Summary of Safety and Effectiveness Data

I. GENERAL INFORMATION

Device Generic Name:	Total Artificial Heart
Device Trade Name:	CardioWest temporary Total Artificial Heart (TAH-t)
Applicant's Name and Address:	SynCardia Systems, Inc. 1992 East Silverlake Road Tucson, Arizona 85713
PMA Application Number:	P030011
Date of Panel Recommendation:	March 17, 2004
Date of Notice of Approval to the Applicant:	October 15, 2004

II. INDICATIONS FOR USE

The SynCardia Systems, Inc., CardioWest temporary Total Artificial Heart (hereinafter called the TAH-t) is indicated for use as a bridge to transplantation in cardiac transplant-eligible candidates at risk of imminent death from biventricular failure. The CardioWest TAH-t System is intended for use inside the hospital.

III. CONTRAINDICATIONS

Patients who are not cardiac transplant eligible.

Patients who do not have sufficient space in the chest area vacated by the natural ventricles. Generally this includes patients who have body surface areas $<1.7m^2$, or who have a distance between the sternum and the 10^{th} anterior vertebral body measured by computed tomography imaging (CT scan) ≤ 10 cm.

Patients who cannot be adequately anticoagulated on the TAH-t.

IV. WARNINGS AND PRECAUTIONS

All Warnings and Precautions can be found in the attached labeling.

V. DEVICE DESCRIPTION

The SynCardia CardioWest TAH-t system is a pulsatile biventricular device that is placed after the native ventricles are excised. The implantable device consists of two artificial

ventricles, each made of a semi-rigid polyurethane housing with four flexible polyurethane diaphragms separating the blood chamber from the air chamber. These diaphragms allow the ventricles to fill and then eject blood when compressed by air from the external drive console. Mechanical valves mounted in the inflow (27 mm) and outflow (25 mm) ports of each artificial ventricle control the direction of blood flow. The maximum dynamic stroke volume of each artificial ventricle is 70 ml, which allows for generating a flow rate up to 9.5 l/min. The right artificial ventricle is connected via the right atrial inflow connector to the right atrium and via the pulmonary artery outflow cannulae to the pulmonary artery. The left artificial ventricle is connected via the left atrial inflow connector to the left atrium, and via the aortic outflow cannulae to the aorta. Each artificial ventricle's driveline conduit is tunneled through the chest. The driveline conduit is covered with velour fabric on its external surface to promote tissue growth. The right and left driveline conduits are attached to seven-foot drivelines that connect to the back of the external drive console.

The console includes a monitoring computer that provides noninvasive diagnostic and monitoring information to the user. Device pumping rate, noninvasive dynamic stroke volumes, and calculated cardiac outputs are displayed on a beat-to-beat basis. Drive pressure and flow waveforms, along with cardiac output trends are provided. Patient related alarms (e.g., low cardiac output) are also displayed on the computer screen. A separate alarm panel on the console provides information on critical drive pressure and backup systems. All alarms generate audio and visual feedback to the user.

A backup air supply (two air tanks) and electrical power (backup power supply and console battery) are automatically activated if the external compressed air and /or AC power are interrupted. This can occur during patient transport or in the event of a failure in the hospital's air or electrical supply.

The controller is the major component of the external console, and supplies pulses of pneumatic pressure to the right and left drivelines, which connect into the air chambers of the respective implanted artificial ventricles. These pulses cause the diaphragms to distend and thereby eject blood from the right artificial ventricle into the pulmonary circulation and from the left artificial ventricle into the systemic circulation.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

One device, the Thoratec Ventricular Assist Device System, is approved for use as a bi-VAD device. The TAH-t is the only device tested that replaces a patient's native ventricles and valves so as to completely take over pumping of blood to both the pulmonary and systemic circulation, and bridge the patient to transplant.

VII. MARKETING HISTORY

Under the authority of 21 CFR §801(e), SynCardia has permission to export, and has distributed the CardioWest Total Artificial Heart to Canada, France, and Germany. The SynCardia CardioWest TAH-t has not been withdrawn from marketing for any reason related to safety and effectiveness of the device.

VIII. ADVERSE EFFECTS

Adverse events collected for all implant patients while on the TAH-t are presented in descending order below. The adverse events represent 19.7 device years of experience while on the device awaiting transplant, and 25.0 man years from date of implant through 30 days post transplant.

Table 1
Incidence of Adverse Events by Decreasing Frequency

	All Patients During Implant Period		All Patients from Implant to 30-days Post Transplant	
Adverse Event	**Number of Events**	**Number (%) of Patients n=95**	**Number of Events**	**Number (%) of Patients n=95**
Any Adverse Event	478	88 (92.6%)	589	93 (97.9%)
Infection	142	66 (69.5%)	172	73 (76.8%)
a. respiratory	58	44 (46.3%)	70	51 (53.7%)
b. urinary tract	32	25 (26.3%)	37	27 (28.4%)
c. device/driveline	18	16 (16.8%)	18	16 (16.8%)
Bleeding	71	42 (44.2%)	102	59 (62.1%)
Respiratory Dysfunction	53	29 (30.5%)	61	34 (35.8%)
Hepatic Dysfunction	34	33 (34.7%)	37	35 (36.8%)
Neurological Event	27	21 (22.1%)	35	26 (27.4%)
a. strokes	11	10 (10.5%)	14	13 (13.7%)
b. TIA	4	3 (3.2%)	4	3 (3.2%)
Renal Dysfunction	28	26 (27.4%)	34	29 (30.5%)
a. elevated creatinine	3	3 (3.2%)	3	3 (3.2%)
b. dialysis	25	24 (25.3%)	31	27 (28.4%)
Reoperation	21	19 (20.0%)	31	23 (24.2%)
Device Malfunction	19	16 (16.8%)	19	16 (16.8%)
a. Driveline kink/leaks	16	14 (14.7%)	16	14 (14.7%)
b. Controller	1	1 (1.1%)	1	1 (1.1%)
c. Air tank	1	1 (1.1%)	1	1 (1.1%)
d. Diaphragm	1	1 (1.1%)	1	1 (1.1%)

	All Patients During Implant Period		All Patients from Implant to 30-days Post Transplant	
Adverse Event	**Number of Events**	**Number (%) of Patients n=95**	**Number of Events**	**Number (%) of Patients n=95**
Reduced Blood Pressure	30	18 (18.9%)	33	22 (23.2%)
Peripheral Thromboembolism	14	9 (9.5%)	18	13 (13.7%)
a. visual	6	5 (5.3%)	6	5 (5.3%)
b. extremities	5	4 (4.2%)	8	7 (7.4%)
c. abdominal	3	2 (2.1%)	4	3 (3.2%)
Reduced Cardiac Index	13	9 (9.5%)	16	12 (12.6%)
Technical/Procedural	11	3 (3.2%)	11	3 (3.2%)
Miscellaneous	5	5 (5.3%)	10	9 (9.5%)
Fit Complication	5	5 (5.3%)	5	5 (5.3%)
Hemolysis	5	4 (4.2%)	5	4 (4.2%)

The adverse events for all patients while on the total artificial heart represented 7079 days on the device. This equates to an adverse event rate on the device of 0.067 events per day while on the device.

The adverse events for all patients from the time of total artificial heart implant to 30 days post transplant (30 days after the implanted TAH-t has been removed) represents an additional 1931 days, for a total time to collect adverse events of 9010 days. The event rate for all implanted patients out to 30 days post transplant is comparable, at 0.065 events per day.

Infections were the largest contributing category to overall adverse events. The majority of infections (150/172 [87.2%]) did not affect patient outcome. Most were respiratory infections followed by genitourinary infections which occurred the first few weeks following implant. Driveline infections were predominantly superficial skin infections treated with routine dressing changes.

Bleeding was related to the surgical implant and transplant procedures. In some cases, reoperations for bleeding (30/102 [29.4%]) were also required for excessive bleeding around the heart or lungs. Fifty-nine [57.8%] of the 102 bleeding events occurred during the first 3 weeks after implant with another 30 events (29.4%) occurring within 2 days after transplant.

Respiratory dysfunction was also surgically related with most events (40/61 [65.6%]) occurring during the first 3 weeks following the implant surgery and 8/61 (13.1%) occurring after the transplant surgery. Hepatic and renal dysfunction occurred in the first 3 weeks following the implant. By 4 weeks, hepatic and renal markers were at normal levels.

