PANEL PACK CLINICAL SUMMARY
November 30, 2007

THORATEC®
HEARTMATE® II LEFT VENTRICULAR ASSIST SYSTEM
(HM II LVAS)

Sponsored by:

Thoratec Corporation
6035 Stoneridge Drive
Pleasanton, CA 94588

Telephone: 925-847-8600
Facsimile: 925-847-8574

CLINICAL SUMMARY - TABLE of CONTENTS

Volume I

List of Tables vii
List of Figures xv
List of Abbreviations xvii

7.1 Executive Summary 1
7.1.1 Study Purpose and Endpoints 1
7.1.2 Results 1

CLINICAL SUMMARY - TABLE of CONTENTS

CLINICAL SUMMARY - TABLE of CONTENTS

CLINICAL SUMMARY - TABLE of CONTENTS

List of Tables

≥

[redacted]

≥

Key to Patient Code:
Patient number assignments are displayed as the two digit site number, plus 2P, plus patient number **(***e.g. 012P101 is site number 01+2P+patient number***)**.

List of Abbreviations

ACE……..Angiotensin Converting Enzyme
AICD……Automated Implantable Cardiac Defibrillator
ALT ……..Alanine Aminotransferase
AST ……..……Asparate Aminotransferase
AVR……...Aortic Valve Replacement or Repair
BMI……Body Mass Index (kg/m^2)
BP……..Blood Pressure
bpm……...Beats per minute
BSA……...Body Surface Area (m^2)
BTT……Bridge to Transplantation
BUN……..Blood urea nitrogen
CABG……...Coronary Artery Bypass Graft
CAP…….. Continued Access Protocol
CEC……..Clinical Events Committee
CI…….. Confidence Interval
CRF…….. Case Report Form
CRT…….. Cardiac resynchronization therapy
CSS…….. Clinical Summary Score of KCCQ
CVA…….. Cerebral Vascular Accident (stroke)
CVP……...Central venous pressure
CVVHD…….Continuous Veno-Veno Hemodialysis
DSMB……...Data Safety Monitoring Board
DT……Destination Therapy
GCP……..Good Clinical Practice
g/dL…….. Grams per deciliter
Hct ……..……Hematocrit
Hgb……Hemoglobin
HMI……HeartMate IP (Implantable Pneumatic), VE (Vented Electric), or XVE (Extended Lead Vented Electric) LVAS; ref. PMA P920014
HMII……..HeartMate II
HMII LVAS….. HeartMate II Left Ventricular Assist System
HMII LVAD….. HeartMate II Left Ventricular Assist Device
IABP……. Intra-Aortic Balloon Pump
IRB……... Institutional Review Board
ICD……Implantable Cardiac Defibrillator
INR……International Normalized Ratio
INTERMACS…Interagency Registry for Mechanical Circulatory Support
IV…….. Intravenous

IVAD…….Thoratec Implantable VAD; ref. PMA P870072/S27
IVIG…….. Intravenous Immunoglobulin Therapy
KCCQ ……..Kansas City Cardiomyopathy Questionnaire (quality of life instrument)
LCL…….. Lower Confidence Limit
LDH ……..…Lactic Acid Dehydrogenase
L/min…….Liters per minute
L/min/m^2…….. Liters per minute per meter squared
LOS…….. Length of Stay (for hospitalization)
LV……..Left Ventricle
LVAS…… Left Ventricular Assist System
LVEF…… Left Ventricular Ejection Fraction
MCS……..Mechanical Circulatory Support
MET……..Metabolic Equivalent Score
mg/dL……Milligrams per deciliter
MI……..Myocardial Infarction
MLWHF……Minnesota Living with Heart Failure (quality of life instrument)
mmHg…….. Millimeters of mercury
mM/L…… Millimoles per liter
Mo……Month
MVR……..Mitral Valve Replacement or Repair
n…… Number of Patients
na or n/a…….. Not Applicable
ND…….Not Done
NYHA……New York Heart Association (heart failure classification)
OMM…….Optimal Medical Management
OPC……..Objective Performance Criteria
OSS……..Overall Clinical Summary Score of KCCQ
PA……..Pulmonary artery
PBU……...Power Base Unit
PCWP……...Pulmonary capillary wedge pressure
PFO……...Patent Foramen Ovale
PhgB…….Plasma free hemoglobin
PI……Principal Investigator
Plt……..Platelets
POD…… Post Operative Day
Pt / Pts……. Patient / Patients
PTT…….. Partial Thromboplastin Time
PVAD……Thoratec Paracorporeal VAD; ref. PMA P870072
PVR…….. Pulmonary Vascular Resistance
QOL……..Quality of Life
RFA…….. Radio Frequency Ablation
RVAD……Right Ventricular Assist Device
SD……Standard Deviation
SE……Standard Error

Status 1A…… Highest medical urgency transplant status per UNOS criteria. Patients must have certain devices or therapies in place; e.g. IABP, ECMO or high doses of inotropes.
Status 1B……. Next highest (after 1A) medical urgency transplant status per UNOS criteria. Patients must be supported by continuous IV inotropes or a ventricular assist device.
TE……. Thromboembolic Event
TIA……. Transient Ischemic Attack
tPA……. Tissue Plasminogen Activator
TPN…….. Total Parenteral Nutrition
TVR…….. Tricuspid Valve Replace/Repair
TX……. Transplant
UCL…….. Upper Confidence Limit
U/L……. Units per liter
VE LVAD……. Vented Electric Left Ventricular Assist Device
VE LVAS……. Vented Electric Left Ventricular Assist System
VO2 max……..Maximal Rate of Oxygen Consumption
WBC……. White blood count
XVE LVAS….. Extended Lead Vented Electric Left Ventricular Assist System

[This page intentionally left blank]

7.1 EXECUTIVE SUMMARY

7.1.1 STUDY PURPOSE AND ENDPOINTS

Purpose: Evaluate the safety and effectiveness of the HeartMate II LVAS as a bridge to cardiac transplantation in patients who are at imminent risk of death from non-reversible end-stage heart failure.

Primary Endpoint: Study success is defined as survival to transplantation or 180 days of LVAD support while remaining listed as status 1A or 1B. The success rate is compared to an Objective Performance Criterion (OPC) of 75% and considered to be non-inferior if the 95% lower confidence interval is at least 65% (10% margin of non-inferiority).

Secondary Endpoint: Characterize the incidence of adverse events, clinical reliability, functional status, quality of life and neurocognitive status while on HeartMate II LVAS support. Assess post-transplant survival at 30 days and one year.

7.1.2 RESULTS

Patient Population:

Two hundred seventy-nine (279) patients were enrolled from March 2005 to March 2007 under the HeartMate II Pivotal Study Protocol. One hundred and thirty-three (133) were enrolled in the Original PMA Study Cohort (7 were later removed) and 146 were enrolled under FDA's procedures for continued access to investigational devices. Continued access patients were enrolled using the same criteria and followed in the same way as the Primary Study Cohort patients. The total of 279 patients are analyzed in three data cohorts, the Primary Study Cohort (n=126), the Continued Access Cohort (CAP, n=138) and the Small BSA Cohort (patients having a BSA < $1.5m^2$,n=15), as described in Section 7.4.3 of this Panel Pack. In addition, as described in Section 7.9, Thoratec proposes that the final device labeling be based on an analysis of the first consecutive 194 of the 279 total patients, all those that have been followed for at least 180 days since implantation of the HeartMate II LVAS.

Effectiveness:

The success rate for the Primary Study Cohort was 67% and the lower one-sided 95% confidence limit was 60% at the March 16, 2007 data follow-up cut-off date, which did not meet the pre-specified OPC for survival to

transplant or 180 days of LVAD support while remaining listed 1A or 1B. As the patients continued to be followed over the next six months the success rate increased to 71% with a lower one-sided 95% confidence limit of 64% due to additional patients being subsequently transplanted or explanted due to myocardial recovery.

This end-point analysis counted patients who were not listed 1A or 1B as failures who by all other measures, including functional status and quality of life, were clinical successes. Therefore, Thoratec also provides an adjunctive analysis of the primary study endpoint in which patients who were successfully supported with no irreversible contraindications for transplant but not listed 1A or 1B at 180 days were counted as successes. This adjunctive analysis, henceforth referred to as the "Alternate Analysis", is presented in Section 7.8 to allow a more direct survival comparison to data from which the OPC was derived. When the 10 clinically successful, yet non-listed patients, are counted as successes, the study meets the OPC at the March 16, 2007 data follow-up cut-off date with a success rate of 75% (95% LCL = 68%).

The Kaplan-Meier estimate of survival (± standard error) on the HeartMate II LVAS for the patients in the Primary Study Cohort was 75% ± 5% at 180 days and 69% ± 6% at 360 days.

Effectiveness of the HeartMate II LVAS was consistent throughout all study cohorts, one factor supporting the use of the Thoratec Proposed Labeling Cohort in the final labeling. The pre-specified analysis of the study endpoint in the Thoratec Proposed Labeling Cohort met the OPC at the September 14, 2007 data follow-up cut-off date, 70% success (95% LCL = 65%). The Alternate Analysis showed an even higher success rate, 76% (95% LCL = 71%). The Kaplan-Meier estimate of survival (± standard error) on the HeartMate II LVAS for the patients in the Thoratec Proposed Labeling Cohort was 78% ± 3% at 180 days and 72% ± 4% at 360 days.

Safety:

The types and incidence of adverse events are similar to those seen in previous studies of ventricular assist devices and consistent throughout all study cohorts. For adverse events with comparable definitions to the HeartMate VE bridge to transplant clinical study, the HeartMate II demonstrated a statistically significant reduction in adverse event rates. Clinical reliability results were consistent with pre-clinical bench-testing.

Secondary Endpoints:

Three measures of functional status were collected during the study (NYHA Class, Six Minute Walk Test and Patient Activity Evaluation/METs). All three demonstrate statistically significant improvement at follow up durations of 30 days, 3 months and 6 months post implant when compared to baseline. In addition, for the two measures that have published benchmarks, clinically meaningful improvement was observed at these same follow up intervals. Results were consistent throughout all study cohorts

This study evaluated two measures of Quality of Life (Minnesota Living with Heart Failure and Kansas City Cardiomyopathy Questionnaire). Using both of these measures, the data demonstrate statistically significant and clinically meaningful improvement at all follow up intervals in all study cohorts.

Eleven of the 32 investigational sites, representing a wide range of VAD experience, were selected at the onset of the study to conduct Neurocognitive (NC) testing. Because of the small sample size (n=86), it is difficult to draw conclusions; however, important trends were seen. There was no significant cognitive decline in patients assessed between baseline and the 3 month or 6 month interval. There were significant improvements in cognitive test performance at 3 and 6 months over baseline for auditory memory, visual memory delay and processing speed.

Post-transplant survival rates were comparable to one year survival rates of the HeartMate VE and the one year survival rates reported by the ISHLT Registry for the contemporary cohort of primary transplants, demonstrating that the HeartMate II does not introduce additional risks to transplantation.

[This page intentionally left blank]

7.2 DEVICE DESCRIPTION

7.2.1 HEARTMATE II SYSTEM OVERVIEW

The HeartMate II (HM II) Left Ventricular Assist System (LVAS) consists of an implanted axial flow blood pump and external components as shown in Figure 1. The HeartMate II is significantly smaller than the currently approved HeartMate XVE LVAS, allowing implantation in a wider range of patients, yet it provides flow equivalent to the XVE LVAS.

Electrical power to the blood pump is delivered through a percutaneous cable that connects to an external System Controller. The System Controller itself is powered by a Power Base Unit (PBU) that connects to AC mains power, or by two batteries that the patient carries or wears in shoulder holsters. These two power configurations are shown in Figures 2 and 3. The PBU, System Monitor and batteries are identical to the components approved for use with the HeartMate XVE LVAS (ref. PMA P920014).

Figure 1 – HeartMate II LVAS, Implantable and External Components

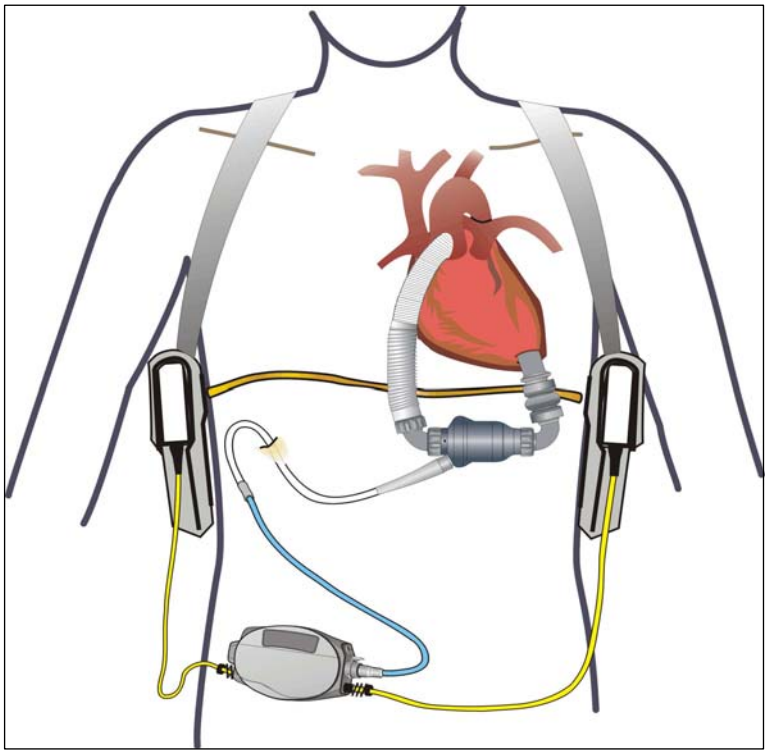


Figure 2 – HeartMate II LVAS Configuration with Power Base Unit and System Monitor

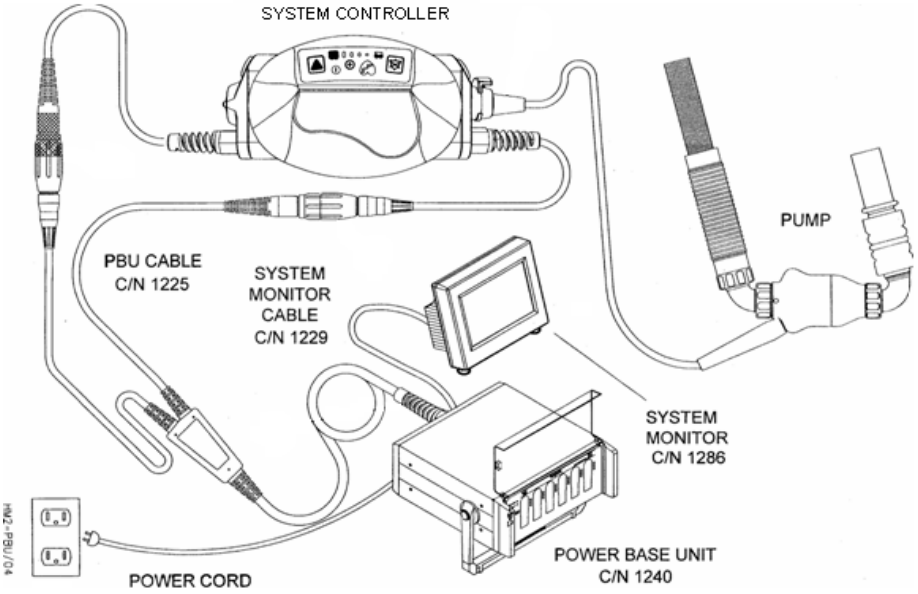
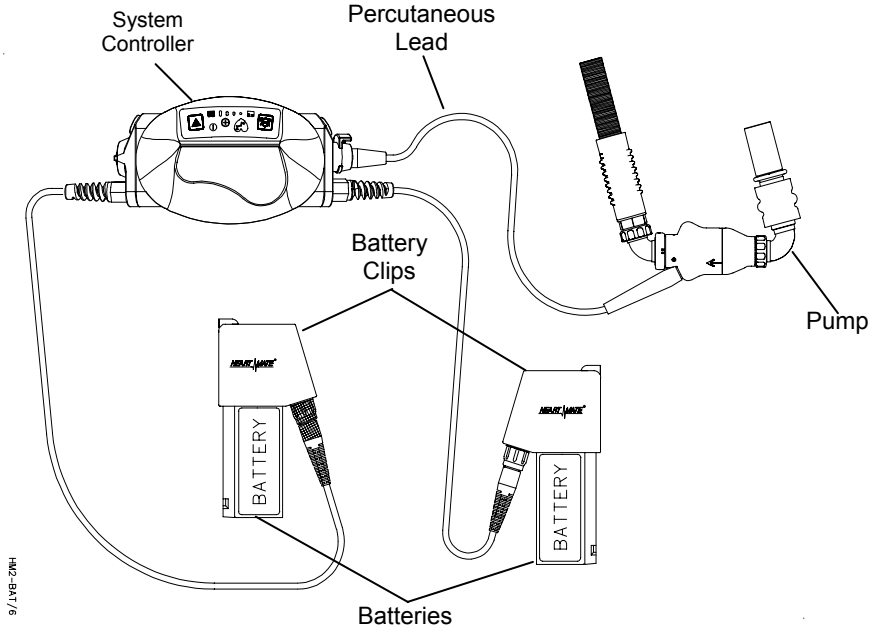


Figure 3 – HeartMate II LVAS Configuration with Batteries



7.2.2 HEARTMATE II LEFT VENTRICULAR ASSIST DEVICE (LVAD)

7.2.2.1 Pump

The HeartMate II LVAD embodies an implanted axial flow rotary blood pump having an operating speed range of 8,000 to 15,000 RPM. With that range, the HeartMate II is capable of cardiac support for a wide size range of patients. As shown in Figure 1, the blood pump is connected in parallel with the native circulation. The pump's inlet is placed in the apex of the left ventricle, while its outlet is connected to the ascending aorta. Forward fixed rate of flow is generated by a rotor located within the bore of the pump. The rotor spins on inlet and outlet bearings and is integrated into a brushless DC motor. The integration is achieved by a magnet located within the rotor and by the adjacent motor coils that surround the blood tube within the pump assembly. Power and commutation logic are delivered to the motor through the percutaneous cable. Since the HeartMate II LVAS is not a positive displacement pump with a blood chamber that is compressed, as is the HeartMate XVE, a vent or compliance chamber is not required to "make up" the volume change as the pump ejects. A cross-section schematic diagram of the pump assembly and a photo of the pump impeller with stators and bearings are provided in Figure 4 and Figure 5 respectively.

Figure 4 – HeartMate II Pump Cross-section

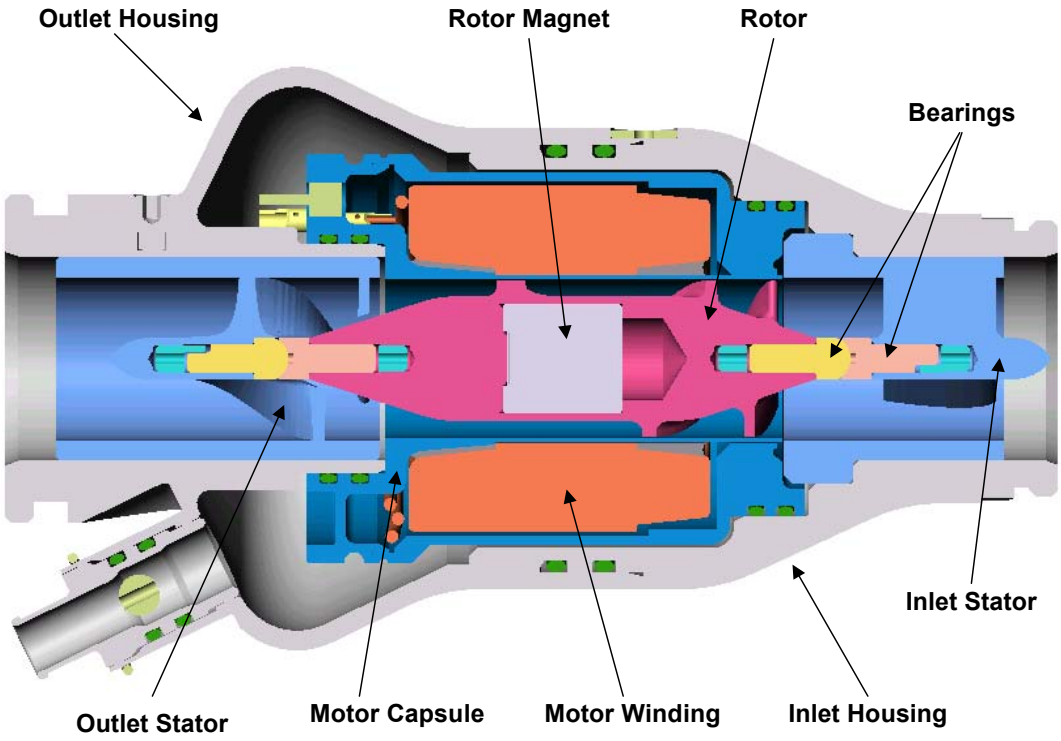


Figure 5 – Pump Impeller, Stators and Bearings

7.2.2.2 Cannulae

The inlet cannula of the LVAD is inserted into the left ventricle, while the outlet cannula is anastamosed to the ascending aorta. The device is intended for implantation in the sub-diaphragmatic position. As shown in Figure 6 and Figure 7, the HeartMate II cannulae are secured to the pump by self-locking screw rings on both the inlet and outlet cannulas. This feature, which is also used with the FDA approved HeartMate XVE LVAD, provides a secure locking mechanism. The outflow cannula is provided with a bend relief, a three or four inch long tube of reinforced ePTFE surrounding the outflow graft proximal to the pump, which is designed to prevent kinking of the outflow graft.

Figure 6 – Inflow Cannula Assembly Attachment to the Blood Pump Assembly

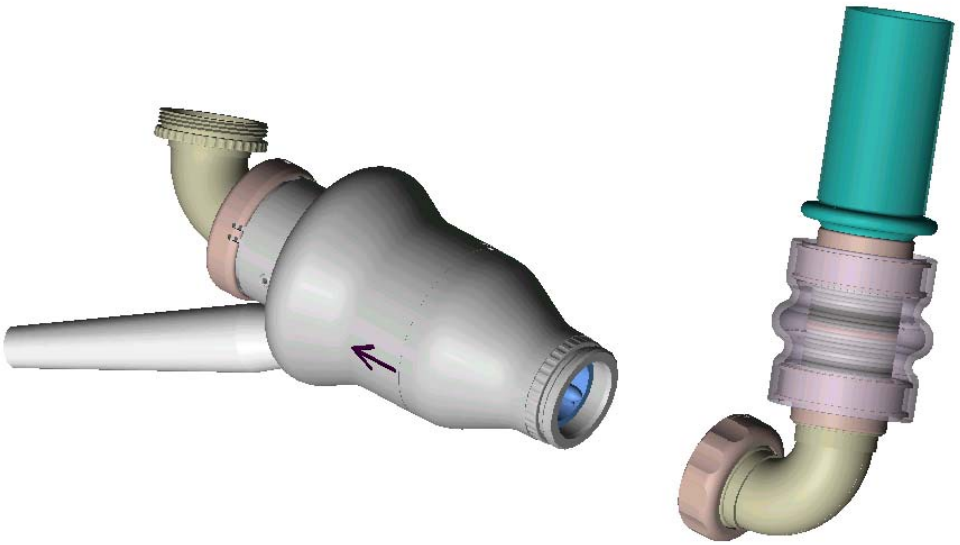
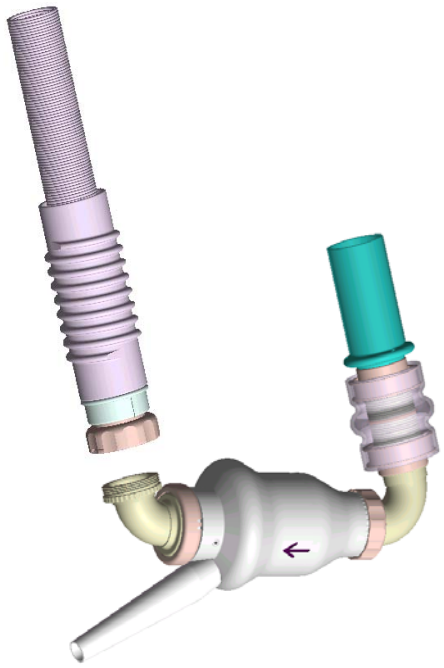


Figure 7 – Outflow Cannula Assembly Attachment to Blood Pump



7.2.2.3 Percutaneous Cable

The percutaneous cable is attached to a bulkhead fitting located at the outlet end of the pump's housing. A polyester velour covers the 14 inch section of cable proximal to the pump end. This velour covering extends out beyond the skin penetration site to allow for tissue ingrowth. The cable's exterior section terminates in a "quick" latch-type connector that plugs into the System Controller. The cable design includes redundant conductors to prevent any interruptions in pump operation should a single wire break occur.

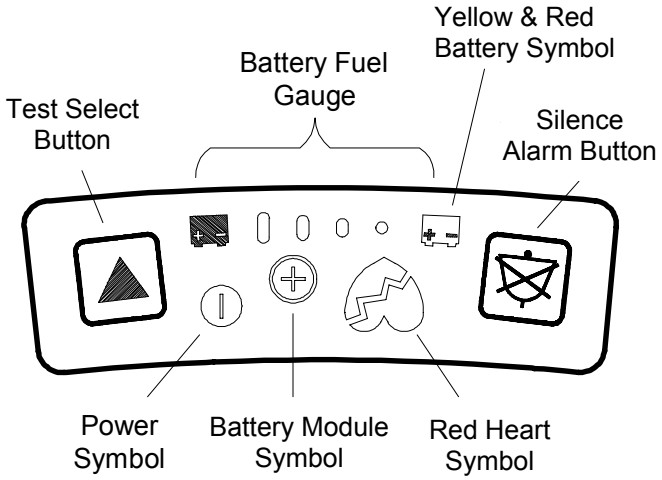
7.2.2.4 LVAD and Conduit Surface Finish

A textured surface composed of titanium microspheres is incorporated as a key feature of the pulsatile HeartMate LVAS products. Extensive clinical history of these devices substantiates that the neointima layer that forms on the textured surface provides excellent biocompatibility with minimal anticoagulation requirements. Therefore, textured surfaces are incorporated into the HeartMate II inflow and outflow conduits, since in large bore blood path zones, the promotion of an adherent neointimal layer on the textured surface reduces the risk of thromboembolism and does not have a negative impact on pump performance. In contrast, all of the blood surfaces within the blood pump itself are smooth.

7.2.3 SYSTEM CONTROLLER

Figure 8 – System Controller

Figure 9 – System Controller Keypad



The HeartMate II System Controller (Figure 8) is the externally worn control unit for the implanted pump. The primary functions of the system controller include motor speed control and performance evaluation (flow, self-test, advisory and hazard alarms). The LVAD connects to the system controller via the percutaneous cable described above. Power is supplied to the system from any of the three power sources (Power Base Unit, Battery, or Emergency Power Pak) that are attached to the system controller by the two power cables. The dual power cables provide redundancy as well as allow the power source to be changed without interruption in pump function. The system controller has a user interface panel that indicates that the LVAS is operational and that power is properly connected The controller provides a mixed rate single mode of operation, audio/visual advisory and hazard alarm indication, a button for silencing audio alarms, and a button to perform a system controller self-test. The alarm silence button also enables a check of the battery charge level.

The system controller contains a fully redundant backup circuitry capable of full operation of the LVAS to reduce risk of functional loss in the event of a single component or subsystem failure. The system controller housing is double shielded to provide maximum protection from electrostatic discharge.

7.2.4 SYSTEM COMPONENTS IN COMMON WITH HEARTMATE XVE LVAS

The components and accessories described below are shared in common with the currently commercialized HeartMate XVE LVAS (ref. PMA P920014). No changes have been made to the hardware or packaging to enable their use within HeartMate II LVAS.

