Summary of Safety and Effectiveness Data

The Heart Laser™ CO_2 TMR System

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The Heart Laser™ CO_2 TMR System
PLC Medical Systems, Inc.

1. General Information

Device Generic Name:.....Transmyocardial Revascularization (TMR) device
Device Trade Name:.....The Heart Laser™ CO_2TMR System
Applicant's Name and Address:.....PLC Medical Systems, Inc.
10 Forge Park
Franklin, MA 02038
PMA Application Number:.....P950015
Date of Panel Recommendation: .....April 24, 1998
Date of Notice of Approval to the Applicant: ..August 20, 1998

2. Indications For Usage

Transmyocardial revascularization with The Heart Laser System is indicated for the treatment of patients with stable angina (Canadian Cardiovascular Society class 3 or 4) refractory to medical treatment and secondary to objectively demonstrated coronary artery atherosclerosis not amenable to direct coronary revascularization.

3. Contraindications

No contraindications known.

4. Warnings and Precautions

See WARNINGS AND PRECAUTIONS in the final draft labeling (Information for Use)

5. Device Description

The Heart Laser™ CO_2 TMR System (The Heart Laser System) is a 1000 watt, fast axial flow, CO_2 laser, operated in a pulsed-only mode, producing pulses of 10 to 99 milliseconds at 8 to 80 Joules. The energy is delivered directly to the heart through a seven mirror articulated arm terminated with a 125 millimeter focal length hand piece producing an approximately 1 mm diameter hole. The CO_2 laser beam is combined with a helium-neon (visible) laser beam as it exits the laser tube to facilitate aiming.

The Heart Laser System is a pulsed, ECG synchronized 10.6 μm CO_2 laser intended for use in transmyocardial revascularization. The 1000 watt laser is set to deliver a maximum power of 800 watts in pulses 10 to 99 msec long at energies of 8 to 80 joules. Laser energy is delivered to the tissue through an articulated arm terminated with a single use, sterile, handpiece.

The laser housing contains all systems components, including the laser head, cooling system, power supply, and computer. All laser functions are controlled from the computer touch screen. The computer interfaces directly with the system H/P Model 78352C ECG monitor to trigger laser actuation at the peak of the R-wave. Laser pulse and ECG signals are displayed on the touch screen to allow the operator to see the timing of the laser pulse in relation to the R-wave.

The sterile disposable TMR kit contains a straight and right angle handpieces to access different sections of the myocardium. The Heart Laser System components, which include the laser resonator, the optical delivery system, the power supply system, the cooling system, the gas and vacuum system, computer control and the safety system, are described below.

5.1 Laser Resonator

The laser resonator is built of several major components including the gas and cooling manifolds, and the mounting surfaces for the laser cavity optics. To the top of the laser body are mounted the gas cooling and distribution manifolds which supply cooled gas to the quartz tubes and cools return gas from the tubes. The gas is pushed through this manifold system by a speed turbine, which is mounted to the bottom of the laser body.

5.1 Optical Delivery System

The optical delivery system includes the helium neon (HeNe) aiming laser and the seven mirror articulated arm. The optic in this mount allows the CO_2 beam to pass through but reflects the HeNe beam up at 45 degrees. By adjusting these two optics, the red beam and the CO_2 beam are made coincident. The two concentric beams are now reflected off the two remaining mirrors so that the concentric beams exit the tower perpendicular to the top of the tower. By adjusting the last two mirrors in the tower the laser beams are made to exit the arm perpendicular and centered.

5.2 Power System and Cooling System

The laser resonator uses RF energy to excite the CO2 laser gas mix. The laser energy is derived from a DC power supply (four, sealed , lead-acid type, 12 volt, storage batteries). The storage batteries are recharged automatically as needed from AC power (220/230 volts wall outlet).

The laser resonator and power supply are cooled by a built in circulating chilled water system including a compressor, a heat exchanger, a liquid pump, a cooling fan and an electronic controller. This system cools the resonator, which in turn cools the circulating laser gas, the turbine motor, and the RF power supply.

5.3 Gas and Vacuum System

The gas and vacuum system controls the flow and the pressure of the laser gas. The gas and vacuum system maintains this pressure within the narrow pressure range necessary to operate the laser. The laser gas is stored in a high pressure tank in the storage compartment.

5.4 Computer Control and EKG Synchronization

A Pentium computer with a DOS operating system is the central control unit. Custom software written by PLC Medical Systems controls laser firing and provides system safety, system monitoring, and system control.

Laser firing is controlled by Hewlett Packard, model 78352C, ECG monitor to occur at the peak of the R-wave. If "arm laser" button has been activated on the control panel and the surgeon is depressing the foot switch, the laser will fire one pulse of the duration set on the control panel.

5.5 Safety System

Protections for the user and the patient include the safety shutter, the watch dog circuits, the power feedback system, the calibration test port. The safety shutter ,which opens when the foot switch is depressed, keeps unintended laser power from escaping out of the system. The watch dog circuits monitor the operation of the software and shut down the main power relay if the software stops, hangs up or malfunctions. The power feedback system warns the operator if the SET and REAL pulse widths do not agree (within 18%).

The calibration test port allows the operator to check the actual output energy of the resonator and decide whether the laser energy is at an acceptable level to continue with the procedure.

6. Alternative Practices and Procedures

The alternative for the treatment of ischemic myocardium that cannot be revascularized by CABG or PTCA therapy is continued pharmacological management using cardioactive medications .

7. Marketing History

The Heart Laser CO_2 Laser System is commercially available in the countries listed below. The device has received the European Community CE mark (excluding France). No device has been withdrawn from any country or site for any reason relating to safety or effectiveness.

Marketing outside of the United States (as of May 1997)

Australia	Greece	Norway	Spain
Austria	Hong Kong	Pakistan	Switzerland
Brazil	India	Philippines	Thailand
China	Indonesia	Poland	United Kingdom
Columbia	Italy	Saudi Arabia	Venezuela
France	Japan	Singapore	
Germany	Mexico	South Africa	

8. Adverse Events

8.1 Observed Adverse Events

Since the beginning of the clinical studies in the U.S. in 1990, a total of 650 patients have been treated with The Heart Laser System. The randomized trial of TMR using The Heart Laser System versus medical management (MM) involved 192 patients who were followed for an average of 8.75 months per patient or a total of 140 patient-years. These 192 patients are the focus of the analyses shown hereafter. The incidence of adverse advents in the 458 additional patients was similar.

