (210 meters and 201 meters for study and control subjects, respectively). Patients in both arms also showed comparable improvement in quality of life from baseline to 3 months as measured by EQ-5D-5L and KCCQ, and the results were sustained through 2 years.

The ENDURANCE Supplemental trial did not meet its pre-specified primary endpoint, a demonstration of non-inferiority of the HVAD to the control device for freedom from neurologic injury (stroke with mRS >0 at 24 weeks post stroke or a transient ischemic attack) at 12 months (HVAD: 14.7% vs control: 12.1%). The combined rate of stroke and TIA in HVAD patients at one year did not meet a performance goal derived from the rate observed in ENDURANCE. Survival at 1 year free from the composite of disabling stroke or device exchange favored the HVAD System (HVAD: 75.3% vs control: 66.7%), though the trend diminished in magnitude over time (at 2 years, HVAD: 59.2% vs Control: 55.2%). The HVAD System and Control both demonstrated sustained improvements in quality of life, functional capacity, and NYHA classification.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in a clinical study conducted to support PMA approval as described above. The serious adverse events that occurred in more than 5% of the patients in the ENDURANCE trial included: Overall Bleeding events (HVAD: 60.1% vs control: 60.4%), Cardiac Arrhythmia (37.8% vs 40.9%), Hepatic Dysfunction (4.7% vs 8.1%), Hypertension (15.9% vs 16.8%), Sepsis (23.6% vs 15.4%), Driveline Exit Site Infection (19.6% vs 15.4%), Stroke (29.7% vs 12.1%), TIA (8.4% vs 4.7%), Renal Dysfunction (14.9% vs 12.1%), Respiratory Dysfunction (29.1% vs 25.5%), Right Heart Failure (38.5% vs 26.8%), Pump Replacement (7.8% vs 13.4%), and Device Malfunction or Failure (31.4% vs 25.5%).

The serious adverse events that occurred in more than 5% of the patients in the ENDURANCE Supplemental trial included: Overall Bleeding events (HVAD: 51.6% vs control: 56.7%), Cardiac Arrhythmia (34.1% vs 31.2%), Hypertension (13.0% vs 12.7%), Major Infection (53.9% vs 59.2%), Stroke (16.9% vs 14.6%), Renal Dysfunction (10.4% vs 14.6%), Respiratory Failure (19.8% vs 19.7%), Right Heart Failure (35.4% vs 38.2%), Pump Replacement (5.2% vs 11.5%), and Device Malfunction or Failure (24.0% vs 24.2%).

The overall safety comparisons in both the ENDURANCE and ENDURANCE Supplemental trials resulted in similar mortality rates and adverse event profiles. Pump thrombosis rates for the sintered HVAD and the Control LVAD were similar, but a higher proportion of Control pump thrombosis events resulted in device exchange. The incidence of stroke was 2.5 times higher in the patients receiving an HVAD compared to control in the ENDURANCE trial. The ENDURANCE Supplemental trial, which included implementation of a blood pressure management strategy for HVAD recipients, demonstrated a reduction in the overall stroke rates in patients receiving an HVAD System, though HVAD failed to demonstrate non-inferiority compared to Control for incidence of neurological injury at one year.

C. Benefit-Risk Determination

The probable benefits of the device are based on data collected in clinical studies conducted to support PMA approval as described above.

The HeartWare™ HVAD™ System has demonstrated a 55% chance of DT patients surviving to 2 years free from debilitating stroke and without the need for a reoperation to replace the pump, and it has demonstrated a 75.3% chance of surviving to one year in the same manner when a blood pressure protocol is employed. Although these rates may not equal those of the Control device used in the studies, they do represent a substantial probable benefit for the DT population. A probable benefit of the HVAD is that the device does not require placement of the pump in an abdominal position.

The risk of undergoing subsequent surgery for pump exchange due to device failure or malfunction was lower in the HeartWare™ HVAD™ System compared to the only other commercially available LVAD for destination therapy. This observation reflects another probable benefit of the device.

The probable risks of the HeartWare™ HVAD™ System include serious adverse events such as stroke and other neurological events, major infection, bleeding, and right heart failure, all of which could led to death. Of these, the neurological event rate, in particular the stroke rate, associated with the HeartWare™ HVAD™ System in DT patients is the principal probable risk for patients.

When compared to all available therapies except mechanical circulatory support, the probable benefits of HeartWare™ HVAD™ System clearly outweigh the probable

risks, since the DT candidate by definition has exhausted those therapies and is at exceedingly high risk of serious adverse events and death. When compared to all available therapies inclusive of currently marketed LVADs, the benefit-risk determination changes. Overall, the probable risks of the HVAD appear to be greater than the alternatives, predominantly because of comparative rates of neurological dysfunction. However, the HVAD also has the clinically important benefit of not requiring an abdominal pocket for its pump, and the need for device exchange due to pump thrombosis may be less than the LVAD currently marketed for DT. Accordingly, when considering all therapeutic options for a DT patient, the probable benefits of the HVAD still outweigh its probable risks, provided patients and physicians fully consider the adverse event data which illustrate the probable risks. The most important risks for patients and providers to fully understand are stroke and device failure/malfunction.