7.2.4.1 Power Base Unit

The primary functions of the Power Base Unit (PBU) are to provide isolated power to the LVAS, charge batteries, echo System Controller alarm conditions, provide short term power (via a back up battery) and to provide an interface between the System Controller and System Monitor or Display Module. The PBU is designed for hospital and home operation.

7.2.4.2 System Monitor

The System Monitor is a device that allows clinicians to monitor LVAS operation (flow, speed, operating mode, and system alarm status), modify LVAS parameters (speed and limits), and save records of LVAS performance. The System Monitor plugs into the PBU via a detachable cable as shown in Figure 2. It is intended for use in the hospital. The System Monitor software detects the type of LVAS to which it is connected, either HeartMate II or HeartMate XVE, and uses the software routines appropriate for that device.

7.2.4.3 Display Module

The Display Module provides a read-only display of the primary performance parameters for the device. The Display Module software detects the type of LVAS to which it is connected, either HeartMate II or HeartMate XVE, and uses the software routines appropriate for that device. It does not allow any changes to the operating parameters of the system. When the HeartMate II LVAS is connected to the Display Module, the following information is displayed:

- LVAD pump speed
- Estimated LVAD flow
- LVAD power consumption
- Calculated pulsatility index (PI)
- Current operating mode
- Hazard and advisory alarm status

The Display Module is typically used in the patient's home, enabling the patient to view, and if necessary, report to the clinic, the HeartMate II LVAS operating parameters and any alarm messages

7.2.4.4 Battery

The Battery is a 12-volt, 2.3 amp-hour, rechargeable, lead-acid battery. Two batteries are used simultaneously to power the LVAS. However, the LVAS will also operate on a single battery, facilitating battery changes without interruption of VAD support. The battery is lightweight to allow full patient mobility outside of and within the hospital and home setting.

7.2.4.5 Battery Clip

A pair of Battery Clips is used with a pair of batteries and a battery holster in order to provide mobility to the patient. The batteries snap into the battery clips, and the battery clips connect to the System Controller power leads supplying the LVAS with portable power. When the batteries are discharged, as indicated by the System Controller, the patient releases the discharged batteries from the clip one at a time and replaces them with freshly charged batteries.

7.2.4.6 Emergency Power Pak (EPP)

The emergency Power Pak is a single-use battery pack in a plastic carrying case with a shoulder strap. The EPP is designed to provide enough power to run the LVAS for approximately 12 hours. The System Controller plugs directly into the EPP.

7.2.4.7 LVAS Accessories

The following accessories facilitate various patient activities while on LVAS support.

- Shower Kit: The Shower Kit enables the patient to place the System Controller and batteries in a water resistant pouch to allow the patient to shower.

- Battery Holster: The Battery Holster facilitates the convenient mounting of batteries to the patient's torso allowing hands free movement while on LVAS support.

- Pocket Pak: The Pocket Pak is a pouch worn about the patient's waist to hold the System Controller, Batteries, and Battery Clips.

- Stabilization Belt: The Stabilization Belt with Lead Locks is used to immobilize and provide strain relief to the percutaneous lead at the exit site through the skin.

7.2.5 SURGICAL IMPLANT TOOLS

7.2.5.1 HeartMate II Implant Kit

The HeartMate II Implant Kit contains the following items in addition to the pump, cannula and System Controller:

- Coring knife – creates circular incision in LV apex for inflow cannula
- Apical sewing ring – secures inflow cannula to LV apex
- Skin coring punch – creates circular incision in dermis for percutaneous lead exit site
- Thread protectors – connect cannulae to sizer, assist in priming and deairing pump
- Tunneling bullet – connects tunneler to percutaneous lead for passing through tissue

7.2.5.2 HeartMate II Sizer

The HeartMate II Surgical Sizer tool approximates the size and shape of the HeartMate II LVAD and can be used at the beginning of the surgical procedure to assist in positioning the HeartMate II pump inside the patient, creating a pocket of appropriate size and determining the length of the outflow cannula. The Surgical Sizer is machined from a solid block of acetal and is provided as a non-sterile reusable device.

7.2.5.3 HeartMate II Tunneler

The HeartMate II Tunneler is a stainless steel surgical accessory used to create a tunnel for the percutaneous lead from the abdominal cavity to the skin exit site. Its use is described on page 57 of the Instructions for Use (ref.Section 9.1). It is provided non-sterile.

7.2.6 HEARTMATE II TRAINING

Thoratec has developed a comprehensive education and training program for both medical personnel and patients. This includes the following: an off-site training session including animal implant of the device; on-site training for health-care providers at the implanting center; web-based training which covers patient selection, implant technique and post-operative management; educational literature and DVD's for patients and caregivers; 24-hour availability to Thoratec representatives for guidance and troubleshooting; and, ongoing maintenance of a dedicated Thoratec staff that is available for training and education.

7.3 PRINCIPLES OF OPERATION

7.3.1 HEARTMATE II PUMP

The HeartMate II pump is an axial flow device, where the path of the entering and exiting flow stream is parallel to the pump's axis. Flow is transferred from the left ventricle to the pump inlet via the inflow cannula. This cannula is similar to the one used for current HeartMate XVE LVAD, with the exception that there is no valve. Similarly, the outflow cannula carrying pump flow to the aorta is patterned after the one used for the XVE device but with no valve, as shown in Figure 1 and Figure 7. The pump itself has but one moving part, the rotor assembly that spins on bearings located at either end of the assembly. Torque that drives the rotor is developed by an integral electric motor. A thin wall, 12-mm diameter titanium duct (blood tube) passes through the bore of the motor's coil windings. The component functioning as the rotating piece of this motor is a permanent magnet located in the pump rotor (or impeller) hub. Three-phase excitation current sequentially commutated to the coils creates a spinning magnetic field, thereby imparting rotary motion and torque to the magnet (i.e. pump rotor). Individual blades located on the spinning rotor move the blood through the pump. Physically, the coils are isolated from blood and tissue by a hermetically sealed capsule.

Flow enters the pump, passing across guide vanes comprised of three blades that structurally support the inlet stator hub. These are of a neutral airfoil shape that straightens the flow field prior to entering the rotor. Three blades on the rotor pick up the flow, supplying kinetic energy in the form of radial velocity. Upon leaving the influence of the rotor, the flow enters the exit stator. It too has three blades, but these are twisted such that a radial velocity imparted to the flow filed by the rotor is turned back to the axial direction. At the same time the flow field is being turned, net flow area increases, thereby converting kinetic energy into static pressure. In such manner, the pressure increases across the pump.

7.3.2 HEARTMATE II LVAD BEARING DESIGN

The axial flow impeller assembly is the only moving component within the HeartMate II device, and the impeller's blood–immersed spherical bearings constitute the interface between the rotating and stationary elements. The bearings in the HeartMate II LVAD have been designed to leverage the benefits of fluid film bearings. In the case of most bearing designs, the goal is to reduce the coefficient of friction between moving surfaces. An efficient means for reducing friction is the maintenance of a separation between rotating surfaces via a fluid film. Bearing sets are located at the leading and

trailing edge of the impeller. After an extensive evaluation of numerous materials and configurations, Thoratec Corporation designed each set to consist of a precision matched ball and cup of dissimilar ceramic materials. The spherical shape of the ball and cup bearings not only allows for omni-directional load carrying capacity, but a degree of overall bearing misalignment. Fluid-film or hydrodynamic action of the bearings is present over the full operating speed of the pump, 6000-15000 rpm.

The outer boundary of the bearing's adjacent static and moving surfaces is washed by blood in the main flow path. The hydrodynamic bearing design is ideal for long term, implantable blood pumps to optimize efficiency and for achieving intended duration of use of the device. The combination of bearing geometry, surface finish, loads, lubricant viscosity and operational speed place the bearing into the fluid film realm of mixed or fully developed lubrication.

7.3.3 PRESSURE—FLOW (H-Q) CHARACTERISTICS

The volume of flow generated by the pump is determined by the speed of rotation of the rotor and by the pressure differential that exists across the pump. For a specified pump speed, flow varies inversely with pressure (i.e., increasing pump pressure differential decreases flow rate).

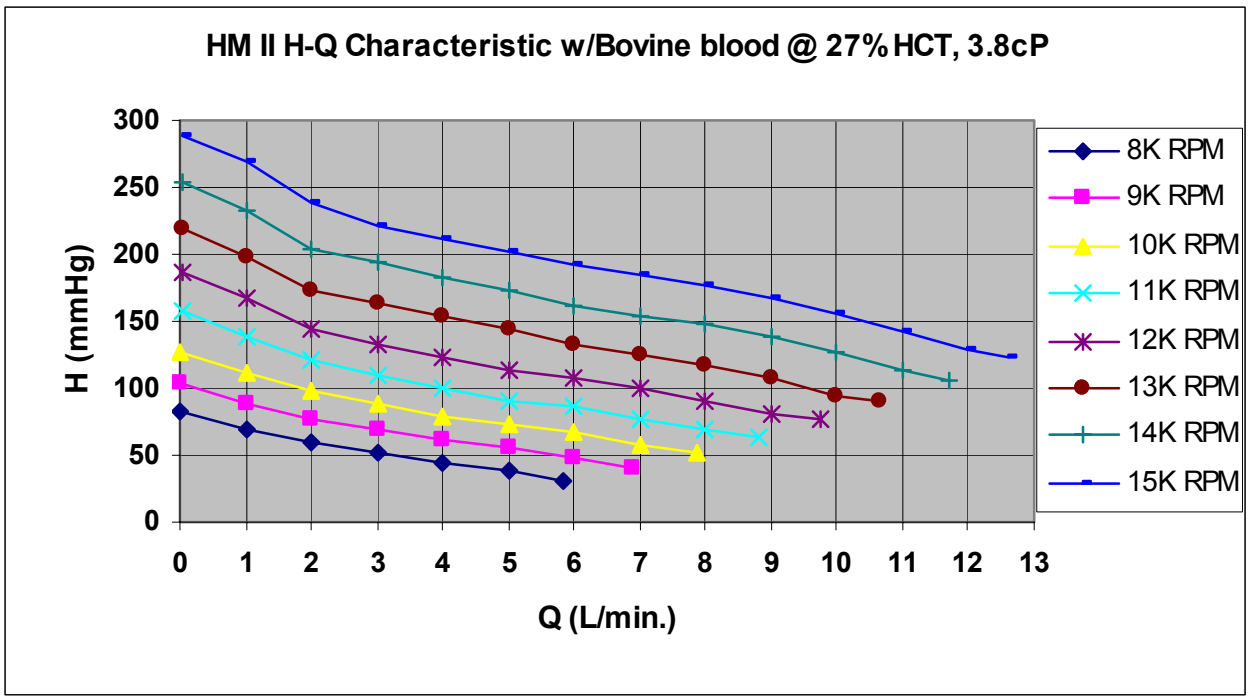
The pressure-flow (H-Q) curve characteristics of the HeartMate II blood pump are fundamental to understanding the interactions between the pump and the physiologic circulation system. As an LVAD, the pump is connected into the systemic circulation via an inlet and outlet cannula connected to the left ventricle and aorta, respectively (ref. Figure 1). With these connections, at any point during a cardiac cycle, differential pressure across the pump is equal to aortic pressure minus left ventricle pressure, plus the combined pressure loss across the inlet and outlet cannulae.

In nominal operating conditions, a patient's aortic pressure is in a normal range, and the net cannula pressure drop is at some value set by flow rate (for example, 10 mm Hg at 6 L/min). Hence, the dynamic parameter that determines pump differential pressure is left ventricular pressure, which in turn is dependent upon the contractile state of the ventricle itself. Even a severely depressed heart will have some residual rhythmic contraction, and any contraction will create a pressure pulse.

This pressure fluctuation at the pump inlet associated with ventricular contraction decreases pump pressure differential, and from the pressure-flow relation, flow rate will increase accordingly. A relatively small change in pump differential pressure causes a significant change in flow rate. The net result is that any contraction by the left ventricle (LV) is amplified as a flow

pulse delivered to the aorta. Thus, under most circumstances, systemic flow will be pulsatile. It takes a completely flaccid heart or one in fibrillation to have no left ventricular contribution to the flow pulse at all.

Figure 10 – HeartMate II H-Q Curve Relationship

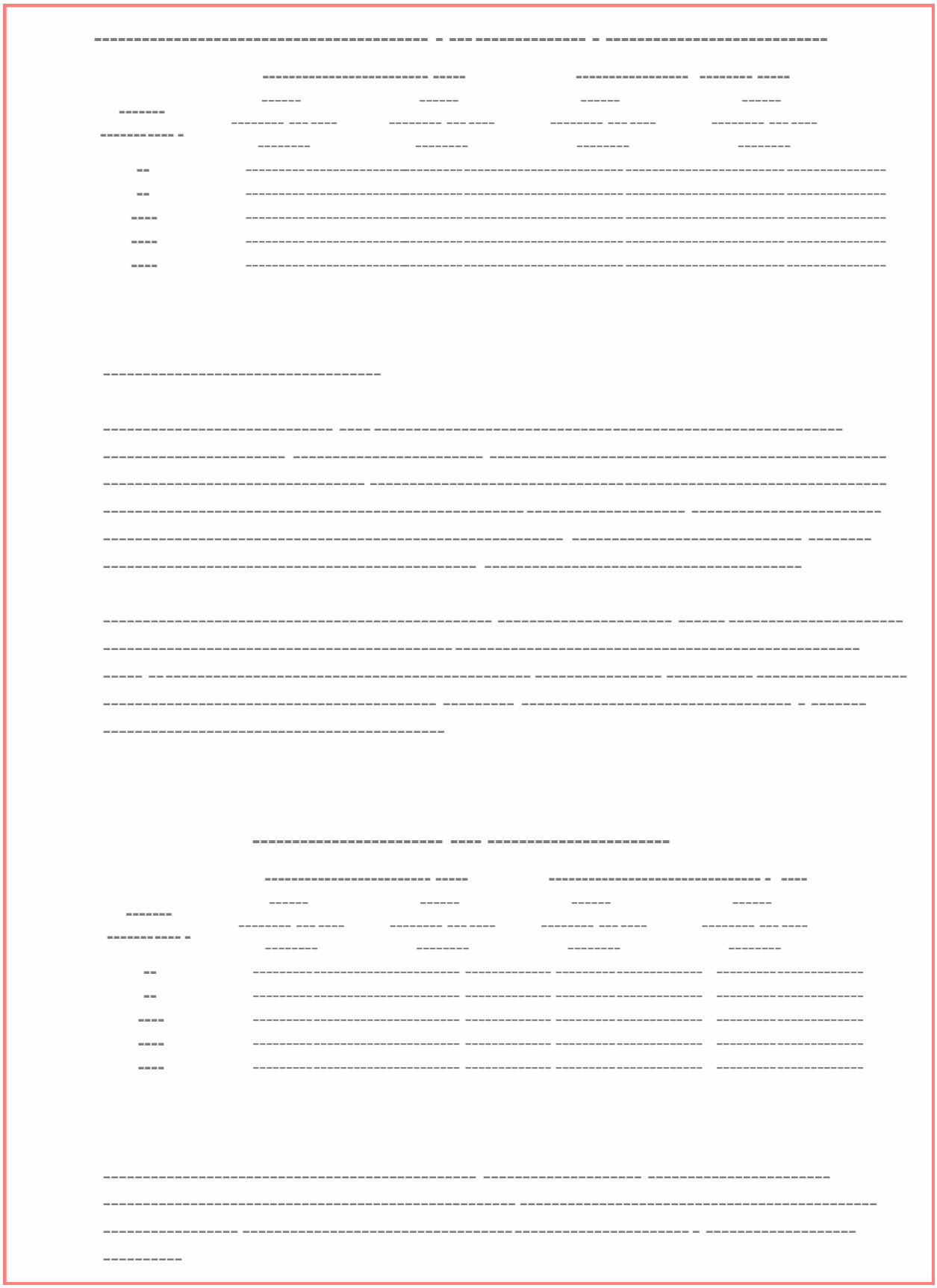


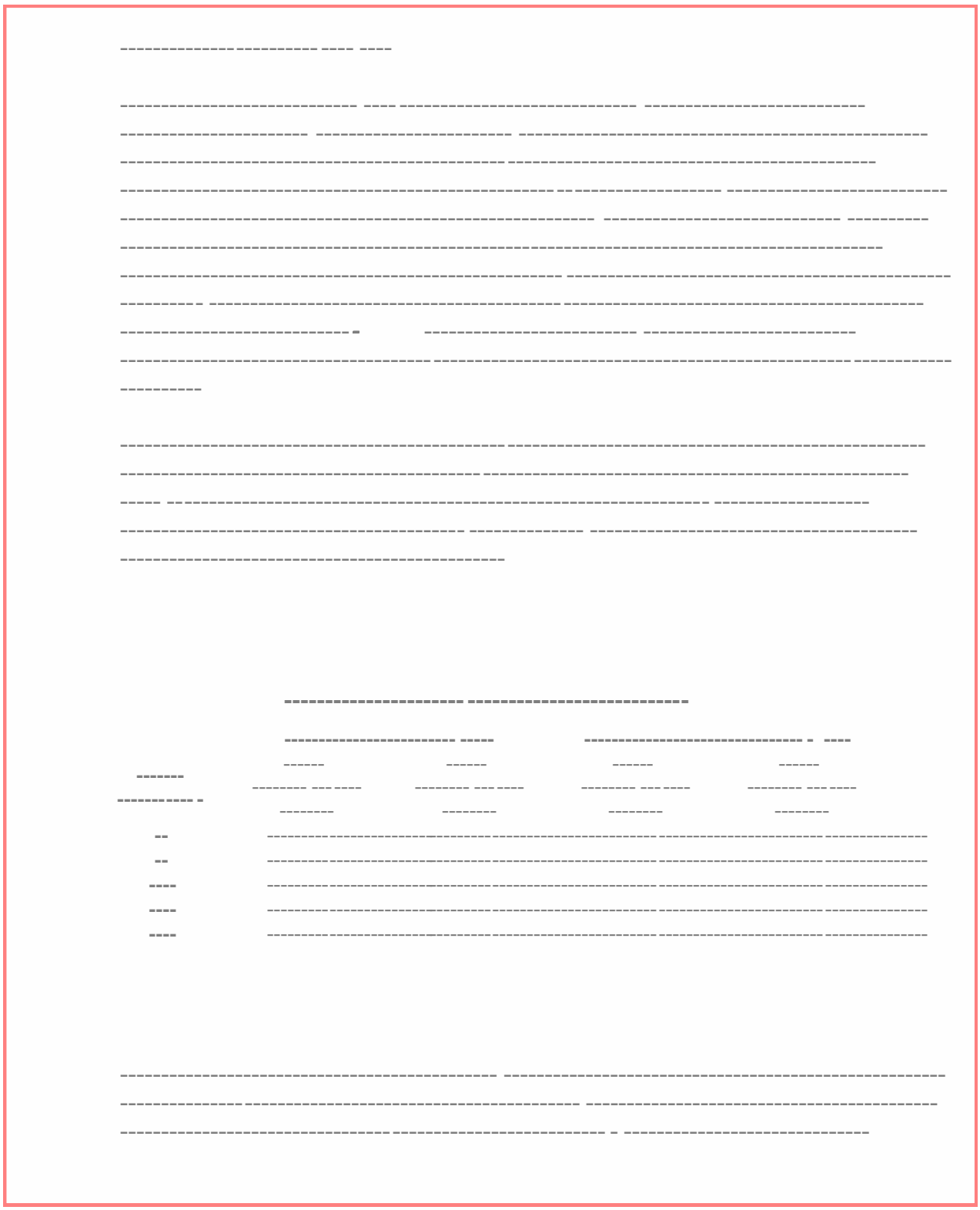
7.3.4 CONTROL MODE FIXED SPEED

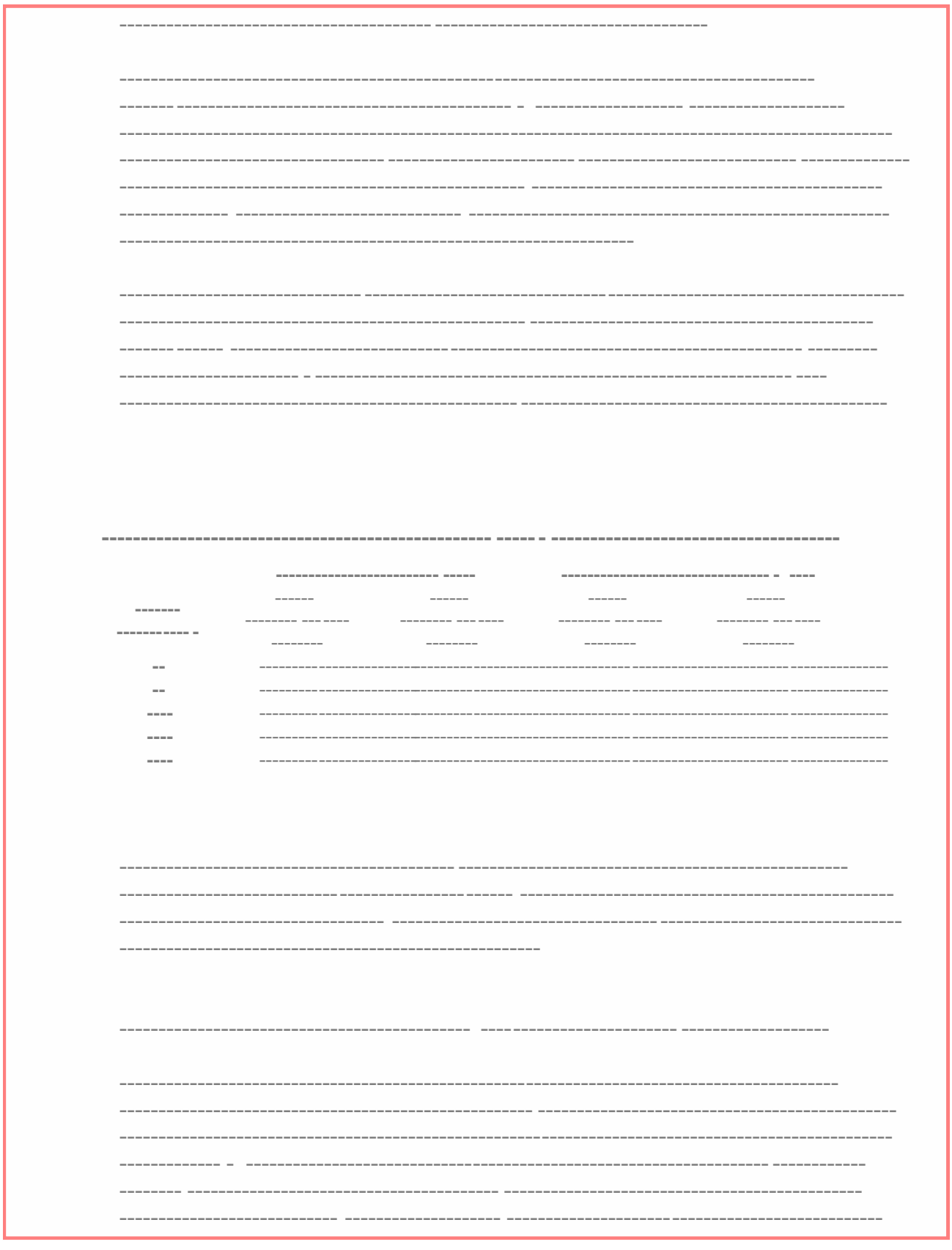
The HeartMate II LVAS intended for commercial distribution operates in a constant, fixed speed mode. This fixed speed may be varied via commands from the System Monitor under the control of qualified, trained medical personnel. The ability to change the fixed speed is not accessible through the wearable System Controller.

7.3.5 HEARTMATE II SYSTEM RELIABILITY

Reliability testing has been conducted on critical components of the HeartMate II system; the pump, outflow cannula, inflow cannula and percutaneous lead. For each *in vitro* reliability test that has been conducted, data are presented below that compare the observed clinical reliability of that component with the *in vitro* results. With one exception, the strain relief at the external end of the percutaneous lead, the clinical reliability confirms the estimated reliability from the *in vitro* studies. The clinical data comparison is based on 133 patients that were presented in the original PMA (refer to “Clinical Data Cohort Identification”, Table 8, pg 23).







7.4 CLINICAL STUDY DESIGN AND MANAGEMENT

7.4.1 BACKGROUND

Mechanical circulatory support (MCS) for treatment of end stage heart failure provides therapy that no drug or drug combination can provide. As evidenced by previous ventricular assist studies, by increasing systemic blood flow, a profound salutary effect is achieved in all organ systems that have not sustained irreversible damage. For damaged organ systems, restoration of perfusion speeds recovery, often providing a starting point for chronic compensation. Extensive experience in the long-term, implantable, circulatory support of transplant eligible patients, along with a lack of growth in worldwide organ availability, has driven the design and development of the next generation of small rotary blood pumps. Smaller than the currently PMA-approved VADs, the Thoratec Corporation HeartMate II Left Ventricular Assist System (LVAS) will allow implantation in a wider range of patients, yet provide flows up to 10L/min. The design intent of this device is for long-term use.

FDA approved IDE G010230 for the HeartMate II Pilot study in the US on May 28, 2003. The same protocol was used to conduct another pilot study simultaneously in Europe. Fifty-three (53) patients were enrolled from November 2003 to December 2004, 31 in the US and 22 in Europe. In November 2005, Thoratec was authorized to apply the European CE Mark to the device, and nearly 300 patients have been implanted commercially in Europe since that time.

On February 18, 2005, the HeartMate II Pivotal protocol was conditionally approved, and the first patient was implanted on March 8, 2005. Full study approval was obtained on May 4, 2005. The HeartMate II Pivotal Trial study protocol was designed to enroll both Bridge to Transplant (BTT) and Destination Therapy (DT) patients under two distinct entry criteria and study endpoints. This Pre-Market Approval (PMA) application is specifically for the BTT indication. The DT study is still underway and will be the subject of another PMA application. BTT enrollment under the HeartMate II Pivotal study was completed upon reaching 133 patients on May 24, 2006. After this date, enrollment for BTT continues under a Continued Access Protocol (CAP) that is identical to the Pivotal study protocol. A copy of the study protocol is provided in Section 7.13 of this Panel Pack.

Key milestones and chronology of the clinical study are shown in Table 6.

Table 6 – HeartMate II Clinical/Regulatory Chronology

Date	Event Description
May 2003	Pilot Study IDE approved
February 2005	Pivotal Study IDE approved (BTT & DT)
November 2005	CE mark authorization
May 2006	Pivotal BTT study enrollment complete (n=133)
	1st BTT CAP approval (90 patients)
November 2006	2nd BTT CAP approval (90 patients)
December 2006	Clinical data module of original PMA submitted to FDA (n=133)
April 2007	Major deficiency letter received from FDA – data update requested
May 2007	Day-100 Meeting between FDA and Thoratec
	3rd BTT CAP approval (60 patients)
July 2007	Major reanalysis submitted to FDA – data updated as of March 16, 2007 (Primary, CAP, Small BSA and Proposed Labeling Cohorts, n=286)
September 2007	4th BTT CAP approval (40 patients)

As shown in Table 7, the HeartMate II has now been implanted in over 1000 patients.

Table 7 – Total HeartMate II Patients (as of September 7, 2007)

Pilot Study (US IDE and EU)	----
US IDE (Pivotal and CAP)	
BTT Arm	----------
DT Arm	----------
Emergency or Compassionate Use	--
Canada Clinical Study	----
Commercial Distribution (EU)	-----
TOTAL:	-------

7.4.2 STUDY ADMINISTRATION AND DESIGN

7.4.2.1 Administration of the Study

The HeartMate II study was administered by Thoratec Corporation with oversight by two committees, the Data and Safety Monitoring Board and Clinical Events Committee. These committees are further described below.