Thirty-five neurologic events occurred in 26 implant patients during the implant and 30-days post transplant periods. Fourteen strokes occurred in 13 patients during the implant to 30-days post transplant period. One stroke temporarily affected patient outcome, and that patient was successfully transplanted after 332 days on the device. Other neurologic events were encephalopathy (6/35 [17.1%]), seizures (7/35 [20.0%]), transient ischemic attacks (4/35 [11.4%]), loss of consciousness (2/35 [5.7%]) and related to metabolic imbalances (2/35 [5.7%]).

There were 11 driveline kinks that occurred when patients rolled over or sat on their drivelines, and 5 driveline leaks. A design change was implemented to relocate the wire reinforcement within the driveline. There have been no reports of driveline leaks since the change was implemented. One malfunction, a diaphragm tear, was a primary cause of death. .The patient had hemodynamic insufficiency, was carefully monitored, and on post-operative day 115, a clot caused cardiac output to decrease, requiring removal of a large hemo-pneumothorax. The family refused another implant and the patient developed multi-organ failure and died on day 124. Although extensively investigated, the cause of the failure was never determined and could never be duplicated. There have been no additional instances of diaphragm tears found during production or experienced clinically, since the incident.

Reduced blood pressure was secondary to sepsis (12/33 [36.4 %]), volume depletion 11/33 [33.3%]), medication (1/33 [3.0%]) and hematuria (1/33 [3.0%]).

All technical/procedural events (11/11 [100%]) were related to a central catheter obstruction of the artificial valve within the TAH-t. Labeling has been modified to include a warning based on these clinical events. The warning advises physicians to not allow any catheter near the left or right inflow valves.

IX. SUMMARY OF NON-CLINICAL LABORATORY TESTS

A. Biocompatibility/Sterilization

The implantable hearts were sterilized by the validated EtO sterilization cycle, extracted and tested in accordance with ISO 10993, *Biological Evaluation of Medical Devices*, test methods, and in accordance with Good Laboratory Practices. Results of the testing are summarized below.

Table 2
Biocompatibility Testing

Test Performed	Result
Cytotoxicity	Non-cytotoxic
Acute Systemic Toxicity	No systemic toxicity
Subchronic Toxicity	No histological evidence of subchronic toxicity
Ames Mutagenicity	Non-mutagenic
Chromosomal Aberration Assay	No induced chromosomal aberrations
Mouse Micronucleus Mutagenicity	Non-mutagenic
Pyrogen	Nonpyrogenic
Sensitization	Non-sensitizing
Hemocompatibility	Hemocompatible

B. In-vitro Studies

1. *In-vitro* Characterization

In-vitro characterization of the TAH-t on a mock circulatory loop demonstrated the performance of TAH-t under normal, hypotensive and hypertensive simulated operating conditions as indicated below.

Table 3
Conditions for Mock Circulation Testing

Setting/Parameter	Hypotensive	Normal	Hypertensive
BPM ± 5	80	120	140
% systole ± 5	55	50	60
LDP ± 15 mmHg	150	200	280
RDP ± 15 mmHg	40	75	135
Vacuum ± 5 mm Hg	none	10	15

The TAH-t provided a range from 2.6-9.5 l/min flow, which is sufficient to support total circulation under the expected clinical conditions.

2. *In-vitro* System Testing

Laboratory testing was performed to demonstrate that the TAH-t system met its intended functional specifications. Testing included pull tests and torque tests on the ventricle-to-connector joints and drivelines, and sterility and packaging testing on the implantable components of the system. Console testing included controller performance of alarms, system connections, battery longevity, electrical safety and electro-magnetic compatibility. Software verification and validation was performed and back-up air and power performance were verified under simulated use conditions.

C. Reliability

The purpose of reliability testing is to determine with reasonable assurance, how long a given device will perform as intended, without failure.

Three separate sets of *in vitro* reliability testing were conducted. In one test, four TAH-t units were run for a period of 180 days. During this time there were no failures or abnormalities observed.

In a second *in vitro* reliability trial initiated in December 1998, four TAH-t units were tested in a "run to failure" study design and are ongoing. To date, there have been no failures or abnormalities observed.

A third test was initiated using three TAH-t units which had expired their 3 year sterilization expiration date. This provided information about the effects of long-term storage on the fatigue resistance properties of the TAH-t. To date, there have been no failures or abnormalities observed.

In conclusion, a total of eleven units have been run for various lengths of time over the last six years with no device-related failures. The cumulative number of days used for calculation was 6715 and there have been no failures or signs of appreciable wear observed. When the 11 units are used to calculate reliability with a 90% confidence, the reliability at 30, 60 and 365 days is as reported in the table below.

Table 4
Reliability Test Results with 90% Confidence

# days run	MTBF*	Reliability in number of days run		
		30	60	365
6715	2916	0.99	0.98	0.88

X. SUMMARY OF CLINICAL STUDIES

A. Study Objective

The purpose of this study was to demonstrate that the CardioWest Total Artificial Heart is safe and effective in providing circulatory support as a bridge to cardiac transplantation in patients with biventricular failure. Bridge to transplant is defined as the use of a circulatory support device to maintain viability for transplantation until a donor organ is procured.

B. Study Design

The study was approved under IDE G920101 as a non-randomized, multi-centered trial with both historical and concurrent controls. Patients were transplant candidates who were at risk of imminent death from biventricular heart failure. The overall objective of this study was to determine if the TAH-t was safe and effective for bridging patients to cardiac transplantation. A total of 95 patients were enrolled. Of these, 81 formed the core implant group and an additional 14 patients did not meet study entrance criteria and were considered an out-of-protocol cohort, treated under compassionate use. IRB acknowledgments were obtained for each patient. The data used to demonstrate safety and effectiveness were collected from patients enrolled at five U.S. investigational sites.

1. Effectiveness Parameters

Treatment success was defined as patients who, at 30 days post transplant, were 1) alive; 2) New York Heart Association Class I or II; 3) not bedridden; 4) not ventilator dependent; and 5) not requiring dialysis. Overall survival, hemodynamics and kidney and liver end organ function were secondary effectiveness endpoints.

2. Safety Parameters

Patients were clinically assessed and adverse events were evaluated for safety.

C. Study Protocol

1. Inclusion Criteria

Patients who met all of the following inclusion criteria were eligible for the study:

- Signed informed consent
- Eligible for Transplant
- New York Heart Association Functional IV

- Body surface area 1.7-2.5 m^2, or have a distance between the sternum and the 10^{th} anterior vertebral body measured by computed tomography imaging (CT scan) ≥ 10 cm.
- Hemodynamic insufficiency demonstrated by A or B below:

  A: Cardiac index ≤2.0 l/min/M^2 and one of the following:
  Systolic arterial pressure ≤90 mm Hg
  Central venous pressure ≥18 mm Hg

  B: Two of the following:
  Dopamine ≥ 10 μg/kg/min
  Dobutamine ≥ 10 μg /kg/min
  Epinephrine ≥ 2 μg /kg/min
  Isoproterinol ≥2 μg /kg/min
  Amrinone ≥ 10 μg /kg/min
  Other drugs at maximum levels
  Intra-aortic balloon pump (IAPB)
  Cardiopulmonary bypass (CPB)

2. *Exclusion Criteria*

Patients with any of the following conditions were excluded from the study:

- Use of any ventricular assist device
- Pulmonary Vascular Resistance ≥ 8 Wood (640 Dynes-sec/cm5).
- Dialysis in previous 7 days
- Serum Creatinine ≥ 5 mg/dl
- Cirrhosis with Bilirubin ≥ 5 mg/dl
- Cytotoxic antibody ≥ 10%

3. *Treatment Procedures*

All patients were screened for study eligibility. The treatment group met eligibility criteria within 48 hours of the implant procedure, signed an informed consent and received a TAH-t implant.

4. *Term of Study*

Patients were followed through the primary endpoint of 30 days post transplant, and then monitored for survival annually.