1. Patient Perspectives

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

In conclusion, given the available information above, the data support that for patients with advanced refractory heart failure, the probable benefits from implanting the HeartWare™ HVAD™ System outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of the HeartWare™ HVAD™ System for hemodynamic support in patients with advanced, refractory left ventricular heart failure; either as a bridge to cardiac transplantation (BTT), myocardial recovery, or as destination therapy (DT) in patients for whom subsequent transplantation is not planned.

XIII. CDRH DECISION

CDRH issued an approval order on September 27, 2017. The final conditions of approval cited in the approval order are described below.

1. **ODE Lead PMA Post-Approval Study - Continued Follow-up of HW004-A ENDURANCE Supplemental Study Cohort:** The study will consist of all living subjects who are currently enrolled in the ENDURANCE Supplemental Study, including the continued access investigation, at participating institutions and who consent to be followed per protocol up to 5 years. The study objective is to compare the safety and effectiveness of a prospective blood pressure management strategy with particular focus on stroke rates in subjects receiving the HeartWare HVAD system, and to compare the safety and effectiveness of the HeartWare HVAD system for destination therapy to other FDA-approved LVADs approved for destination therapy in subjects with end-stage heart failure who are ineligible for heart transplantation.

For continued follow-up of patients, the primary and secondary endpoints are listed in the protocol as follows: The primary endpoint is a non-inferiority test comparing HVAD to Control considering the incidence at 12 months on the originally implanted device of neurologic injury, defined as an ICVA or HCVA with an MRS > 0 at 24-weeks post-stroke, or a TIA, or as a spinal cord infarction. The first secondary endpoint is the reduction in stroke/TIA incidence at 12 months on the originally implanted HVAD. The second secondary endpoint is stroke-free success (Modified Rankin Scale < 4 at 24weeks post-stroke) at 12 months comparing HVAD to Control. Additional endpoints include the primary endpoint excluding subjects with baseline MRS >0, overall survival, incidence of all serious adverse events, neurocognitive status and unanticipated adverse device effects, maintenance of mean arterial pressure per IBPM Guidelines, stroke incidences and rates, incidence of all device failures and device malfunctions, health status improvement, and functional status improvement.

2. **OSB Lead PMA Post-Approval Study - ENDURANCE Supplemental PAS:** A confirmatory study of the safety and effectiveness of the HeartWare Ventricular Assist Device (HVAD) for destination therapy (DT), with special attention paid to the occurrence, risk factors, and severity of stroke. This prospective, non-randomized, multi-center, observational study will be conducted through Medtronic's Product Surveillance Registry (PSR). A total of 300 subjects will be enrolled. Approximately 50 study sites will be enrolled, and no more than 20% of these sites will be located outside of the United States. Study subjects will be newly enrolled (using the HVAD system as DT). Subjects will be followed through five years post-implant. However, the FDA agrees to reevaluate the need for continued data collection to address study objectives once all eligible subjects have completed two years of follow-up. This evaluation will take into consideration primary and secondary endpoints/objectives from this PAS, as well as from the other required PAS (continued follow-up of the ENDURANCE Supplemental IDE cohort #G090243 and the Continued Access Protocol cohort), and other clinical data available at the time of evaluation.

   The primary endpoint/objective is survival free of disabling stroke or device malfunction requiring exchange, explant, or urgent transplant. There will be three (3) secondary endpoints/objectives. The first secondary endpoint/objective is to determine the observed early stroke rate (stroke occurring ≤2 years post-implant), and stroke risk factors. The second secondary endpoint/objective is to determine the late stroke rate (stroke occurring >2 years post-implant) and to evaluate risk factors for late stroke. Stroke rate will be estimated using Kaplan-Meier methods, and Cox proportional hazards modeling will be used to determine factors that influence time to first stroke post-HVAD implant. The third secondary endpoint/objective is to evaluate stroke severity for all subjects who experience a stroke on device while in this study. Stroke severity will be assessed through modified Rankin Scale (mRS) scoring which will be conducted by trained individuals. The mRS scoring will be conducted at the time of stroke, 12 weeks post-stroke, and 24 weeks post-stroke. Rates and their corresponding 95% confidence intervals will be reported, where appropriate, for each endpoint/objective.

Additionally, the following will be evaluated: the effectiveness of Improved Blood Pressure Monitoring (IBPM), a summary of neurologic dysfunction events (ischemic cerebrovascular accidents, hemorrhagic cerebrovascular accidents, and transient ischemic attacks), overall survival on device, INTERMACS adverse event rates, quality of life measures (measured by EuroQol EQ-5D-DL and Kansas City Cardiomyopathy Questionnaire), and functional status (measured by the 6-minute walk test). Patients will be followed at 3 months, 6 months, and every 6 months thereafter or as reportable adverse events prompt. PAS progress reports will be provided to the FDA biannually for the first 2 years following approval, and annually thereafter.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order