7.4.2.2

7.4.2.3

7.4.2.4 Study Design

The purpose of the HeartMate II study was to determine the safety and efficacy of the HeartMate II as a Bridge to Transplant (BTT) in end-stage heart failure patients who are listed for cardiac transplant but at imminent risk of dying. The HeartMate II BTT pivotal trial was a prospective, non-randomized trial. Study success was defined as survival to transplantation or 180 days of LVAD support while remaining listed as status 1A or 1B. The success rate was compared to an Objective Performance Criterion (OPC) of 75% and considered to be non-inferior if the 95% lower confidence limit is at least 65% (10% margin of non-inferiority).

7.4.2.5 ----------

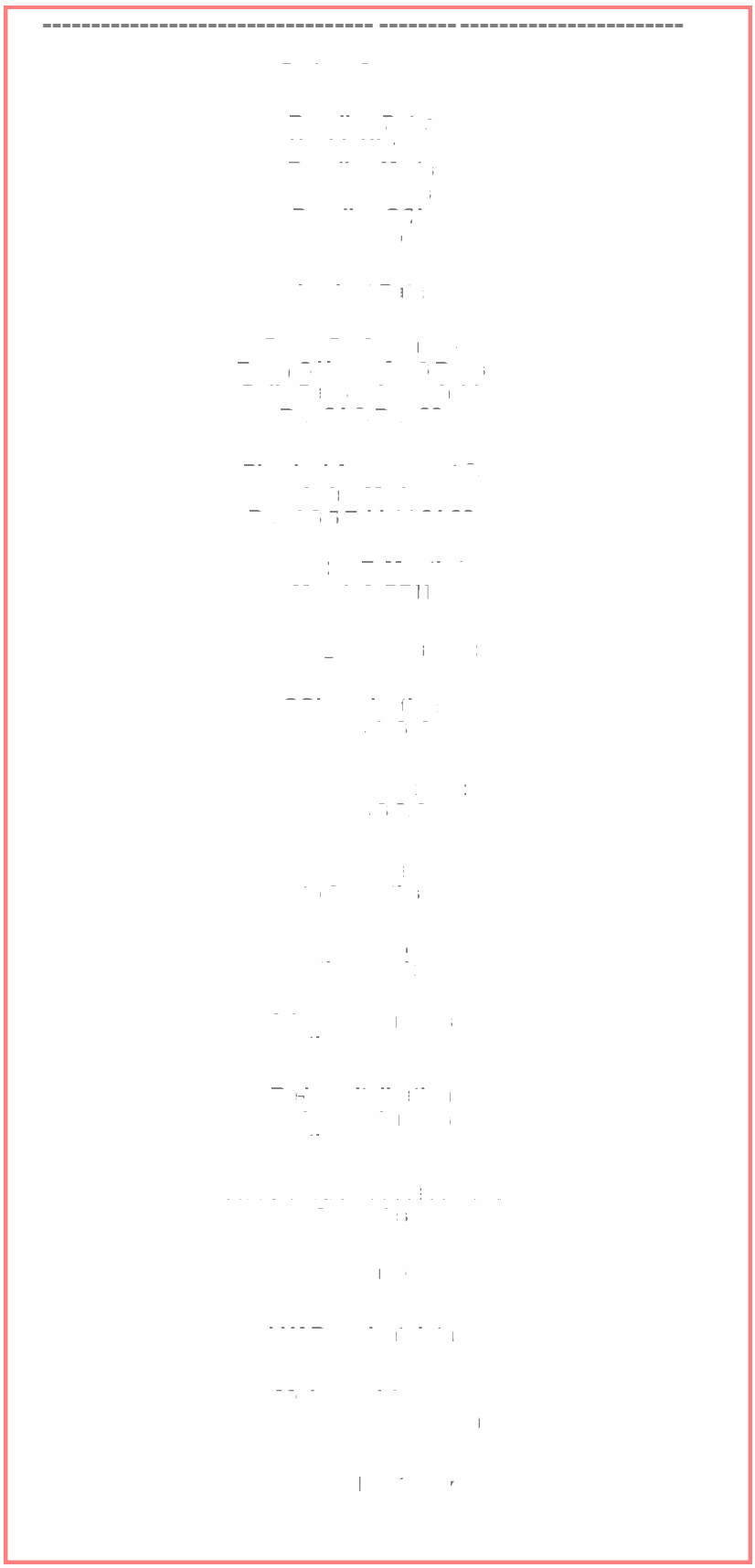
[redacted]

7.4.2.6 [redacted]

[redacted]

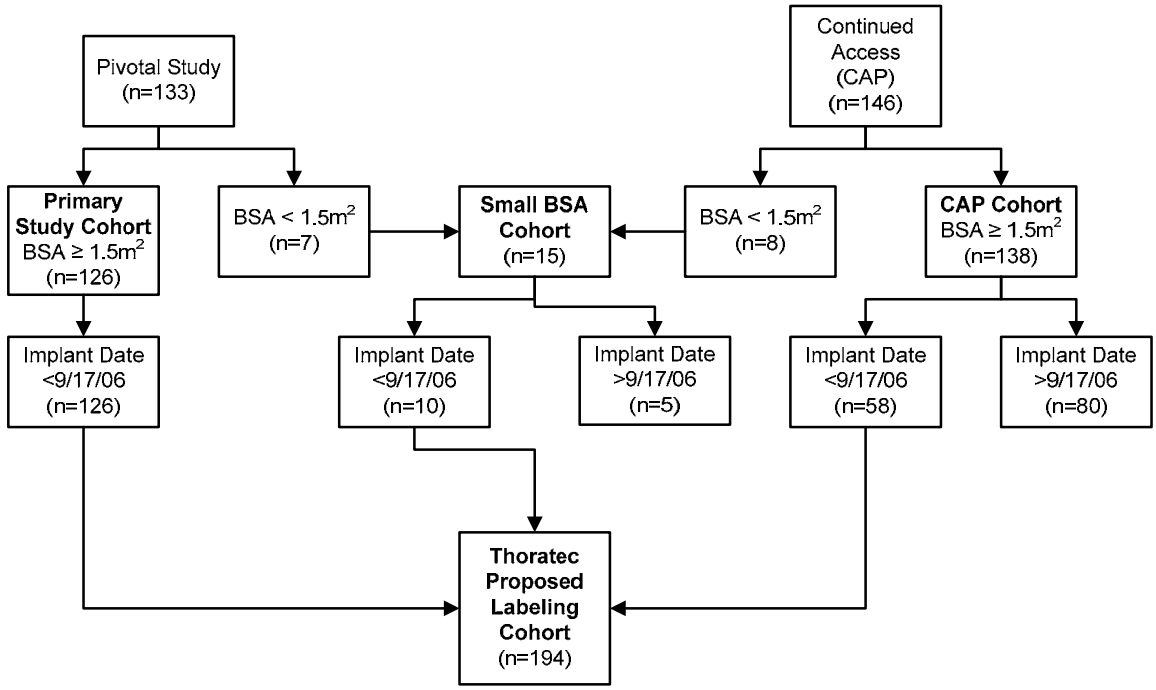
[redacted]

7.4.2.7 [redacted]



[redacted]

Figure 12 – Thoratec Proposed Labeling Cohort



*Patients implanted before September 17, 2006 have been followed for at least 180 days as of the date of the last full data analysis, March 16, 2007

[This page intentionally left blank]

7.5 PRIMARY STUDY COHORT (N=126)

7.5.1 SUMMARY OF PRIMARY STUDY COHORT (N=126)

Adverse event rates are similar to or better than currently approved Thoratec devices. The majority of adverse events occurred within the first 30 days, and then adverse event rates stabilized over time

Three measures of functional status were collected during the study (NYHA Class, Six Minute Walk Test and Patient Activity Evaluation/METs). All three demonstrate statistically significant improvement at follow up durations of 1 month, 3 months and 6 months post implant when compared to baseline. In addition, for the two measures that had published benchmarks, clinically meaningful improvement was observed at these same follow up intervals.

This study evaluated two measures of Quality of Life (Minnesota Living with Heart Failure and Kansas City Cardiomyopathy Questionnaire). Using both of these measures, the data demonstrate statistically significant and clinically meaningful improvement at all follow up intervals.

Multi-center neurocognitive testing was conducted during this study. Because of the small sample size, it is difficult to draw conclusions, however important trends were seen. Significant improvements over time were seen in some of the neurocognitive tests and no significant cognitive decline was

noted. Over time, as the patients stabilized, neurocognitive functions improved and the incidence of adverse events declined.

The data presented also demonstrate the clinical utility of the HeartMate II as a Bridge to Transplant and reasonable assurance of safety and efficacy as evidenced by the following clinical measures:

- The 30-day peri-operative mortality is 10%, which is half of what was observed in the HeartMate VE bridge to transplant study.
- Eighty-four percent (84%) of the HeartMate II patients survived to hospital discharge or transplant.
- Kaplan-Meier analysis of survival to transplant or recovery demonstrates the HeartMate II is non-inferior to the HeartMate VE.
- The cumulative duration of support on the HeartMate II is 22,307 patient days or 61.1 years of support of which 75% was spent outside of the hospital.
- Thirty day post-transplant survival is 97% and 1 year post-transplant survival is 83%.

7.5.2 DATA PRESENTED FOR PRIMARY COHORT

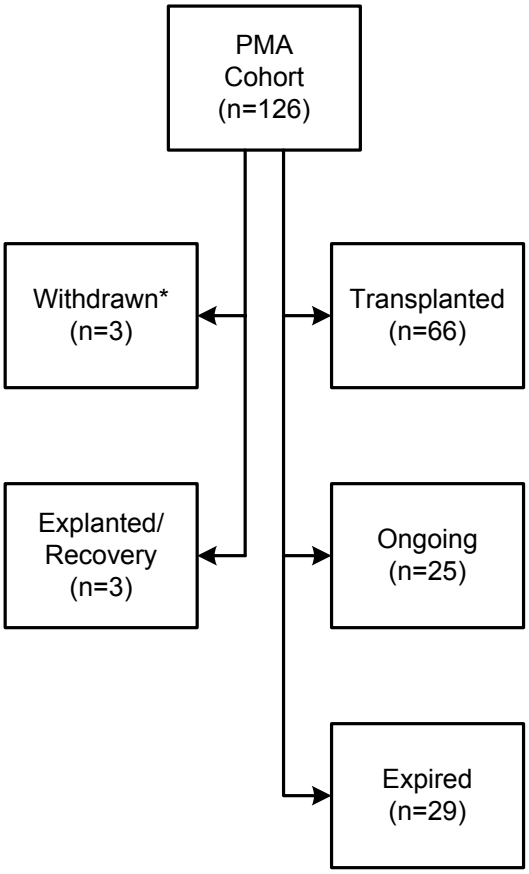
The data presented in this analysis includes the 126 BTT Pivotal study patients with a BSA $\geq$ 1.5. These patients were enrolled from March 8, 2005 to May 24, 2006. Study data presented includes all follow-up data as of March 16, 2007, except where noted otherwise.

7.5.3 STUDY SITES AND ENROLLMENT FOR PRIMARY COHORT

The 126 patients were enrolled at 26 study sites. The list of study sites, investigators and patients enrolled per site can be found in Table 9. Figure 13 displays the patient status.

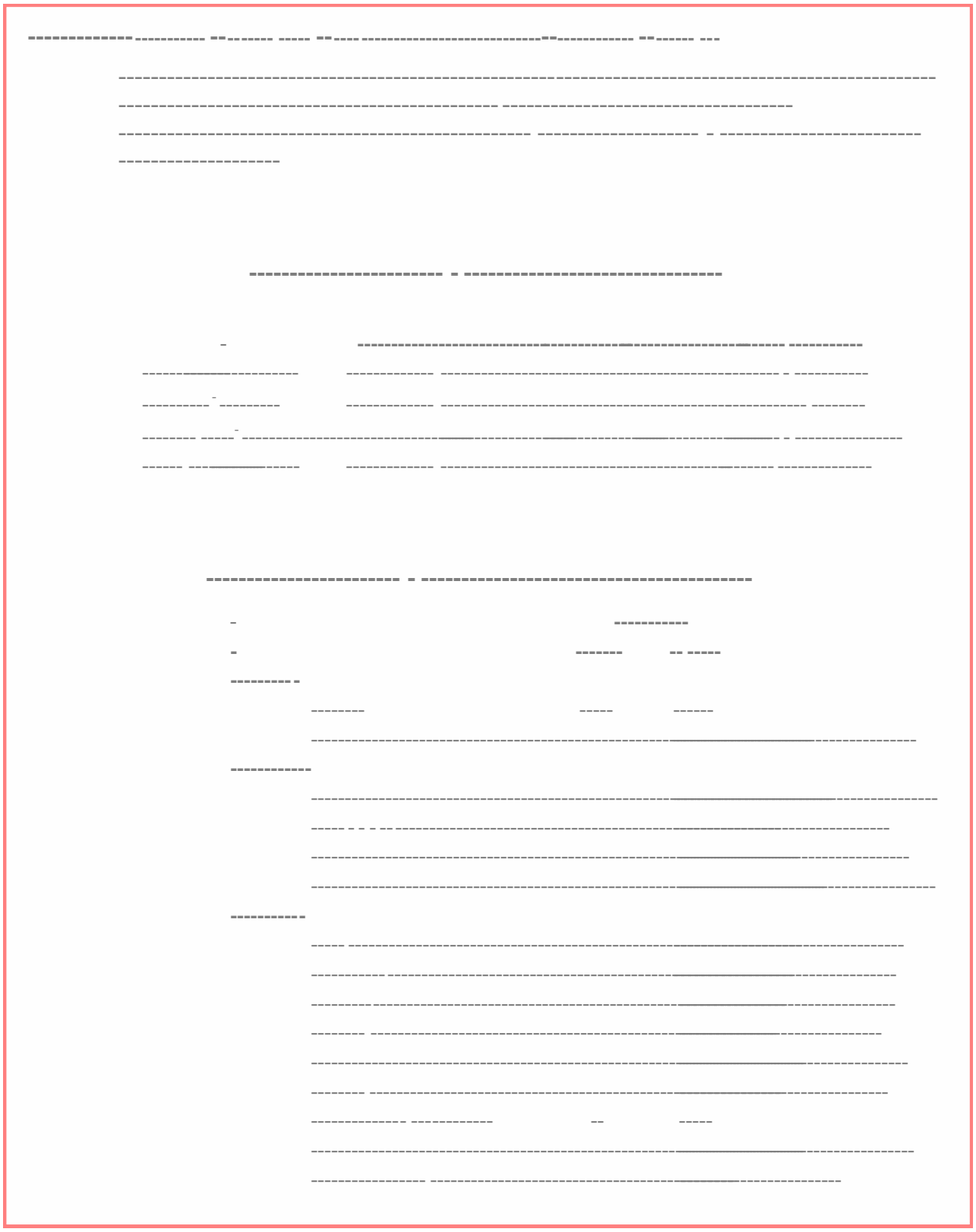
Table 9 – Primary Cohort: Study Sites and Investigators

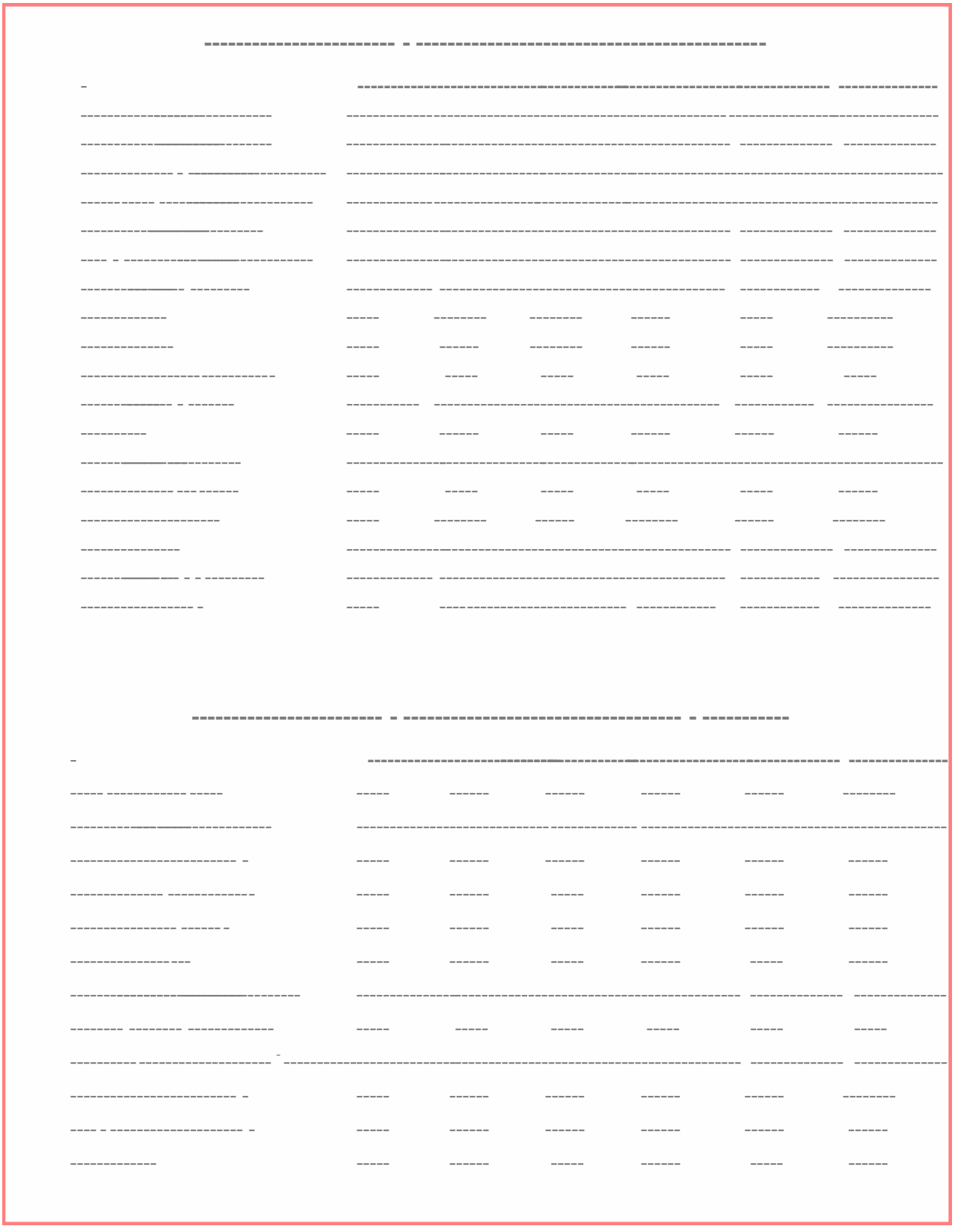
Figure 13 – Primary Cohort: Enrollment and Patient Follow-up as of March 16, 2007

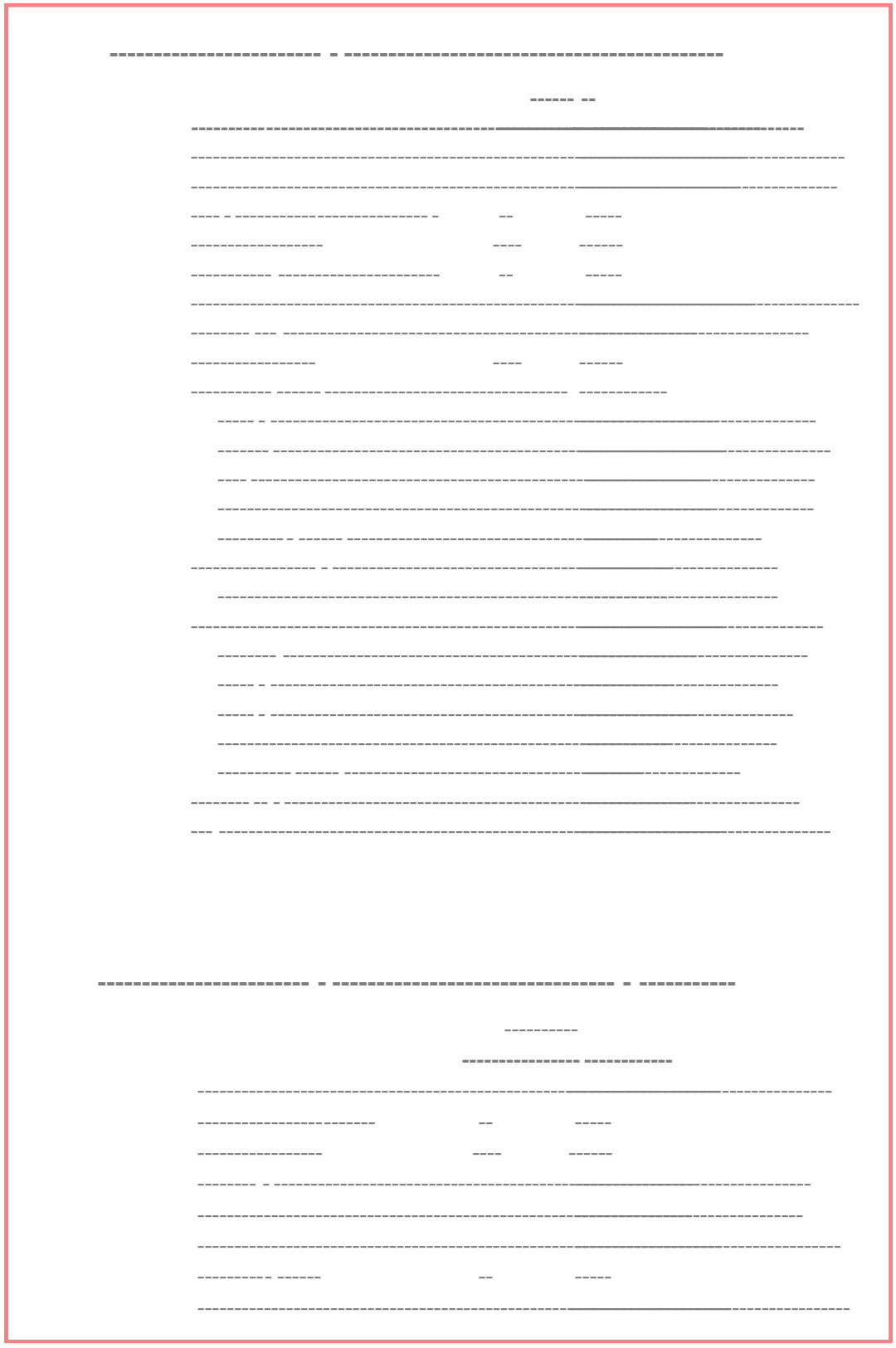


* HeartMate® II Replaced with other devices
(2 received XVE, 1 PVAD devices)

7.5.4 [redacted]







7.5.6 PRE-SPECIFIED PRIMARY ENDPOINT: TRANSPLANT OR SURVIVAL TO 180 DAYS FOR PRIMARY COHORT

As of March 16, 2007, all 126 pivotal patients had achieved a study endpoint defined as survival to transplant or VAD supported for 180 days and UNOS status 1A or 1B listed for transplant. Eighty-four (84) of the 126 HeartMate II patients (67%, 95% LCL 60%) were considered successes. Of these 84, 66 patients received a heart transplant, 3 patients were explanted due to recovery, and 15 patients were supported for more than 180 days while remaining listed 1A or 1B. Forty-two (42) patients were counted as failures, including 14 patients that were supported at least 180 days but not listed 1A or 1B at 180 days. Using a z-statistic:

- The null hypothesis is not rejected that the HeartMate II success is less than or equal to the OPC – 10% delta (P=0.3474, one-sided), and
- The alternative hypothesis is not accepted that the HeartMate II success is greater than the OPC – 10% delta
- The primary study endpoint has not been achieved on the basis of hypothesis testing using the pre-specified endpoint defined in the protocol

Table 18 provides a summary of the successful and not successful patient endpoints as of March 16, 2007

Table 18 – Primary Cohort: Pre-specified Analysis of Patient Status as of March 16, 2007

Success	**# Pts**	**% Pts**	**LCL**
Transplanted	66	52.4%	
Recovered	3	2.4%	
Supported ≥ 180 days and Status 1A or 1B	15	11.9%	
Total Success	**84**	**66.7%**	**59.8%**
Not Success	**# Pts**	**% Pts**	**LCL**
Expired < 180 days	25	19.8%	
Supported ≥ 180 days but not Status 1A or 1B	14	11.1%	
Received other VAD; Treatment failure	3	2.4%	
Total Not Success	**42**	**33.3%**	**26.4%**

Table 19 provides an update of the pre-specified study endpoint as requested by FDA. Between March 16, 2007 and September 14, 2007, five patients originally counted as "not success" due to not being listed 1A or 1B at 180 days were subsequently transplanted or explanted due to myocardial recovery and are now counted as study "success" patients.

Table 19 – Primary Cohort: Pre-specified Analysis of Patient Status as of September 14, 2007

Success	**# Pts**	**% Pts**	**LCL**
Transplanted	72	57.1%	
Recovered	4	3.2%	
Supported ≥ 180 days and Status 1A or 1B	13	10.3%	
Total Success	**89**	**70.6%**	**64.0%**
Not Success	**# Pts**	**% Pts**	**LCL**
Expired < 180 days	25	19.8%	
Supported ≥ 180 days but not Status 1A or 1B	9	7.1%	
Received other VAD; Treatment failure	3	2.4%	
Total Not Success	**37**	**29.4%**	**26.4%**

7.5.7 OUTCOMES FOR PRIMARY COHORT

7.5.7.1 Overall Outcomes for Primary Cohort

This section analyzes outcome data, which is based on the actual patient status as of March 16, 2007, regardless of the patient's pre-specified endpoint status. Patients who were ongoing at day 180 (the pre-specified study endpoint) but expire thereafter are counted as "expired", and patients who were ongoing at day 180 and remain ongoing as of March 16, 2007 are counted as "ongoing."

As of March 16, 2007, 52% (66/126) of patients have received a heart transplant, 2% (3/126) of patients have been explanted for myocardial recovery, 23% (29/126) of patients have expired on support, 2% (3/126) of patients have withdrawn from the study after re-implantation with a VAD other than the HeartMate II, and 20% (25/126) of patients remain on HeartMate II support. Ninety-eight of the 126 patients (78%) were either transplanted, recovered, or supported 180 days without regard for transplant status at 180 days.

The 30 day (peri-operative) mortality was 10% (12/126 patients). This is half the peri-operative mortality reported in the HeartMate VE Trial (20%). Eighty-four percent (106/126) of patients survived to hospital discharge or transplant.