D. Comparison Population

A comparison group was initially identified by retrospective review during a time period when the TAH-t was not available to the participating centers. Analysis of the baseline data from this group of patients revealed they were not comparable to

the treatment group. An imbalance in the year of implant and in multiple baseline covariates made statistical comparisons inappropriate. Therefore, a survival to transplant performance goal (65%) that had been developed for bridge to transplant in univentricular devices (LVADs) was used as a guideline. It should be noted that the adverse events were not compared to a performance goal due to different definitions. The LVAD performance goal was established from a literature search of articles published in 1997 or after for the bridge to transplant indication. The criteria for inclusion were: at least 20 adult patients, original data, wide geographic distribution, and enough detailed data to determine the results in LVAD adult patients. The criteria for exclusion were: duplicate papers reporting the same population, registries, meta-analyses, RV support at initial implant, and cardiogenic shock patients.

E. Description of Study Population

There were 81 patients entered into the core treatment group. The patients were predominantly male (86%) with average age of 51 (range 16-67), and average body weights and surface areas of 85.3 kg and 2.0 m^2. All patients were NYHA functional Class IV at the time of enrollment. The etiology of the heart disease was ischemic (53%) or idiopathic (47%).

Patients enrolled in the clinical trial were not candidates for VAD devices as evidenced by at least one of the following:

Contraindications to VAD Use	n
Refractory Arrhythmias/Unresuscitatable cardiac arrest	25
Hypokinetic right/left/global ventricle	23
Aortic regurgitation, stenosis, prosthesis	13
Massive myocardial infarction or direct myocardial injury that affects technical insertion of a VAD through the ventricle.	10
Failure to wean from cardiopulmonary bypass with biventricular injury	4
Left Ventricular/Right Ventricular/Mural Thrombus	3
Ventricular Septal Defect	3

Analysis of baseline covariates at the completion of the study indicated that the control and core implant patients were not statistically comparable. No valid statistical comparisons could be made between the two groups. Therefore, the results for the control group are not included in this summary.

The study was designed as a multi-institutional study. The following distribution of implants occurred for the core patients.

Table 5 Enrollment by Center

Center Code	Center	Number (%) Core Patients
UMC	University Medical Center, Tucson, AZ	58 (72%)
LOY	Loyola University Medical Center, Chicago, IL	13 (16%)
LDS	LDS Hospital Salt Lake City, UT	8 (10%)
STL	St. Luke's Medical Center Milwaukee, WI	1 (1%)
UPM	Univ. of Pittsburgh Medical Center Pittsburgh, PA	1 (1%)
	Total	***81***

No gender requirements were identified for inclusion into the trial. The United Network for Organ Sharing (UNOS) August 1, 2001 database of all patients receiving heart transplants, heart-lung transplants or multiple organ transplants, divides gender into 73.3% males and 26.7% females for cardiac transplants.. For the 64 patients who received a heart transplant in this trial, 86.4% were males vs. 13.6% females, indicating similar characteristics as the UNOS data.

The inclusion criteria were broad and it is recognized that the diagnosis of RV failure is difficult. The following are the inclusion criteria for the study and the prevalence of patients meeting each part of the inclusion criteria:

- Hemodynamic insufficiency demonstrated by A or B below:

  A: Cardiac index $\leq$ 2.0 l/min/M^2 and one of the following:
  Systolic arterial pressure $\leq$ 90 mm Hg
  Central venous pressure $\geq$ 18 mm Hg

  B: Two of the following:
  Dopamine $\geq$ 10 µg/kg/min
  Dobutamine $\geq$ 10 µg /kg/min
  Epinephrine $\geq$ 2 µg /kg/min
  Isoproterinol $\geq$ 2 µg /kg/min
  Amrinone $\geq$ 10 µg /kg/min
  Other drugs at maximum levels
  Intra-aortic balloon pump (IAPB)
  Cardiopulmonary bypass (CPB)

Table 6
Inclusion Criteria of Core Implant Patients

Inclusion Criteria Met	Number of Patients (%) n=81
Only A (SAP <90 or CVP >18)	25 (30.9%)
Only B (drugs, IABP, CPB)	30 (37.0%)
Both A and B	26 (32.1%)

Baseline characteristics for the core patients are provided in the table below.

Table 7
Baseline Demographics, Risk Factors and Clinical Characteristics for Core Implant Patients

Characteristic	n=81
Age (years) Mean ± SD	51.1 (10.3)
Male	70 (86.4%)
Height (mean in cm) ± SD	176.2 (11.1)
Weight (mean in kg) ± SD	85.3 (13.2)
BSA (mean as m^2) ± SD	2.0 (0.18)
NYHA Class IV	81 (100.0%)
Cardiac index L/min/m^2 ± SD	1.9 (0.5)
Etiology – Ischemic	43 (53.1%)
Etiology -Non-ischemic (idiopathic)	38 (46.9%)
History of smoking	44 (54.3%)
History of excessive alcohol use	37 (45.7%)
Hypertensive	26 (32.1%)
Prior cardiac arrest	30 (37.0%)
Anticoagulated on entry	38 (46.9%)
Insulin-dependent Diabetes Mellitus	5 (6.2%)
Non- insulin-dependent Diabetes Mellitus	15 (18.5%)
Entry on Cardiopulmonary bypass	15 (18.5%)
Entry on intra-aortic balloon pump	29 (35.8%)
Entry with ventilator	34 (42.0%)
Entry obtunded/drowsy	28 (34.6%)

Characteristic	n=81
Prior mediastinal surgery	31 (38.3%)
Prior percutaneous angioplasty	12 (14.8%)
Pacemaker	10 (12.3%)
Automatic implantable cardioverter defibrillator	24 (29.6%)

Baseline hemodynamics, hematology and blood chemistry for the core implant group is presented below. At entry, 15 patients were supported by cardiopulmonary bypass and 29 patients were supported on intra-aortic balloon pumps to maintain hemodynamics.

Table 8
Baseline Hemodynamics – Core Implant Patients

Hemodynamic Measurement	Mean Value (SD) n = 81
Cardiac Index (L/min/M^2)	1.9 (0.5) n = 65
Cardiac Output (L/min)	3.9 (1.1) n = 65
Systemic Vascular Resistance (dyne-sec/cm^5)	1108.9 (393.7) n = 68
Pulmonary Vascular Resistance (dyne-sec/cm^5)	221.7 (116.8) n = 78
Heart Rate (bpm)	101.3 (20.7) n = 81
Systolic Arterial Pressure (mm Hg)	92.8 (15.2) n = 79
Mean Arterial Pressure (mm Hg)	68.1 (9.1) n = 79
Pulmonary Artery Systolic Pressure (mm Hg)	55.2 (13.5) n = 72
Pulmonary Artery Mean Pressure (mm Hg)	41.1 (10.8) n = 72
Pulmonary Capillary Wedge Pressure (mm Hg)	29.6 (10.6) n = 68
Central Venous Pressure (mm Hg)	19.7 (6.9) n = 77
Organ Perfusion Pressure (mm Hg)	48.6 (10.9) n = 75

Table 9
Baseline Blood Chemistry and Hematology
Core Implant Patients

Chemistry/Hematology Measurement	Mean Value (SD) n = 81
Chemistry	
Sodium (mEq/L)	132.0 (6.7) n = 79
Potassium (mEq/L)	4.4 (0.9) n = 80
Chloride (mEq/L)	96.1 (6.7) n = 79
Blood Urea Nitrogen (mg/dL)	36.2 (18.7) n = 79
Creatinine (mg/dL)	1.7 (0.6) n = 81
Total Bilirubin (mg/dL)	2.0 (1.3) n = 79
SGOT (IU/L)	189.9 (773.1) n = 77
Hematology	
White Blood Cell Count ($10^3/\mu L$)	11.4 (4.1) n = 80
Red Blood Cell Count ($10^6/\mu L$)	3.8 (0.7) n = 80
Hematocrit (%)	33.7 (6.1) n = 80
Platelet Count ($10^3/\mu L$)	213.0 (93.6) n = 77
Plasma Free Hemoglobin (mg/dL)	11.5 (16.0) n = 64
Coagulation Panel/Cytotoxicity	
Prothrombin Time (sec)	16.4 (4.4) n = 79
International Normalization Ratio (INR)	2.0 (1.5) n = 79
Partial Thromboplastin Time (sec)	37.3 (12.7) n = 75
Fibrinogen (mg/dL)	467.4 (198.6) n = 62
Cytotoxic Antibody (%)	0.0 (0.3) n = 76