There were no intra-operative deaths in the TMR group, but three patients (3%) died in the perioperative period. One patient died in cardiogenic shock (day 5 post procedure), one of cardiac arrest (day 9), and one with an acute myocardial infarction (day 12). There were also three deaths (3%) in the MM group; two from acute myocardial infarction (days 13 and 24 after enrollment), and one from coronary artery disease (day 30). Nine of the 60 patients (15 %) treated with TMR after failing medical management(crossover patients) died. Three died with ventricular fibrillation (two on day 0 and one on day 2), one with an acute myocardial infarction (day 7), two with strokes (day 7 and day 14), one in cardiogenic shock (day 9), one with low cardiac output (day 11), and one died a cardiac death of unknown cause (day 7).

All deaths and other adverse events were reviewed by an independent Data and Safety Monitoring Board (DSMB) for severity and relation to the procedure (TMR). Table 8-1 shows the incidence of major adverse events which were judged by the DSMB as probably or possibly related to TMR from the Phase III trial.

Table 8-1. Incidence of Major Cardiac Adverse Events

All patients in the Phase III Randomized Trial (N=192)

Cardiac Related Event	TMR assigned (N=91)		Crossovers[c] (N=60)		MM (N=101)
	Day 1-30	Month 1-12[a]	Day 1-30	Month 1-12[a]	Month 1-12[a]
Acute myocardial infarction	6.6%	7.7%	6.7%	6.7%	11.9%
Arrhythmia: Atrial	2.2%	2.2%	5.0%	5.0%	-
Arrhythmia: Ventricular[b]	9.9%	9.9%	11.7%	11.7%	-
Cardiogenic Shock/Low output	3.3%	3.3%	6.7%	6.7%	-
Chest Pain	1.1%	1.1%	-	-	1.0%
Congestive heart failure	11.0%	11.0%	5.0%	5.0%	9.9%
Laser Hit – Mitral Regurgitation	1.1%	1.1%	1.7%	1.7%	-
Left Ventricular Bleeding	1.1%	1.1%	1.7%	1.7%	-
Mitral Valve Regurgitation	-	1.1%	-	-	-
Pericardial Tamponade	-	-	1.7%	1.7%	-
Pericarditis	-	1.1%	-	-	-
Ruptured Left Ventricle	-	-	1.7%	1.7%	-
Unstable Angina	1.1%	2.2%	3.3%	5.0%	69.3%

[a] *Includes first month (days 1-30). Average duration of follow-up was 10.4 mos for the 91 TMR patients, 8.7 mos for the 60 crossover patients, and 7.2 mos for the 101 MM patients*

[b] *One patient had 2 events – a peri-operative event and a long-term event*

[c] *Control patients that failed medical therapy and received TMR during the 12 month study.*

Adverse events judged by the DSMB to be not related to the TMR procedure were reported in 1% to 8% of the patients. These adverse events included anemia, cancer, cerebrovascular accident, edema, GI complications, hemothorax, hyperglycemia, hypotension, infection, pleural effusion, pulmonary complications, renal complications, and syncope.

8.2 Potential Adverse Events

Adverse events potentially associated with the use of TMR include (in alphabetical order):

- Acute Myocardial Infarction
- Accidental Laser Hit
- Arrhythmia
- Congestive Heart Failure
- Conduction Pathway Injury
- Cerebrovascular Accident
- Death
- Mitral Valve Damage
- Pulmonary Complications
- Unstable Angina

9. Summary of Preclinical Studies

9.1 Biocompatibility Testing

Biocompatibility testing of all blood-contacting components of the Heart Laser System was conducted in accordance with the FDA-modified matrix of International Standard ISO-10993, "Biological Evaluation of Medical Devices Part 1: Evaluation and Testing." Testing was conducted in accordance with the "limited exposure/indirect blood path" category. The following tests were conducted: cytotoxicity, dermal sensitization, intracutaneous injection testing, systemic toxicity, pyrogenicity, prothrombin time assay, unactivated partial thromboplastin time, in vitro hemocompatibility and complement activation analysis. All device materials were demonstrated to be nontoxic, nonsensitizing, nonpyrogenic, and hemocompatable. In addition, these components did not adversely effect the prothrombin coagulation time or the clotting time of human plasma and they did not induce complement activation. Based on these results the device components are biocompatible for their intended use.

9.2 Bench Testing

Laser Standards

The Heart Laser System contains a Class IV laser that conforms to 21 CFR 1040.10 and 1040.11 Radiological Health requirements. The system was designed to the international standard IEC 601-2-22.

Device Functionality Testing

Functionality of the right angle handpiece and the laser lens cell was tested by firing a single heart laser beam at a known power level through the assembly and determining the power output. All power output readings for the laser lens cells and right angle handpieces were within ±5% of the known power output. The straight handpiece was tested by passing a HeNe laser beam through the handpiece attached to an inspection jig. The laser beam passed through the straight handpiece and was not occluded by the handpiece. These results support the functionality of the components following sterilization.

ECG Synchronization Validation

The synchronization of the R-Wave peak to the ECG Output Sync Pulse for the Hewlett Packard model 78354A Patient Monitor was measured using a digitizing oscilloscope. Twelve electronically simulated and twelve *in vivo* ECG tracings confirmed the timing and accuracy of the ECG trigger and subsequent laser firing. The Patient Monitor consistently produced an ECG Output Sync Pulse within ten milliseconds of the R-Wave peak, while the laser consistently fired within three milliseconds after receiving the synch pulse. Six additional electronically simulated ECG tracings verified the ability of the system to perform correctly in the presence of negatively directed R-Waves. The data also verified the accuracy of the laser marker on the Patient Monitor's display screen.