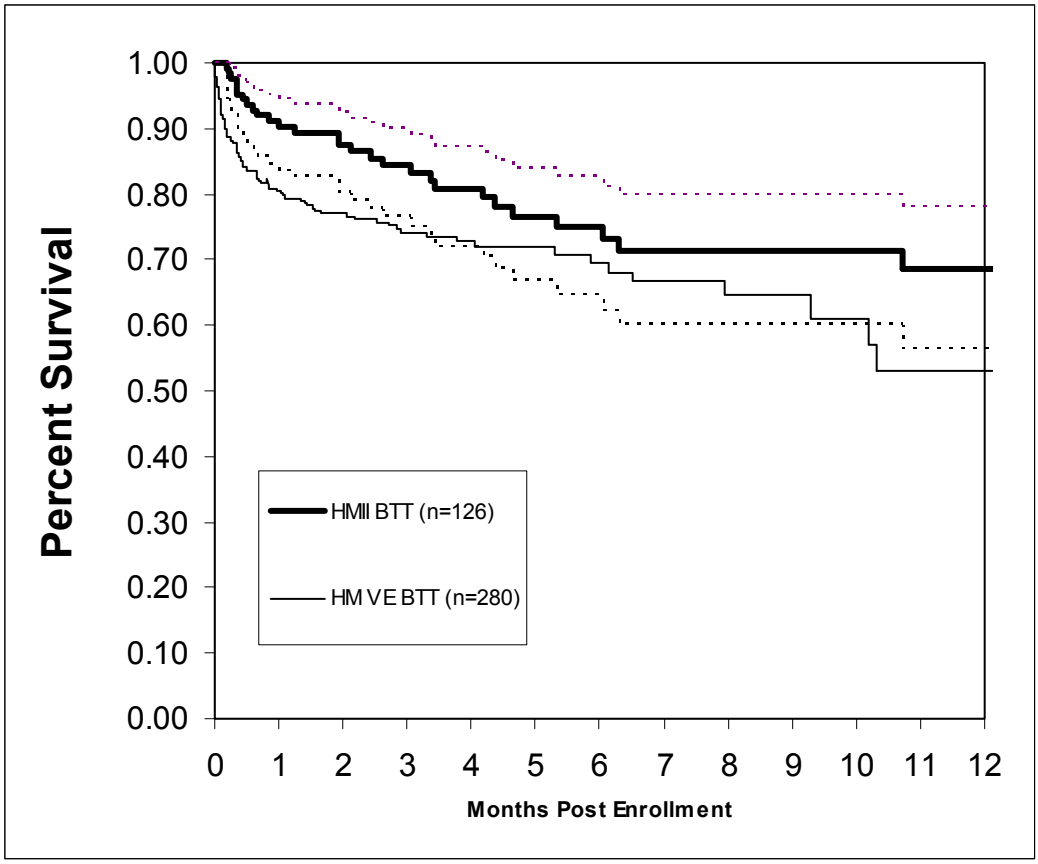
As of March 16, 2007, 52% (66/126) of patients have received a cardiac transplant. The median time to transplant for patients that received a transplant was 96.5 days with a range between 15 and 471 days. Post-transplant survival for these patients is presented in Section 7.5.16 and was 97% at 1 month and 83% at 1 year.

The overall median duration of support was 117 days (mean = 177 days, range = 1–672 days). The cumulative duration of support was 61 patient years.

A Kaplan-Meier curve demonstrating survival to transplant or recovery is provided in Figure 14 and Table 20. The Kaplan-Meier only counts patient deaths as an event and patients are censored at the time of transplant, recovery, study withdrawal, or ongoing day at the time of analysis. The 30 day survival was 90.3% ± 2.7% (survival ± SE %), the 90 day survival was 84.5% ± 3.4%, the 180 day survival = 74.9% ± 4.6%, and the 360 days survival =

68.5% ± 5.5%. For comparison purposes the Kaplan-Meier curve of the HeartMate VE LVAS Bridge to transplant trial is included[1] which was 80.5% at 30 days, 69.5% at 180 days, and 53.1% at 360 days.

Figure 14 – Primary Cohort: Kaplan Meier Plot Illustrating the Probability of Survival to Transplant or Recovery; HeartMate II vs. HeartMate VE LVAS Clinical Trial Data



Note: Dotted lines represent 95% confidence interval for HeartMate II patients
See Table 20 for tabular data

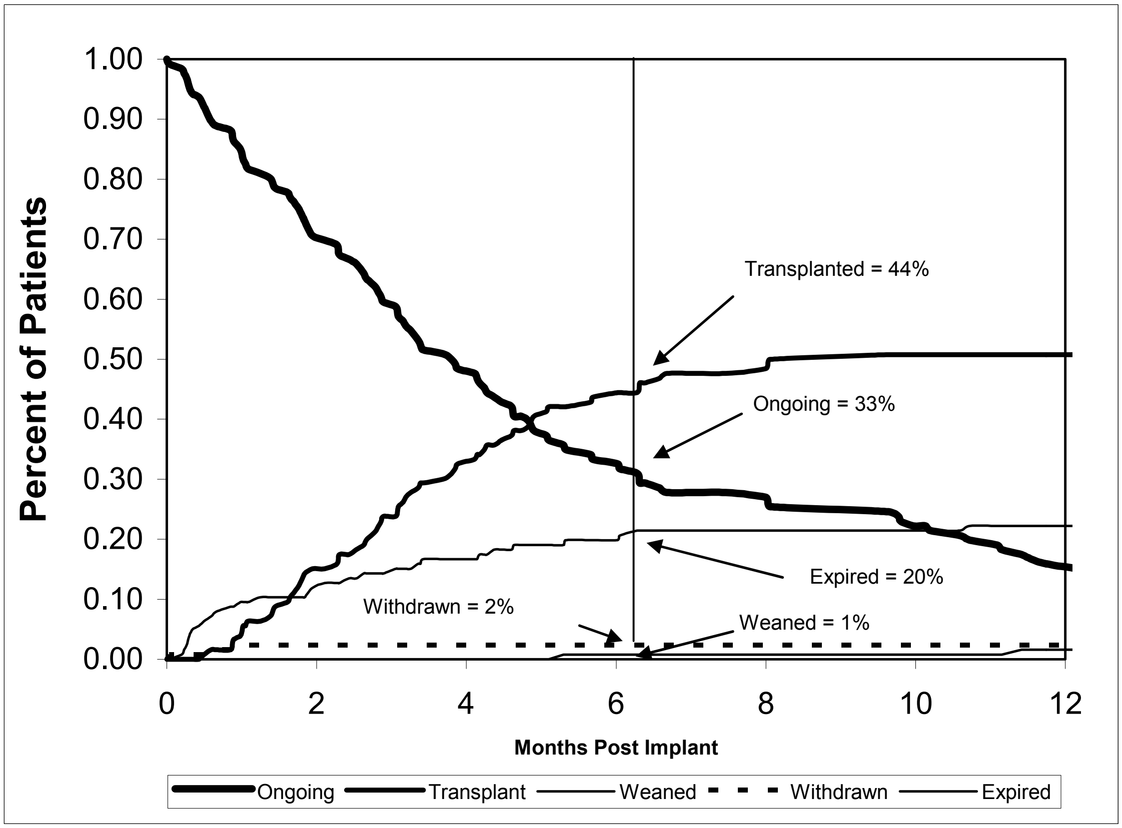
[1] HeartMate VE LVAS; IDE G900049, PMA P920014/S7

Table 20 – Primary Cohort: HeartMate II Survival with HeartMate VE LVAS Clinical Trial Data as Comparison

HeartMate II								
	Time Interval (Months)							
	0 - 1	**1 - 2**	**2 -3**	**3 - 4**	**4 - 5**	**5 - 6**	**6 - 12**	**12 - 24**
Number of patients starting interval	126	107	89	75	61	48	42	20
Number of patients who died this interval	12	3	3	3	3	1	3	1
Number of cumulative patient deaths	12	15	18	21	24	25	28	29
Number of patients censored in interval	7	15	11	11	10	5	19	19
Number of cumulative censored patients	7	22	33	44	54	59	78	97
Probability of surviving interval	0.903	0.875	0.845	0.809	0.766	0.749	0.685	0.000
+/- 95% Confidence Limit at end of interval	0.05	0.06	0.08	0.09	0.10	0.11	0.17	---
HeartMate VE LVAS								
	Time Interval (Months)							
	0 - 1	**1 - 2**	**2 -3**	**3 - 4**	**4 - 5**	**5 - 6**	**6 - 12**	**12 - 24**
Number of patients starting interval	280	215	179	129	96	66	53	13
Number of patients who died this interval	54	9	6	2	1	2	6	2
Number of cumulative patient deaths	54	63	69	71	72	74	80	82
Number of patients censored in interval	11	27	44	31	29	11	34	2
Number of cumulative censored patients	11	38	82	113	142	153	187	189
Probability of surviving interval	0.805	0.770	0.741	0.728	0.720	0.695	0.531	0.000
+/- 95% Confidence Limit at end of interval	0.05	0.05	0.07	0.08	0.09	0.10	0.20	---

A competing outcomes plot of the HeartMate II Primary Study Cohort data (n=126) is provided in Figure 15 to allow comparison of the HeartMate II outcomes to other VAD post approval commercial experience collected and summarized in INTERMACS quarterly reports. The data show that at six months, 44% of the HeartMate II patients were transplanted, 32% were ongoing, 20% had expired, 2% were withdrawn and 1% had recovered sufficiently to have the device removed.

Figure 15 – Primary Study Cohort: Competing Outcome Plot of HeartMate II BTT Data (n=126) as of March 16, 2007



[redacted]

7.5.8 SAFETY: ADVERSE EVENTS FOR PRIMARY COHORT

Table 28 presents all of the adverse events experienced in the study cohort, and Table 29 presents only the serious events. Adverse events were classified as serious if they resulted in death or were life threatening, resulted in permanent disability, required hospitalization or a prolonged hospital stay. The number of patients, percent of patients, number of events and number of serious events for each adverse event is presented. Further tables present the time to adverse events. In addition, detailed tables are presented for strokes, other neurological events, right heart failure and hemolysis.

Table 28 – Primary Cohort: All Adverse Events

	n = 126				
	# Pts	**% Pts**	**UCL**	**LCL**	**# Events**
Bleeding*	87	69%	77%	61%	163
Bleeding requiring surgery	37	29%	37%	21%	42
Stroke	11	9%	14%	4%	11
Peri-operative (≤ POD2)	5	4%	7%	1%	5
Post-operative (> POD2)	6	5%	8%	1%	6
Other Neurological**	11	9%	14%	4%	12
Local Infection	36	29%	36%	21%	69
Percutaneous Lead Infection	17	13%	19%	8%	22
Pocket Infection	2	2%	4%	0%	2
Sepsis	26	21%	28%	14%	37
Right Heart Failure	22	17%	24%	11%	23
Peripheral TE	10	8%	13%	3%	11
Respiratory Failure	32	25%	33%	18%	41
Cardiac Arrhythmias	76	60%	69%	52%	135
Renal Failure	17	13%	19%	8%	18
Hepatic Dysfunction	3	2%	5%	0%	3
Device Thrombosis	2	2%	4%	0%	2
Hemolysis	3	2%	5%	0%	3
Psychological	8	6%	11%	2%	10
Myocardial Infarction	1	1%	2%	0%	1
Confirmed Malfunctions	39	31%	39%	23%	62

*Bleeding requiring PRBC ≥ 2 units or surgery
**Includes transient ischemic attacks (TIA) and non-stroke neurological events.

Table 29 – Primary Cohort: Serious Adverse Events

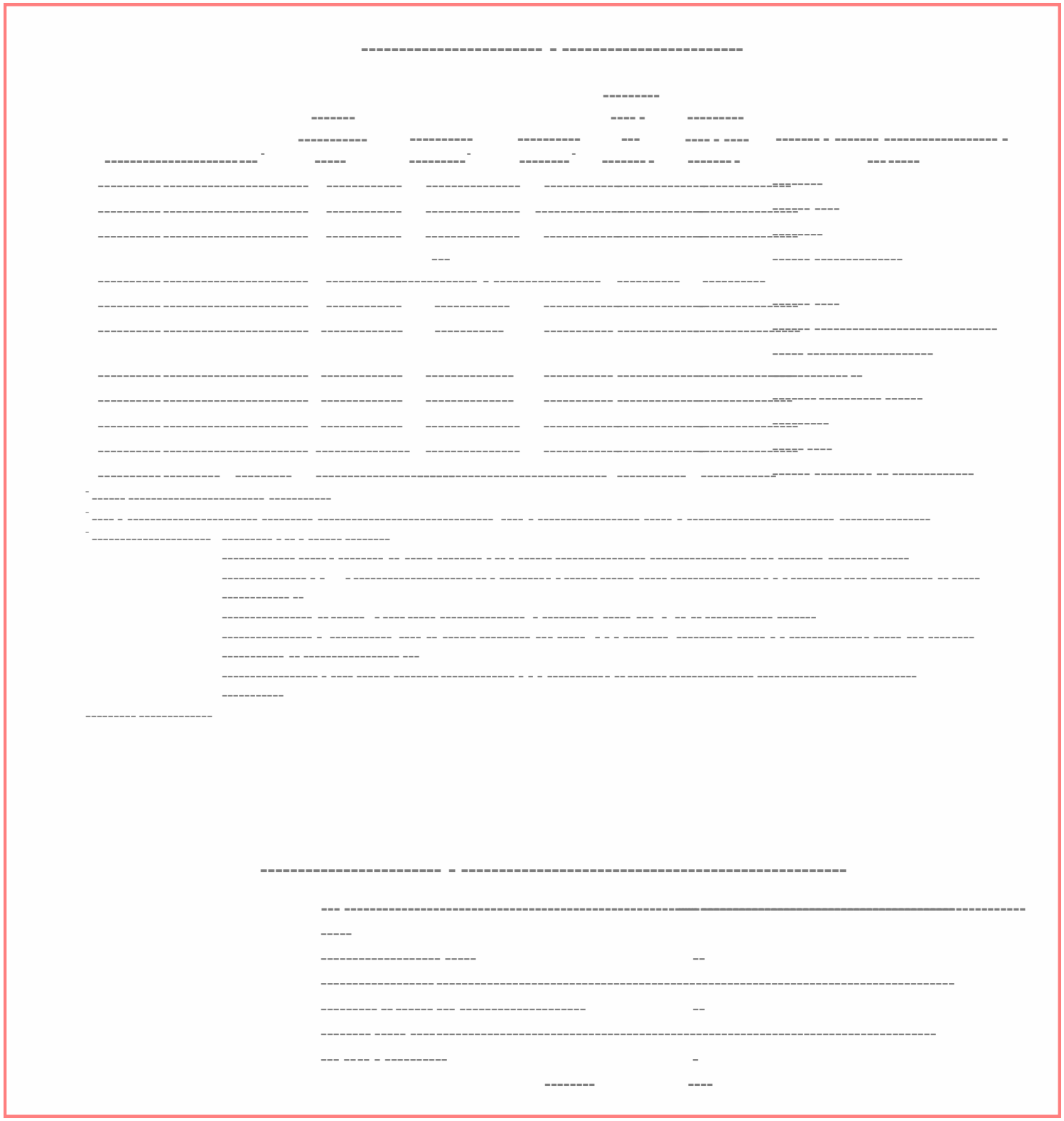
	n = 126				
	# Pts	% Pts	UCL	LCL	# Events
Bleeding*	74	59%	67%	50%	132
Bleeding requiring surgery	37	29%	37%	21%	42
Stroke	11	9%	14%	4%	11
Peri-operative (≤ POD2)	5	4%	7%	1%	5
Post-operative (> POD2)	6	5%	8%	1%	6
Other Neurological**	10	8%	13%	3%	11
Local Infection	25	20%	27%	13%	41
Percutaneous Lead Infection	9	7%	12%	3%	11
Pocket Infection	2	2%	4%	0%	2
Sepsis	25	20%	27%	13%	36
Right Heart Failure	22	17%	24%	11%	23
Peripheral TE	9	7%	12%	3%	10
Respiratory Failure	32	25%	33%	18%	41
Cardiac Arrhythmias	55	44%	52%	35%	91
Renal Failure	17	13%	19%	8%	18
Hepatic Dysfunction	3	2%	5%	0%	3
Device Thrombosis	2	2%	4%	0%	2
Hemolysis	3	2%	5%	0%	3
Psychological	2	2%	4%	0%	4
Myocardial Infarction	1	1%	2%	0%	1
Confirmed Malfunctions	8	6%	11%	2%	8

*Bleeding requiring PRBC ≥ 2 units or surgery
**Includes transient ischemic attacks (TIA) and non-stroke neurological events.

Table 30 – Primary Cohort: All Adverse Event Rates per Patient Year by Time Interval

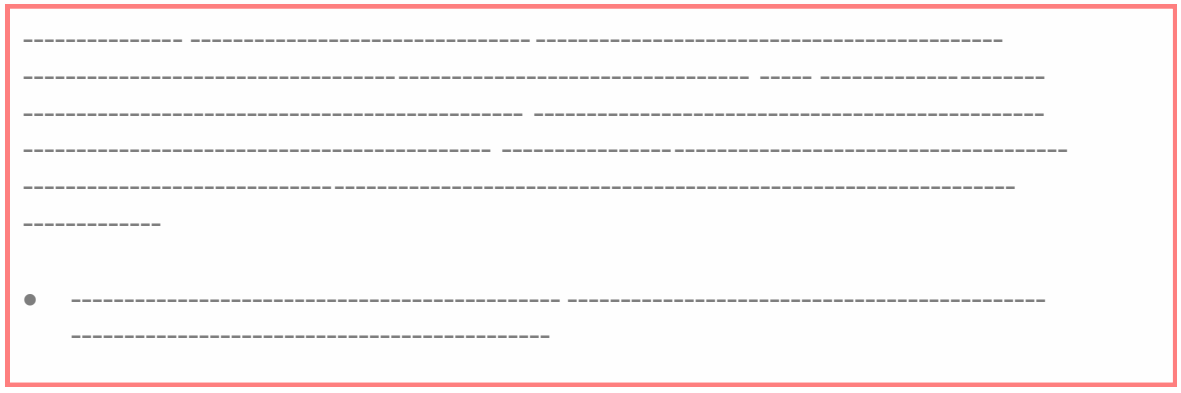
	n = 126				
	0 – 7 days	**8 - 30 days**	**31 – 90 days**	**91 - 180 days**	**> 180 days**
Cumulative years support	2.40	7.24	15.00	13.71	22.71
Adverse Event					
Bleeding	35.42	5.25	1.53	0.58	0.40
Stroke	1.25	0.28	0.00	0.22	0.04
Other Neurological*	1.25	0.41	0.27	0.15	0.09
Local Infection	2.92	0.69	0.33	0.15	0.00
Percutaneous Lead Infection	0.00	0.00	0.13	0.07	0.00
Pocket Infection	0.00	0.00	0.00	0.00	0.04
Sepsis	0.83	0.28	0.00	0.07	0.04
Right Heart Failure	2.08	1.66	0.33	0.00	0.04
Peripheral TE	1.25	0.83	0.13	0.00	0.00
Respiratory Failure	7.50	1.66	0.47	0.22	0.04
Cardiac Arrhythmias	24.58	4.01	1.47	1.09	0.44
Renal Failure	3.75	0.69	0.13	0.15	0.00
Hepatic Dysfunction	0.42	0.14	0.07	0.00	0.00
Device Thrombosis	0.42	0.00	0.07	0.00	0.00
Hemolysis	0.83	0.00	0.00	0.00	0.04
Psychological	1.67	0.14	0.07	0.29	0.00
Myocardial Infarction	0.00	0.00	0.07	0.00	0.00
Confirmed Malfunctions	7.08	1.38	0.60	0.95	0.57

*Includes transient ischemic attacks (TIA) and non-stroke neurological events.



7.5.13 FUNCTIONAL STATUS OF PRIMARY COHORT

One of the secondary objectives of the HeartMate II study was to obtain information on the patients' functional status during VAD support. Functional status was measured by the NYHA classification, the Six Minute Walk Test, and patient activity score.



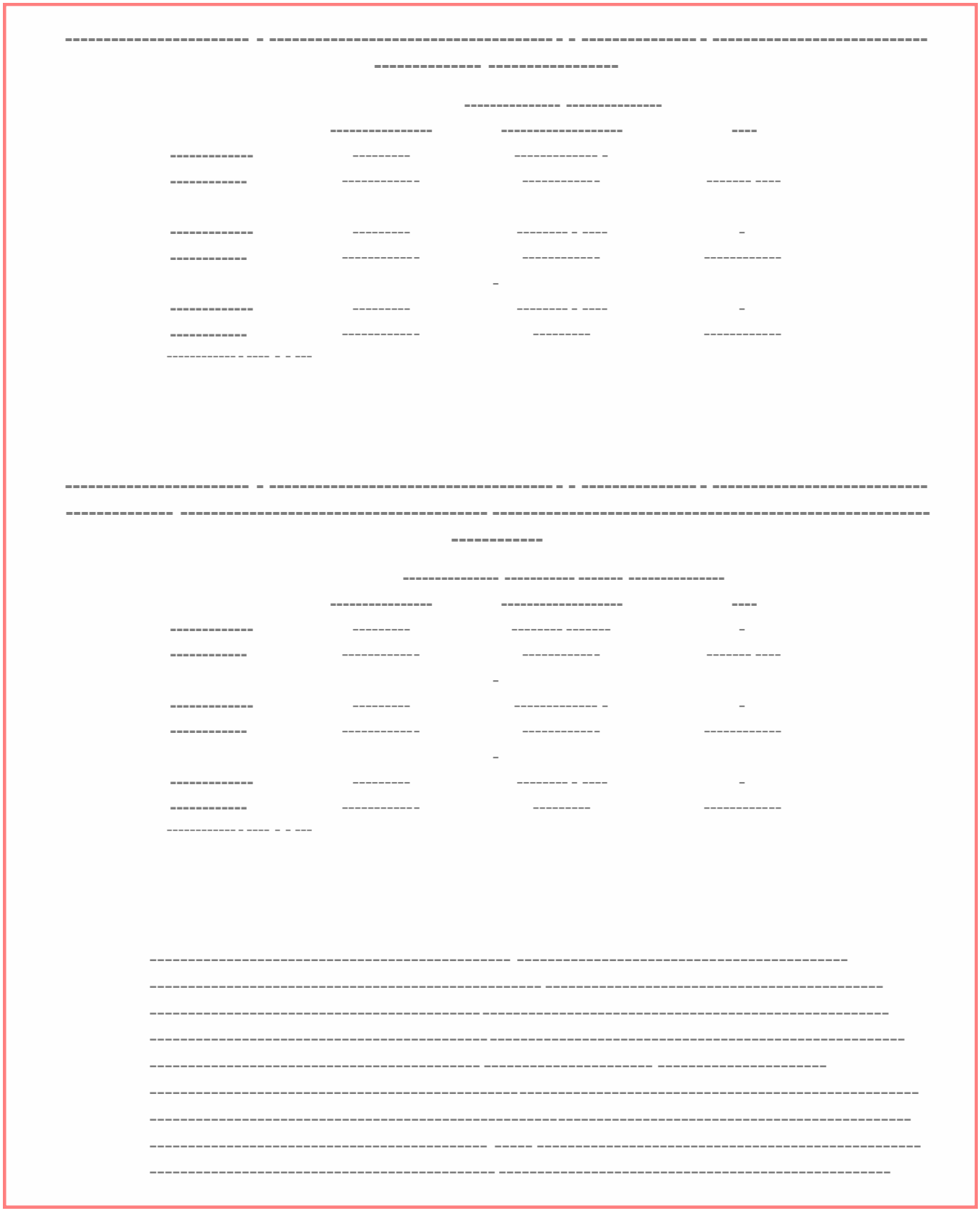
7.5.13.1 NYHA Classification for Primary Cohort

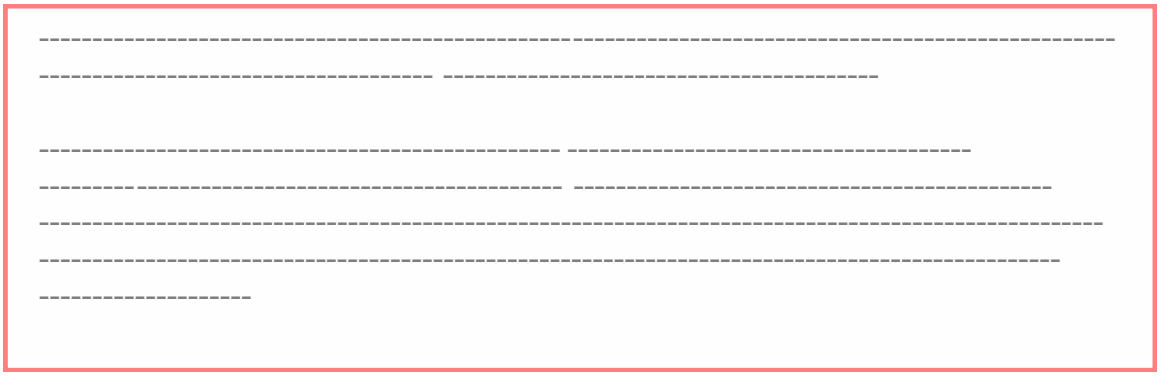
NYHA functional class was assessed by an independent assessor at baseline and post implant at month 1, initial hospital discharge, 3 and 6 months. The independent assessor was defined as a nurse, cardiologist or other medical staff not directly involved with the patients care at that time. NYHA status over time is displayed in the next three tables.

The analysis is performed in two ways. First by ignoring the missing data, and then by assigning the worst case (NYHA Class IV) to the missing follow-up data.

Table 42 – Primary Cohort: NYHA Class over Time

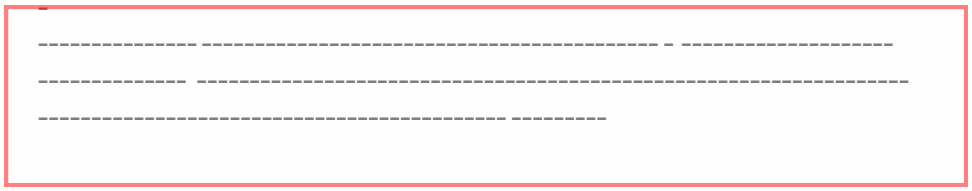
Interval	Baseline	Month 1	Month 3	Month 6
Number of patients at interval	126	107	75	41
Number of patients with missing data	0	8	4	0
Patients at NYHA IV	125 (99%)	4 (4%)	2 (3%)	0 (0%)
Patients at NYHA IIIB	1 (1%)	13 (13%)	2 (3%)	1 (2%)
Patients at NYHA IIIA	0 (0%)	18 (18%)	7 (10%)	2 (5%)
Patients at NYHA II	0 (0%)	47 (47%)	36 (51%)	19 (46%)
Patients at NYHA I	0 (0%)	17 (17%)	24 (34%)	19 (46%)





7.5.13.2 Six Minute Walk Test for Primary Cohort

A second measure to assess functional improvement was the six minute walk test, which documented the number of meters a patient could walk in six minutes. Assessments were performed at baseline (if the patient was able to perform) and post implant at 1 month, 3 months and 6 months. Patients unable to walk due to a medical condition (ie; IABP in place; IV Inotropes; in ICU; leg or foot problem) and patients who refused to walk were assigned a score of zero meters walked.