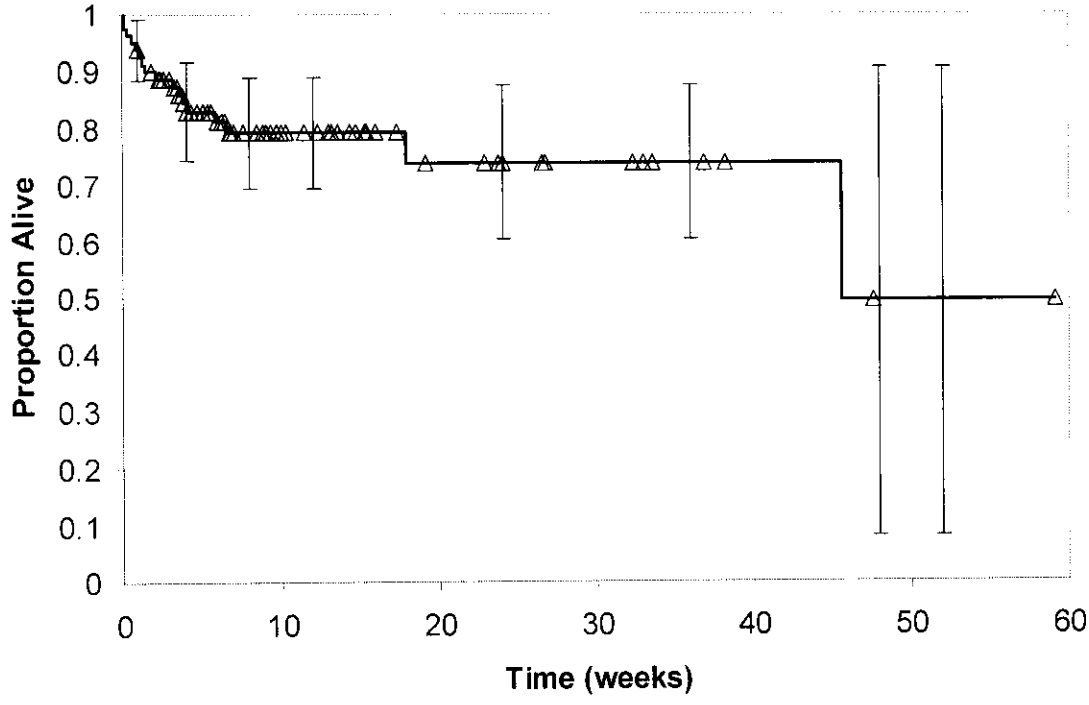
The mean core patient wait for a donor heart was 79 days, with a median wait time of 47 days.

Table 10 Time to Transplant or Death

Time	Statistic	Core n = 81
Duration (days)	Mean (SD)	79.1 (83.9)
	Median	47.0
	Min-Max	1.0 - 414.0
Total Duration (days)		6411

Figure 1 graphically shows the estimate of survival to transplant or death for the core implant group by time.

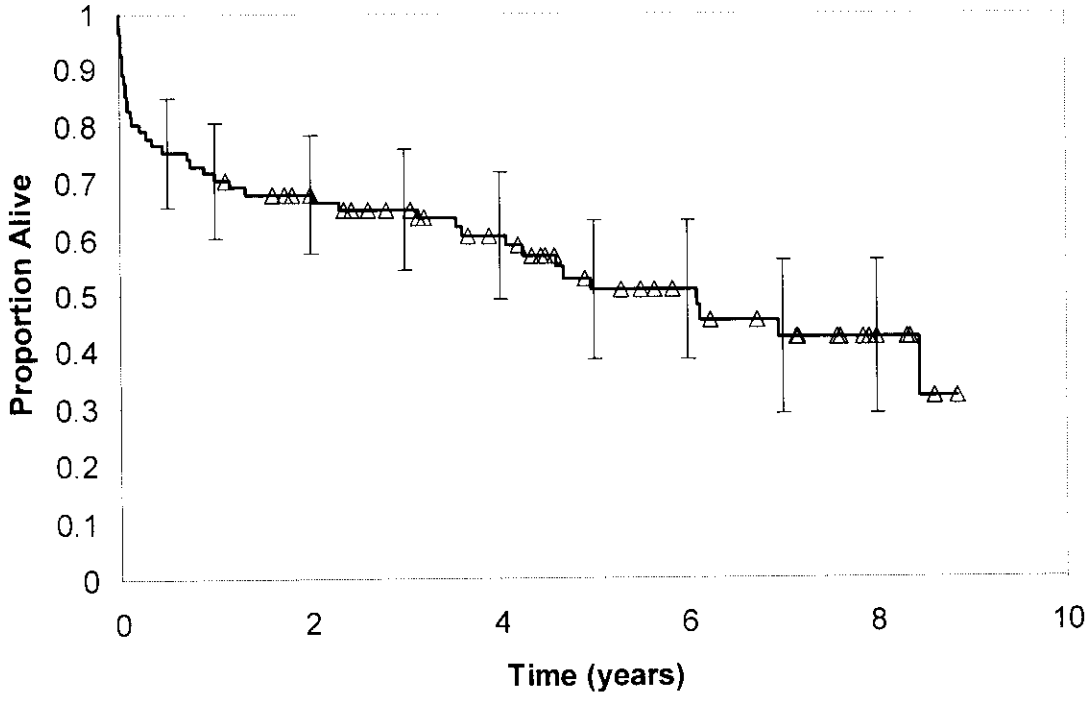
Figure 1 – Kaplan-Meier Estimate of Duration of Survival to Transplant or Death (Core Patients)



Time (weeks)								
	1	4	8	12	24	36	48	52
Core (n=81)								
Survival rate (%)	93.8	83.1	79.3	79.3	74.0	74.0	49.4	49.4
Standard error (%)	2.7	4.3	4.9	4.9	6.8	6.8	20.7	20.7
n	75	55	37	26	10	5	1	1

All patients in this study reached at least the 2 year post transplant interval and at 2 years the survival was 68%.

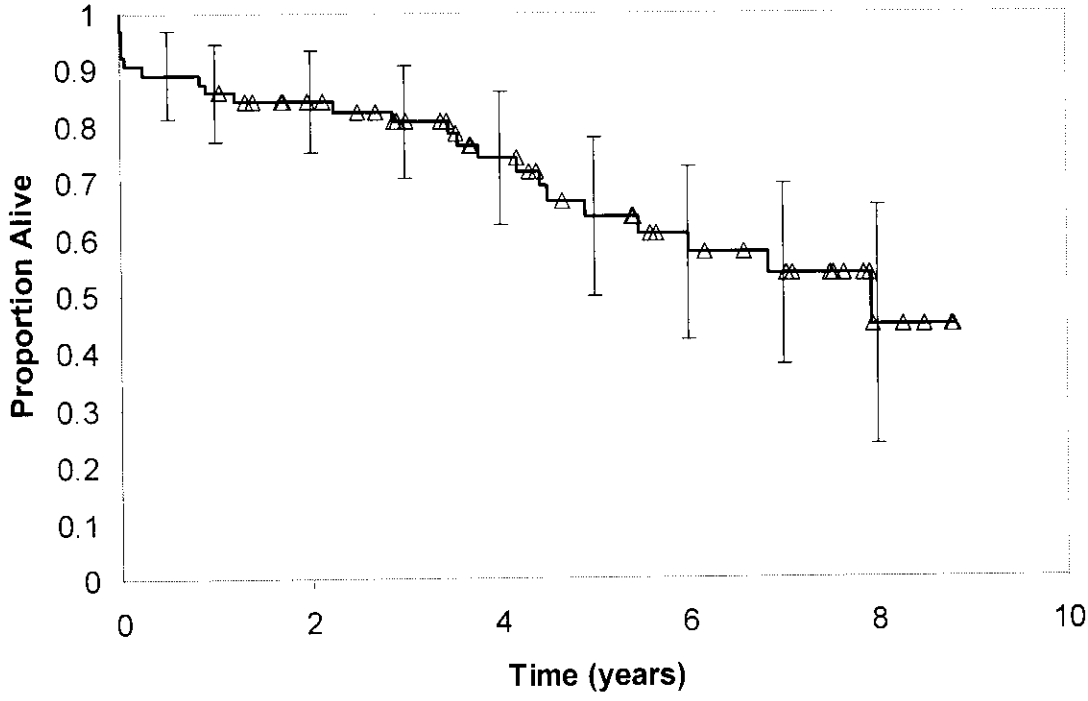
Figure 2 – Kaplan-Meier Estimate of Overall Duration of Survival (Core Patients)



Time (years)								
	0.5	1	2	3	4	5	6	7
Core (n=81)								
Survival rate (%)	75.3	70.4	67.9	65.1	60.4	50.8	50.8	42.4
Standard error (%)	4.8	5.1	5.2	5.3	5.6	6.2	6.2	6.8
n	61	57	51	44	35	24	19	14

Survival post transplant was comparable between the core patients and published survival of all cardiac recipients on the UNOS list. Sixty four of 81 core patients received transplants, with a post transplant survival rate at 1 year of 85.9% (vs. 84.7% UNOS), and a 5 year survival rate of 63.8% (vs. 69.8% UNOS).