Battery Pack Performance Testing

The endurance level of the battery pack was evaluated following repeated firing of the laser, set at the maximum energy level of one 80 Joule pulse every minute, for one hour. The terminal voltage and current delivered by the battery pack during the testing were recorded, as well as the time needed to recharge the battery. The test results indicated that the battery endurance level is adequate and that the battery pack is recharged in fifteen seconds after every firing.

Software Validation

V1.09 is the current version of the software used in The Heart Laser System. The software is utilized in most of the key functions of the system. These functions include setting and displaying system parameters; starting, firing, and shutting down the laser; monitoring the laser status; and storing system data. The software was treated as a system component and was verified as part of the device in system integration tests. The tests performed included a complete software function test, during which the functionality of the software was evaluated. No critical faults were identified, and the results met the respective acceptance criteria. A "Requirements Traceability Matrix", document which relates the verification and validation tests to the software and system requirements, was provided.

Electrical Safety & Electromagnetic Compatibility

The Heart Laser System has been tested to and conforms to the requirements of the domestic and international standards listed below.

Electrical Safety

IEC 601-1, UL 2601-1, CSA 22.2 No. 601-1-M90

The Hewlett Packard model 78352C ECG Patient Monitor used in the Heart Laser System has been tested to and meets the following electrical safety standards: CSA 22.2 No. 125, UL 544, IEC 601-1. Additionally, it meets the requirements of AAMI EC13-1983, standard for cardiac monitors.

Electromagnetic Compatibility

IEC 601-1-2
IEC 1000-4-2,3,4,5 (formerly IEC 801-2,3,4,5)
FCC part 18
EN 55011

Reliability Testing

The continuous test results indicate that the Heart Laser System can operate reliably for up to 10 years. Likewise, the interruptible test results indicate that the system can operate reliably for up to 5.3 years. These conclusions are based on the Heart Laser System performing an expected 100 procedures per year with an average of 36 transmyocardial channels per procedure.

9.3 Sterility and Packaging Testing

Sterility

The TMR Disposable kit is sterilized by a validated 100 percent ethylene oxide sterilization process. The validated protocol was based on the ANSI/AAMI/ISO 11135-1994 Standard: "Medical devices - Validation and routine control of ethylene oxide sterilization". The validation results demonstrated that the sterilization process achieved a sterility assurance level of 10^{-6}.

Shelf Life Studies

Sterility testing and a microbial challenge were performed to evaluate the ability of the TMR Disposable Kit packaging to maintain sterility over a period of one year. The sterility testing was conducted on 20 samples real-time aged for one year. All samples were found to be sterile. The microbial challenge test was conducted on 3 samples real-time aged for one year. The test results showed negative growth for all of the samples. Based on these results, a shelf life of one year for the TMR Disposable Kits has been established.

Shipping tests

TMR Disposable Kit

Drop, vibration and compression testing, in accordance with International Safe Transit Association Test Procedure 1A, was conducted on 67 TMR Disposable Kits packaged in shipping containers. Additionally, thirty samples each of the right angle and straight handpieces were evaluated functionally for alignment and three right angle handpieces were evaluated for strength. The labels of all kits evaluated remained legible and intact; the pouches and handpieces were free from damage; and pouch seals remained intact. Handpieces passed the alignment and strength tests. The results of the study support the ability of the packaging to protect the kits from physical damage during transit.

Heart Laser System

The Heart Laser System was retrospectively evaluated for damage during transport. The current design of the wooden crate customized for the transportation of the system prevents movement of the system during shipment. Retrospective analysis of fifty-one shipments using the customized crates has shown no failures at installation related to shipping.

10. Summary of Clinical Studies

The Heart Laser System was evaluated in three clinical studies involving 691 patients a pilot study (Phase I), an open safety/effectiveness study (Phase II) and a randomized parallel study

with unstable angina arm and a continuation arm (Phase III). Table 10-1 summarizes the baseline description of these patients.

Table 10-1. Summary of Clinical Studies

N (percent), mean (range), mean [95% confidence interval], All patients enrolled in all studies, N=691

Study	Phase I	Phase II	Phase III					Total
Description of Study								
Type of Study	Pilot/ Safety Open	Safety/ Effectiveness Open	Randomized Parallel Study blinded core laboratory SPECT		Crossover Arm	Unstable angina arm	Continuation arm	
Treatment	TMR	TMR	TMR	MM (control)	TMR	TMR	TMR	-
# Patients Enrolled	15	201	91	101	-	66	217	691
# Centers (a)	1	8	12	12	-	10	16	16
Primary outcome measures	Feasibility	Angina, SPECT	Myocardial Perfusion Improvement (pharmacological stress SPECT studies) Angina Improvement					
Other outcomes	Morbidity /Mortality	Morbidity /Mortality	Morbidity/Mortality, Unstable Angina Events, Quality of Life					
Description (at baseline) of Patients Treated								
# TMR treated	15	201	91	0	60	66	217	650
Age, mean (range)	62 (42,82)	63 (35,85)	61 (30,82)	61 (37,83)	61 (37, 83)	64 (41,87)	63 (37, 85)	-
Females, N (%)	3/13 (23%)	44/201 (22%)	17/91 (19%)	23/101 (23%)	11/60 (18%)	22/66 (33%)	62/215 (29%)	-
s/p AMI, N (%)	9/13 (69%)	163/201 (81%)	75/91 (82%)	78/101 (77%)	47/60 (78%)	51/66 (77%)	156/215 (73%)	-
s/p CABG, N (%)	12/13 (92%)	167/201 (83%)	84/91 (92%)	92/101 (91%)	56/60 (93%)	55/64 (86%)	192/215 (89%)	-
s/p PTCA, N (%)	4/13 (31%)	56/149 (38%)	43/91 (47%)	53/101 (53%)	32/60 (53%)	36/66 (55%)	108/214 (51%)	-
CHF, N (%)	1/13 (8%)	34/127 (27%)	31/91 (34%)	35/101 (35%)	22/60 (37%)	33/66 (50%)	81/212 (38%)	-
Ejection fract % (range)	-	47% (15,77)	50% (24,75)	50% (21,73)	51% (21,69)	47% (23,82)	50% (19, 74)	-

The balance of this section describes the Phase III randomized trial.