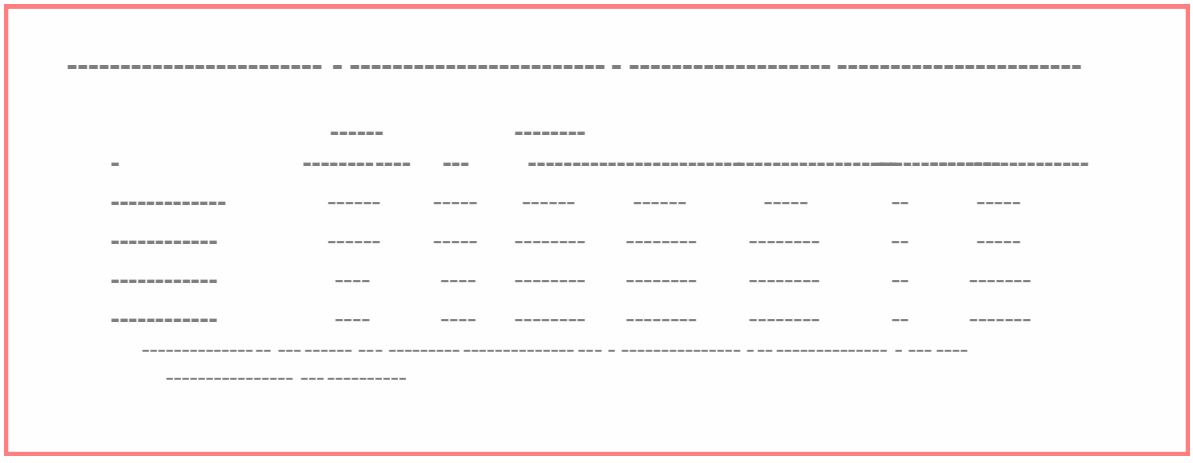
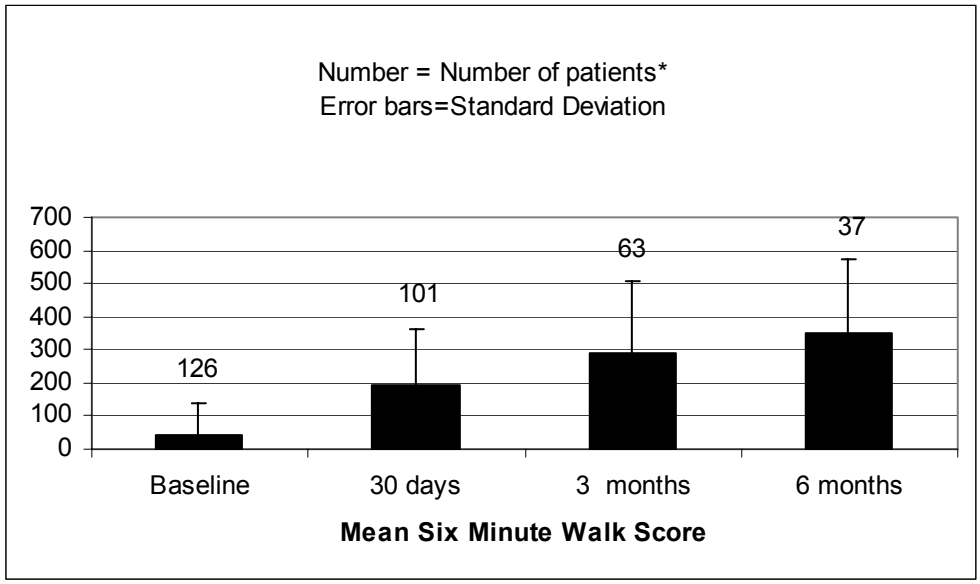


Table 47 – Primary Cohort: Median Distance Walked during Six Minute Walk Test; Change over Time Compared to Baseline

	Baseline	Month 1	Month 3	Month 6
Number of patients at interval	126	106	75	41
Number of patients who performed test	23	69	49	33
Number of patients unable to perform test due to medical reason or refusal[1]	103	32	14	4
Number of patients with missing data	0	5	12	4
Worse than baseline	na	9	4	2
Same as baseline	na	29	12	2
1 - 200m better than baseline	na	20	10	5
200 - 499m better than baseline	na	41	32	24
500+m better than baseline	na	2	5	4

1. patient assigned score of 0 meters walked

Figure 16 – Primary Cohort: Six Minute Walk; Mean Meters Walked over Time



*patients with data who perform test, or who are medically unable to perform test and assigned zero

In summary, the improvements in six minute walk test results were both statistically significant and clinically meaningful.

[2] Abraham WT, et al. Cardiac Resynchronization in Chronic Heart Failure. New England Journal of Medicine, 2002; 346: 1845-1851.

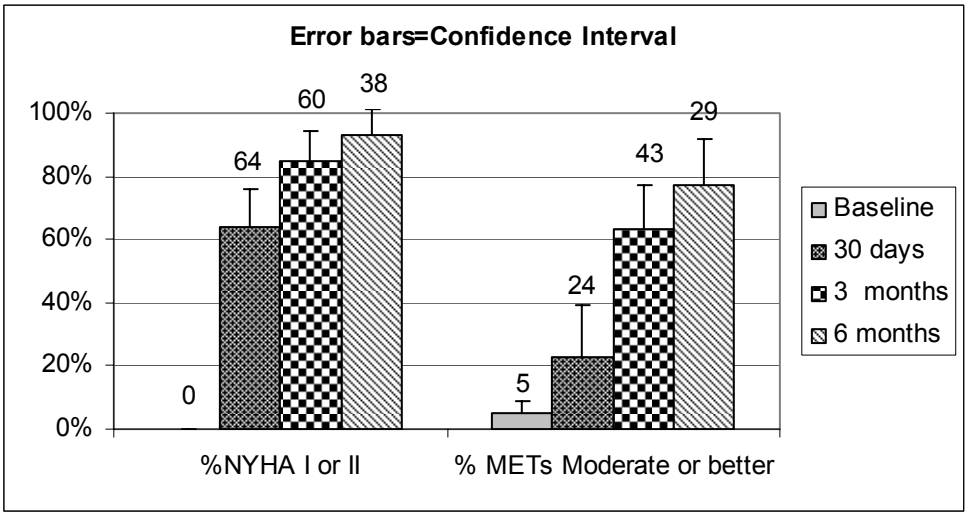
7.5.13.3 Patient Activity Evaluation for Primary Cohort

A third measure to assess functional improvement was documenting the patient's level of activity via a Metabolic Equivalent score (METs). Patients were asked to describe their highest level of activity for the reporting period. This was collected at baseline and post-implant at 1 month, 3 months and 6 months. A summary of patients' MET scores over time is provided in Table 50.

Table 50 – Primary Cohort: MET Scores over Time

	# of Patients			
	Baseline	**Month 1**	**Month 3**	**Month 6**
# Patients at interval	126	106	75	41
# Patients with missing data	2	1	4	2
Very Low (METs < 1)	64	12	4	0
Low (METs 1-2)	54	68	22	9
Moderate (METs 2-4)	6	23	25	10
High (METs 4-6)	0	2	12	13
Very High (METs >6)	0	0	8	7

Figure 17 – Primary Cohort: Percent of Patients Achieving NYHA Class I/II or METs Moderate or Better



In summary, patients experienced a highly significant improvement in Patient Activity Score at all intervals tested when compared to baseline scores. Highly significant improvements were also seen when patients with missing baseline data were assigned a 'best case' score of Very High, and patients with missing follow up data were assigned a 'worst case' score of Very Low.

7.5.14 QUALITY OF LIFE ASSESSMENT FOR PRIMARY COHORT

The quality of life (QOL) was assessed by administering the following QOL instruments:

- Minnesota Living with Heart Failure Questionnaire (MLWHF)
- Kansas City Cardiomyopathy Questionnaire (KCCQ)

Patients completed the MLWHF questionnaire and the KCCQ at baseline and post implant at 1 month, 3 months and 6 months. Both questionnaires show improvement in QOL.

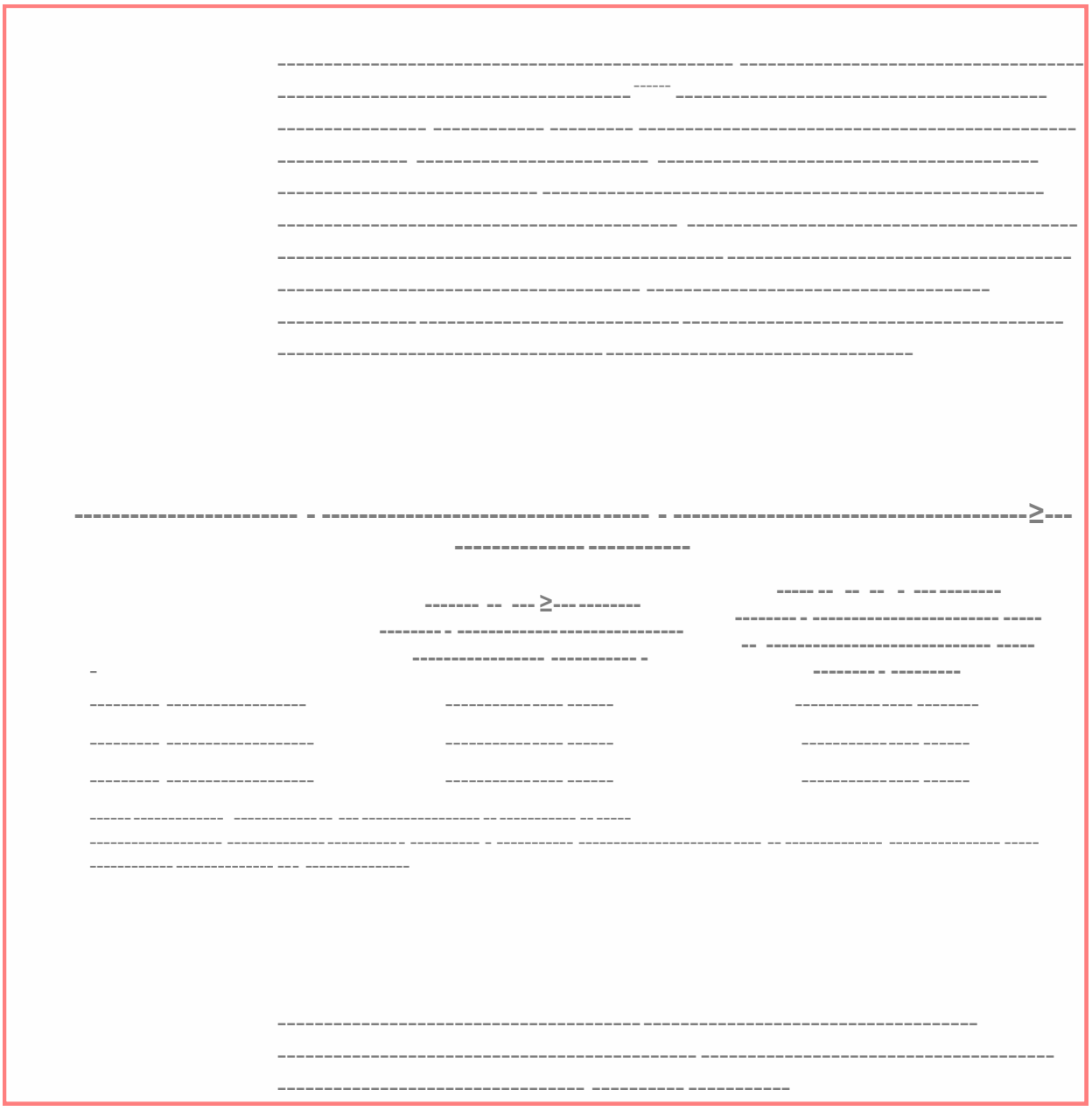
7.5.14.1 Minnesota Living with Heart Failure (MLWHF) for Primary Cohort

The MLWHF tests how heart failure affects various activities. The greater the effect heart failure has on preventing activities such as working, walking, sexual activity, and recreation, the higher the MLWHF score. Ther---------- better quality of life. ----------

---

Table 53 – Primary Cohort: MLWHF Scores over Time

	n at Interval	n with Scores	Mean	SD	Median	Min	Max
Baseline	126	108	73.6	23.7	80.5	5	105
Month 1	105	93	58.9	25.2	63.0	2	101
Month 3	74	67	43.0	25.9	40.0	0	104
Month 6	41	39	39.4	26.2	37.0	0	105



[3] Majani G, Giardini A, Opasich C, et. Al. Effect of Valsartan on Quality of Life when Added to Usual Therapy for Heart Failure: Results from the Valsartan Heart Failure Trial. Journal of Cardiac Failure, 2005; 11: 253-259.

[4] Rector TS, Cohn JN. Assessment of Patient Outcome with the Minnesota Living with Heart Failure Questionnaire: Reliability and Validity during a Randomized, Double-blind, Placebo-controlled Trial of Pimobendan. Pimobendan Multicenter Research Group. American Heart Journal, 1992; 124: 1017-1025

[5] Rector TS, Kubo SH, Cohn JN. Validity of the Minnesota Living with Heart Failure Questionnaire as a Measure of Therapeutic Response to Enalapril or Placebo. American Journal of Cardiology, 1993; 71: 1106-7.

7.5.14.2 Kansas City Cardiomyopathy Questionnaire (KCCQ) for Primary Cohort

The KCCQ quantifies physical function, symptoms (frequency, severity and recent change), social function, self-efficacy and knowledge, and quality of life. An overall summary score (OSS) is derived by combining scores in each domain. A clinical summary score (CSS) is derived by combining the physical function and symptoms scores. For both parameters, a higher score represents a better quality of life. In a separate analysis to account for missing data, patients with either missing baseline or interval scores were assumed to have no clinical improvement.

Table 56 – Primary Cohort: KCCQ Scores over Time

Overall Summary Score (OSS)							
Interval	**n at Interval**	**n with Scores**	**Mean**	**SD**	**Median**	**Min**	**Max**
Baseline	126	109	30.2	20.2	25.3	0.5	87.2
Month 1	105	93	44.6	21.1	43.8	4.6	90.1
Month 3	75	68	57.2	22.1	58.3	7.3	97.9
Month 6	41	39	60.2	26.1	54.4	0.0	100.0
Clinical Summary Score (CSS)							
Interval	**n at Interval**	**n with Scores**	**Mean**	**SD**	**Median**	**Min**	**Max**
Baseline	126	109	38.0	22.2	35.9	0.0	91.67
Month 1	105	93	53.0	23.2	56.0	1.6	94.3
Month 3	75	68	65.9	22.3	66.7	10.4	100.0
Month 6	41	39	69.4	25.8	75.0	0.0	100.0

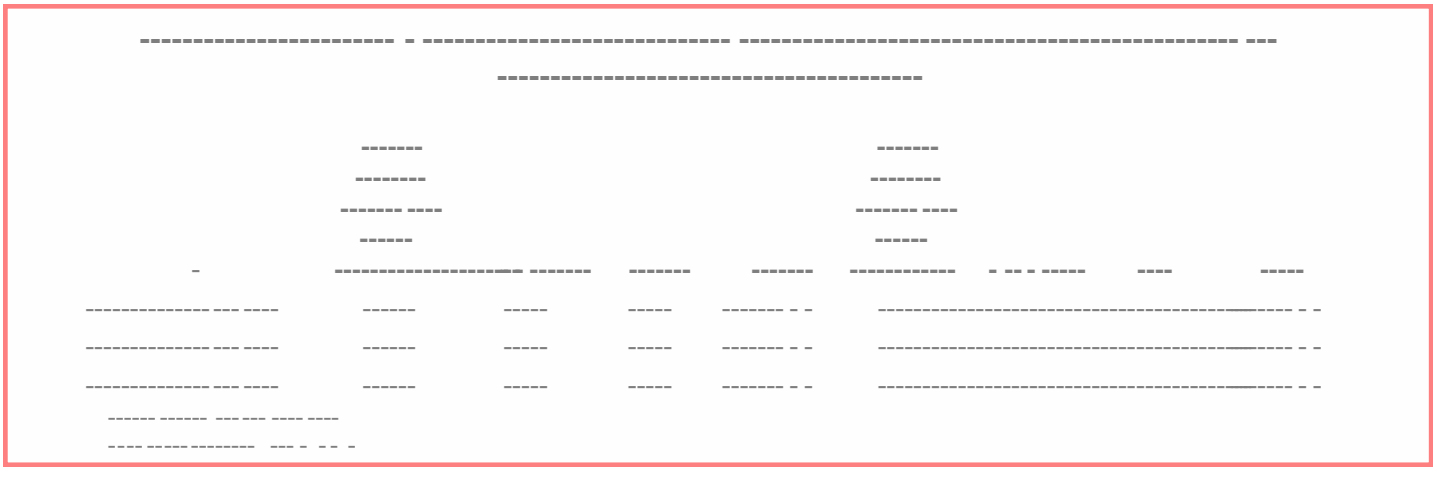
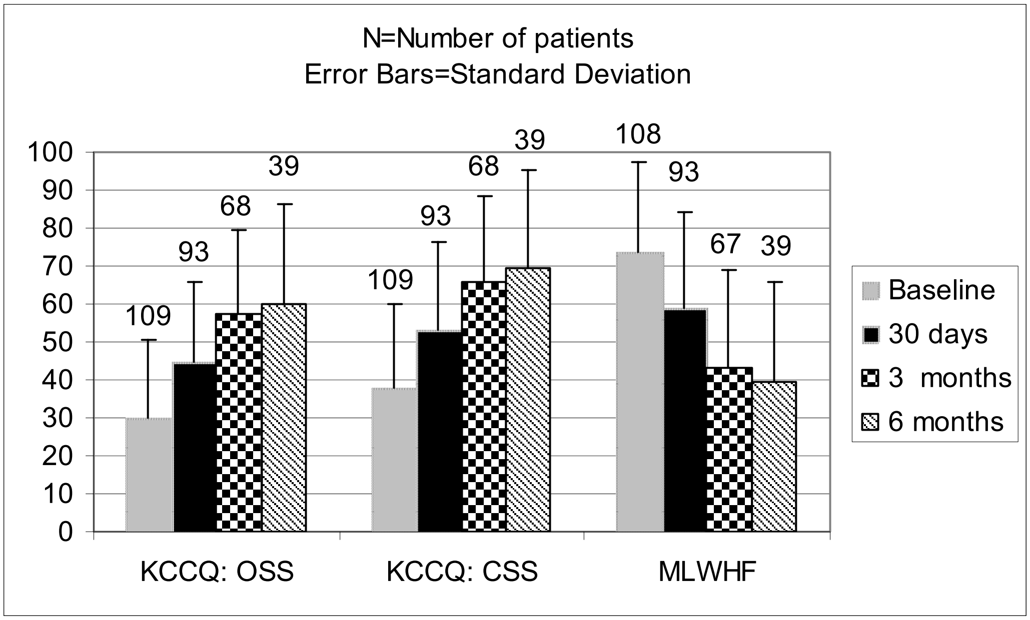


Figure 18 – Primary Cohort: Quality of Life Mean Scores over Time

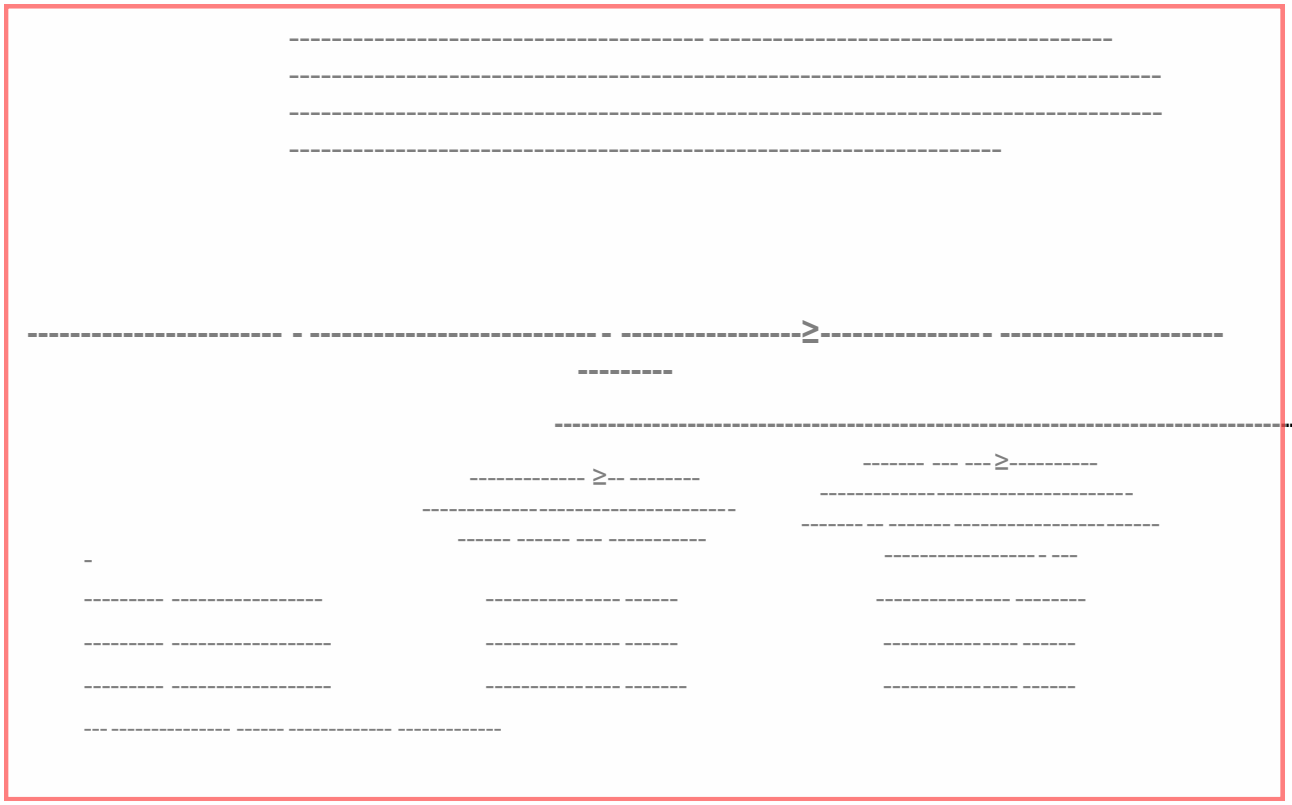


[redacted]

[redacted]

[redacted]

[6] Spertus J, Peterson E, Conrad MW, et. al. Monitoring Clinical Changes in Patients with Heart Failure: A Comparison of Methods. American Heart Journal, 2005; 150: 707-715.



These data demonstrate that patients supported with the HeartMate II achieved both statistically significant and clinically meaningful improvement in quality of life.

[redacted]

[7] Frazier OH, Rose EA, Oz MC, et. al. Multicenter Clinical Evaluation of the HeartMate Vented Electric Left Ventricular Assist System in Patients Awaiting Heart Transplantation. Journal of Thoracic and Cardiovascular Surgery, 2001; 122: 1185-1195.

[8] Taylor DO, Edwards LB, Boucek MM, et. al. Registry of the International Society for Heart and Lung Transplantation: Twenty-second Official Adult Heart Transplant Report– 2005. Journal of Heart and Lung Transplantation, 2005; 24: 945-955.

[This page intentionally left blank]

7.6 CONTINUED ACCESS PROTOCOL (CAP) COHORT (N=138)

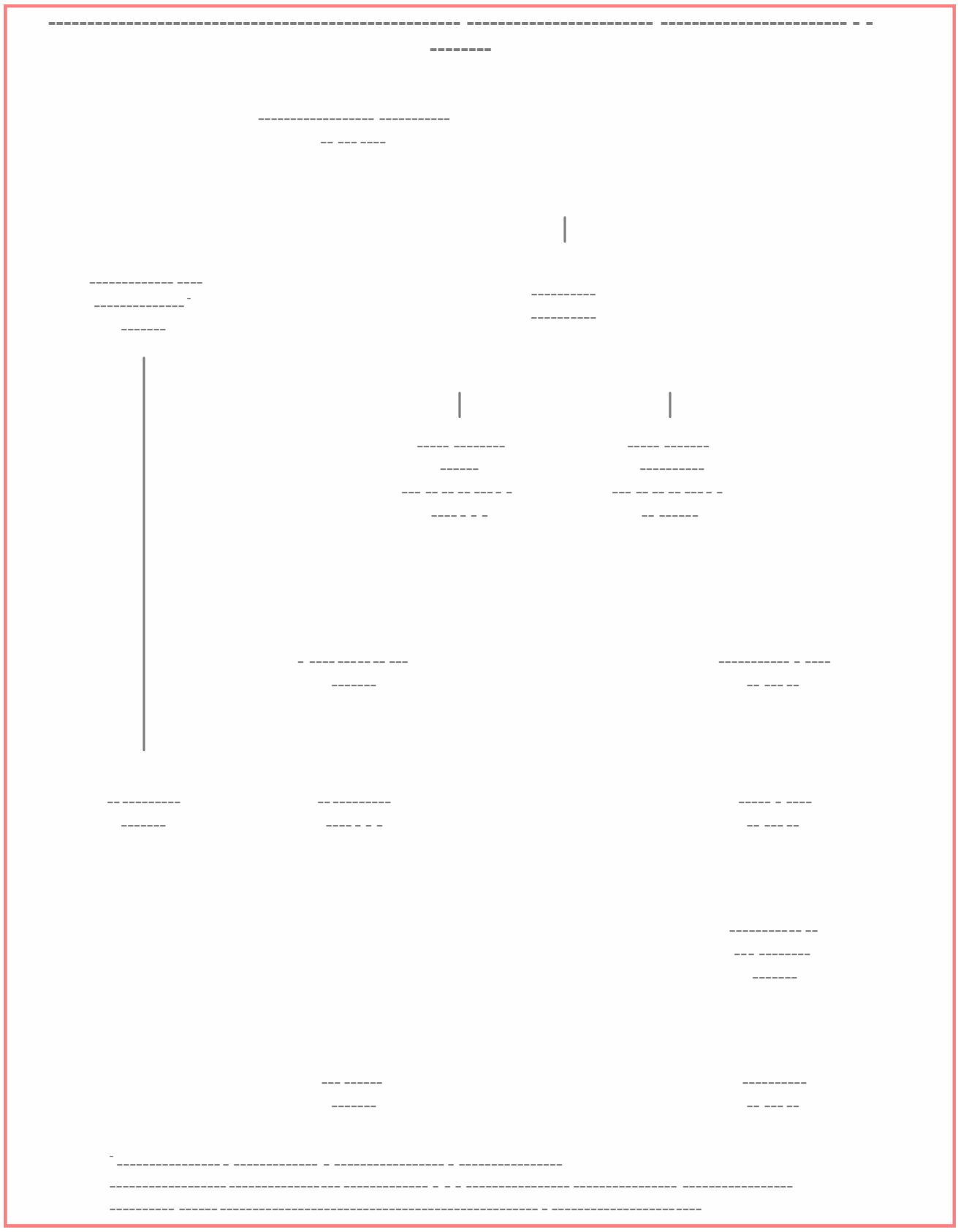
7.6.1 SUMMARY OF CAP COHORT (N=138)

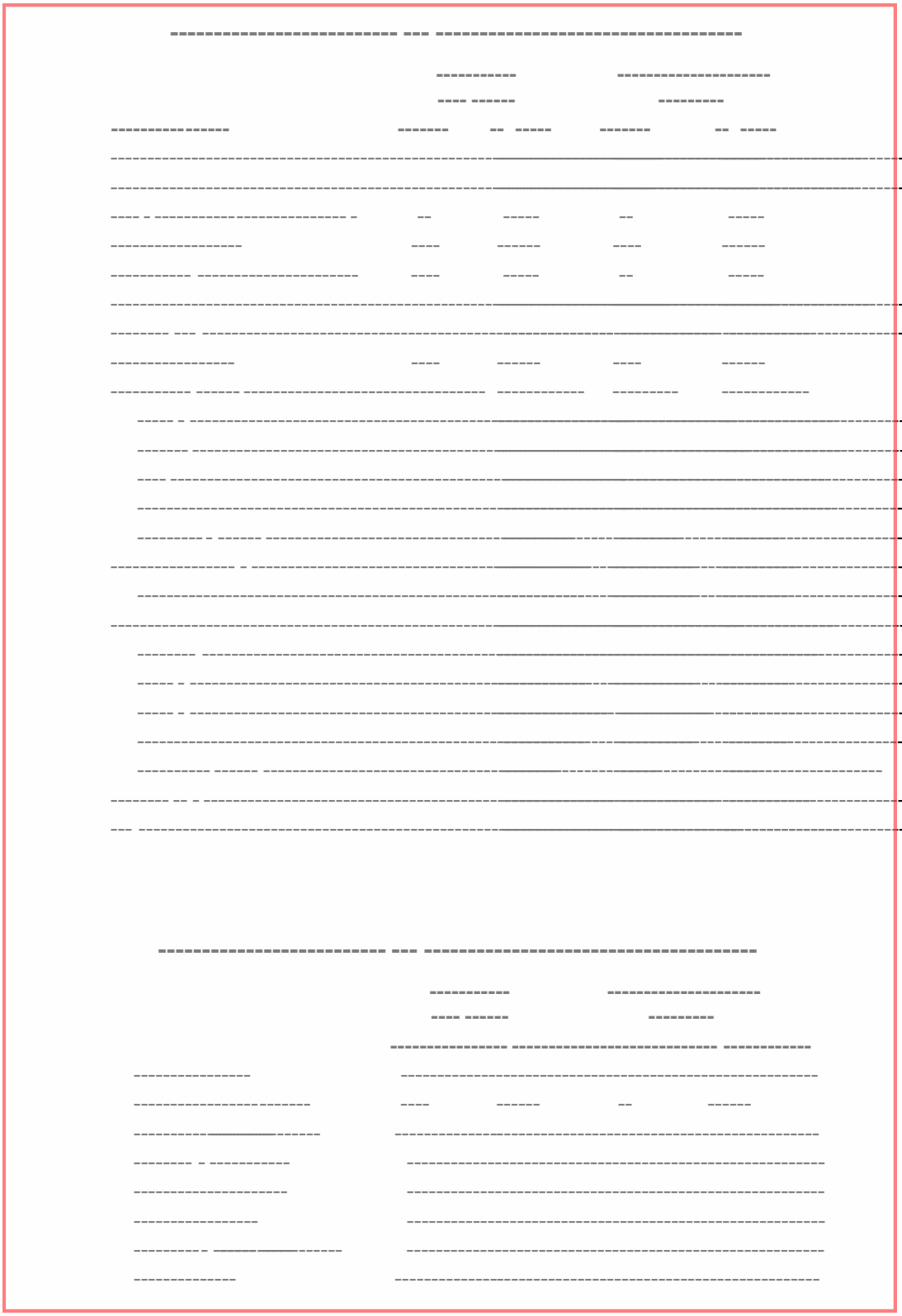
This section presents data on all Continued Access Protocol (CAP) Cohort patients (n=138) updated as of March 16, 2007. As described in Section 7.4.3.3, these patients were enrolled following completion of enrollment in the Primary Study Cohort. All patients were followed under the same protocol as the Primary Study Cohort patients. These data include 58 patients that have been followed for at least 180 days.