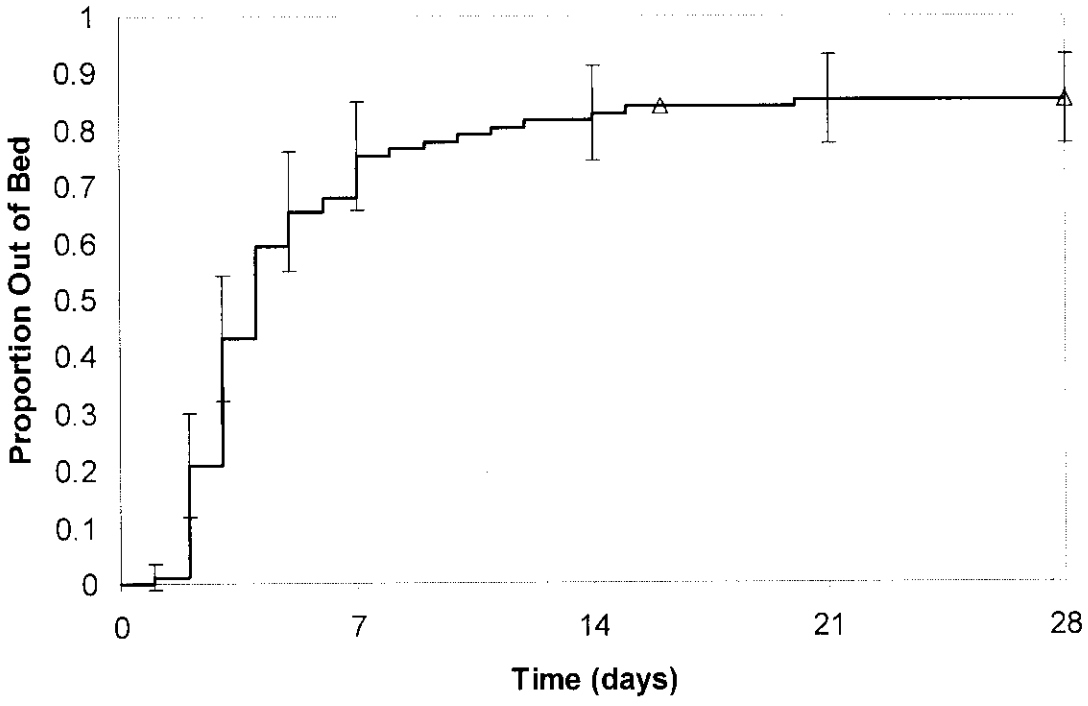
Figure 3 – Kaplan-Meier Estimate of Duration of Survival from Transplant (Core Patients)



Time (years)								
	0.5	1	2	3	4	5	6	7
Core (n=64)								
Survival rate (%)	89.1	85.9	84.3	80.7	74.1	63.8	57.4	53.5
Standard error (%)	3.9	4.3	4.5	5.0	5.9	7.0	7.6	8.0
n	57	55	48	41	32	23	17	14

The core TAH-t patients' ability to get out of bed and ability to walk over 100 feet was significantly improved. Approximately 65% of the core patients were out of bed by the 5th day after implant. Two weeks after implant, 60% of core patients were walking over 100 feet.

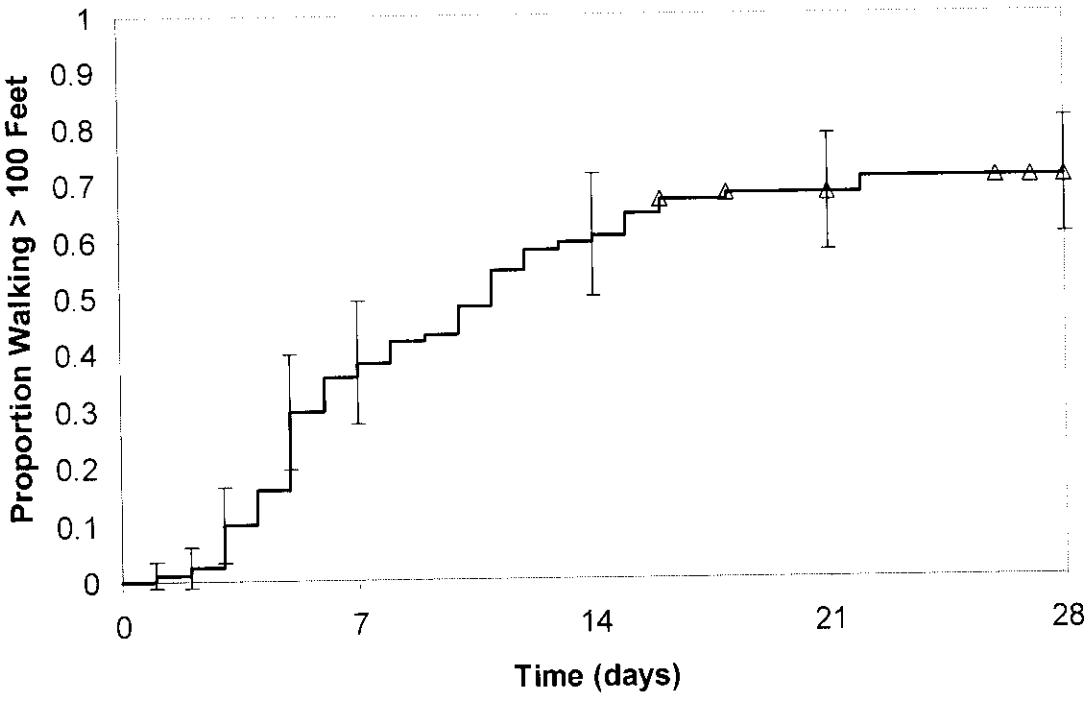
Figure 4 – Kaplan-Meier Estimate of Time to First Getting Out of Bed (Core Patients)



	Time (days)							
	1	2	3	5	7	14	21	28
Core (n=81)								
% walking	1.2	21.0	43.2	65.4	75.3	82.7	85.3	85.3
Standard error (%)	1.2	4.5	5.5	5.3	4.8	4.2	4.0	4.0
n	80	64	46	28	20	14	11	11

Note: *Time to getting out of bed is the number of days from enrollment/implant to first getting out of bed or transplant. Patients who die before getting out of bed are censored at 9999 days; patients transplanted before getting out of bed are censored at day of transplant.*

Figure 5 – Kaplan-Meier Estimate of Time to First Walking > 100 Feet (Core Patients)



Time (days)								
	1	2	3	5	7	14	21	28
Core (n=81)								
% walking > 100 ft	1.2	2.5	9.9	29.6	38.3	60.5	67.9	70.7
Standard error (%)	1.2	1.7	3.3	5.1	5.4	5.4	5.2	5.1
n	80	79	73	57	50	32	23	19

Note: *Time to walking>100 ft is the number of days from enrollment/implant to first walking > 100 ft or transplant. Patients who die before walking >100 ft are censored at 9999 days; patient transplanted before walking >100 ft are censored at the day of transplant.*

Core patients had an immediate and sustained improvement in their hemodynamic variables while on the TAH-t awaiting transplantation. Cardiac index improved from 1.9 L/min/m² to 3.0 L/min/m² immediately after implant, a 58% improvement, with sustained levels throughout the implant period. Systolic blood pressure increased from a baseline 92.8 mm Hg to 122.7 mm Hg, a 32% improvement, immediately following transplant, and was also sustained through the implant period.