10.1 Phase III Study Design

Twelve US centers participated in a prospective, randomized, controlled, multi-center study. Patients were randomized to receive treatment with The Heart Laser System or continued medical management (MM). Patients enrolled into the study had: 1)medically refractory Canadian Cardiovascular Society (CCS) Class 3 or 4 angina, 2) reversible ischemia of the left ventricular free wall and, 3) coronary anatomy that precluded CABG or angioplasty. Patients were excluded from the study if their left ventricular ejection fraction (LVEF) was < 20% or if they had a concurrent major illness.

MM patients who failed medical management (developed unstable angina requiring ≥48 hours of intravenous anti-anginal therapy in an intensive care unit) were eligible for TMR treatment (crossovers). TMR crossover patients were followed up for 12 months after TMR treatment.

Angina Assessment: Each patient's angina was evaluated at baseline and at 3, 6 and 12 months follow-up and was classified using the Canadian Cardiovascular Society (CCS) guidelines. .An independent assessor, who was masked as to the treatment received, validated angina classification at the end of the study. The independent assessment was conducted an average of 5 months following the angina evaluation at 12 months. In 80% of the cases, the independent survey classification was within one class of the site score. Evaluations were similar between the two treatment groups and across the 12 investigational sites when the site and independent evaluations were compared.

Radionuclide Scans: All patients underwent baseline radionuclide scanning with follow-up scans at 3, 6 and 12 months post-randomization. Thallium-201 single-positron emission tomography (^{201}Tl:SPECT) was performed to assess the extent and reversibility of myocardial ischemia at rest and during exercise. Dipyridamole (0.56 mg/kg up to 6 mg) was infused over 4 minutes. If feasible, the patient walked in place for 4 minutes to minimize side effects and improve image quality. Subsequently, 3.5 to 4.0 mCi of thallium-201 was injected, after which the patient was monitored for 13 minutes. Image acquisition was started 10 to 20 minutes after thallium-201 injection. Three to 4 hours later, redistribution imaging was performed. Half of the initial thallium-201 dose was then reinjected, and reinjection imaging was performed after 10 to 20 minutes.

The radionuclide scans were processed at two independent core laboratories masked as to the patient's treatment and the timing of the scan in the patient's treatment course. The images were divided into apical, middle, and basal slices and a 24 segment model was used in which each slice was further divided into 8 segments. The 6 segments that formed the lateral, anterolateral, and posterolateral walls represented the left ventricular free wall (TMR-treated myocardium). The remaining 2 segments represented the intraventricular septum (non-TMR-treated myocardium).

Redistribution/stress and reinjection/stress images were displayed side by side, and myocardial segments with fixed perfusion defects were recorded. Stress images were compared to redistribution/reinjection images to detect reversible defects. Each segment was scored as representing normal tissue, a fixed defect (scarred or hibernating tissue), a reversible defect, or both types of defects. The defects were then totaled for the left ventricular free wall and intraventricular septum, providing perfusion information concerning the entire left side of the heart.

Quality of Life Assessment: Each patient completed the Short Form-36 (SF-36) and the Seattle Angina Questionnaire (SAQ) at the time of enrollment and at 3, 6, and 12 months follow-up.

TMR Treatment: With the patient under general anesthesia, transesophageal echocardiography (TEE) was performed to assess regional wall abnormalities and mitral valve anatomy. A left anterolateral thoracotomy was performed between the fifth and sixth intercostal space. Areas of reversible ischemia were treated with The Heart Laser System. At a peak power of 800 watts, 1-mm-diameter transmural laser channels were created with a single pulse through the left ventricle, spaced at approximately 1 channel per cm^2 of myocardial surface. The laser was synchronized to fire at the electrocardiographic R-wave, when the left

with unstable angina arm and a continuation arm (Phase III). Table 10-1 summarizes the baseline description of these patients.

Table 10-1. Summary of Clinical Studies

N (percent), mean (range), mean [95% confidence interval], All patients enrolled in all studies, N=691

Study	Phase I	Phase II	Phase III					Total
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# Patients Enrolled	15	201	91	101	-	66	217	691
# Centers (a)	1	8	12	12	-	10	16	16
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Other outcomes	Morbidity /Mortality	Morbidity /Mortality	Morbidity/Mortality, Unstable Angina Events, Quality of Life					
Description (at baseline) of Patients Treated								
# TMR treated	15	201	91	0	60	66	217	650
Age, mean (range)	62 (42,82)	63 (35,85)	61 (30,82)	61 (37,83)	61 (37, 83)	64 (41,87)	63 (37, 85)	-
Females, N (%)	3/13 (23%)	44/201 (22%)	17/91 (19%)	23/101 (23%)	11/60 (18%)	22/66 (33%)	62/215 (29%)	

ventricle is maximally blood-filled and the heart is electrically quiescent. Transmural penetration by the CO_2 laser was confirmed by the TEE.

10.2 Patient Description and Gender Bias

Patients were enrolled into the study between July 1995 and September 1996 at the 12 United States centers and were randomly assigned to the two treatment groups: 91 to Transmyocardial Laser Revascularization (TMR) and 101 to continued medical management (MM). The study population (N=192) is described in Table 10-2.