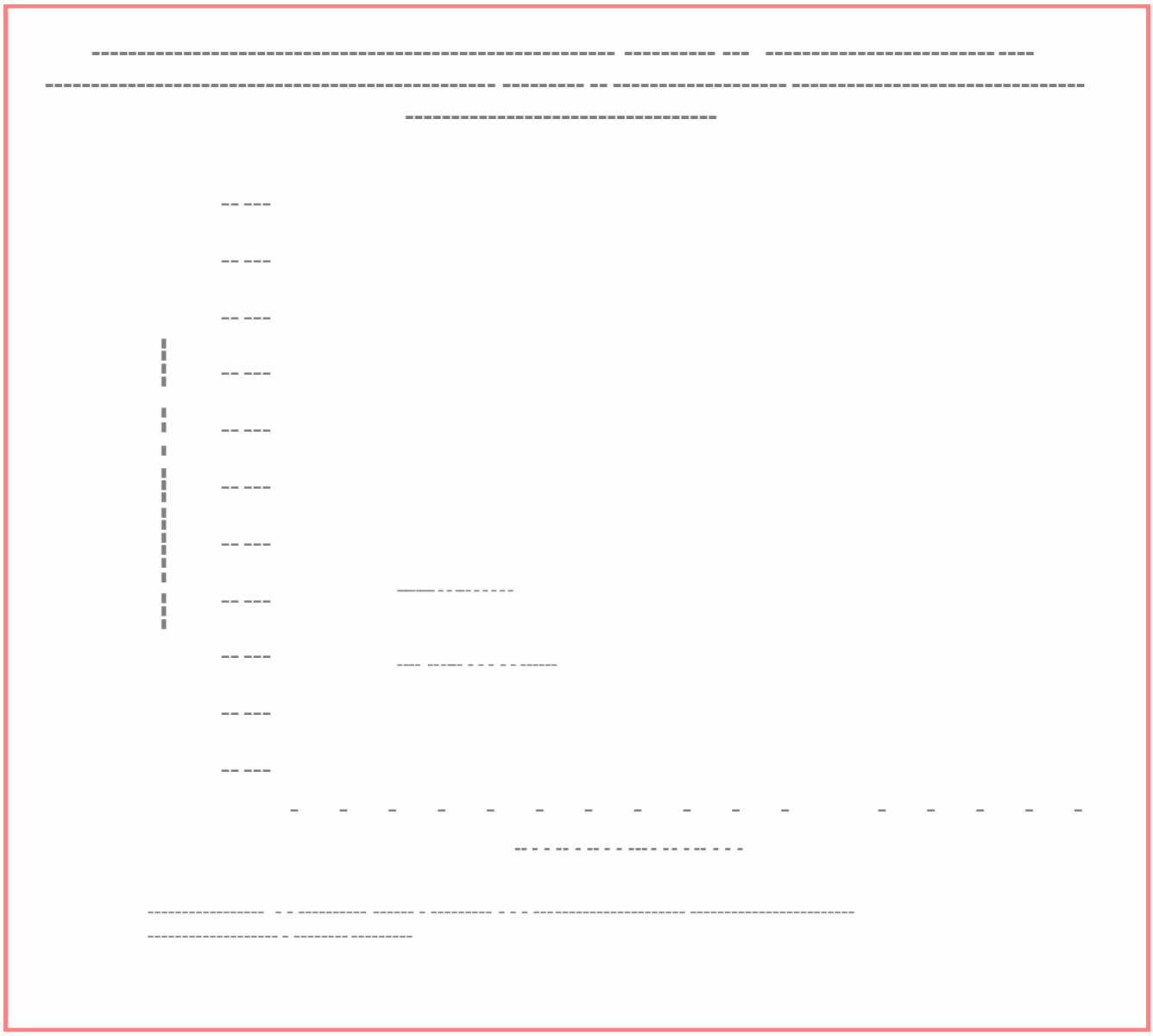
Adverse event results, functional status, and quality of life measures show the same trends as seen in the Primary Study Cohort. Thirty-day peri-operative mortality continues to be low at 7%, Quality of Life and functional assessments show clinically meaningful and statistically significant improvement and post-transplant survival continues to be strong. There are no new adverse events or significant changes in frequency of adverse outcomes.

The experience with these additional 138 patients reaffirms the evidence seen in the Primary Study Cohort of reasonable assurance of safety and efficacy of the HeartMate II for the Bridge to Transplant indication.

7.6.2







PAGES 125 - 201 HAVE BEEN REDACTED PER MFR

[This page intentionally left blank]

This page intentionally left blank

7.9 THORATEC PROPOSED LABELING COHORT (N=194)

7.9.1 SUMMARY OF THORATEC PROPOSED LABELING COHORT (N=194)

The Labeling Cohort proposed by Thoratec represents the totality of the bridge to transplant experience gathered during the HeartMate II LVAS pivotal study and therefore, it is the most appropriate data set for the final device labeling. This cohort provides increased statistical power for the primary and secondary endpoints as compared with the analysis of any individual study cohorts. This cohort is comprised of 194 patients, all of which have reached the 180 day study endpoint. The 194 patients include the Primary Study Cohort (n=126), the CAP Endpoint cohort (n = 58) and Small BSA cohort (n=10). As of the date of this Panel Pack, FDA has not yet concurred with this approach.

Using the pre-specified study endpoint analysis, the HeartMate II achieved a success rate of 70% (95% LCL 65%) as of September 14, 2007. The primary study endpoint is achieved.

The alternate analysis, as described in Section 7.8, is also presented because it is more clinically meaningful for both patients and physicians. Successful endpoints are defined as survival to transplant or survival to 180 days without irreversible contraindication to transplantation. This analysis demonstrates that the HeartMate II achieved a success rate of 76% (95% LCL 71%).

The types and incidence of adverse event rates are similar to those seen in previous studies of ventricular assist devices. For adverse events with comparable definitions to the HeartMate VE bridge to transplant clinical study, the HeartMate II demonstrated a statistically significant reduction in adverse event rates. The majority of adverse events occurred within the first 30 days, and then adverse event rates stabilized over time.

Three measures of functional status were collected during the study (NYHA Class, Six Minute Walk Test and Patient Activity Evaluation/METs). All three demonstrate statistically significant improvement at follow up durations of 1 month, 3 months and 6 months post implant when compared to baseline. In addition, for the two measures that had published benchmarks, clinically meaningful improvement was observed at these same follow up intervals.

This study evaluated two measures of Quality of Life (Minnesota Living with Heart Failure and Kansas City Cardiomyopathy Questionnaire). Using both of these measures, the data demonstrate statistically significant and clinically meaningful improvement at all follow up intervals.

Multi-center neurocognitive testing was conducted during this study. Because of the small sample size, it is difficult to draw conclusions, however important trends were seen. Significant improvements over time were seen in some of the neurocognitive tests and no significant cognitive decline was noted. Over time, as the patients stabilized, neurocognitive functions improved and the incidence of adverse events declined.

The data presented also demonstrate the clinical utility of the HeartMate II as a Bridge to Transplant and reasonable assurance of safety and efficacy as evidenced by the following clinical measures:

- The 30-day peri-operative mortality is 10%, which is half of what was observed in the HeartMate VE bridge to transplant study.
- Eighty-five percent (85%) of the HeartMate II patients survived to hospital discharge or transplant.
- Kaplan-Meier analysis of survival to transplant or recovery demonstrates the HeartMate II is non-inferior to the HeartMate VE.
- The cumulative duration of support on the HeartMate II is 33,740 patient days or 92.4 years of support of which 74% was spent outside of the hospital.
- Thirty day post-transplant survival is 97% and 1 year post-transplant survival is 83%.
- The outcomes observed in this study compare favorably to the latest INTERMACS[16] statistical summary of commercial mechanical circulatory support experience for bridge to transplantation.

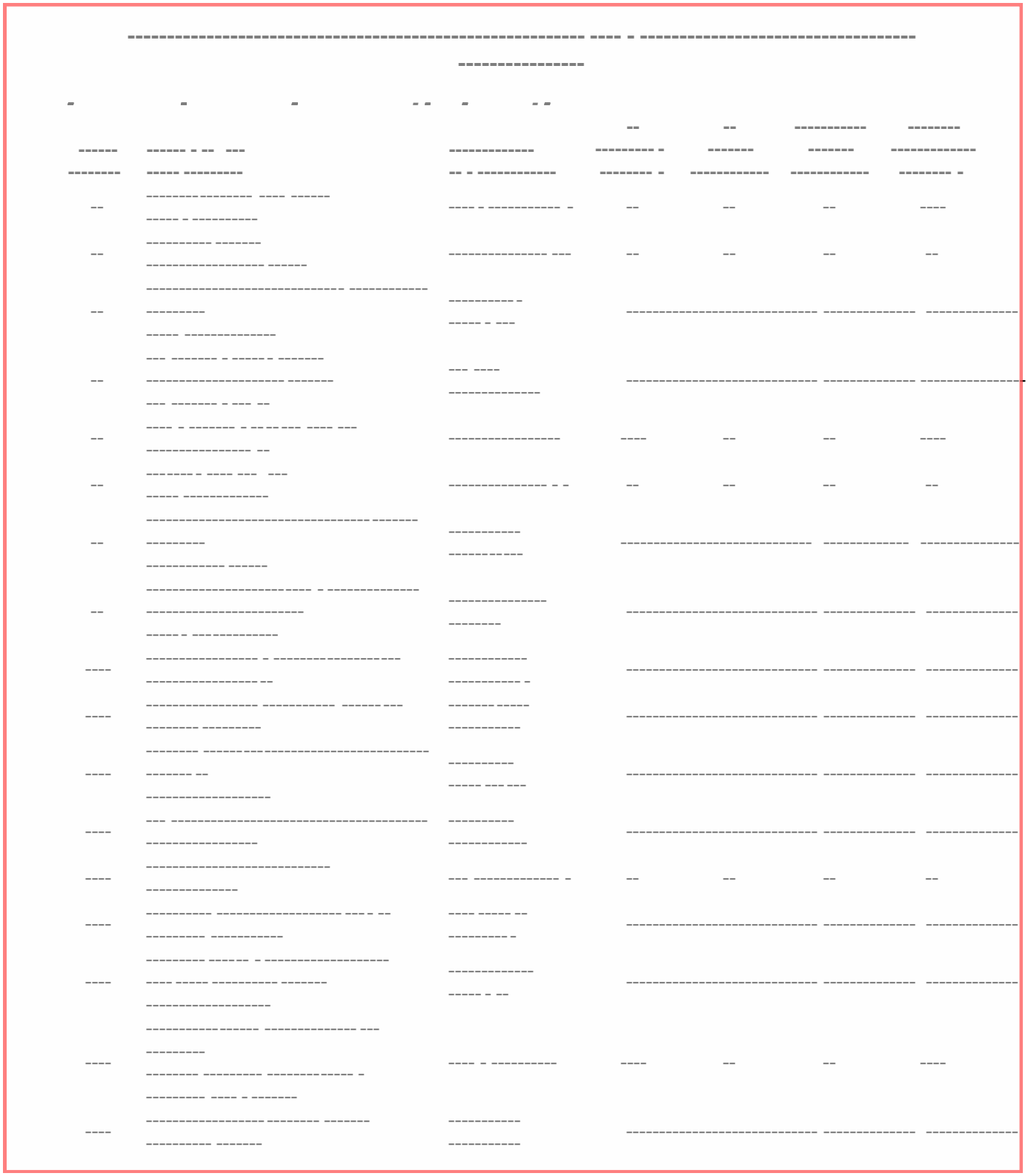
7.9.2 DATA PRESENTED FOR THORATEC PROPOSED LABELING COHORT

This cohort is comprised of 194 patients from the Primary Study Cohort, the CAP Cohort and the Small BSA Cohort, all of which have reached the 180 day study endpoint as of March 16, 2007. These patients were enrolled from March 8, 2005 to September 17, 2006. Study data presented includes all follow up data as of March 16, 2007.

7.9.3 STUDY SITES AND ENROLLMENT FOR THORATEC PROPOSED LABELING COHORT

The 194 patients were enrolled at 32 study sites. The list of study sites, investigators and number of patients enrolled per site can be found in Table 167. Figure 29 displays the patient status.

[16] INTERMACS Quarterly Statistical Report, implant dates March 1, 2006 – May 31, 2007, dated June 28, 2007.



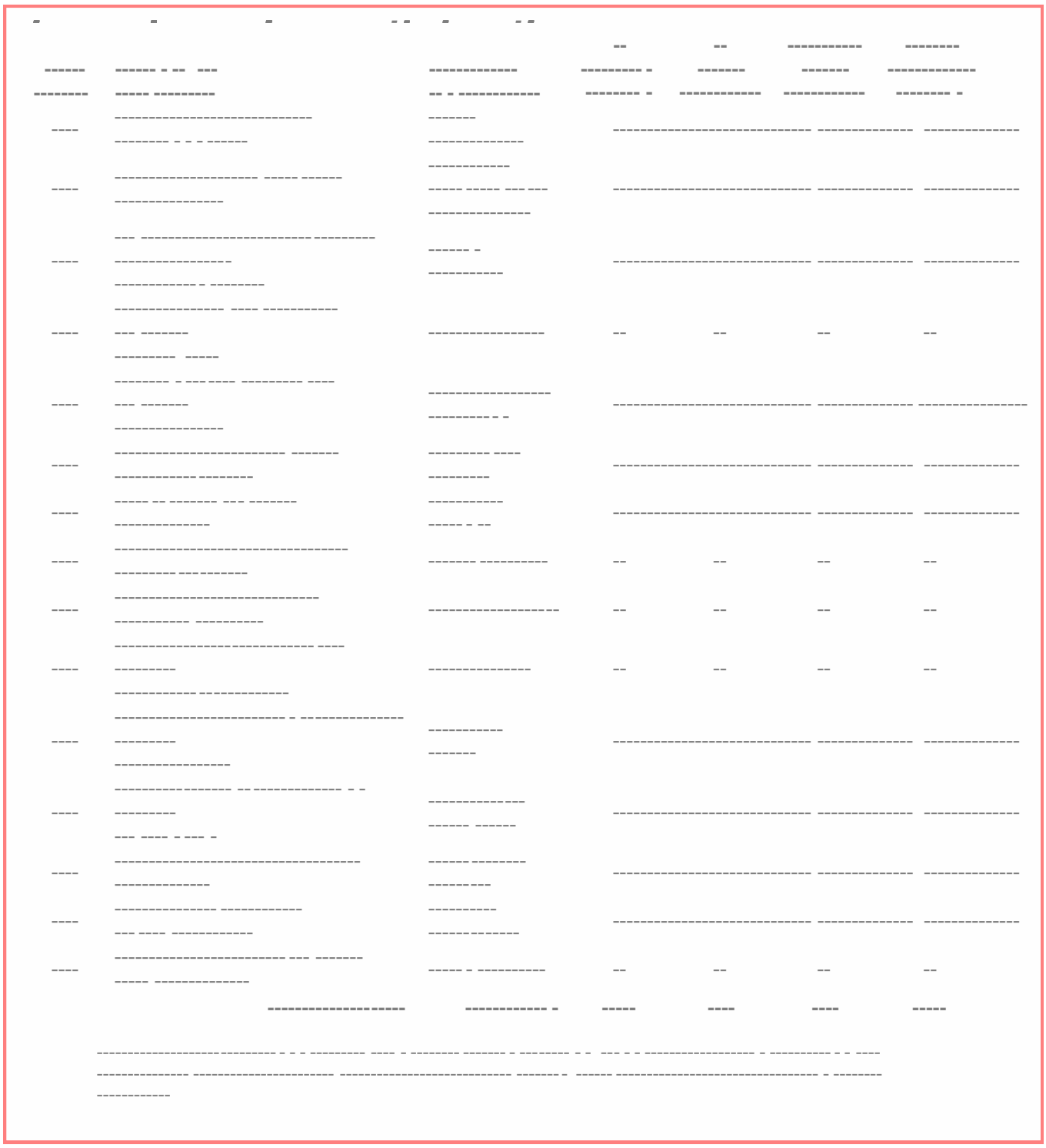
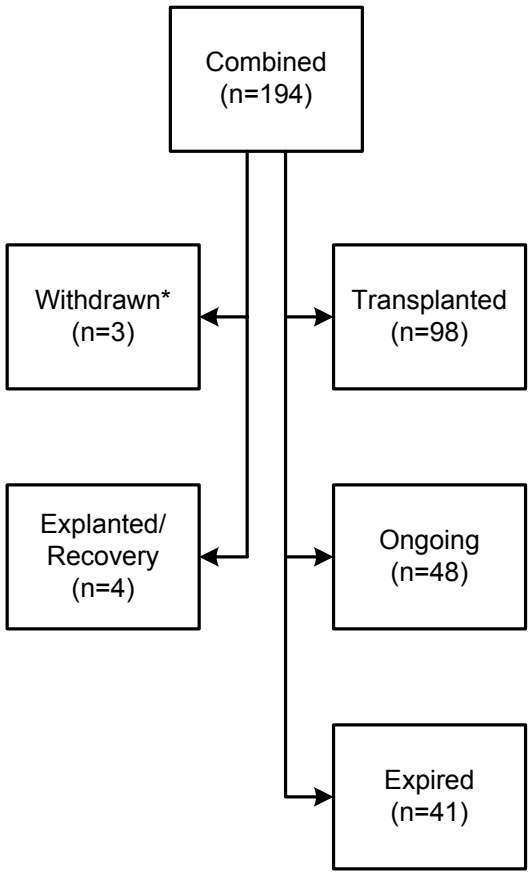


Figure 29 – Proposed Labeling Cohort: Enrollment and Patient Follow-up as of March 16, 2007



* HeartMate® II Replaced with other devices
(2 received XVE, 1 PVAD devices)

7.9.5 PATIENT BASELINE CHARACTERISTICS FOR THORATEC PROPOSED LABELING COHORT

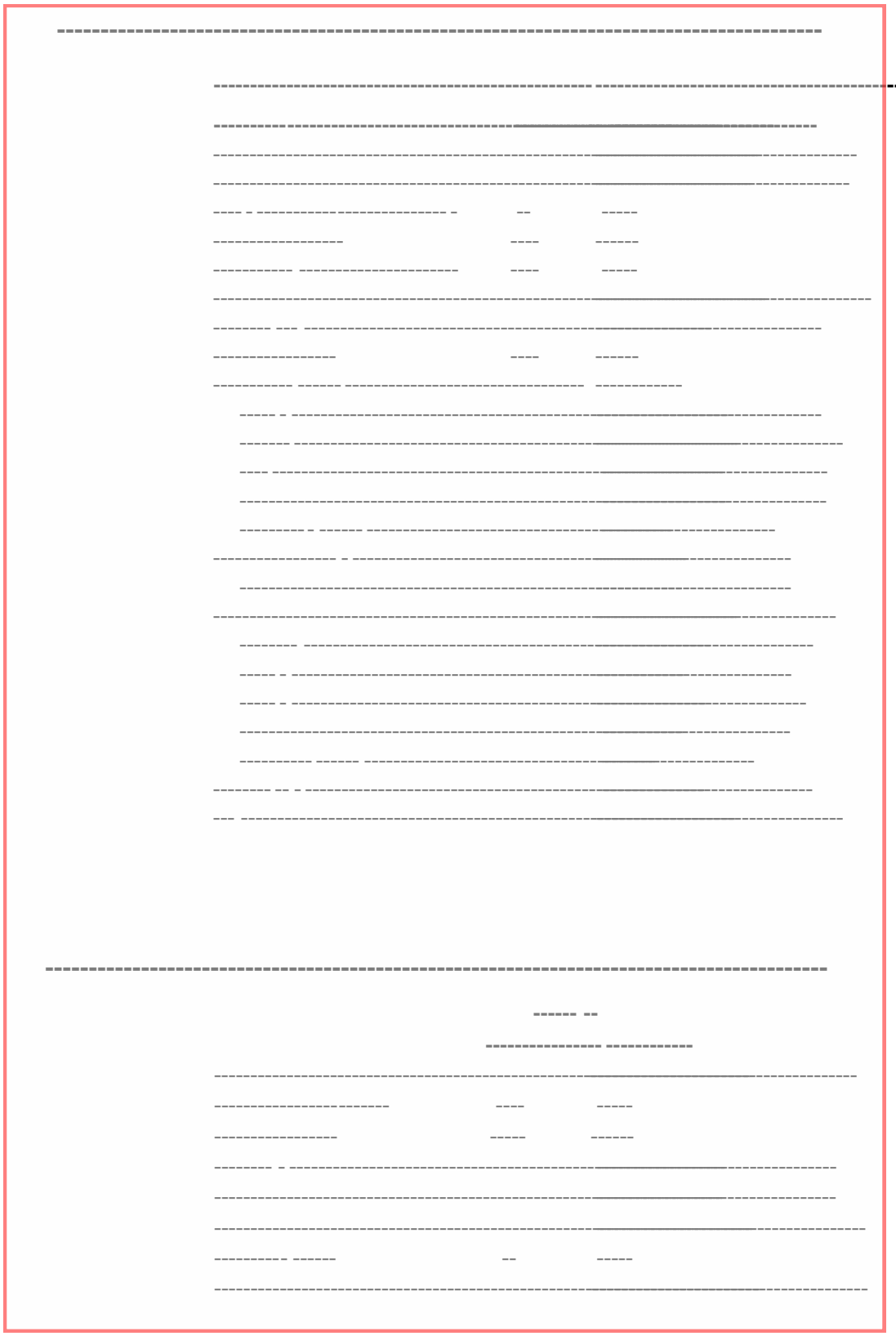
The tables below present the patient baseline characteristics, including: age and size, gender and etiology, baseline biochemistry, baseline hemodynamics, cardiovascular history, baseline medications and baseline patient status.

Table 169 – Proposed Labeling Cohort: Age and Size

	n	Mean	SD	Median	Range
Age (years)	194	50.6	13.0	55.0	16.0-69.1
BSA (m^2)	194	1.99	0.29	1.99	1.33-2.62
BMI (kg/m^2)	194	27.0	5.8	26.6	15.6-44.0
Weight (kg)	194	82.9	21.4	83.5	40-135.4

Table 170 – Proposed Labeling Cohort: Gender and Etiology

	n=194	
	#Pts	%Pts
Gender		
Male	150	77%
Female	44	23%
Ethnicity		
Black	41	21%
Caucasian	135	70%
Hispanic	12	6%
Asian	3	2%
Other	3	2%
Etiology		
Ischemic	79	41%
Idiopathic	94	48%
Alchoholic	1	1%
Myocarditis	5	3%
Valvular	4	2%
Peripartum	2	1%
Sarcoid	1	1%
Adriamycin induced	2	1%
Amyloid	1	1%
Hyperthyroidism	1	1%
Familial	1	1%
Congenital	2	1%
Dilated	1	1%



7.9.6 PRIMARY ENDPOINT: PRE-SPECIFIED ANALYSIS

As of March 16, 2007, all 194 patients in the Proposed Labeling Cohort had achieved a study endpoint defined as survival to transplant or VAD supported for 180 days and UNOS status 1A or 1B listed for transplant. One hundred twenty-nine (129) of the 194 HeartMate II patients (67%, 95% LCL 61%) were considered successes. Of these 129, 98 patients received a heart transplant, 4 patients were explanted due to recovery, and 27 patients were supported for more than 180 days while remaining listed 1A or 1B. Sixty-five (65) patients were counted as failures, including 26 patients that were supported at least 180 days but not listed 1A or 1B at 180 days.

Table 176 provides a summary of the successful and not successful patient endpoints as of March 16, 2007

Table 176 – Proposed Labeling Cohort: Pre-specified Analysis of Patient Status as of March 16, 2007

Success	**# Pts**	**% Pts**	**LCL**
Transplanted	98	50.5%	
Recovered	4	2.1%	
Supported ≥ 180 days and Status 1A or 1B	27	13.9%	
Total Success	**129**	**66.5%**	**60.9%**
Not Success	**# Pts**	**% Pts**	**LCL**
Expired < 180 days	36	18.6%	
Supported ≥ 180 days but not Status 1A or 1B	26	13.4%	
Received other VAD; Treatment failure	3	1.5%	
Total Not Success	**65**	**33.5%**	**27.9%**

Table 177 provides an update of the pre-specified study endpoint as requested by FDA. Over the course of six months, seven (7) patients originally counted as “not success” due to not being listed 1A or 1B at 180 days were subsequently transplanted or explanted due to myocardial recovery and are now counted as study “success” patients.

Table 177 – Proposed Labeling Cohort: Pre-specified Analysis of Patient Status as of September 14, 2007

Success	**# Pts**	**% Pts**	**LCL**
Transplanted	112	57.7%	
Recovered	6	3.1%	
Supported ≥ 180 days and Status 1A or 1B	18	9.3%	
Total Success	**136**	**70.1%**	64.7%
Not Success	**# Pts**	**% Pts**	**LCL**
Expired < 180 days	36	18.6%	
Supported ≥ 180 days but not Status 1A or 1B	19	9.8%	
Received other VAD; Treatment failure	3	1.5%	
Total Not Success	**58**	**29.9%**	24.5%

Table 176 and Table 177 are provided for comparison purposes only. Thoratec intends to present only Table 178, as described in the following section, in the final labeling.

7.9.7 PRIMARY ENDPOINT: ALTERNATE ANALYSIS

To present the data in the labeling in a clinically meaningful way for both patients and physicians, success is defined as survival to transplant or survival to 180 days without irreversible contraindication to transplantation.

As shown in Table 178, the HeartMate II is non-inferior to an OPC of 75% of patients transplanted or supported 180 days with no irreversible contraindication to transplant, with a non-inferiority margin of 10%. The HeartMate II achieved a success rate of 76% (95% LCL 71%).

Table 178 – Proposed Labeling Cohort: Alternate Analysis of Patient Status as of March 16, 2007

Success	**# Pts**	**% Pts**	**LCL**
Transplanted	98	50.5%	
Recovered	4	2.1%	
Supported ≥ 180 days and Status 1A or 1B	27	13.9%	
Supported ≥ 180 days but not Status 1A or 1B due to reversible reason	18	9.3%	
Total Success	**147**	**75.8%**	**70.7%**
Not Success	**# Pts**	**% Pts**	**LCL**
Expired < 180 days	36	18.6%	
Supported ≥ 180 days but not Status 1A or 1B due to irreversible reason	8	4.1%	
Received other VAD; Treatment failure	3	1.5%	
Total Not Success	**47**	**24.2%**	**19.2%**

7.9.8 OUTCOMES FOR THORATEC PROPOSED LABELING COHORT

7.9.8.1 Overall Outcomes for Thoratec Proposed Labeling Cohort

This section analyzes outcome data, which is based on the actual patient status as of March 16, 2007, regardless of the patient's pre-specified endpoint status. Patients who were ongoing at day 180 (the pre-specified study endpoint) but expired thereafter are counted as "expired", and patients who were ongoing at day 180 and remain ongoing as of March 16, 2007 are counted as "ongoing."