Organ perfusion pressure (transcapillary or whole body perfusion pressure) increased by 42% immediately following implant with the TAH-t. An increase in perfusion pressure is a measurement of increased whole-body perfusion which leads to organ recovery. Perfusion pressure is calculated by subtracting the central venous pressure from the mean arterial pressure. Perfusion pressure was improved and maintained throughout the implant period for core implant patients.

Figure 6 – Mean (+/- 2SE) Cardiac Index by Study Period (Core Patients)

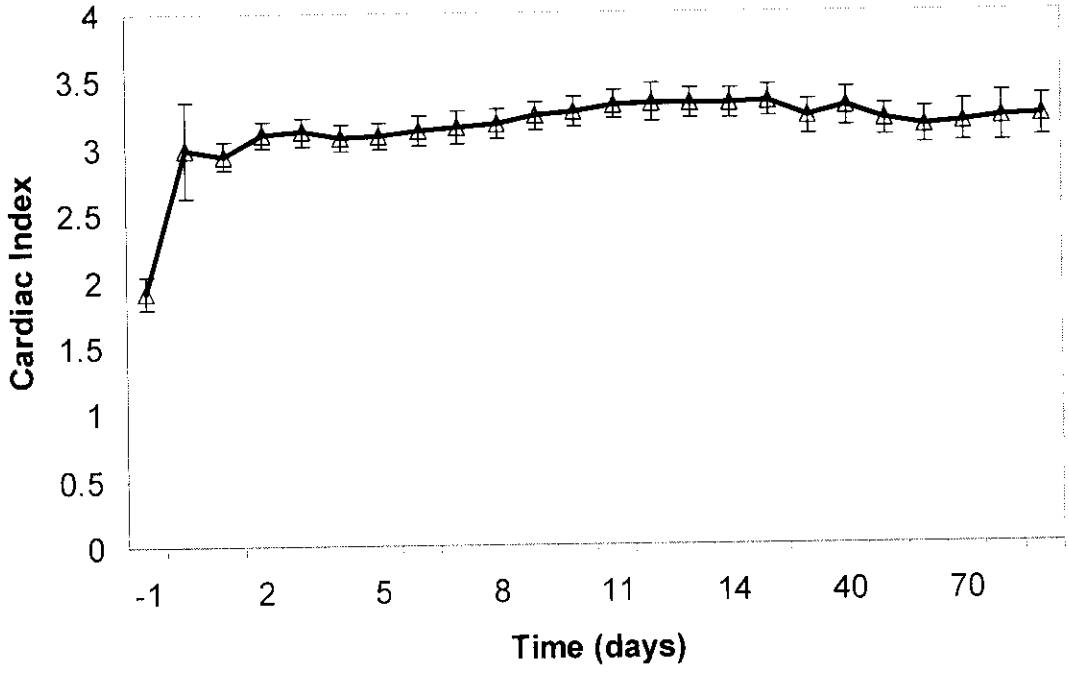


Figure 7 – Mean (+/- 2SE) Systolic Arterial Pressure by Study Period (Core Patients)

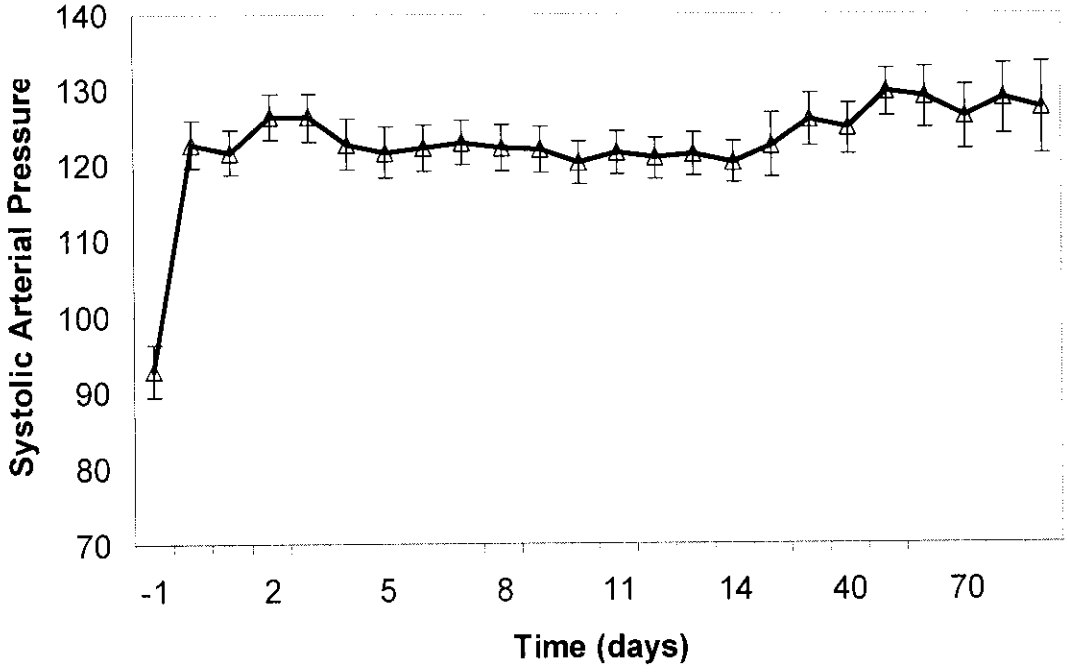
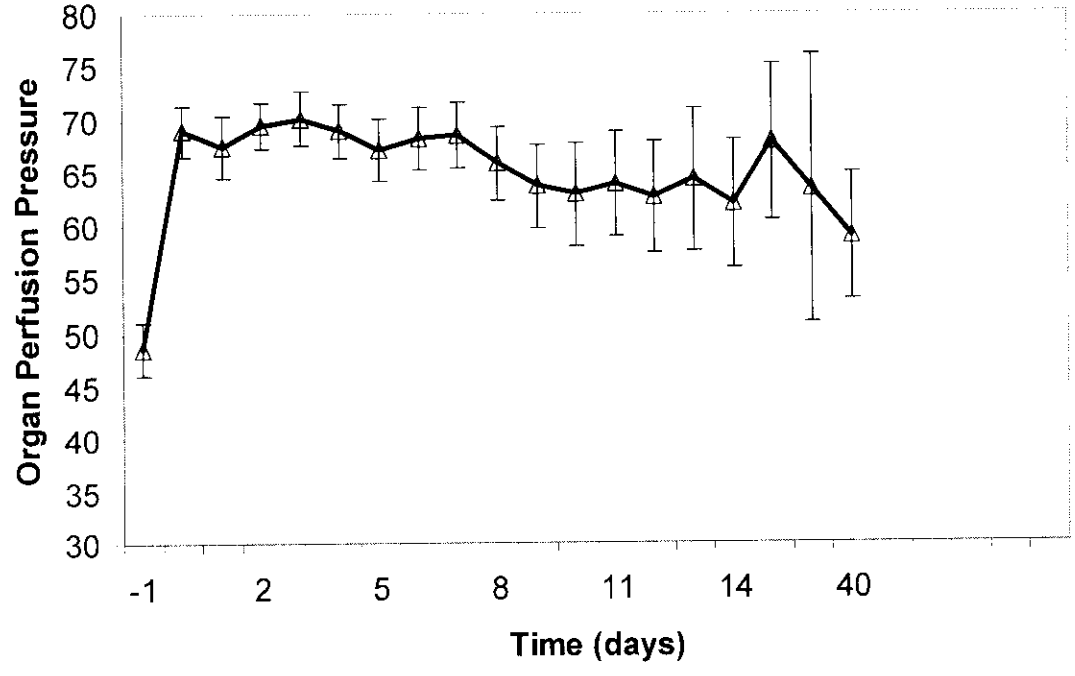


Figure 8 – Mean (+/- 2SE) Organ Perfusion Pressure by Study Period (Core Patients)



Both renal and hepatic function in the core implant population normalized after 3 weeks. At study entry the renal and hepatic functions were adversely affected by the patients' heart conditions shown by elevated blood urea nitrogen (BUN), creatinine, total bilirubin and SGOT levels above maximum normal. After the TAH-t implant surgery and recovery from surgery (approximately 3 weeks) the levels normalized in the core group and were often in the normal range for these markers of renal and hepatic function.