Table 10-2. Description of patients at Baseline and Laser Treatment

Number (%), Mean± SD, {range}, All patients enrolled in the Phase III Trial, N=192

Descriptor	TMR (N=91)	MM (N=101)	Difference [95% CI]
Female	17 (19%)	23 (23%)	-4.1% [-15.5%, 7.4%]
Age (yr)	61±10	61±11	0.0 [-3.0, 3.0]
CCS Class 4 Angina	63 (69%)	64 (63%)	5.9% [-7.5%, 19.2%]
CCS Class 3 Angina	28 (31%)	37 (37%)	5.9% [-19.2%, 7.5%]
Unstable Angina	7 (8%)	13 (13%)	-5.2% [-13.7%, 3.3%]
LVEF (%)	50±11	50±11	0.0 [-3.1, 3.1]
LVEF ≤ 45%	42 (46%)	54 (53%)	-7.3% [-21.4%, 6.8%]
AMI History	75 (82%)	78 (77%)	5.2% [-6.1%, 16.5%]
CHF	31 (34%)	35 (35%)	-0.6% [-14.0%, 12.9%]
CABG: History	84 (92%)	92 (91%)	1.2% [-6.6%, 9.0%]
PTCA: History	42 (46%)	54 (53%)	-7.3% [-21.4%, 6.8%]
Hypertension	59 (65%)	65 (64%)	0.5% [-13.1%, 14.0%]
Diabetes	36 (40%)	52 (51%)	-12% [-25.9%, 2.1%]
Hypercholesterolemia	52 (57%)	66 (65%)	-8.2% [-22.0%, 5.6%]
Current Smoker	8 (9%)	7 (7%)	1.9% [-5.8%, 9.5%]
CABG Risk*	6.1±3.4	5.8±2.9	0.3 [-0.6, 1.2]
High CABG Risk*	54 (59%)	58 (57%)	1.9% [-12.0%, 15.9%]
Laser shots fired	36 {15, 75}	-	-
TEE confirmed channels	30 {4, 50}	-	-

95% CI = confidence interval by normal approximation

**High CABG risk by the Cleveland Clinic CABG Surgery Risk stratification risk model is defined as a risk number of 5 or higher.*

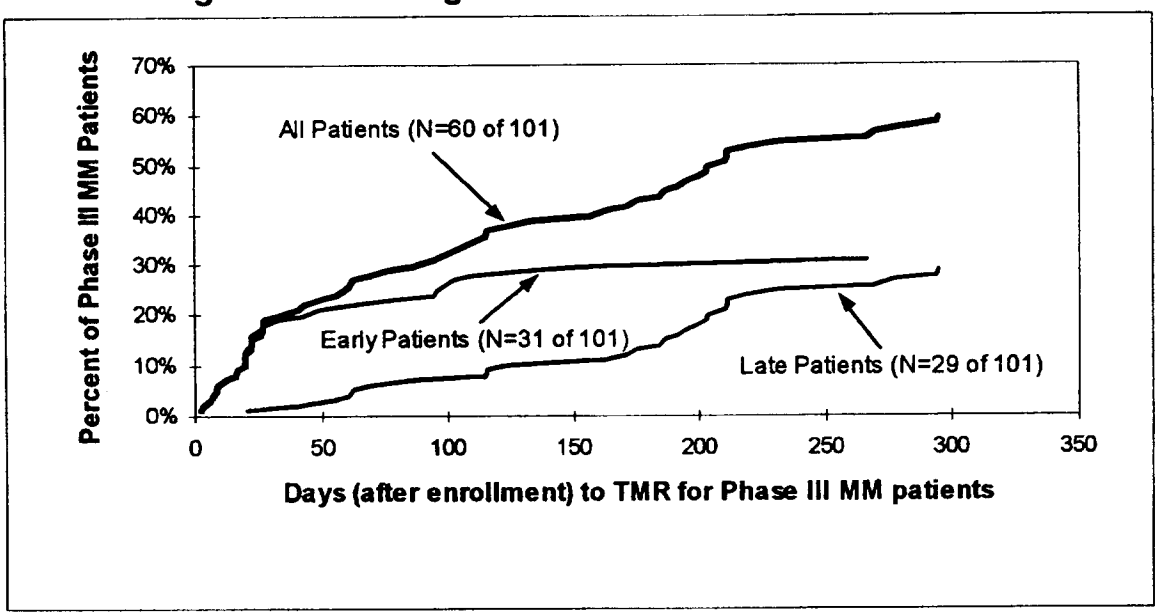
Study inclusion and exclusion criteria were designed and the study carried out to avoid gender bias in patient enrollment. Of the 192 patients enrolled, 40 (21%) were female. This proportion of females is consistent with the female to male incidence of patients presenting for coronary artery bypass graft surgery. In a study published in the JACC, 1,148 patients (20%) were female out of 5,517 patients participating in the study.[1]

[1] Tu JV, Sykora K, Naylor CD. Assessing the outcomes of coronary artery bypass graft surgery: How many risk factors are enough? **JACC** 1997, 30; 1317-23.

Based on univariate analyses, there was no association between any of the study endpoints and patient gender so subsequent results are considered relevant to both males and females.

MM treatment crossovers . Of the 101 MM patients, 70 (69%) failed due to unstable angina and 60 (59%) received TMR treatment (crossovers). During the first half of the study, the median time to crossover was 26 days. To limit the incidence of crossover, a 6 month mandatory waiting period was implemented . After 7/8/96, the median time to crossover was 186 days (Figure 10-1). The TMR and MM crossover patients had similar baseline characteristics except for the presence of pre-operative unstable angina in 70% of the MM crossover patients compared to 13% of the MM patients.