As of March 16, 2007, 98/194 or 51% of patients have received a heart transplant, 4/194 or 2% of patients have been explanted for myocardial recovery, 41/194 or 21% of patients have expired on support, 3/194 or 2% of patients have withdrawn from the study after re-implantation with a VAD other than the HeartMate II, and 48/194 or 25% of patients remain on HeartMate II support.

The 30 day (peri-operative) mortality was 10% (19 of 194 patients). Eighty-five percent (164 of 194) of patients survived to hospital discharge or transplant.

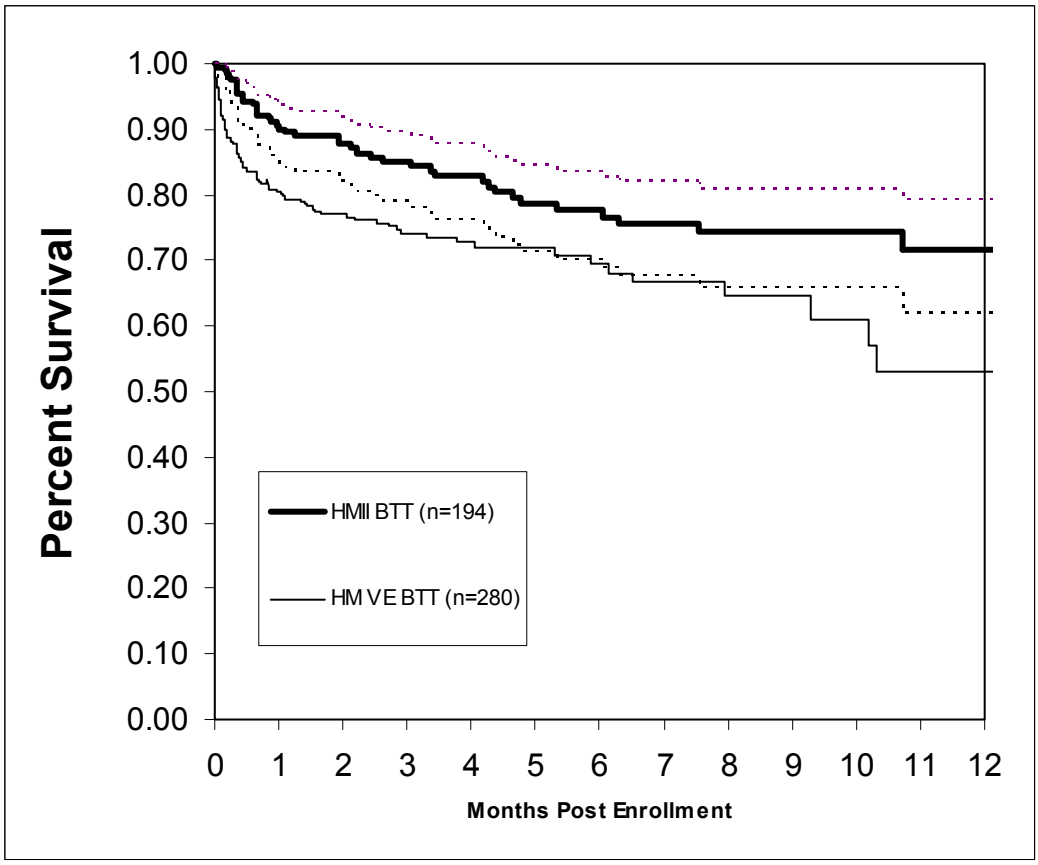
Ninety-eight (51%) of patients have received a cardiac transplant. The median time to transplant for patients who received a transplant was 96 days with a range between 15 and 498 days. Post-transplant survival for these patients is presented in Section 7.9.17.

The overall median duration of support was 131.5 days (mean = 173.8 days, range = 1– 672 days). The cumulative duration of support was 92 patient years.

A Kaplan-Meier curve demonstrating survival to transplant or recovery is provided in Figure 30 and Table 179. The Kaplan-Meier only counts patient deaths as an event and patients are censored at the time of transplant, recovery, study withdrawal, or ongoing day at the time of analysis. The 30 day survival was 90.0% ± 2.2% (survival ± SE %), the 90 day survival was 85.1% ± 2.7%, the 180 day survival = 77.7% ± 3.4%, and the 360 days survival = 71.7 ± 4.4%. For comparison purposes the Kaplan-

Meier curve of the HeartMate VE LVAS Bridge to transplant trial is included.[17]

Figure 30 – Proposed Labeling Cohort: Kaplan Meier Plot Illustrating the Probability of Survival to Transplant or Recovery; HeartMate II Proposed Labeling vs. HeartMate VE LVAS Clinical Trial Data



Note: Dotted lines represent 95% confidence interval for HeartMate II patients
See Table 179 for tabular data

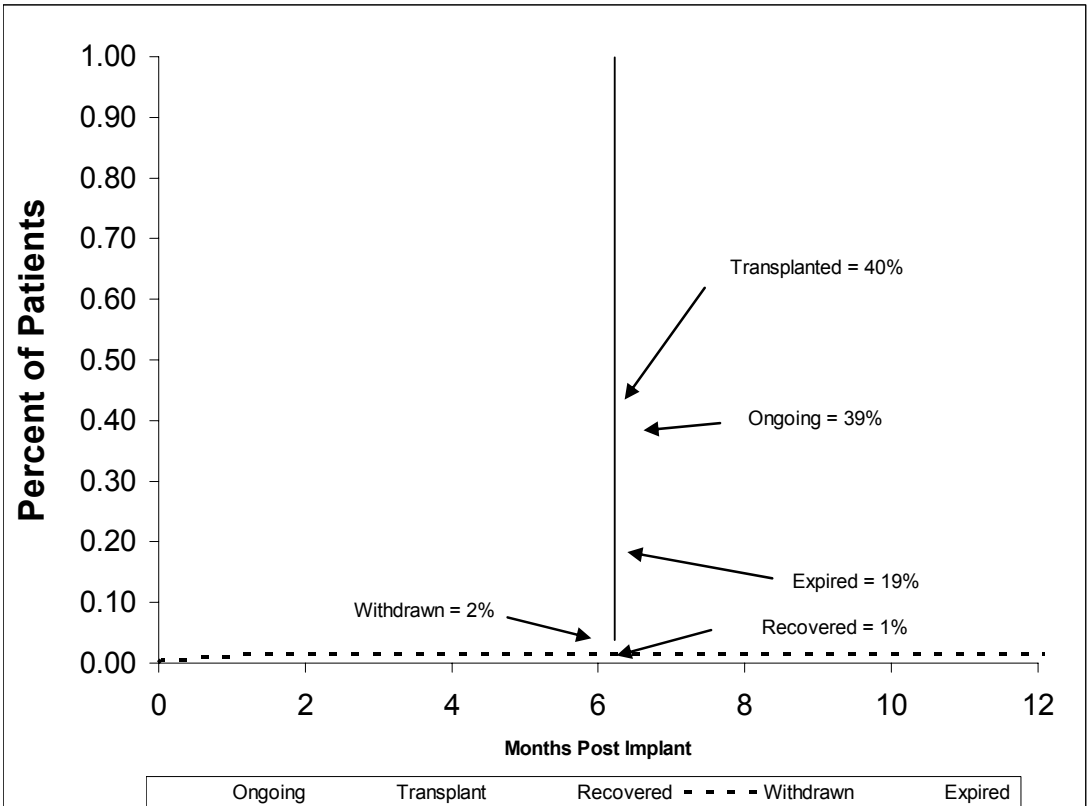
[17] HeartMate VE LVAS; IDE G900049, PMA P920014/S7

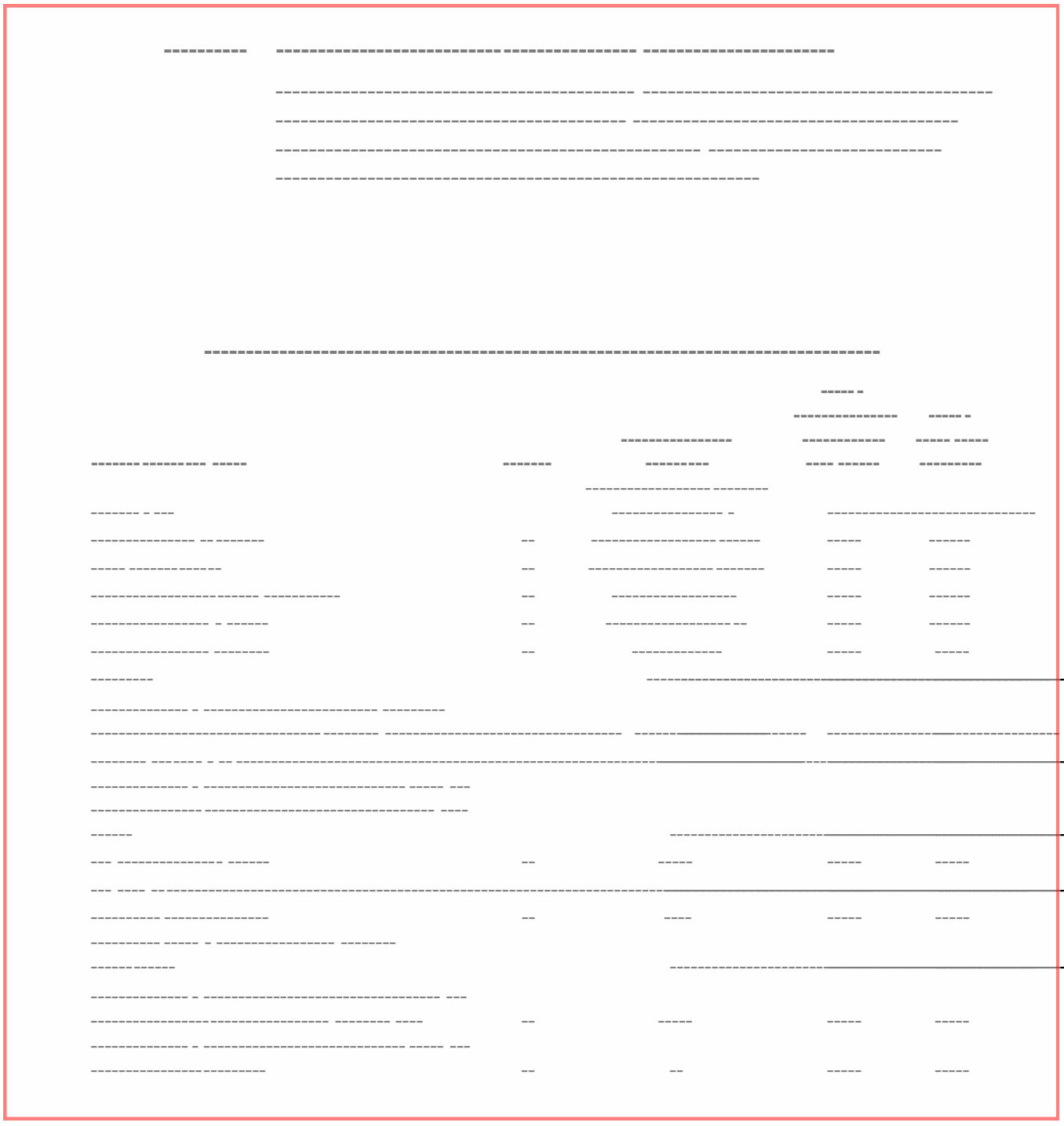
Table 179 – Proposed Labeling Cohort: HeartMate II Survival with HeartMate VE LVAS Clinical Trial Data as Comparison

HeartMate II								
	Time Interval (Months)							
	0 - 1	1 - 2	2 -3	3 - 4	4 - 5	5 - 6	6 - 12	12 - 24
Number of patients starting interval	194	165	140	120	103	87	76	23
Number of patients who died this interval	19	4	4	3	5	1	4	1
Number of cumulative patient deaths	19	23	27	30	35	36	40	41
Number of patients censored in interval	10	21	16	14	11	10	49	22
Number of cumulative censored patients	10	31	47	61	72	82	131	153
Probability of surviving interval	0.901	0.877	0.851	0.829	0.787	0.777	0.717	0.000
+/- 95% Confidence Limit at end of interval	0.04	0.05	0.06	0.07	0.08	0.08	0.16	---
HeartMate VE LVAS								
	Time Interval (Months)							
	0 - 1	1 - 2	2 -3	3 - 4	4 - 5	5 - 6	6 - 12	12 - 24
Number of patients starting interval	280	215	179	129	96	66	53	13
Number of patients who died this interval	54	9	6	2	1	2	6	2
Number of cumulative patient deaths	54	63	69	71	72	74	80	82
Number of patients censored in interval	11	27	44	31	29	11	34	2
Number of cumulative censored patients	11	38	82	113	142	153	187	189
Probability of surviving interval	0.805	0.770	0.741	0.728	0.720	0.695	0.531	0.000
+/- 95% Confidence Limit at end of interval	0.05	0.05	0.07	0.08	0.09	0.10	0.20	---

A competing outcomes plot of the HeartMate II Proposed Labeling Cohort data (n=194) is provided in Figure 31 to allow HeartMate II comparison to other VAD post approval commercial experience collected and summarized in INTERMACS quarterly reports. The data shows that at six months, 40% of the HeartMate II patients were transplanted, 39% were ongoing, 19% had expired, 2% were withdrawn and 1% had recovered sufficiently to have the device removed.

Figure 31 – Proposed Labeling Cohort: Competing Outcome Plot of HeartMate II BTT Proposed Labeling Data (n=194) as of March 16, 2007





7.9.9 SAFETY: ADVERSE EVENTS FOR THORATEC PROPOSED LABELING COHORT

Table 187 presents all of the adverse events experienced in this study cohort, and Table 188 presents only the serious events. Adverse events were classified as serious if they resulted in death or were life threatening, resulted in permanent disability, required hospitalization or a prolonged hospital stay. The number of patients, percent of patients, number of events and number of serious events for each adverse event is presented. Further tables present the time to adverse events, in addition detailed tables are presented for strokes, other neurological events, right heart failure and hemolysis.

Table 187 – Proposed Labeling Cohort: All Adverse Events

	n = 194				
	# Pts	% Pts	UCL	LCL	# Events
Bleeding*	128	66%	73%	59%	253
Bleeding requiring surgery	55	28%	35%	22%	65
Stroke	16	8%	12%	4%	17
Peri-operative (≤ POD2)	5	3%	5%	0%	5
Post-operative (> POD2)	11	6%	10%	3%	12
Other Neurological**	16	8%	12%	4%	19
Local Infection	57	29%	36%	23%	104
Percutaneous Lead Infection	23	12%	16%	7%	30
Pocket Infection	3	2%	3%	0%	3
Sepsis	34	18%	23%	12%	45
Right Heart Failure	35	18%	23%	13%	36
Peripheral TE	11	6%	9%	2%	12
Respiratory Failure	50	26%	32%	20%	63
Cardiac Arrhythmias	107	55%	62%	48%	188
Renal Failure	25	13%	18%	8%	26
Hepatic Dysfunction	3	2%	3%	0%	3
Device Thrombosis	3	2%	3%	0%	3
Hemolysis	6	3%	6%	1%	6
Psychological	12	6%	10%	3%	14
Myocardial Infarction	2	1%	2%	0%	2
Confirmed malfunctions	55	28%	35%	22%	84

*Bleeding requiring PRBC ≥ 2 units or surgery.
**Includes transient ischemic attacks (TIA) and non-stroke neurological events.

Table 188 – Proposed Labeling Cohort: Serious Adverse Events

	n = 194				
	# Pts	**% Pts**	**UCL**	**LCL**	**# Events**
Bleeding*	113	58%	65%	51%	210
Bleeding requiring surgery	55	28%	35%	22%	65
Stroke	16	8%	12%	4%	17
Peri-operative (≤ POD2)	5	3%	5%	0%	5
Post-operative (> POD2)	11	6%	10%	3%	12
Other Neurological**	14	7%	11%	4%	17
Local Infection	41	21%	27%	15%	64
Percutaneous Lead Infection	13	7%	10%	3%	15
Pocket Infection	3	2%	3%	0%	3
Sepsis	33	17%	22%	12%	44
Right Heart Failure	35	18%	23%	13%	35
Peripheral TE	10	5%	8%	2%	11
Respiratory Failure	50	26%	32%	20%	62
Cardiac Arrhythmias	77	40%	47%	33%	125
Renal Failure	25	13%	18%	8%	26
Hepatic Dysfunction	3	2%	3%	0%	3
Device Thrombosis	3	2%	3%	0%	3
Hemolysis	4	2%	4%	0%	4
Psychological	3	2%	3%	0%	5
Myocardial Infarction	2	1%	2%	0%	2
Confirmed Malfunctions	15	8%	11%	4%	15

*Bleeding requiring PRBC ≥ 2 units or surgery.
**Includes transient ischemic attacks (TIA) and non-stroke neurological events.

Table 189 – Proposed Labeling Cohort: All Adverse Event Rates per Patient Year by Time Interval

	n = 194				
	0 - 7 days	**8 - 30 days**	**31 - 90 days**	**91 - 180 days**	**> 180 days**
Cumulative years support	3.68	11.22	23.37	23.50	30.60
Adverse Event					
Bleeding	34.78	4.81	1.54	0.81	0.52
Stroke	1.36	0.27	0.13	0.21	0.03
Other Neurological*	0.54	0.45	0.26	0.17	0.07
Local Infection	8.42	2.41	1.33	0.43	0.16
Percutaneous Lead Infection	0.00	0.00	0.26	0.51	0.39
Pocket Infection	0.00	0.09	0.00	0.00	0.07
Sepsis	1.63	1.52	0.34	0.26	0.26
Right Heart Failure	2.72	1.69	0.21	0.00	0.07
Peripheral TE	1.09	0.53	0.09	0.00	0.00
Respiratory Failure	8.15	1.60	0.39	0.21	0.03
Cardiac Arrhythmias	20.65	4.28	1.20	0.89	0.49
Renal Failure	3.80	0.62	0.09	0.13	0.00
Hepatic Dysfunction	0.27	0.09	0.04	0.00	0.00
Device Thrombosis	0.54	0.00	0.04	0.00	0.00
Hemolysis	0.82	0.00	0.00	0.09	0.03
Psychological	1.90	0.18	0.04	0.17	0.00
Myocardial Infarction	0.00	0.00	0.04	0.04	0.00
Confirmed Malfunctions	6.50	1.10	0.43	0.86	0.59

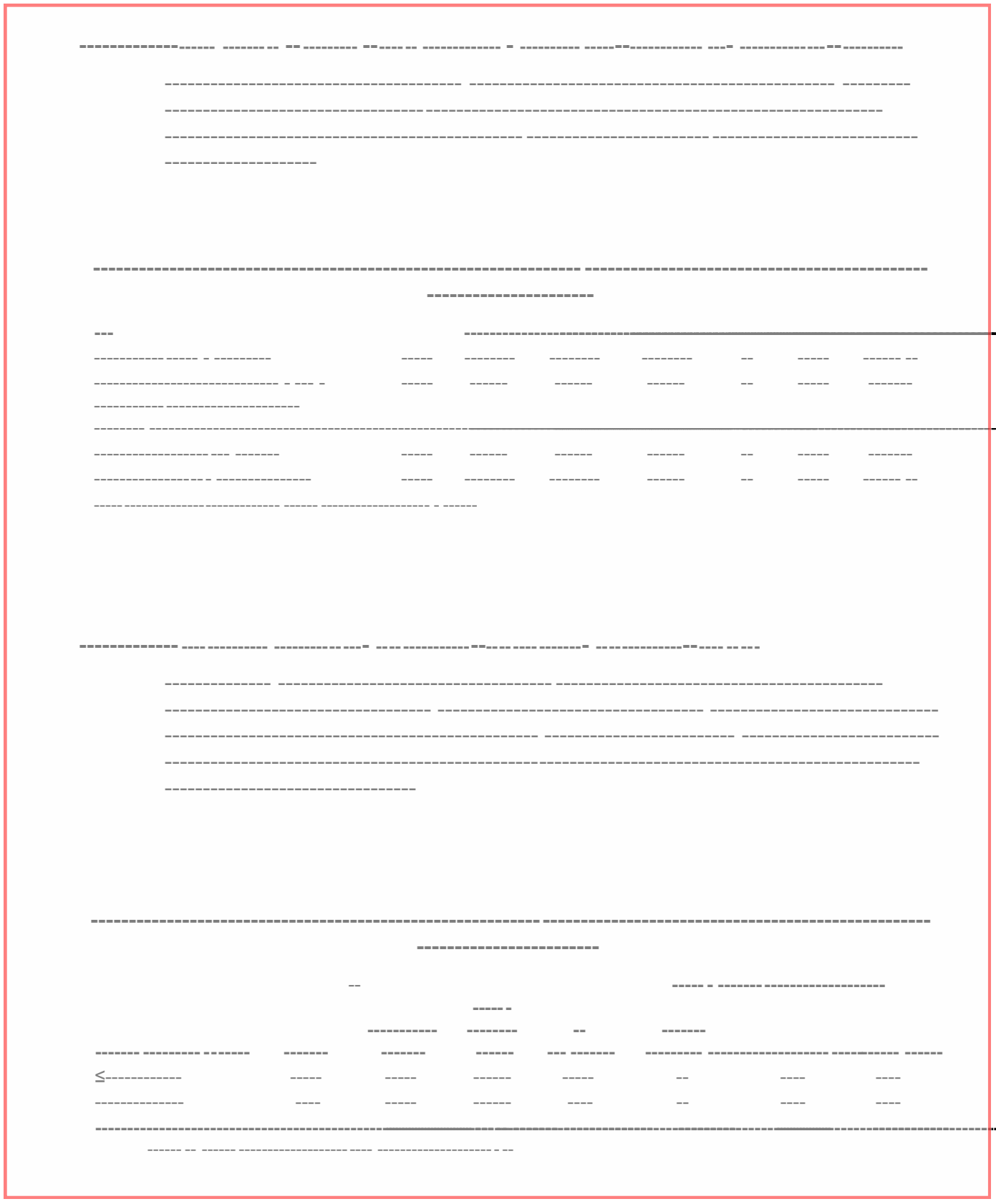
*Includes transient ischemic attacks (TIA) and non-stroke neurological events.

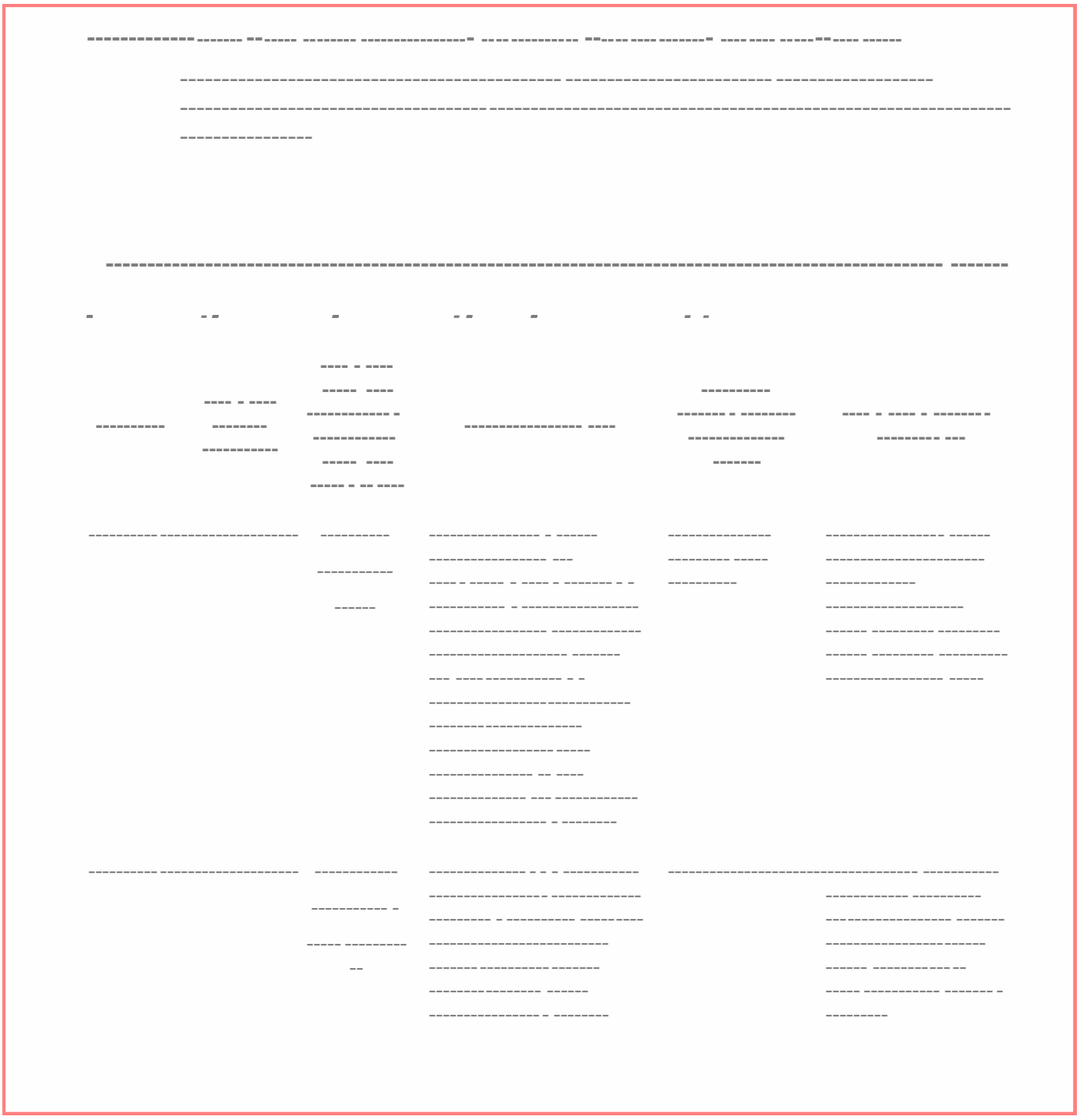
7.9.9.1 Adverse Event Comparison to HeartMate VE BTT for Thoratec Proposed Labeling Cohort

The rates of HeartMate II adverse events, where common definitions could be used, were compared to rates observed in the HeartMate VE Bridge to Transplant Study. The comparable adverse events include: bleeding events requiring surgery, strokes, other neurologic events (including TIAs, seizures, and metabolic encephalopathy), percutaneous lead infections, and right heart failure that requires RVAD insertion. As can be seen in Table 195, the HeartMate II adverse event rates are significantly better than the HeartMate VE BTT study rates.

Table 195 – Proposed Labeling Cohort: Comparison of the HeartMate II (n=194) Adverse Events and HeartMate VE Bridge Study (n=280) Adverse Events

	HeartMate II Proposed Labeling Cohort (92.4 pt yrs)		***HeartMate VE BTT (86.2 pt yrs)***		
Event	**# Events**	**Events/pt yr**	**# Events**	**Events/pt yr**	**Risk Ratio (95% CI)**
Stroke	17	0.18	38	0.44	0.42 (0.22 - 0.79)
Other Neurologic Event	19	0.21	58	0.67	0.31 (0.17 - 0.55)
Bleeding requiring Surgery	65	0.70	127	1.47	0.48 (0.31 - 0.73)
Percutaneous Lead Infection	30	0.32	301	3.49	0.09 (0.06 - 0.15)
RHF requiring RVAD	10	0.11	26	0.30	0.36 (0.16 - 0.79)





7.9.14 FUNCTIONAL STATUS OF THORATEC PROPOSED LABELING COHORT

One of the secondary objectives of the HeartMate II study was to obtain information on the patients' functional status. Functional status was measured by the NYHA classification, the Six Minute Walk Test, and patient activity score (METs).