Figure 9 – Mean (+/- 2SE) BUN by Study Period (Core Patients)

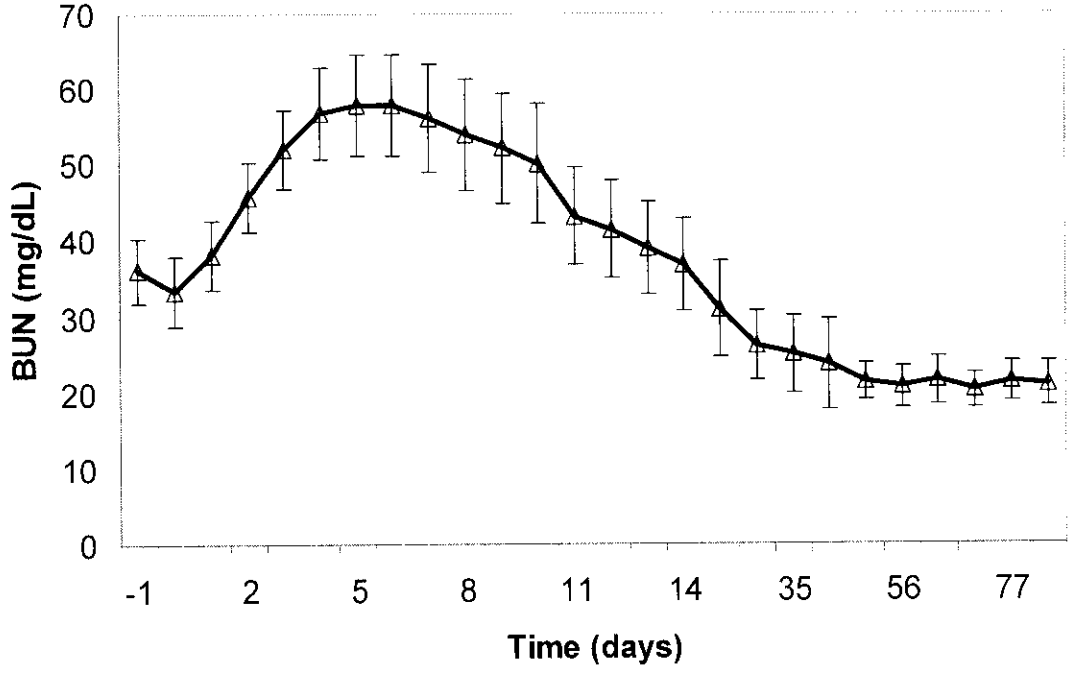


Figure 10 – Mean (+/- 2SE) Creatinine by Study Period (Core Patients)

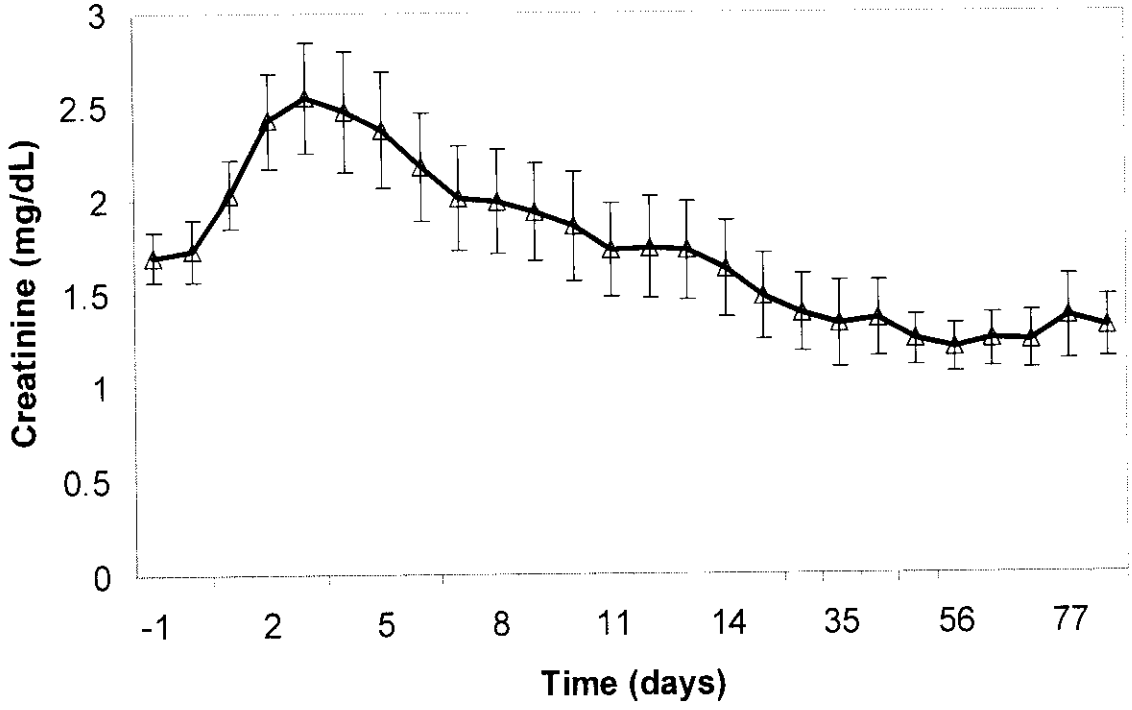


Figure 11 – Mean (+/- 2SE) Total Bilirubin by Study Period (Core Patients)