Figure 10-1. Timing of TMR Treatment of MM Patients



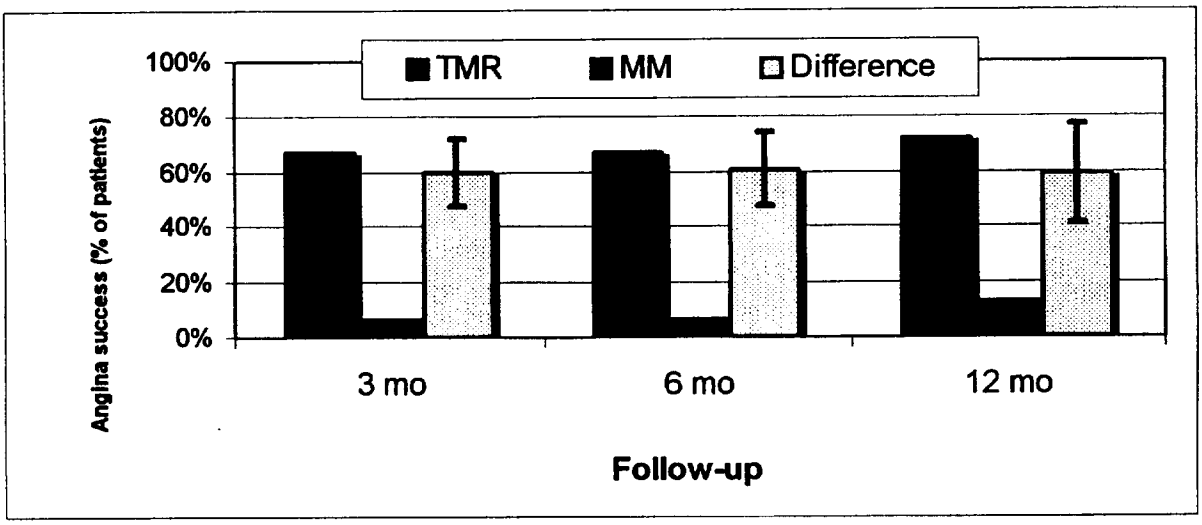
Percent of all Phase III MM patients enrolled, N=101

Measure	Early Patients (through 7/8/96)	Late Patients (after 7/8/96)	All Patients
Number (of 101)	31	29	60
Percent (of 101)	31%	29%	59%
Mean (days)	52	167	107
Median (days)	26	186	90
Minimum (days)	2	21	2
Maximum (days)	266	295	295

10.3 Results

Angina Class. Success in angina reduction was defined as improvement from baseline by at least 2 angina classes. Figure 10-2 shows the percent of patients showing angina success at 3, 6 and 12 months.

Figure 10-2. Angina Success at 3, 6, and 12 months



Number, %, Difference, 95% confidence intervals, All Phase III patients evaluated for angina, N=138

When	Follow-up at 3 months			Follow-up at 6 months			Follow-up at 12 months		
Treatment	TMR	MM	Difference	TMR	MM	Difference	TMR	MM	Difference
# Successes	52	4		45	3		44	3	
# Evaluated	78	60		67	47		61	23	
% Success	67%	7%	60%*	67%	6%	61%*	72%	13%	59%*
CI-Low	56%	0%	48%	56%	-1%	48%	61%	-1%	41%
CI-High	77%	13%	72%	78%	13%	74%	83%	27%	77%

CI = confidence interval (95%) by normal approximation

- *Difference statistically significant (p<0.05) by chi-square*

In the MM crossover group, 3 month angina assessment on 41 patients found that 32 patients (78%) had no angina (class 0) or were in class 1 to 2; 5 (12%) were in class 3; and 4 (10%) were in class 4. At the 6 month follow-up angina assessment in 37 patients found that 27 patients (73%) were in class 0 to class 2; 8 (22%) were in class 3; and 2 (5%) were in class 4. Twenty-three MM crossover patients were eligible for the 12 month follow-up. Of these 23 patients, 16 (69%) were in class 0 to 2; 3 (13%) were in class 3; and 4 (18%) were in class 4.

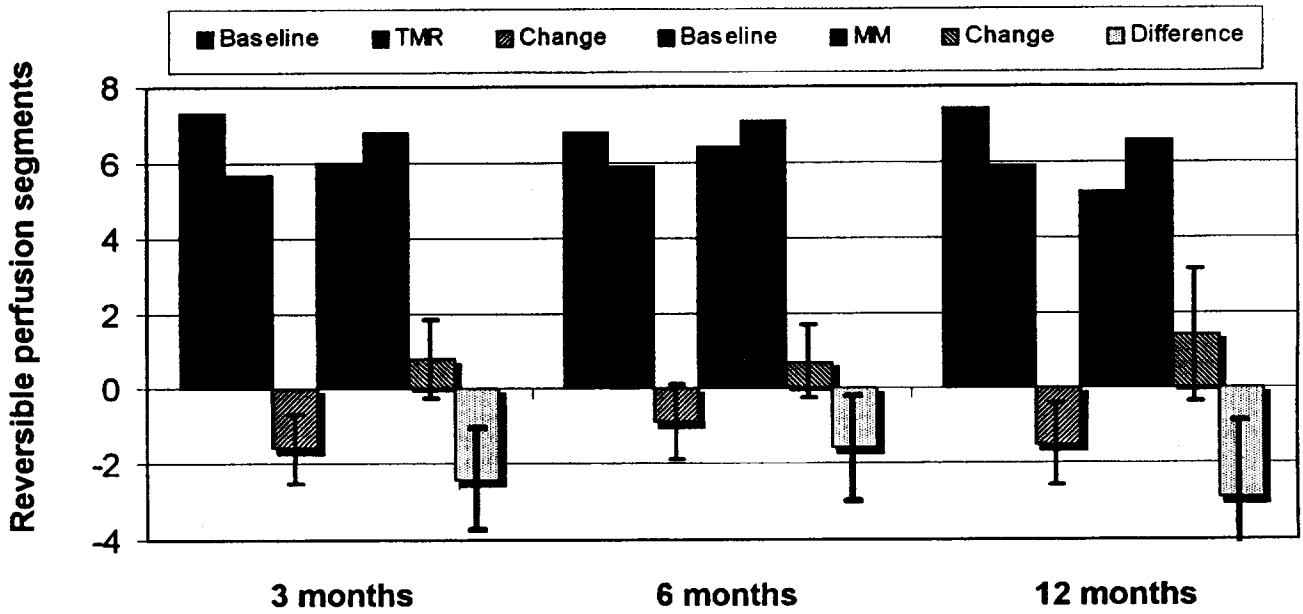
Radionuclide Scans: The TMR and MM treatment groups had similar follow-up rates (compliance: TMR, 81%; MM, 79%; usability: TMR, 72%; MM, 69%) with respect to follow-up TI:SPECT scanning. However, many imaging studies were ineligible for analysis due to additional revascularization procedures, patient death, withdrawal, missed or non-protocol imaging conducted studies or technical problems such as improper formatting of the disk. Figure 10-3 shows the average number of segments with a reversible perfusion defect at baseline and 3, 6, and 12 months. The difference between TMR treated patients and MM patients that have not crossed over is statistically significant as shown by the 95% confidence

intervals that exclude the 0 value. However, a comparison between the patient's perfusion measurements and their angina status lacked a strong correlation.