The number of patients available (had not been transplanted, explanted, died or withdrawn from the study) at each study interval for the evaluation of survival, functional status and quality of life varies. Differences in patients reported in the Kaplan-Meier analysis and patients available for the functional and quality of life assessment is due to the following:

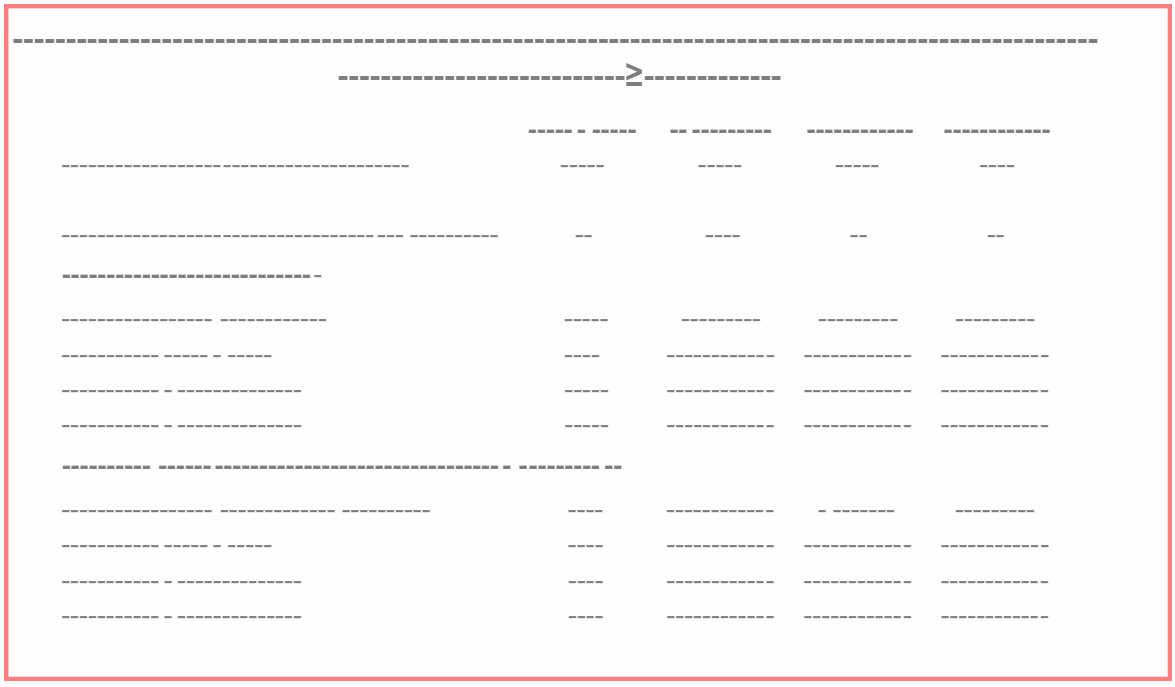
- The Kaplan-Meier analysis reports the number of patients ongoing at day 30, 90 and 180 post-implant.
- The functional status and quality of life data is collected within a test window that extends one week before and after day 30, 90 and 180 days post-implant.
- Patients who had an outcome (transplant or death) within the test window and did not complete functional status and quality of life tests are judged to be not available for that test interval.
- Patients who had an outcome (transplant or death) within the test window but completed all of the functional status or quality of life tests prior to their outcome have their scores included in the analysis.
- Patients who had an outcome (transplant or death) within the test window but completed only some of the functional status and quality of life tests prior to their outcome have the completed scores included in the analysis, but are judged to be not available for the tests that were not completed.

7.9.14.1 NYHA Classification for Thoratec Proposed Labeling Cohort

NYHA functional class was assessed by an independent assessor at baseline and post implant at month 1, initial hospital discharge, 3 and 6 months. The independent assessor was defined as a nurse, cardiologist or other medical staff not directly involved with the patients care at that time. NYHA status over time is displayed in the next three tables.

Table 201 – Proposed Labeling Cohort: NYHA Class over Time

Interval	Baseline	Month 1	Month 3	Month 6
Number of Patients at Interval	194	164	120	75
Patients with missing data	0	12	6	5
Patients at NYHA IV	191 (98%)	9 (6%)	2 (2%)	0 (0%)
Patients at NYHA IIIB	1 (1%)	17 (11%)	6 (5%)	3 (4%)
Patients at NYHA IIIA	2 (1%)	31 (20%)	10 (9%)	7(10%)
Patients at NYHA II	0 (0%)	65 (43%)	58 (51%)	29 (41%)
Patients at NYHA I	0 (0%)	30 (20%)	38 (33%)	31 (44%)



7.9.14.2 Six Minute Walk Test for Thoratec Proposed Labeling Cohort

A second measure to assess functional improvement was the six minute walk test, which documented the number of meters a patient could walk in six minutes. Assessments were performed at baseline (if the patient was able to perform) and post implant at 1 month, 3 months and 6 months. Patients unable to walk due to a medical condition (ie; IABP in place; IV Inotropes; in ICU; leg or foot problem) and patients w----------

---

Table 205 – Proposed Labeling Cohort: Summary of Six Minute Walk over Time

	n at interval	n with scores	Mean (m)	SD	Median	Min	Max
Baseline	194	194	30.7	85.6	0.0	0	445.0
Month 1	163	151	177.3	163.4	152.4	0	570.0
Month 3	120	101	268.4	208.3	286.5	0	1057.0
Month 6	75	64	318.8	217.0	374.6	0	1176.0

In summary, the improvements in six minute walk test results were both statistically significant and clinically meaningful.

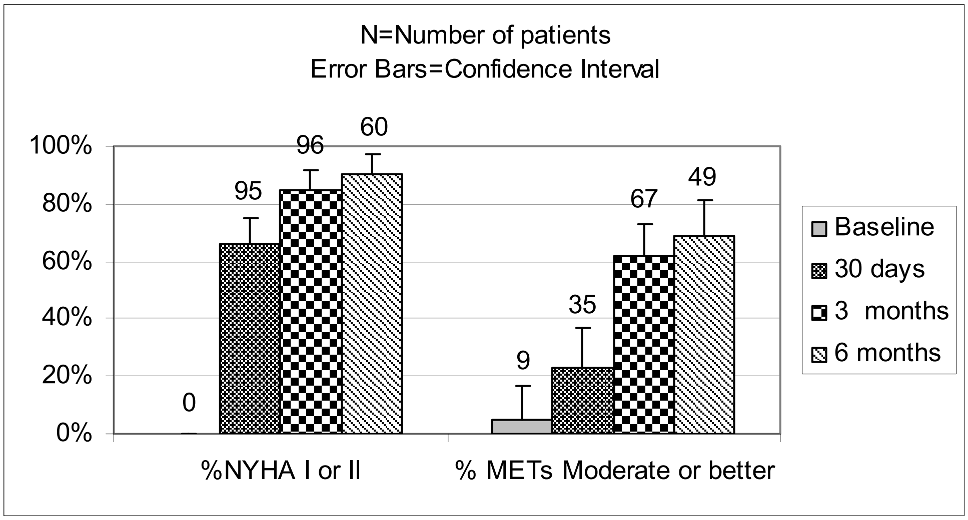
7.9.14.3 Patient Activity Evaluation for Thoratec Proposed Labeling Cohort

A third measure to assess functional improvement was documenting the patient's level of activity via a Metabolic Equivalent score (METs). Patients were asked to describe their highest level of activity for the reporting period. This was collected at baseline and on post-implant at 1 month, 3 months and 6 months. A summary of patients METs scores is provided in Table 209.

Table 209 – Proposed Labeling Cohort: MET Scores over Time

	# Pts Baseline	# Pts 1 Month	#Pts 3 Months	#Pts 6 Months
#Patients at interval	194	162	119	76
#Patients with missing data	4	2	4	2
Very Low (METs < 1)	101	19	8	1
Low (METs 1-2)	79	105	36	22
Moderate (METs 2-4)	10	34	40	17
High (METs 4-6)	0	2	20	21
Very High (METs >6)	0	0	11	13

Figure 33 – Proposed Labeling Cohort: Percent of Patients Achieving NYHA Class I/II or METs Moderate or Better



In summary, patients experienced a highly significant improvement in Patient Activit---- -- compared to baseline scores.--- ---------------- ------------------------
----

7.9.15 QUALITY OF LIFE ASSESSMENT FOR THORATEC PROPOSED LABELING COHORT

The quality of life (QOL) was assessed by administering the following QOL instruments:

- Minnesota Living with Heart Failure Questionnaire (MLWHF)
- Kansas City Cardiomyopathy Questionnaire (KCCQ)

Patients completed the MLWHF questionnaire and the KCCQ at baseline and post implant at 1 month, 3 months, and 6 months. Both questionnaires show improvement in QOL.

7.9.15.1 Minnesota Living with Heart Failure (MLWHF) for Thoratec Proposed Labeling Cohort

The MLWHF tests how heart failure affects various activities. The greater the effect heart failure has on preventing activities such as working, walking, sexual activity, and recreation, the higher the MLWHF score. The----------

Table 212 – Proposed Labeling Cohort: MLWHF Scores over Time

	n at Interval	n with Scores	Mean	SD	Median	Min	Max
Baseline	194	158	72.7	21.6	76	4	105
Month 1	162	141	57.3	26.0	62	1	105
Month 3	119	107	42.9	25.8	40	0	105
Month 6	75	69	38.4	25.6	37	0	105

In summary, MLWHF Scores---------- improvement in quality of life.

[19] Majani G, Giardini A, Opasich C, et. Al. Effect of Valsartan on Quality of Life when Added to Usual Therapy for Heart Failure: Results from the Valsartan Heart Failure Trial. Journal of Cardiac Failure, 2005; 11: 253-259.

[20] Rector TS, Cohn JN. Assessment of Patient Outcome with the Minnesota Living with Heart Failure Questionnaire: Reliability and Validity during a Randomized, Double-blind, Placebo-controlled Trial of Pimobendan. Pimobendan Multicenter Research Group. American Heart Journal, 1992; 124: 1017-1025

[21] Rector TS, Kubo SH, Cohn JN. Validity of the Minnesota Living with Heart Failure Questionnaire as a Measure of Therapeutic Response to Enalapril or Placebo. American Journal of Cardiology, 1993; 71: 1106-7.

7.9.15.2 Kansas City Cardiomyopathy Questionnaire (KCCQ) for Thoratec Proposed Labeling Cohort

The KCCQ quantifies physical function, symptoms (frequency, severity and recent change), social function, self-efficacy and knowledge, and quality of life. An overall summary score (OSS) is derived by combining scores in each domain, with a higher score reflecting a better health status. A clinical summary score (CSS) is derived by combining the physical function and symptoms scores. For b---------- ---------- quality of life.------- ---------- - ---------- ---------- ---------- ----------

Table 215 – Proposed Labeling Cohort: KCCQ Scores over Time

Overall Summary Score (OSS)							
Interval	**n at Interval**	**n with Scores**	**Mean**	**SD**	**Median**	**Min**	**Max**
Baseline	194	158	30.6	19.1	25.3	0.5	87.24
Month 1	162	142	45.8	22.4	44.7	2.1	91.67
Month 3	119	109	58.3	21.6	59.4	7.3	97.92
Month 6	75	70	61.9	24.5	60.6	0.0	100
Clinical Summary Score (CSS)							
Interval	**n at Interval**	**n with Scores**	**Mean**	**SD**	**Median**	**Min**	**Max**
Baseline	194	158	38.7	21.4	35.9	0.0	100
Month 1	162	142	53.5	24.8	56.3	0.0	100
Month 3	119	109	67.2	21.9	67.5	10.4	100
Month 6	75	70	70.7	24.5	75.8	0.0	100

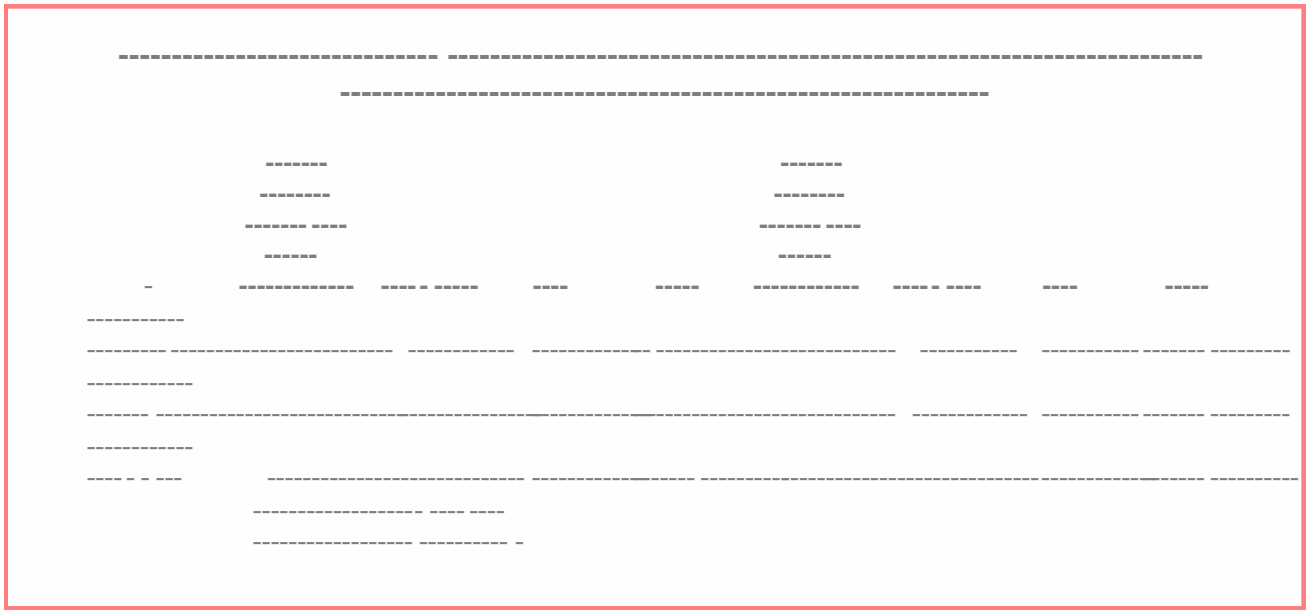
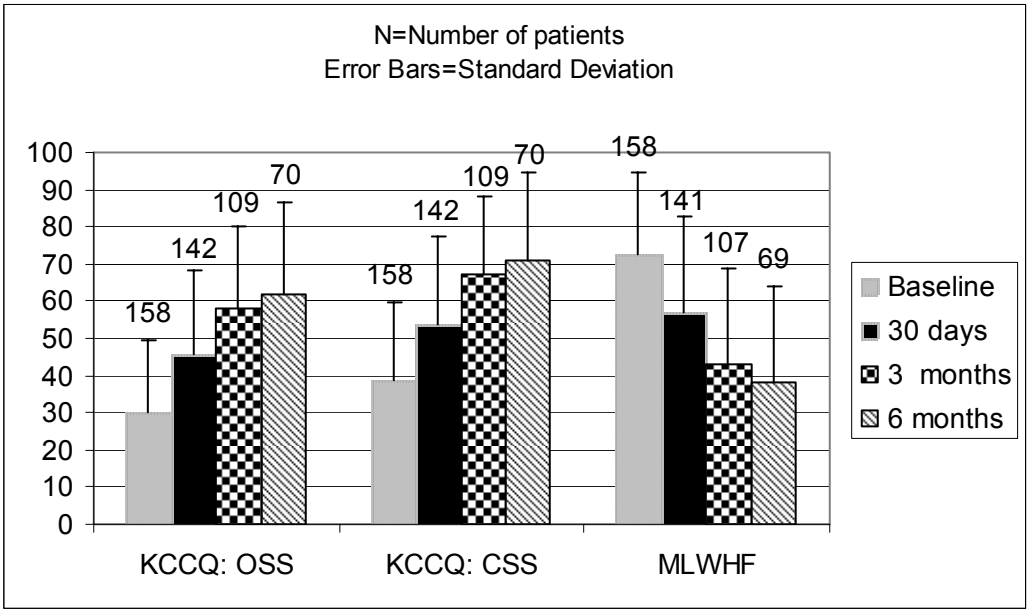


Figure 34 – Proposed Labeling Cohort: Quality of Life Mean Scores over Time



As presented in Table 215, mean and median overall summary and clinical summary scores improved over time. When compared to their baseline score, highly significant ($p<0.0001$) improvement was measured at all intervals following implant.

[22] Spertus J, Peterson E, Conrad MW, et. al. Monitoring Clinical Changes in Patients with Heart Failure: A Comparison of Methods. American Heart Journal, 2005; 150: 707-715.

These data demonstrate that patients supported with the HeartMate II achieved both statistically significant and clinically meaningful improvement in quality of life.

[redacted]

[redacted]

[redacted]

PAGES 261 - 270 REDACTED PER MFR

7.11 OBJECTIVE PERFORMANCE CRITERIA (OPC)

White Paper

Justification for the use of historical / concurrent comparison group in the HeartMate II Bridge to Transplant Pivotal trial

Over the last two decades the implantable left ventricular assist device (LVAD) has become the standard of care for providing circulatory support to patients awaiting transplant who are refractory to intravenous inotropic medical therapy. Jaski et al have reported that the percentage of patients who received LVADs as a function of total transplants has increased from 2% in 1990 to 16% in 1997 (1). The HFSA position paper on key issues for trial designs for LVADs states that since there is widespread acceptance that current generation VADs improves the likelihood of survival to transplant in the population described above, it is appropriate to encourage the application of objective performance measures within uncontrolled trials of newer VADs as long as the target population remains similar to that for which the current generation of VADS is indicated (2). Thoratec proposes a single- arm trial to evaluate the HeartMate II as a bridge to transplant in which the outcomes associated with the HeartMate II will be compared to the expected outcomes associated with approved devices. This approach is proposed based on analysis of aggregate data from all Thoratec implantable VAD databases. This analysis as reported in the following pages, has confirmed that the patient population and survival has not changed appreciably over two decades of use, thereby validating Thoratec's intention to use the outcomes obtained from the aggregate data as a performance objective against which the HeartMate II will be compared.

The following sections will review Thoratec's aggregate data and address concerns regarding the ability to compare the new treatment against historical data.

Thoratec maintains databases (device tracking, study and registry databases) on all Thoratec device implants. Since 1986, over 3500 patients in the United States have been implanted with Thoratec Left Ventricular Assist Devices (HeartMates and IVAD)) as a bridge to cardiac transplantation (see table 1). Approximately 100 new patients are implanted every quarter.. This database, containing both historic and concurrent data will serve as the comparison group for the HMII.

Table 1. HeartMate II Bridge to Transplant Comparison Group.

Database	***Study Dates***	***Number Pts***	***Number Hospitals***
HeartMate IP Clinical Trial	1/86 - 9/94	223	22
HeartMate VEDL Trial	5/91 - 6/96	71	11
HeartMate VESL Trial	2/96 - 9/98	280	24
IVAD Clinical Trial[1]	1/03 – 6/04	16	6
HeartMate IP Device Tracking Registry (USA)	10/94 - 8/04[2]	931	79
HeartMate VE Device Tracking Registry (USA)	10/98 - 8/04[2]	1980	99

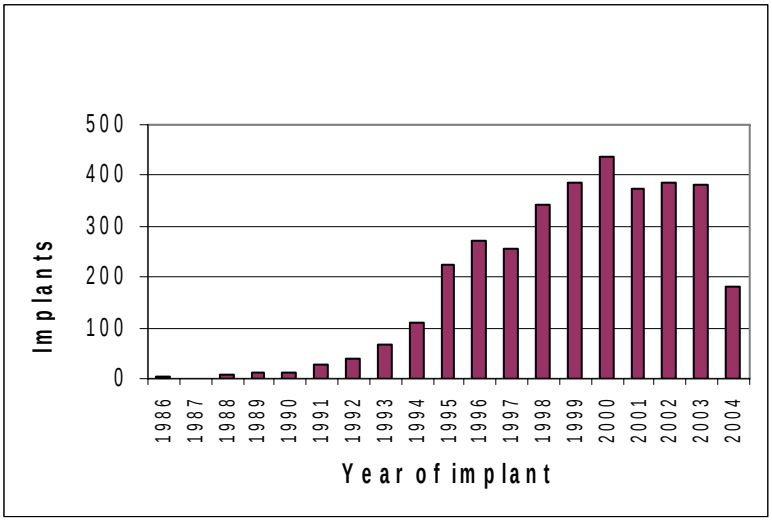
1. Only LVAD Bridge to Transplant patients
2. Thoratec will continue to follow and add concurrent BTT patients

Long has stated that the leading implantable circulatory support technology today is the pulsatile Thoratec HeartMate LVAD (3). This is supported by data reported by the ISHLT in its 2003 report of the Mechanical Circulatory Support Database that showed that the HeartMate represents 69% of LVADs reported (4). Thus, Thoratec implantable LVADs represent the current use of LVAD technology and can serve as the basis for performance standards, assuming there have not been significant changes in the patient population.

Have there been changes to the patient population and do these changes impact outcome?

The first HeartMate patient was implanted in 1986, however, as can be seen in Table 2 below, the majority of efficacy data has been collected in the last 6 years, from 1998 on

Table 2. Implant trend for HeartMate and IVAD LVAD Bridge to transplant patients in the United States



Given that the historical and concurrent control represents nearly 2 decades of data potential changes in the patient population must be explored. These potential changes include the following five areas:

- Changes in the transplant population
- Changes in the transplant population requiring an LVAD
- Changes in patient selection
- Changes in patient management
- Changes in the VAD

Changes in the transplant population:

While it appears that there are some patient characteristics changes in the transplant population as reported by UNOS, these changes have not been seen in the Thoratec VAD treated population. UNOS data as reported in Transplant Statistics: 2003 Annual Report demonstrates some shifts in patient characteristics and outcomes over the last 10 years. Only 4.5% of transplant recipients were aged 65 years or older in 1993 compared to 10.3% in 2002. No changes in the race of the recipient were noted. Hispanic recipients have nearly doubled from 4.9% in 1993 to 8.0% of cardiac transplants in 2002. The percentage of females receiving transplants rose from 21.6% in 1993 to 27.8% in 2002. The percentage of patients in intensive care at the time of transplant dramatically fell from 54.7% in 1993 to 34.1% in 2002 (this trend is due to a change in the transplant allocation algorithm that removed patient location as a dominant factor). The primary diagnosis for heart transplant recipients has remained constant over the last decade. Konstam has reported that transplant patients now have more comorbidities and are more likely to be receiving intravenous inotropes or vasoactive drugs (2).

Have there been similar changes to the VAD Bridge to Transplant comparison group over the last decade?

The Thoratec VAD Bridge to Transplant population characteristics have not changed over the last decade. Patients enrolled into Thoratec bridge to transplant clinical trials all met inclusion criteria designed to identify patients at imminent risk of death (see Table 3). LVADs continue to be used mainly in patients with hemodynamic instability despite maximum medical therapy (2). Thus VAD use is generally restricted to patients listed for transplant who have a cardiac index less than 2 L/min/m^2 and a pulmonary wedge pressure more than 20 mmHg.

Table 3. Summary of HeartMate and IVAD Clinical Trial Inclusion Criteria

Inclusion Criteria	***HM-IP***	***HM-VEDL***	***HM-VESL***	***IVAD - BTT***
Signed consent	Y	Y	Y	Y
Tx List	Y	Y	Y	Y
PCWP	>20 mmHg	>20 mmHg	>20 mmHg	>20 mmHg
Systolic BP	< 80 mmHg	< 80 mmHg	< 80 mmHg	< 90 mmHg
LAP	>20 mmHg	>20 mmHg	>20 mmHg	NA
Cardiac Index	< 2 L/min/sqm	< 2 L/min/sqm	< 2 L/min/sqm	< 2 L/min/sqm
Mixed venous O2 Sat	NA	NA	NA	< 50%
Inotropes	Y	Y	Y	NA
NA = Not Applied to Study				

Age at implant has remained consistent for Thoratec VAD patients over time (Table 4). Four percent of the patients implanted in 1994 were aged 65 years or older compared to 10 percent in 2003, however, since 1997 there has been no trend in more patients 65 years or older. Gender ratios have remained constant. In 2003, 17% of patients were female, the same percentage of patients as in 1994.

Table 4. Age of Thoratec US Bridge to Transplant LVAD patients over time

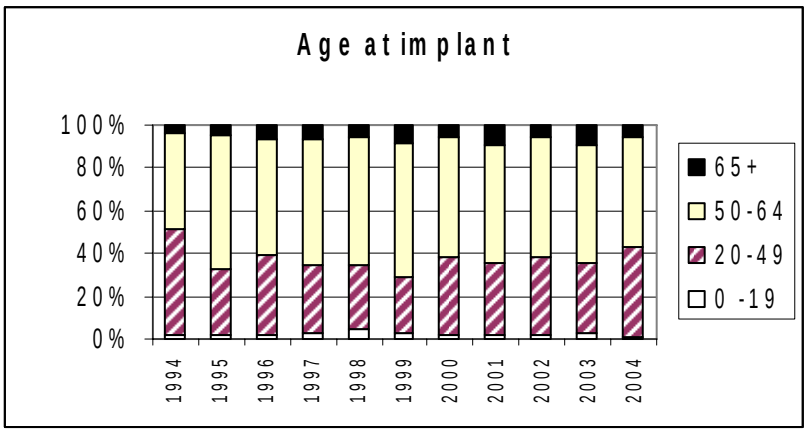
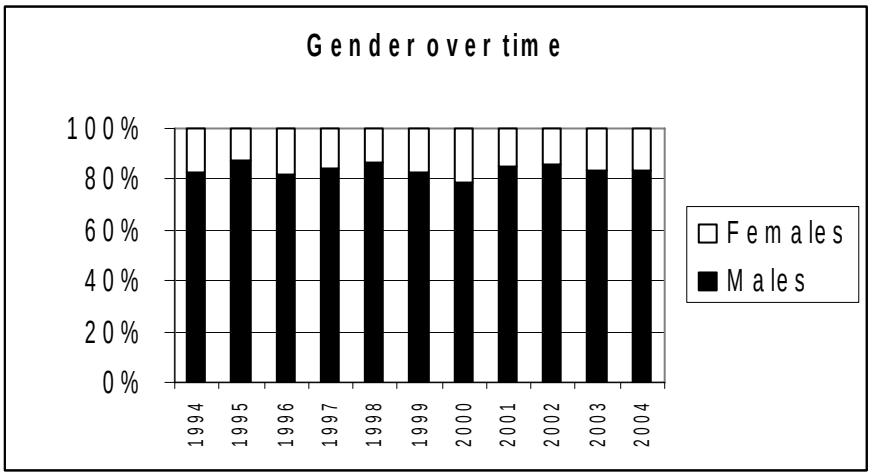


Table 5. Gender of Thoratec US Bridge to Transplant LVAD patients over time



Baseline hemodynamic and biochemical variables, designed to select patients at imminent risk of death, have remain constant over time. The IVAD is a smaller pump than the HeartMate and allowed for a larger proportion of women to be enrolled into the trial.

PAGES 278 - 288 REDACTED PER MFR

7.12 NEUROCOGNITIVE EVALUATIONS

Neurocognitive Evaluations

PAGES 291 - 340 REDACTED PER MFR

7.13 STUDY PROTOCOL

The HeartMate II LVAS Pivotal Study Protocol

Sponsor: **Thoratec Corporation**
6035 Stoneridge Drive
Pleasanton, CA 94588
(925) 847-8600
(925) 847-8574

PAGES 343 - 378 REDACTED PER MFR