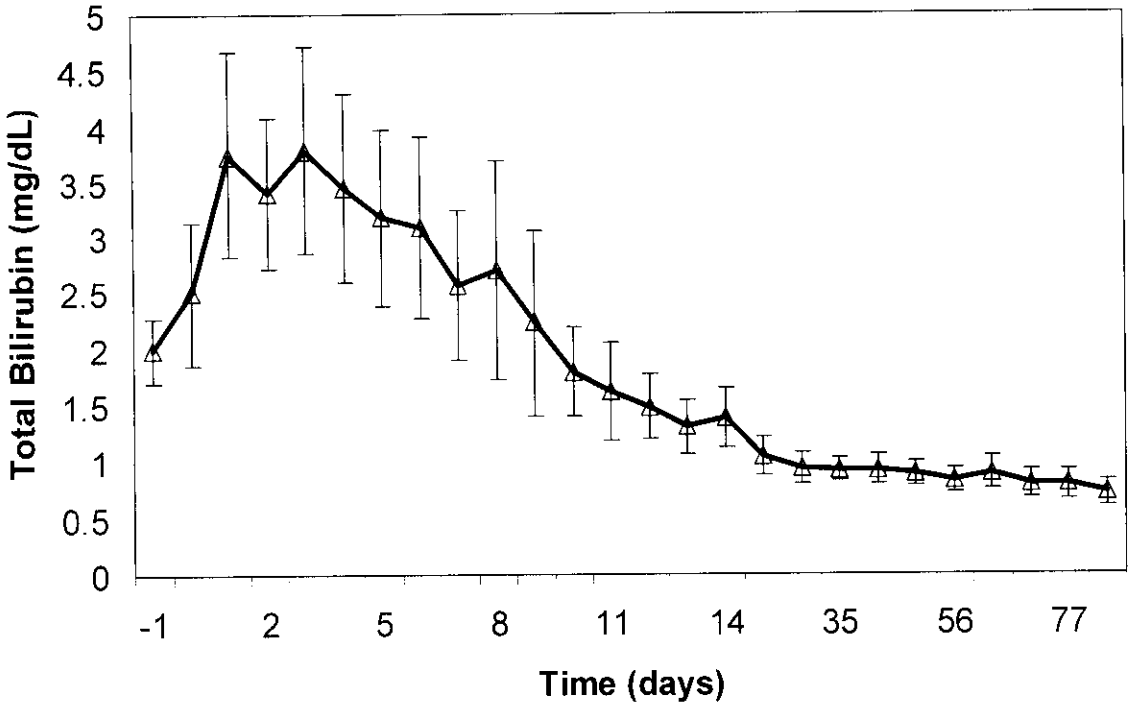
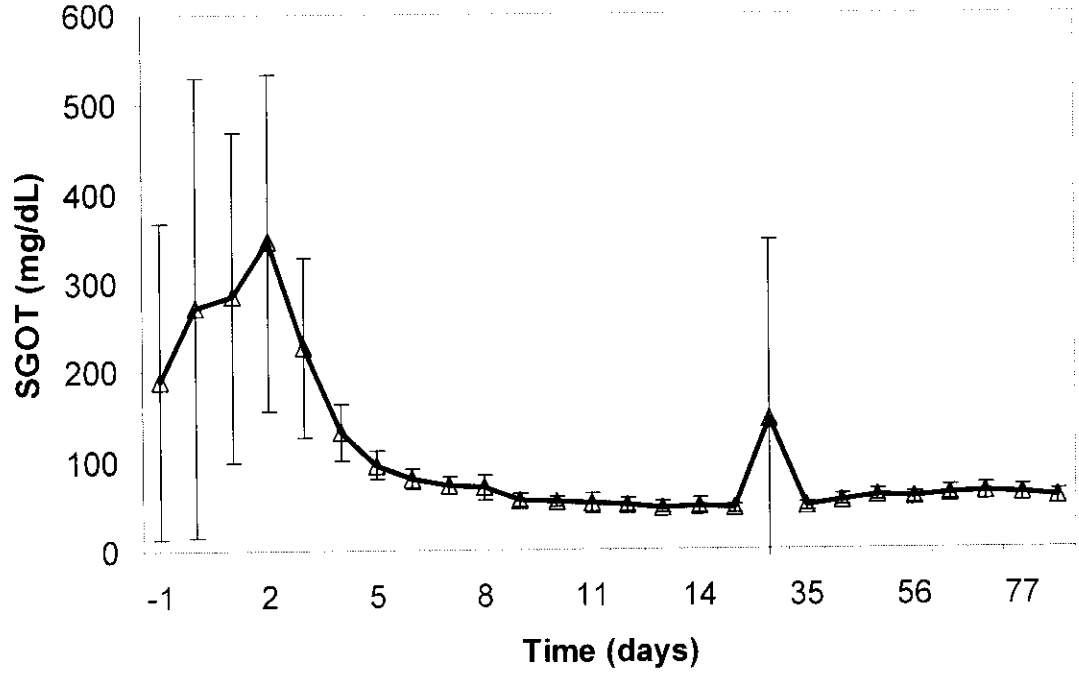


Figure 12 – Mean (+/- 2SE) SGOT by Study Period (Core Patients)



F. Results

The primary endpoint of the study was treatment success. To be considered a success the patient must have been, at 30-days post transplantation: 1) alive; 2) NYHA Class I or II; 3) ambulatory; 4) not ventilator dependent; and 5) not on dialysis. Patients who failed these criteria were considered failures with respect to the study. At 30 days post transplant, 69.1% (56/81) of the core implant group met the criteria for treatment success.

Table 11- Clinical Trial Outcomes - Core Patients

Outcome n(%)a (95% CI)	Core Patients N=81
Survived to transplant	64 (79.0%) (68.5% - 87.3%)
Survived to 30 days post Transplant	58 (71.6%) (60.5% - 81.1%)
Treatment success (30 days post Transplant)	56 (69.1%) (57.9% - 78.9%)

Device effectiveness results establish that the SynCardia CardioWest temporary Total Artificial Heart is effective in providing bridge to transplant circulatory support in cardiac transplant candidates at risk of imminent death from biventricular failure. Secondary effectiveness parameters measured the improvement in hemodynamics, the ability to ambulate and to walk 100 feet for core patients awaiting transplant. At the time of TAH-t implantation, cardiac index increased to an average of 3.0 l/min/m^2, an increase of 58% from baseline. Following TAH-t implant, systolic blood pressure increased to an average of 123 mm Hg (32% from baseline), and mean transcapillary perfusion pressure (mean blood pressure minus central venous pressure) increased to an average of 69 mm Hg, up 42% from baseline, an indication of improved organ perfusion. This near normalization of hemodynamic parameters corresponded to the ability of core patients to ambulate and walk more than 100 feet. By two weeks 71.6% of core patients were ambulatory, and 60.5% could walk >100 feet.

Both renal and hepatic recovery with normal laboratory parameters was evident within one month after implant of the TAH-t.

XI. CONCLUSIONS

Results demonstrate that the SynCardia CardioWest temporary Total Artificial Heart performed reliably on the bench and as intended during the clinical trial. The materials used in its composition are biocompatible with human tissue and blood. The device meets the FDA and ISO guidelines to assure sterility.

All patients enrolled in the study had the opportunity to reach at least 24 months follow-up. Outcomes are summarized in the table below.

Table 12
Summary of Outcomes

Outcome	Core
Overall Survival	
Survival overall at 6 months	75.3%
Survival overall at 12 months	70.4%
Survival overall at 24 months	67.9%
Survival to Transplant	
Survival to transplant	79.0%
Time to Transplant	
Mean time to Transplant or death	79.1 days
Eligibility for Transplant	
Hepatic function normalization	21 days
Renal function normalization	28 days
Mean Organ Perfusion (day 1) increase from baseline	Δ 21.1 mm Hg
Quality of Life While Awaiting Transplant	
Cardiac index (day 1) increase from baseline	Δ 1.1 L/min/m^2
% patients ambulatory	86.4%
% patients walking 100 feet	75.3%
Overall Treatment Success	
Alive 30-days post Tx, NYHA Class I or II, and not bedridden, ventilator dependent or on dialysis	69.1%

The clinical study showed that the device is effective as a bridge-to-transplantation in patients who are at imminent risk of dying from biventricular heart failure. The data obtained in this trial demonstrate that the CardioWest temporary Total Artificial Heart is effective support for patients waiting for donor hearts. In patients implanted with the TAH-t, hemodynamic status improved and renal and hepatic function returned to normal within one month. Treatment outcomes post transplant were nearly identical for the core patients compared to all UNOS patients.

The benefits offered to the patients implanted with the SynCardia TAH-t include the additional time to await transplant and, improved hemodynamics resulting in early ambulation. These benefits outweigh the risks associated with adverse events that occurred.

XII. PANEL RECOMMENDATIONS

At an advisory panel meeting held on March 17, 2004, the Circulatory System Devices Panel recommended that the SynCardia System's PMA for the SynCardia Systems, Inc. CardioWest temporary Total Artificial Heart (TAH-t) be approved subject to submission to, and approval by, the Center for Devices and Radiological Health (CDRH) to the following:

1. A year long postmarket study and adding a contraindication that the device should not be used in patient in whom it would not fit.

2. A contraindication for patients who cannot receive anticoagulation therapy.

3. A warning that safety was not assessed in those patients who are not candidates for anti-platelet therapy.

4. Surgeons be required to view a human transplant with the device before attempting their own procedure.

XIII. CDRH DECISION

CDRH concurred with the Panel recommendation of March 17, 2004, and issued a letter to SynCardia Systems, on April 9, 2004, advising that its PMA was approvable subject to SynCardia Systems modifying the Instructions for Use and Summary of Safety and Effectiveness and also agreeing to the conditions of approval as recommended by the Panel and required by FDA. A postapproval study was necessary to provide assurance that the success of the device at one center can be reproduced at different centers. A postapproval study protocol detailing the number of patients (at least 50) that will be followed, the duration of follow-up (at least 1 year), and the endpoints (including, but not necessarily limited to survival to transplant, adverse events, device malfunction, etc) was requested. In an amendment received by FDA on August 16, 2004, SynCardia Systems submitted the

required data regarding their agreement to the postapproval study and Instructions for Use modifications. It should be noted that the postapproval protocol will be submitted as a supplement to the PMA once approval is obtained.

FDA issued an approval order on October 15, 2004. The applicant's manufacturing facility was inspected on January 7, 8, 9, 12 and 13, 2004 and September 21, 22 and 23, 2004, and was found to be in compliance with the Quality System Regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATION

Directions for use: See the labeling.

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

Postapproval Requirements and Restrictions: See approval order.