Figure 10-3. Reversible Segments in the Left Heart by SPECT Scans

Number at baseline, follow-up, change and Difference, 95% confidence intervals

All Phase III patients evaluated for perfusion, N=138



When	Follow-up at 3 months							Follow-up at 6 months							Follow-up at 12 months						
Treatment	TMR			MM			Diff	TMR			MM			Diff	TMR			MM			Diff
Which	Mo 0	Mo 3	Chge	Mo 0	Mo 3	Chge	TMR	Mo 0	Mo 6	Chge	Mo 0	Mo 6	Chge	TMR	Mo 0	Mo 12	Chge	Mo 0	Mo 12	Chge	TMR
N	50	59	50	38	45	38	-MM	47	57	47	35	40	35	-MM	38	46	38	13	15	13	-MM
Mean	7.3	5.7	-1.6*	6.0	6.8	0.8	-2.4*	6.8	5.9	-0.9	6.4	7.1	0.7	-1.6*	7.4	5.9	-1.5*	5.2	6.6	1.4*	-2.9*
% Mo 0		78%	-22%		113%	13%	35%		87%	-13%		111%	11%	24%		80%	-20%		127%	27%	47%
Std Dev		3.6	3.3		3.6	3.1			3.7	3.5		3.1	2.8			3.6	3.4		3.5	2.4	
CI-Lo		4.8	-2.5		5.8	-0.2	-3.8		4.9	-1.9		6.1	-0.2	-3.0		4.9	-2.6		4.8	0.1	-4.6
CI-Hi		6.6	-0.7		7.9	1.8	-1.1		6.9	0.1		8.1	1.6	-0.2		6.9	-0.4		8.4	2.7	-1.2

CI = confidence interval (95%) by normal approximation

** Difference statistically significant (p<0.05) by t-test*

Cardioactive Medications. Changes in the usage of cardioactive medications (nitrates, beta blockers, and calcium channel blockers) from baseline to follow-up were cross-checked against the angina success of TMR or angina failure of MM for their potential influence on the angina outcomes. Most (83%) of the successful TMR patients had a decreased or an unchanged medication regimen. Conversely, 86% of patients who were MM failures had an increased or unchanged medication regimen.

Quality of Life. Based on the results of the SF-36 questionnaire, patients felt less limited physically after TMR (38% improvement) than after MM (6% improvement). This difference was statistically significant ($p<0.01$) at 3, 6, and 12 months. The TMR patients also felt less mentally stressed by their disease post-operatively (23% improvement), while MM patients felt little change (1% improvement). These differences were statistically significant ($p<0.005$) at 3, 6, and 12 months.

The overall SAQ scores improved by 143% in the TMR group and by 39% for patients who continued medical therapy. For the overall score each component of the SAQ (exertional capacity, angina stability, angina frequency, treatment satisfaction, and disease perception), TMR yielded a statistically significantly better result ($p<0.05$) than did MM.

Peri-Operative Morbidity . Peri-operative complications (those that occurred within 30 days of the TMR surgery) in the 91 TMR patients were as follows: 5 patients (7%) had an AMI, 10 patients (11%) had congestive heart failure (CHF), 7 (8%) had ventricular tachycardia or ventricular fibrillation, and 1 (1%) had unstable angina. The only complication specific to TMR was an accidental laser hit to the mitral valve apparatus, which was successfully repaired. Of the 91 TMR patients, 62 (68%) had no in-hospital complications.

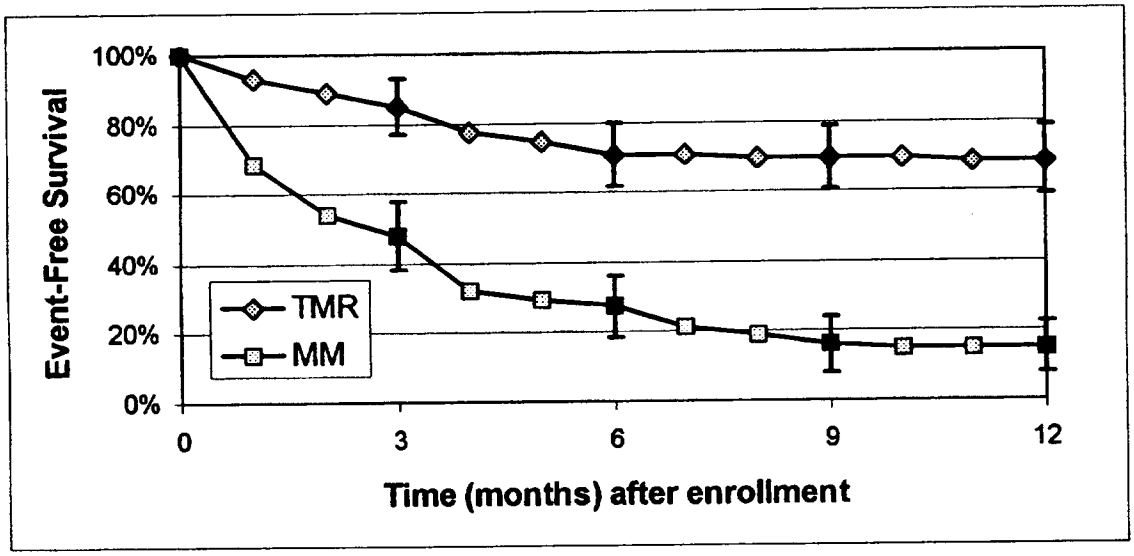
In the 60 patients that crossed over from the MM group the following peri-operative complications were reported: 4 patients (6.7%) had an AMI, 2 patients (3%) had unstable angina, 4 patients (6.7%) had life-threatening arrhythmia (ventricular tachycardia, ventricular fibrillation and cardiac arrest), and 3 patients (5%) had CHF. One patient sustained laser induced damage to the mitral apparatus.

Twelve-Month Morbidity. The incidence of hospital admissions due to unstable angina was 2% after TMR (0.02 ICU admissions/patient/year) and 69% during MM (1.37 ICU admissions/patient/year) ($p<.0001$). Kaplan-Meier estimators, corrected for study dropouts, were used to calculate freedom from AMI, unstable angina and Class 4 angina (Figure 10-4). There was no significant inter-group difference with respect to freedom from AMI (TMR: 89%; MM: 78%) or CHF (TMR: 84%; MM: 77%), but freedom from unstable angina was significantly greater after TMR (86% versus 25%, $p <0.001$).

A total of 11 patients (5 in the TMR group and 6 in the MM group) were lost to follow-up when they refused to return to the treating centers for evaluation.

Figure 10-4. Freedom from Death, AMI, Unstable Angina and Class 4 Angina

Actuarial (Kaplan Meier) survival and 95% confidence interval*, All Phase III patients enrolled, N=192



Month	0	1	2	3	4	5	6	9	12	
TMR (%)	**100%**	**93%**	**89%**	**85%**	**78%**	**75%**	**71%**	**65%**	**64%**	
N	91	85	81	77	71	68	65	59	58	Total
Lost to follow-up		0	0	0	0	0	0	5	0	5
Event (any)		6	4	4	6	3	3	1	1	28
Death		3	1	1	1	2	1	1	0	10
Acute MI		2	2	1	0	1	0	0	0	6
Unstable angina		1	1	2	2	0	2	0	1	9
Angina CCS 4		0	0	0	3	0	0	0	0	3

MM (%)	**100%**	**69%**	**54%**	**48%**	**32%**	**29%**	**27%**	**65%**	**12%**	
N	101	70	55	48	32	29	27	13	12	Total
Lost to follow-up		0	0	0	1	0	0	5	0	6
Event (any)		31	15	7	15	3	2	9	1	83
Death		1	2	0	0	0	0	1	0	4
Acute MI		3	8	1	2	0	0	2	0	16
Unstable angina		27	5	6	7	3	2	5	1	56
Angina CCS 4		0	0	0	6	0	0	1	0	7

** Confidence interval (95%) calculated using SAS PROC LIFETEST for Kaplan-Meier survival estimates.*

Mortality The TMR group had no intra-operative deaths and a 12-month survival rate of 85%, as calculated by Kaplan-Meier estimators. In comparison, the 12-month survival rate was 79% in the MM group for those patients who did not cross over (n=41). Of the TMR patients, 3 (3%) died peri-operatively, and 10 (11%) died during follow-up. Seven (7%) of the 41 MM patients who did not cross over died during the study. Among the MM patients that did cross over (n=60), 15patients (25%) died during the 12 months after TMR treatment. Nine of these 15 patients died within 30 days, for a peri-operative mortality of 15%.

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Univariate and multivariate logistic regression analyses found that unstable angina was the only statistically significant correlate of peri-operative mortality. Furthermore, a correlation exists between the time of an unstable angina event and TMR surgery and TMR peri-operative mortality (peri-operative mortality increases with decreased time between the event and surgery). Likewise greater age and lower LVEF were the predictors of 12-month mortality for the TMR group. The incidence of acute myocardial infarction during the study was a predictor of mortality in both groups. Treatment assignment (TMR vs. MM) was not predictive of a higher mortality.

11. Conclusions Drawn from the Studies

The preclinical studies indicate that The Heart Laser System has the appropriate physical and performance characteristics for its intended use, as stated in the labeling.

Data from the multicenter clinical trial found that treatment with The Heart Laser System provides a reduction in the severity of angina in the majority of patients. Significant risks associated with the procedure include accidental laser hit of the chordae tendinae, life threatening arrhythmias and early death. Based on a Kaplan Meier estimator, the one year survival rates between the TMR group and the MM group that did not cross over were similar. The incidence of unstable angina was significantly lower in the TMR group.

The preclinical and clinical studies demonstrate with reasonable assurance that The Heart Laser System is safe and effective when used in accordance with the approved labeling (Information for Use).

12. Panel Recommendations

The Circulatory System Devices Panel met on July 28, 1997, to consider the application and recommended not approvable pending the completion of the phase III study (to 12 months) and several measures to validate the results.

The Circulatory System Devices Panel reconsidered the application on April 24, 1998, and recommended approval subject to labeling changes, a reanalysis of the angina data, and a post-approval study.

13. FDA Decision

FDA concurred with the Circulatory System Devices Panel's recommendation of April 24, 1998, and issued an approval order advising the sponsor that its PMA was approvable subject to the labeling changes recommended by the Panel and required by FDA in addition to several other requirements described below.

A condition of sale of the device prior to transmyocardial revascularization (TMR) treatment with The Heart Laser CO_2 TMR System, the patient must sign a special consent form to ensure that the risks associated with this treatment have been fully explained to the patient. In addition, all

advertising and promotional materials must include the warning about the use of TMR in a patient with unstable angina, the need for patients to sign a consent form and the requirements that apply to the training of practitioners who may use the device.

Additionally, the applicant must complete a randomized post approval study to further define the 30 day post-operative mortality predictors (risk factors), effectiveness as a function of operator experience (the learning curve), and the medical conditions treated. The study should enroll 600 consecutive patients at all centers to assess clinical status including mortality. A detailed protocol and statistical analysis plan will be submitted to the Agency for review within 30 days of approval. Use of The Heart Laser CO_2 TMR System may continue per the restrictions above at the 33 centers who participated in the IDE studies (a maximum of 10 patients per center). Patient treatment at new centers prior to beginning of the post approval study will be limited to 90 days after the date of the approval order and the total number of patients shall not exceed 90.

FDA performed an inspection and found the applicant in compliance with the Quality System Regulation (21 CFR Part 820).

14. Approval Specifications

Directions for Use: See Final Draft Labeling (Information for Use)

Hazards to Health from Use of the Device: See INDICATIONS, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and ADVERSE EVENTS in the final draft labeling (Information for Use).

Post-approval Requirements and Restrictions: See Approval Order